Göttingen International Health Network (GIHN)

Martin Kappas, Uwe Groß,
Dermot Kelleher (Eds.)

Global Health

A Challenge for Interdisciplinary Research

Universitätsverlag Göttingen

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Address of the Editor
Prof. Dr. Martin Kappas
Geographisches Institut
Abteilung Kartographie, GIS und Fernerkundung
Georg-August-Universität Göttingen
Goldschmidtstr. 5
37077 Göttingen

e-mail: mkappas@uni-goettingen.de

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Acknowledgement

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Christiane Hennecke

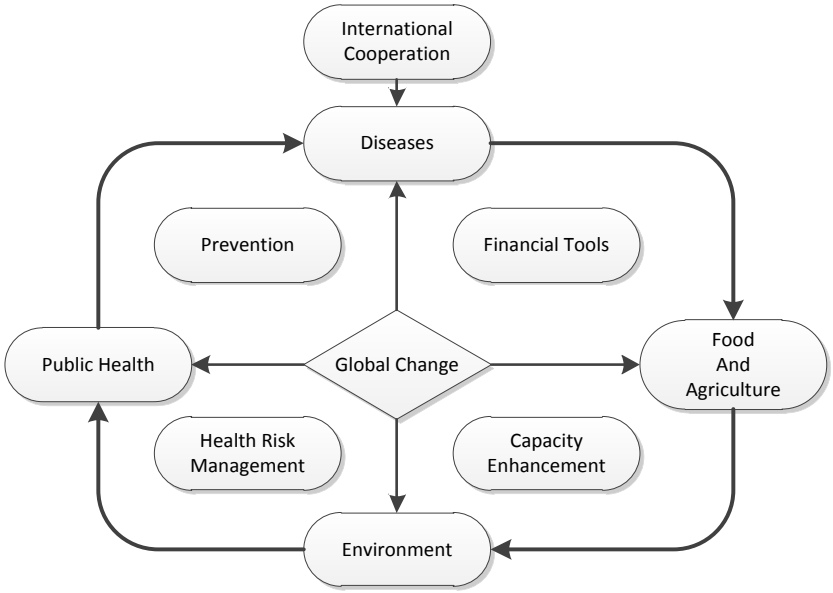
1 Editorial
Global Health
A challenge for interdisciplinary research

International health, global health or one health, are in general synonyms for the same holistic view of human, animal and environmental issues which is not really a new idea over the past decades. The first veterinary schools for instance were created 250 years ago as a response to concerns over food security in and the threat from zoonotic diseases. But over the last decades research lost track of this holistic view on the interconnectedness of all health related issues. In consideration of the fact that climate change is happening and endangering our planet (e.g. AR4-climate report of IPCC 2007) many initiatives have been created to adapt to the projected impacts on the 21st century. The whole range of requirements for human livelihood is at risk and the focus of our future health should be on human, animal and plant diseases together.

Most of the new infectious diseases (around 75%) are of animal origin and the cost of controlling outbreaks can be extremely high. In relation to the risk that a major disease outbreak poses, the costs of prevention are negligible. For this reason decision makers have implemented measures for regulation, surveillance and research networks (like Eurolife or GIHN) to promote prevention. The main health risk drivers are at present:

- Non-Communicable Diseases; Allergies
- Emerging Diseases
- Climate Change, Water Cycle Change and Disturbances of Ecosystem Services
- Food and Agriculture
- Urban Environment (continuation of urbanization to Mega-Cities)

Considering the impact of the above mentioned health risks, a holistic and integrative perspective will be a prerequisite for successful management of Global Health risks in an era of climate change, air pollution, emerging allergies and zoonotic diseases, malnutrition and other development challenges. The integrative approach of global health means the consideration of both the environmental/geo-bio-chemo-physical and socio-economic parameters and is visualized in a simple flowchart



The following list highlights important topics (in bold) and their association with health and global change - related keywords that make the whole story of the flowchart above more complex:

- *Public Health*: healthcare services – pandemics - pet animals – pharmaceuticals - vaccination & resistances - sanitation & hygiene - socio-economic determinants
- *Diseases*: allergies - communicable diseases - emerging diseases - lifestyle diseases - mental illnesses - non-communicable diseases - wildlife diseases – zoonoses
- *Food and Agriculture*: agricultural production - agro chemistry – biofuel - food design - food safety & security - genetically modified organisms - livestock
- *Environment*: biodiversity - ecosystem goods & services - fisheries & wildlife - land degradation - logistics & transportation – natural hazards – pollution - resource – depletion - water & energy
- *Global Change*: climate change – demographics - displacement & migration – globalization – poverty - sustainable development - urbanization
- *Prevention*: early warning - monitoring, surveillance & early detection - predictive modelling - preparedness
- *Health Risk Management*: best practice - ethics & stewardship - integrative risk management - intervention/response - recovery/rehabilitation - resilience & adaptation
- *Capacity Enhancement*: capacity building – education - research, innovation & technology - social learning & behavioural change
- *Financial Tools*: financing methods - funding strategies – insurance - sustainable investments
- *International Cooperation*: alliances & partnerships (Eurolife, GIHN) – communication - corporate social responsibility – institutions - global health strategies - policy & governance - public diplomacy

The assigning of keywords from the above indicates the broad field of interconnected drivers for global health and illustrates relevant scientific disciplines ranging from medicine to geography, sociology, economy and agricultural sciences.

The new **G**öttingen **I**nternational **H**ealth **N**etwork (GIHN) looks at the emergence of "One World, One Medicine, One Health" as the latest instance in a long history of attempts to bring research and treatment of human, animal and plant diseases together. This concept tries to diminish disciplinary and institutional barriers of collaboration. On the other side interdisciplinary research is still weakly elaborated and is often not the focus of funding agencies. What is needed here is a new awareness on the part of politics and funding agencies. Therefore this concept is on probation and has first to show if it could deliver solutions for complex environmental-health problems.

GIHN involves various disciplines in establishing how they could interact and what contemporary interests lead to their co-operation and problem solving. Addressing human, animal and plant diseases within the framework of global change issues (climate change, land use change, lifestyle change) is the outstanding topic of GIHN.

The background for establishing GIHN in 2011 was the strong wish to create a shared vision and to build up the capability of people and institutions in solving

rising health problems which cannot be handled by a mono-discipline view. The global health approach should become the new norm for addressing these complex health issues. Furthermore GIHN encourages bringing together researchers in the relevant areas and facilitating exchange of experience and development of new projects. Networks work best when legitimate interests of different partners combine to further a common goal.

Moreover the implementation of global health approaches are seen as a prerequisite for sustainable life. The adoption of global health itself has a unique value to address health issues at the interface of human and animal ecosystems. For this task cross-sectoral partnerships are needed. The ceremonial launch event of the Göttingen International Health Network on May 24, 2011 was a first response to this challenge. It is no surprise that at the same time other huge joint projects like "Global Strategic Alliances for the Coordination of Research on the Major Infectious Diseases of Animals and Zoonoses" (STAR IDAZ) were created (STAR IDAZ launched in May 2011). Research questions of today read like "Influenza and other Emerging Zoonotic Diseases at the Human-Animal Interface" or "Risk Assessment on West Nile Virus Infection in the European Union" or "Alternatives to Antibiotics" or "Viruses on the Move". Just a few examples of relevant research questions directly connected to Global Health.

The Grand Opening of GIHN was dedicated to the unresolved millennium goal of reducing mother and child mortality in the world. An interdisciplinary research group should deliver approaches for improving maternal and child health. In the light of this a few chapters of the book directly focus on maternal mortality. Other chapters deliver a more general view of conceptual vistas or offer information about very specific health problems such as infectious diseases or the travel behaviour of people and related illnesses. Therefore the book is divided into three sections (I: *"Setting the Scene"*, II: *"Health Risks related to Maternal and Child mortality – examples from Africa and India"*, III: *"Specific initiatives and research topics under the vision of GIHN"*). The chapters of the book reflect the broad variety of topics under the umbrella of global health presented at the GIHN opening event, May 24th /25th 2011 at Göttingen University.

Setting up GIHN and the present book was a great challenge and we should like to thank the members of Eurolife and GIHN and all contributing authors to this book. Finally, in the name of the entire network, we should also like to express our gratitude to the outstanding commitment of Ms Christiane Hennecke (University Medical Center Göttingen, International Affairs) and Ms Martina Beck (Institute of Geography, Göttingen University) for their help in setting up the *Göttingen International Health Network* and creating a first joint publication dedicated to the vision of "global health".

Göttingen, Juli 2012 Martin Kappas, Uwe Groß, Dermot Kelleher

I. Setting the scene

2 Knowledge based approaches to international health: The Eurolife International Health Alliance

Dermot Kelleher

1 Introduction

The world of biomedical science is rapidly changing at an international level at a rate which is frequently not fully appreciated. Arising out of the genome project, we now understand in a lot more detail both the causes of monogenic disorders and the complexities of the genetic components of common human diseases such as diabetes, inflammatory arthropathies and gastrointestinal diseases such as celiac disease or inflammatory bowel disease. However, the genome project although providing huge quantities of data has only provided us with an introduction and a framework on which to base our understanding of human disease. Most importantly, we now appreciate that many diseases occur as a result of an interaction of a series of both environmental and genetic effects. Such interactions could best be illustrated by the example of coeliac disease, a condition also known as gluten-sensitive enteropathy, in which the host's genetic background determines the susceptibility, but exposure to gliadin and related proteins from wheat and other cereals in the diet is the factor which provokes disease. On this background, we can begin to identify a very complex history of evolution of the condition, which is non-fatal and which has developed in geographically distinct parts of the world, including Punjab, North Africa (1) and Ireland (2).

We now have to begin to develop an understanding of the "exposome" (3), ie the disease provoking factors to which we are exposed and to develop the tools to catalogue such interactions and to understand their relationships with the genetic component of disease. The influence of such gene- environment interactions over generations can lead to development of populations which are skewed in a particular direction, as a result of both genetic and environmental factors. Hence, genes which contribute to auto-immune disease might also be favourable in terms of their capacity to skew immune responses towards stronger responses to bacterial or viral infection. In the international health arena conditions such as sickle cell disease represent the outcome of generations of interactions with infectious agents and the processes of natural selection which have enabled survival of the host.

2 The paradigm of gene-environment interactions

Therefore, the concept of gene environment interactions in terms of conventional, common diseases in man has led to an evolving understanding of disease. Most notably, in recent times, we have been able to determine that multiple genes are involved in disease causation, through genome-wide association studies (4). Furthermore, in recent times, we have also been able to identify the cell biology resulting from gene-gene interactions and from protein-protein interactions and the potential for pathogenic processes to have clear pathways towards disease causation. We now increasingly, in terms of modern day science, utilise animal models of disease to determine the true extent of gene-environment interactions in an *in vivo* setting and such models have provided us with very exciting insights into the causation of diseases such as childhood eczema, multiple sclerosis, among others. Ultimately, the process of drug development typically involves the requirement for such animal models, prior to testing of a therapeutic entity in a murine system before our well developed processes for clinical trials.

However, we do know that this paradigm, while extremely valuable in countries with economic resources to take advantage, has limited applicability when it comes to the implementation of change in terms of poverty related disease. At this moment in time, the world is seeing an emergence of a range of epidemic diseases, including conditions such as West Nile Fever, SARS coronavirus, multi-drug resistant salmonella, multi-drug resistant TB and the factors that determine susceptibility and outcome frequently relate to situations over which we have less and less control. Furthermore, the factors that influence health are dependent on such basic environmental issues as the economy, the weather and the food and water supply. Global climate change is emerging as an important factor in the pathogenesis of disease, increasing the migration of disease-causing vectors to areas of the world where they have not been endemic, having substantial effects on water supplies and on food supplies in areas which are vulnerable and hence increasing the potential for food and water borne disease at a global level.

3 Millenium development goals

For these reasons 193 member states of the United Nations and 23 international agencies agreed in 2000 on eight Millenium Development Goals to be achieved by 2015 all of which have substantial impacts on the health of the global populations (5): -

- eradicating extreme poverty and hunger,
- achieving universal primary education,
- promoting gender equality and empowering women
- reducing child mortality rates,
- improving maternal health,
- combating HIV/AIDS, malaria, and other diseases,
- ensuring environmental sustainability, and
- developing a global partnership for development

There has been considerable debate as to the best mechanisms to achieve these goals and it is fair to say that political complexities both North and South have not always been conducive to the delivery of these goals. International health has not traditionally been attractive to the pharmaceutical industry or to the biotechnology industry, because the returns on investments in this sphere have been considerably less than the returns with regard to conditions of the more prosperous nations. Hence, although there is enormous scientific interest in the areas of international infectious disease, very strongly supported by funding bodies and by philanthropic sources, there are a series of bottlenecks in the delivery process including for example a bottleneck at the level of large, controlled clinical trials, which are necessary in order to determine efficacy of drugs, prior to implementation of therapeutic processes in terms of poverty-related disease. The ethical issues involved in the construct of clinical trials with regard to conditions impacting on international health have come to the fore in recent years with consensus that common ethical principles apply at a global level (6).

In this regard, while pharma and biotech and the global medical and political community are frequently dealing with conditions for which many of the mechanisms are known, the outcome does not depend on a simple paradigm, but is strongly influenced by issues such as economics, politics, climate, energy and, indeed, health systems at a global level. Hence, there is an increasing need for new approaches towards the development of synergies in the international health arena, which can contribute to improved outcomes for patients and populations at a global level. In this regard the global academic community has a substantial role to play in developing the agenda not only for the science but also for delivery in the sphere of international health.

4 Biomedical science and international health

There is a very pressing need to substantially facilitate our capacity to make meaningful interventions in the biomedical space in terms of poverty-related disease. Success in this area will require a concerted approach involving Science, Policy and Implementation (Fig 1) and there are important considerations in how we progress across these three themes. Firstly, discovery science is paramount in terms of identifying new mechanisms of disease and in identifying the types of therapeutic approaches that may make a difference at an international level. Secondly, there is an increasing requirement to look at the continuum of activities in international health and to examine such activities in terms of their capacity to substantially modify outcomes. In this context, the development of North-South partnerships in research and education, particularly with regard to the biomedical sciences will have substantial impact on the capacity of countries in the south to develop their own analytical and scientific programmes, which will strongly influence our knowledge of disease.

In this context, the barriers are substantial and they include the very high cost of equipment and reagents necessary to perform biomedical science at the highest level and also the education of staff at PhD and postdoctoral level, in addition to the principal investigator level, to create the human resource capacity to perform such studies in a scenario of real critical mass. Hence, we do need to strongly address our ability to deliver high quality educational programmes at an international level.

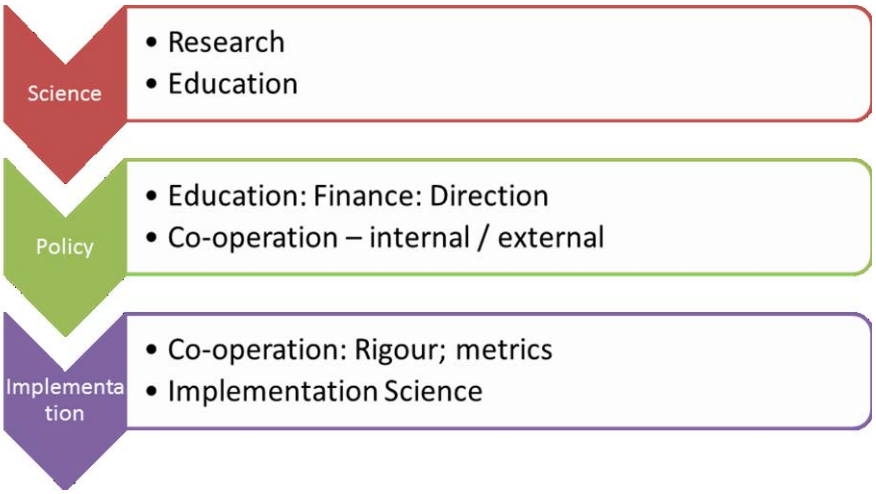


Figure 1: The integration of Science, Policy and Implementation is key to success in the International Health arena

There are even more pressing issues with regard to policy and implementation. Firstly, the capacity to develop and deliver new therapeutic approaches is only of benefit, if such approaches can be advanced and implemented. Laboratory researchers must develop an understanding of the barriers to implementation of successful developments and aim to optimise the discovery process. An example of this is in the field of vaccine design where due concern is needed to ensure that vaccines can be delivered to areas where there is limited capacity for refrigeration. It is critical that these issues are at least considered at an early stage in the development process in order that policy implementation is facilitated at the stage of delivery. In the policy arena, it is critical that all partners must work together to ensure that policy is developed at a sufficient level to deliver across global populations.

It is also critically important that implementation of policies at national and trans-national levels must be accompanied by the introduction of high quality metrics to assess and evaluate the impact of such implementations in a formal and rigorous way. This is the domain in which the academic community typically excels and in which it may have even further potential to develop partnerships that facilitate a growth in knowledge that facilitates delivery. The application of formal metrics to intervention and the examination of case studies of interventions are critical so that we can understand not only what makes us feel good but also what does good.

Thus, it is important that within health systems that the individual components for effective management of health and health-care are brought together in a way that ensures a delivery of the highest possible care at an international level. Without formal implementation science (7,8) to ensure that we are effectively providing improved outcomes, it is highly possible to fool ourselves that well-meaning and benign interventions are making a difference. Hence, the critical components that are needed are an increasing cohesion between north and south, an increasing cohesion between the biomedical sciences and public health and policy and the development and strengthening of bridges to individual networks and institutions and to policy drivers within multiple populations.

5 Eurolife

Eurolife is a consortium of universities in the biomedical space, which includes Leiden University Medical Centre, the University of Barcelona, the Karolinska Institutet, the Université de Strasbourg, the Medizinische Universität Innsbruck, the University of Edinburgh, the Universitätsmedizin Gottingen and Trinity College Dublin (9). This consortium of universities is strongly committed to working together in the biomedical areas in both research and education, and have collaborated substantially in areas such as inflammation, neuroscience, nanotechnology and imaging in the past.

The Eurolife Universities have established strengths in International Health in areas related to both the biomedical sciences and the public health. Some of these strengths are summarised below: -

- CRESIB (www.cresib.cat) The Barcelona Centre for International Health. Universidad de Barcelona
- Division of International Health (IHCAR) Karolinska International Research and Training (KIRT [ki.se/ki/jsp/polopoly.jsp?d=25542&l=en]) Program and the Centre for Global Health (KICGH [ki.se/ki/jsp/polopoly.jsp?d=12350&a = 29787&f=sv&l=en]) Karolinska Institutet,
- Centre for International Public Health Policy (www.health.ed.ac.uk/CIPHP) University of Edinburgh
- Centre for Global Health (www.medicine.tcd.ie/global-health), Trinity International Development Initiative (TIDI), Trinity College Dublin; INDIGO, the International Doctoral School in Global Health
- Female Cancer Programme (FCP) LUMC (www.femalecancerprogram.org/FCP/ The LUMC Center for Infectious Diseases (a center for departments of microbiology, infectious diseases and parasitology to work together and organise education, research and patient care.) web link http://www.lumc.nl/rep/cod/redirect/2010/algemeen/cid-nl.html
- Gottingen University Medical Centre: DAAD Physician Program (between UMG and Banda Aceh/Indonesia) (www.daad.de/entwicklung/de/12.2.8.10.html). Coordinated by the Institute for Medical Microbiology.

Hence, within the academic institutions we have considerable expertise in international health focussed in a number of complementary areas. Hence, we have developed an alliance in the area of international health called the Eurolife International Health Alliance, with a mission statement as follows:

> „The Eurolife International Health Alliance will combine its' complimentary expertise in international health to deliver innovative transnational interdisciplinary education and research programmes in health, healthcare policy and care delivery that best serve the needs of the developing world. The EIHA will utilise its' resources to champion international health as a key priority for improving the health of the human population and will actively engage with policy makers to ensure the realisation of this vision".

This mission statement encompasses the need to not only deliver research programmes but also to utilise our resources to improve the health of the human population. Hence, implicit within the mission statement, is an active engagement with the process of translation into the international health arena.

6 Delivering the EIHA vision

The Eurolife International Health Alliance commits to maximising synergies between the different partners in order to address key international health priorities and develop innovative solutions for poverty related health deficits using our strengths in the areas of *Education and Training, Research, Health Care Policy and Care Delivery*. An unique feature is the ability of EIHA partners to combine research and training. EIHA will engineer capacity building alliances with appropriate partner organisations and stakeholders in both developing and developed countries, advancing a coherent agenda through a series of initiatives in the fight against global disease.

These initiatives will include:

- A Research Partnership that builds on existing programmes of research between individual institutions within Eurolife and their partners in the developing world and provides added value to maximise research excellence in areas of mutual interest that will have broad international application.
- An Educational Alliance that will promulgate innovative inter-institutional programmes of education and training between Eurolife Institutions and Partner Institutions in the developing world, underpinning capacity building within the developing world.
- A Policy Forum that will be nurtured in close partnership with stakeholders in the developing world to position International Health as a key challenge in society.
- A commitment to advancing solutions to particular healthcare problems and healthcare access within partner developing countries.

In this respect we feel that it is important that we utilise our combined strength to leverage an evolving alliance between EIHA and other high profile International Health partners within the developed world to enhance the production of relevant quality solutions in research, education, health care policy and care delivery in International Health for the developing world. Recognising the value of strength through unity and the need to advance the international agenda at a political level, EIHA undertakes to utilise its collective strengths to lobby for the required International Health priorities to be recognised and appropriately resourced at both local and international levels.

7 The importance of networks

It is now critically important that we aim to look at international health problems in an integrated way. There are a range of issues which relate to the interface between Biomedical Sciences and Public Health and in which both components are absolutely required and synergistic in terms of outcomes. Hence multiple skills are needed to address complex problems and the nature of the skills that are required may not be apparent until these issues are addressed. In this respect, we need to identify new modus operandi for the global health space. We need to identify a matrix of both research and educational programmes with international health elements in order to facilitate integration. With regard to research and delivery of health care we also need to develop a real critical mass in interdisciplinary working within the international health space with researchers in public health arena working side by side with the biomedical space and also with educationalists in terms of the delivery of new understanding and knowledge. The European Academic Global Health Alliance has as its two major aims:

- To create a forum for interested academic institutions with involvement in Global Health to exchange views and ideas, so as to develop a European voice on Global Health issues and influence relevant policies.
- To bring together International Health/Tropical Medicine and Public Health institutions

Eurolife members serve as partners in EAGHA while the Eurolife EIHA is itself an affiliated member of EAGHA, emphasizing our strong commitment to interdisciplinary and international work in the field of International Health. Similarly the EIHA aims to work closely with TropEd to promote new educational experiences in International Health. In addition EIHA has liaised directly with the US Consortium of Universities in Global Health to find common ground. Such interactions were best exemplified at a jointly hosted colloquium at the FESTMIH meeting in Barcelona in October 2011 entitled "Embracing pluralism: Networks dedicated to improving global health. In this regard EIHA is positioned very much on the biomedical side of the continuum and sees its interactions with other networks as extremely valuable as we all seek to succeed in the common goal of improving health for the global population.

8 Conclusion

Academic Institutions have made an enormous contribution to research and health care delivery in international health. It is important that we now move to consolidate and develop from such gains by working in an interdisciplinary manner across a range of academic areas including biomedical sciences, public health and education. Key to success will be the capacity to generate and translate new knowledge across disciplines in a manner that creates new knowledge and translates such knowledge into measurable benefits for the health of global populations. Such interactions are key to progress towards the Millenium development Goals and also to our capacity to generate and forge new and more effective ways of working across disciplinary and national boundaries to make substantial improvements in the prevention, diagnosis and cure of poverty-related disease. Our academic social responsibility (10) demands that we should aim to not simply make transitory interventions but to also improve educational and research capacity through our combined interactions.

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3 The One Health Concept in a development context

Kerstin Wydra

1 Population increase, climate change, hunger, poverty, inequality and health

The challenges mankind is facing in the next decades are manifold, encompassing world population growth predicted to reach 9 billion by 2050, climate change with temperature increases and changes in precipitation patterns, and more extreme and unpredictable weather events, which occur with increasingly higher amplitudes and frequencies. Additionally, environmental degradation, in combination with inadequate political frameworks, further contribute to food insecurity, malnutrition, bad health and depletion of natural resources. Among the regions most affected by and most vulnerable to climate change is Sub-Saharan Africa, where variability in onset and extent of rainy seasons, and significant reductions in the length of growing periods forecasted by many of the Global Climate Models as well as steadily increasing desertification and land use and land cover change will have direct impact on agricultural production. Besides the effects of exploitation and further loss of natural resources, the direct drivers of agricultural change, the growing food demand and changes in consumption patterns, are enhanced by factors such as global energy shortage, which further aggravate the situation (IAASTD 2008). As a result, Africa's agriculture, particularly in arid and semi-arid areas, is facing increased abiotic and biotic stress with disease outbreaks and insect epidemics, leading to a decline in crop yields, a decrease in forest and cultivated area shares, and a reduc-

tion in ecosystem integrity, associated with a decline in biodiversity. Thus, for large parts of the Sub-Saharan African region, the percentage of "failing seasons" is likely to be in the range of 20-50% by 2050 (Thornton et al. 2006). Existing farm and pastoralist systems and their agricultural practices and pest control measures are not resilient enough to cope with these challenges. In 2010, Sub-Saharan Africa had with 30 % the highest percentage of undernourished population comparing continents and an extremely alarming global hunger index in some countries, among them East and Central Africa with 25% to more than 35% of the population being undernourished, respectively (FAO 2010). One of the most evident effects of the climate-related, unforeseen disturbancies are the regional disasters in form of hunger catastrophes.

Additionally to the increasing exposure to environmental stress, small-scale farmers are further challenged by changing socio-economic conditions, which increase risk, as there are population growth, large-scale farming and foreign investment ('land grabbing'). In a vicious circle low agricultural production leads to undernourishment and malnutrition as primary causes of illnesses and death, which further negatively impact food production. In these aspects, the linkages between agriculture and health are obvious.

Associated with hunger is poverty. Sub-Saharan Africa counts for about 75% of the ultrapoor of the world, who live on less than 0.50 US$ per day (Ahmed et al. 2007). In combination with low food production, related low water quality, insufficient sanitation and health facilities and lack of education, specifically of mothers, poverty contributes to a high vulnerability of households and an overall poor livelihood. This interrelatedness of factors governing the living conditions in developing countries demands innovative, integrated and interdisciplinary approaches to reach development goals. One prerequisite to reduce poverty and improve nutrition and health is building on agricultural knowledge and innovation in local and traditional societies (IAASTD 2008).

2 Climate change and health

Climate change will have impact on the distribution, epidemiology and severity of diseases, and make controlling existing diseases more difficult (Campbell-Lendrum, 2011). The impact of climate change on health will manifest in direct effects, such as outbreaks of diseases among human populations, and indirect influences such as disease calamities of domesticated animals or plants, which endanger food security, economic stability and trade. Disease control under changing conditions in agricultural production has to be adapted, since host resistance and pathogen virulence may change. Further impacts on crop yields and the environment which indirectly affect health are given below.

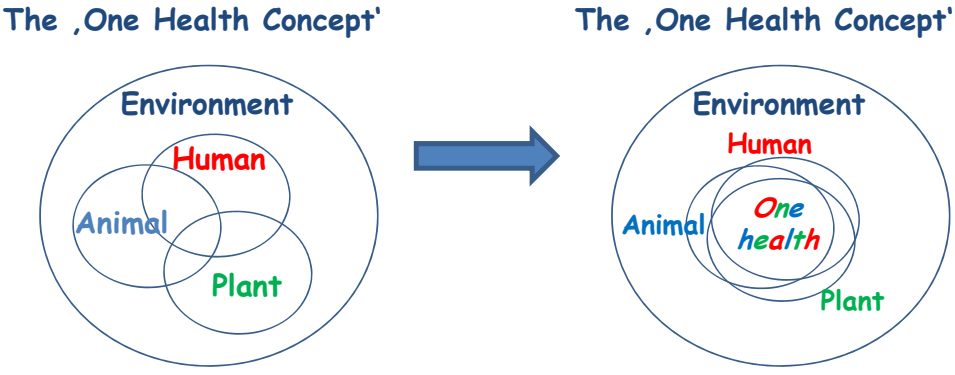
3 Millenium Development Goals

As a response to the challenges of global change and population growth, in year 2000 the eight millennium development goals (MDGs) were defined and adopted by 170 heads of state. To achieve the MDGs as prospected for year 2015, the development of an intersectoral framework is needed that facilitates the exploitation of synergies between agriculture and health and supports joint policy formulation (von Braun et al. 2010). Therefore, the one health concept linking the sectors agriculture, environment and health is important for most of the MDGs. As outlined below, the interactions between the different sectors are numerous, and policy-makers, scientists and donors need to be convinced of the enormous opportunities for development through synergistic effects by a close collaboration between the various sectors.

4 The One Health Concept

Existing and emerging challenges and threats encompassing plant, animal and human diseases, water scarcity, chemicals in the environment, loss of biodiversity and land degradation and loss of agricultural land need to be addressed in a one-health approach which also considers measures to mitigate climate change and socio-economic conditions. The one health concept integrates human medicine, veterinary medicine, plant pathology and plant protection and environmental health, encompassing the natural and the human environment, the latter covering the social, political, structural and institutional framework. Not the overlap of disciplines is searched, but one holistic approach entangling the diverse aspects of each discipline.

One Health is the collaborative effort of multiple disciplines-working locally, nationally, and globally – to attain optimal health for people, animals and our environment.



5 Linkages between agriculture and health

Agriculture is related to many of the world's major health problems, through food production and the environmental impact of agriculture. In the food systems linkages to health occur at all steps along the value chain, from natural resources and inputs to primary production, transport, storage, processing, followed by secondary production, further transport and storage, to consumption (Pinstrup-Anderson 2010). The conceptual framework of linkages between agriculture and health is operating on three levels: across the top level the agricultural supply chain with agricultural producers, agricultural systems and agricultural outputs, which are linked through intermediary processes to the second level – labor processes, access to and impact on natural resources (water, land, biodiversity), income generation and provision of health-related services, and to the bottom level, representing the health problems, undernutrition, water-associated, vector-borne diseases (e.g. in relation to irrigation and land degradation), foodborne diseases and occupational health hazards (Hawkes and Ruel 2006). Through linking the agriculture and food system to health, health becomes a critical driver of agricultural change (Hawkesworth et al. 2010). Health issues linked to agriculture encompass direct effects of low and insufficiently diverse agricultural production such as hunger and malnutrition, and also cover health related indirect consequences of unsustainable production, which can cause foodborne diseases resulting from infections and intoxications, and vector-borne diseases, which are enhanced under specific production systems and occupational health hazards. Nevertheless, agricultural policy to date has been focussing on maximizing production, thereby neglecting environmental health issues as well as biodiversity, which are an important basis for sustainability and sufficient micronutrient supply. The often bidirectional cause-effect relationships between agriculture and health are outlined in detail in the following.

5.1 Hunger and malnutrition

Hunger is the most obvious and direct effect of failed agricultural production on human health. Besides hunger the fact of malnutrition as most important cause of diseases and death worldwide is often neglected. About 53% of deaths among children of below five can be attributed to malnutrition (Caulfield et al. 2004). In the recommendation of the Copenhagen consensus 2008 (http://www.copenhagenconsensus.com), eight world leading economists identified the top ten solutions for the world problems, of which five involve nutrition issues. A balance of nutrients forms the basis of a healthy diet, which should include the four micronutrients zinc, iodine, iron, and vitamin A which are in chronically short supply. This hidden hunger in form of micronutrient deficiencies affects more people – about 2 billion - than the lack of calories which about 800 Mio people in the world suffer from. The promotion of micronutrient-rich food combined with behavioural change is a recommended strategy which has to be fol-

lowed in an intersectorial approach, between farmers, traders and consumers, and on policy level (Hawkes and Ruel 2006).

5.2 Food safety and water safety

Food-borne diseases caused by contaminations through pathogenic micro-organisms and toxic organic and inorganic compounds are among the most important reasons for illnesses in the population of the developing world. Many of these microbiological and chemical hazards originate from agricultural production, such as zoonotic pathogens or toxins, and contaminated water. Specifically aflatoxicoses caused by mycotoxins may be one of the most important and least recognized health problems (Williams et al. 2004). Staple crops such as maize and groundnut can contain highly toxic metabolites from pathogenic and saprophytic fungi, which develop in the field under conditions of drought stress and erratic high rainfall or high moisture, and proliferate under unsuitable storage conditions, favoured by high temperature and humidity (see also below). Generally, contaminations can occur along the whole value chain, from primary production to harvest, storage, processing and transport, and during food preparation.

Water-borne and water-associated, vector-borne diseases are the cause of death for 3.2 million people per year, which to a significant part are due to the impact of agricultural activity (Nugent and Drescher 2006). Irrigation water and stagnant water are related to agricultural practices and provide breeding ground for disease vectors. Further impacts on food safety derive from pesticide residues in intense agricultural production, which endanger humans and the environment. Water-borne diseases including zoonoses as well as contamination of water supplies with chemicals, toxins and by-products of drugs and hormones are typical examples, which demand a solution under the paradigm of an one health approach.

5.3 Zoonotic diseases

Zoonotic diseases are the main factor of infectious illnesses in the developing world. They originate with animals and are transmitted directly from animals or through a large number of pathogen-transmitting insect vectors, contaminated water, or bad sanitary conditions with humans and livestock living closely in the same space. Pathogen transmission for livestock-related zoonoses in more densely populated areas with frequent contact between animals and humans will be increasing, the rate of development of pathogens may become enhanced, the geographic range of vectors and their competence may change with variations in weather (temperature, humidity, rainfall, precipitation) and land use, increasing suitable habitats for water-related vectors. Recent emergence of serious zoonotic diseases such as Salmonella spp. and Campylobacter spp. from poultry, bovine spongiform encephalopathy (BSE), E. coli infections, the severe acute respiratory syndrome (SARS) and avian influenza are all related to animal production practices

(Todd and Narrot 2006). Transmission can be through vectors, but also through contaminated water, crops, other animals, specifically where animals are kept in dense populations and close to human living grounds. All these hazards related to livestock production are expected to increase in the coming decades due to a rapidly increasing demand for animal products. About 21 billion food animals are being produced with 15 millions of tons of animal and agricultural products being transported worldwide. The future increase in animal production will occur predominantly in developing countries which have major deficits in monitoring and controlling disease and thus pose a threat to the global food system and human health worldwide.

5.4 Crop protection and health

Occupational hazards related to crop protection include health risks from pest control through use of chemical pesticides, with both acute effects and long-term harms to health (Williamson et al. 2008). Besides the exposure of farmers during application, toxic compounds occur as residues in the food supply, in the environment and in the water. A wide array of abiotic and biotic factors such as insects and pathogens causes major yield losses through the impact on quantity and quality of crops, which in turn leads to malnutrition and hunger, thereby closing the vicious cycle of negative health-agriculture feedbacks leading to poverty with subsequent negative impact on agricultural production. Mycotoxins produced by pathogenic and saprophytic fungi such as Fusarium spp., and Aspergillus and Penicillium, respectively, have a direct negative health effect on consumers and can cause liver cancer, stunting, low birth weight and other severe impacts on health. Some measures are available to reduce mycotoxin contamination before harvest and in the storage, as recent development of a biological control through application of atoxigenic strains of Aspergillus flavus by the International Institute of Tropical Agriculture (IITA), while awareness among farmers and consumers and suitable monitoring systems are still insufficient or missing.

In reaction to the high pressure from increased populations, climate change and global change, traditional, more resilient production systems are more and more abandoned in favour of high input mostly monocultures based agriculture, which reacts highly sensitive to any stress and to lack of external input, when not available. Only sustainable intensification considering the principles of integrated pest management and biological control, in combination with measures to support soil health and mixed cropping systems, as part of an integrated crop management can contribute to enhanced human, plant and environmental health, and thereby supporting human wellbeing and rural development.

6 Natural environment and health

6.1 Ecosystem degradation

The impact of the environment on health of children < 14 is higher than for the general population. Children are 44% more likely to die as a result of environmental factors. Globally, almost 25% of the diseases are related to environmental factors, with 94% for diarrhoea, 42% for malaria and 41% for lower respiratory infections (Prüss-Üstün and Corvalán 2007). Ecosystem degradation will be enhanced by a predicted 30-85% increase in water withdrawal and a 100 to 1000 fold increased extinction of species for the next 40 years (Millennium Ecosystem Assessment 2005: http://www.millenniumassessment.org/en/index.html). Environmental degradation such as erosion, salinisation, soil nutrient depletion and water contamination and scarcity caused by agricultural practices will contribute to declining agricultural productivity, resulting in malnutrition and illnesses, which again will reduce labour productivity, resulting in unsustainable agricultural production and further negative impact on the environment. The health effects range from undernutrition to increased occurrence of water-borne diseases, altered transmission mechanisms for infectious diseases and intestinal, respiratory and other disorders, leading to decline of farm income with its negative effects on health and health care (Nugent and Drescher 2006).

6.2 Agrobiodiversity and health

Agrobiodiversity is a basis for food security and provides famine food in times of hunger as well as micronutrients to alleviate the effects of malnutrition. Inter- and intraspecific biodiversity is a source of genetic resources and the basis for breeding for more resilience to biotic and abiotic stress and to increase the content of miconutrients. Neglected crops, specifically vegetables, contain high levels of carotinoids such as lycopene and lutein, and beneficial compounds with functional properties, such as flavonoids and phenolics which act as antioxidants and contribute to reducing the risk of chronic diseases and cancer. Successful examples of increased content of micronutrients through introduction of genes from neglected species through classical breeding are available and already propagated in various African countries, such as the Vitamin A rich sweet potato. When plant produce enters the market chain agrobiodiversity can directly contribute to income generation. Moreover, biodiverse systems improve environmental quality and ecosystem services for agriculture, such as nutrient cycling, soil fertility, provisioning services supplying food, water, wood and fiber, regulating services such as climate regulation, disease regulation, water purification and cultural services, which all directly or indirectly impact human health. Thus, agrobiodiversity combined with indigenous knowledge as part of locally available resources has the potential to positively

influence the entire agriculture-food-nutrition-health structure (Gari and Villarreal 2002).

6.3 Environmental pollution

Hazards to the environment and thereby to human health can originate from intense agricultural production, such as contamination of water with fertilizers (nitrates and others), pesticide residues and pollution of water and air through intense livestock production systems with huge amounts of livestock-derived waste (Catelo 2006). Agricultural chemicals accumulate in environmental sinks such as soil, air, water and plants, to which humans are exposed.

6.4 Agroforestry, nutrition and health

Agroforestry systems represent through integration of crop and tree diversity in a production system a sustainable basis for environmentally sound agricultural activity and increase the flexibility and adaptability of the system. They are a source of medicinal products from trees, shrubs and herbs used in traditional medicine across much of Asia, Latin America and Africa. Moreover, agroforestry systems provide fruits, leaves and other products of high nutritious value which increase the dietary diversity for the rural and, if marketed, also the urban population, and which serve as animal feed. Fruits and berries are preferably consumed by children as a study in Zimbabwe showed (cited in Swallow and Ochola 2006) and also contribute to household income when entering the market chain. In terms of environmental impacts, agroforestry systems are the basis for a sustainable crop production by providing niches for beneficial insects such as bees or parasitoids and predators, which have the potential to balance the outbreaks of pests, and by a sustainable nutrient cycling process with positive effects on soil fertility.

7 Human environment: Socio-economic and structural factors influencing health

Demographic factors and conflicts surely play major roles in human welfare in developing countries. Though not neglecting these circumstances, long term changes need sustainable solutions based on well functioning structures. Obstacles for improved strategies in developing countries are besides a lack of coordination and a poor infrastructure the knowledge gaps on the ways of contamination of food, on epidemiological cycles of zoonotic diseases, and thus of adequate management strategies. Successful strategies developed elsewhere, such as agricultural interventions to control the spread of water-associated diseases, are available and can be transferred and adapted to local conditions (Mutero et al. 2006). This implies that a major effort is needed on all levels, from research to implementation,

from community to policy level, including organizational and infrastructure development. To develop efficient intervention strategies to improve food security and food safety in relation to health, risk analyses are one tool to choose among various management options to reduce foodborne diseases and other hazards related to agriculture, which affect human health.

8 Opportunities linking agriculture, environment, food security and health

Linking the agricultural and the health sector provide unique opportunities to improve health and human welfare in the poor countries. Thereby, promotion of agriculture considering health aspects and, in a two-ways approach, improving health-related problems considering their impact on agricultural production and the environment has the potential to significantly and sustainably enhance the nutrition and health status of the poor population. As stated by the IAASTD (2008), a report accomplished by several hundred scientists, signed by 58 countries, agricultural growth of small-scale farms is the best way to generate income and reduce global poverty. Considering environmental factors, as outlined above, the vulnerability of the ecosystem to climate change and changes in land use patterns will clearly influence agricultural production and biodiversity, and thus improvements on one side will positively affect the entangled sectors.

To achieve considerable impact, linked agri-food and health governance structures have to be established, which reduce institutional barriers and are the basis for intersectoral research and policymaking. Encouraging intersectoral initiatives are being developed in the recent years by the World Health Organization (WHO), the Consultative Group on International Agricultural Research (CGIAR) with a platform on 'Agriculture and Health', and by the International Food Policy Research Institute (IFRPI) which organized international conferences on the subject, to name only few.

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4 Commitments on a global level translating into actions locally

Andrea Holzäpfel

1 Maternal and child health: The commitments of the international community

In the year 2000, political leaders from around the world gave the world's biggest promise – to achieve the Millennium Development Goals (MDGs). The MDGs are a global pledge to reduce extreme poverty and human deprivation by half until 2015 through collaborative multilateral action. The MDGs comprise 8 quantifiable goals of which MDG 4,5 and 6 are directly related to improving health outcomes (improving child and maternal health and combating HIV/AIDS). As we move towards the target date of 2015 the critical question needs to be asked whether the MDGs have been a successful approach and what can be learned from the past 10 years for the formulation of the Post-MDG agenda.

Certainly, the MDGs have generated great commitments from governments, international organizations, civil society, and even the private sector (Manning 2010). They have focused attention on key dimensions of human development and progress has been made in many areas. The 2010 UN-MDG Summit however drew attention to the fact that progress towards MDG 5 – improving maternal health – has been unacceptably slow. Child mortality also still remains dramatically high with 9 million children dying each year before their fifth birthday (WHO 2010). At the G8 summit in 2010 the support to significantly reduce maternal and child mortality was reaffirmed by announcing the G8-Muskoka Initiative. In the

framework of the Muskoka-Initiative the G8 states together with other countries, the Gates-Foundation and UN Foundations pledged to mobilize US$ 7.3 billion to improve maternal and child health (BMBF 2010). Germany will contribute US$ 500 million (BMBF 2010). Research and innovation are explicitly part of the initiative. New funding mechanisms however have not been foreseen. Instead each donor is free to choose the mechanisms they consider most effective, like for example placing the focus of funding programmes on reducing the burden of diseases that mainly affect mothers and children. As welcome the renewal of the commitment is, one should realize that for both, the MDGs and Muskoka, much attention is paid to the formulation of goals but less to their implementation.

2 Dimensions of poverty

The prime aim of the MDGs is halving extreme poverty. Poverty is now widely considered to be a multidimensional problem stemming from a complex set of deprivations. In fact, new perspectives on poverty have challenged the focus on income as the defining condition of poor people (Fukuda-Parr 2006). According to the 2000 World Development Report, "poverty is pronounced deprivation in well-being" (Kakwani 2006). Subjective wellbeing in turn seems closely related to people's capabilities and achievements. UNDP's Human Development Report views poverty as "reflecting lack of choices and opportunities in the key areas of education, health, and command over resources, as well as voice related to democratic processes" (Kakwani 2006). Consequently, strategies aiming to reduce poverty require not only economic growth but also direct interventions in many areas such as health and education. As these dimensions are closely intertwined new approaches are needed. For example human health cannot be considered holistically without also looking at the health of animals and plants. Apart from the bodily wellbeing, healthy social relations play an important role for the wellbeing of individuals and communities as a whole. The complexity of the matter therefore calls for holistic approaches to alleviate poverty. In fact, the multidimensional nature of poverty implies that progress is not realistic or sustainable if only one dimension of the problem is addressed in exclusion of others.

It is true that the idea of interdisciplinary projects is not new. Over the past years, funding agencies have become much more receptive and proactive about supporting interdisciplinary approaches. Programmes have been initiated to encourage scientists from various disciplines to work together. However, despite the recognition of the need and potential of interdisciplinary projects their implementation still remains a great challenge.

3 The contribution of GIHN

The Göttingen International health Network (GIHN) has set out to meet this challenge. The Network brings together scientists from disciplines ranging from life sciences to geosciences and economics. Together they design and implement projects aiming to improve maternal and child health. As the health of mothers and children is influenced by a wide range of factors such as the quality of nutrition and water, economic determinants, implications of climate change, social relations and spiritual wellbeing all partners of the network can contribute their expertise to joint projects. Furthermore, GIHN embraces the concept of fostering South-South partnership by bringing together scientists from Ghana, Tanzania and India in equal partnerships. The aims of the Göttingen International Health Network are thus not only in line with the MDG 4,5 but also MDG 8 that calls for global partnership. Its collaborative approach ensures a mutual learning experience and the expansion of knowledge of all partners.

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5 Linkages between economic and health outcomes: Options for interventions for better health

Elena Gross and Stephan Klasen

The United Nations and its member countries have agreed in the year 2000 on the 8 Millennium Development Goals. MDG 4 and 5 are specific sub-targets related to improved morbidity and mortality for children and women. A status of good health is essential for a human's overall well-being, and thus of intrinsic importance. In addition, poor health places significant economic burdens on families. Health costs are often high in developing countries and access to health services is lacking (WDR, 2004). As a result, higher disease prevalence in a poor environment can cause poverty traps where people are too unhealthy to earn money and too poor to pay health costs. Conversely, policies to reduce poverty can be one way to escape this trap. Poor people in developing countries face a higher diseases burden than richer people in the same countries. They also suffer from poor housing conditions and lack of improved water and sanitation facilities which increases the risk of falling ill. Prüss-Üstün et al. (2008) estimate that almost 70% of deaths are related to unhygienic water and sanitation practices.

This chapter briefly discusses how economic factors affect health and vice versa. In a second step, we discuss policy options to improve maternal and child health in developing countries.

1 Why is good health important for economic outcomes?

Under-five mortality in developing countries is still high and many children and adults are malnourished. Table 1 reports economic and health indicators in several regions of the world from the World Development Indicators[1]. Sub-Sahara Africa performs worst among all regions with low income and health expenditure per capita, but high malnutrition and mortality rates. Maternal mortality is more than twice as high as the world average. Stunting (low height for age) is highest in South Asia and Sub-Sahara Africa. Bad health outcomes in nourishment and mortality go in line with low income and health expenditure per capita.

Table 1: GDP and Health Indicators

Regions	GDP per capita (constant 2000 US$)	Health expenditure per capita (current US$)	Prevalence of undernourishment (% of population)	Mortality rate, under-5 (per 1,000)	Maternal Mortality Ratios per 100 000 live births
East Asia & Pacific	1.758,7	83,1	11,4	27,4	89
High income: OECD	29.820,5	4.189,3	5,0	5,7	15
South Asia	682,3	26,1	21,7	78,2	290
Sub-Saharan Africa	618,5	53,5	28,7	146,3	650
World	6.023,6	724,4	14,1	67,8	260

Data Sources: Col1-4 World Development Indicators, Col. 5 WHO/World Bank/UNICEF

The Human Development Report (1993) and, more recently, the Commission on Macroeconomics and Health (2004) addresses 4 crucial factors why good health is essential for economic success:

[1] The most recent data available was taken from years 2001-2009.

1. Good health increases production and productivity of workers because of fewer workdays lost healthier workers
2. Children in school attend class more frequently and learn easier which has positive effects for their future
3. Resources can be used more productively as otherwise they had been used for treating diseases
4. In general, good health increases the efficient use of natural resources, e.g. the use of arable land due to the eradication of insects which transmit diseases as malaria, dengue, river blindness…

On the one hand economic output can be produced more efficiently and production increases because of a lower disease burden. On the other hand people can save time and money when requiring fewer visits to health services.

2 Why are economic conditions important for good health outcomes?

Economic conditions are critical for better health outcomes. At the household level, better-off households benefit from the ability to purchase better nutrition, housing, and other amenities with direct health implications.

Moreover, the richer households often have better access to health services. Often necessary health services are not available for poor people (WDR, 2004). Table 2 shows selected indicators to measure service levels for the population. In Sub-Sahara Africa and South Asia birth attendance is only done for 41-45 percent of births. Similarly, the hospital bed per population rate is very low. Due to illness, households remain or fall into poverty through high spending on disease treatment and lost wages.

There is evidence that in the poorest countries (e.g. Burkina Faso) the share of household expenditures on health items is even higher than that of the rich (Makinen et al, 2000). Out of pocket expenditure is highest in East and South Asia and higher in poor than in rich countries, see Table 2. In high income countries most people are insured and out of pocket health expenditure only account for 36% of total private expenditure. The poor face a higher financial burden in health payments and similarly have a higher disease burden because of poor living conditions.

Table 2: Indicator of Health Services

	Births attended by skilled health staff (% of total)	Hospital beds (per 1,000 people)	Out-of-pocket health expenditure (% of private expenditure on health)
East Asia & Pacific	88,5	2,2	82,1
High income: OECD	99,5	6,1	36,6
South Asia	41,5	0,9	91,4
Sub-Saharan Africa	45,3	1,2	46,4
World	65,4	2,6	43,7

Data Sources: World Development Indicators

In case of illness, services fail to reach the poorest. Income inequality translates into inequalities in the health sector (Wagstaff, 2002). Contributors to health inequalities between the rich and the poor lie in economic as well in social factors. Income and assets are economic determinants of receiving treatment more frequently and of better quality. For women and children, the economic gradient of health and health access is often particularly strong.

3 Why do services fail to reach the poorest?

The following discussion will be on maternal and child health. Here, women are still disadvantaged in many health perspectives and access to services. The World Bank (2004) addresses 4 major factors why women do not seek adequate health care for themselves and their children:

- Distance from health facilities (Babianard and Roberts, 2006)
- Cost (for services and transport)
- Multiple demands on a woman's time (Blackden and Wodon, 2006)
- Women's lack of decision-making power within the family
- Poor quality and availability of services

Distances to health facilities are often very large. Only 40-75% of women in Sub-Sahara Africa were found to have a facility within 5 km distance. This makes it hard to get to the health center in time, especially when (public) transport and roads are poor (Babianard and Roberts, 2006; Gabrysh and Campell, 2009). Transport costs are estimated to be around 25% of total health costs related to the disease (Ensor and Cooper, 2004). As there is often no public insurance available, often health payments are out-of pocket payments (WDR, 2004).

Recent literature on time use data shows that women in developing countries have a double burden of work in agriculture and domestic activities. This burden inhibits them from taking their children to health facilities at the right time (Blackden and Wodon, 2006).

One important finding of economic research is that women rather spend household income on nutritional and health items (Thomas, 1990, 1997) and increasing women's share in income increases expenditure for food and raises anthropometric measures of children in general and for girls relative to boys (Thomas, 1990, 1997). Whether women can earn or increase their income largely depends on the female status in society, as well as their educational opportunities.

As a result, the education of women has been found to be an important determinant for the good health of children (Hill and King, 1995; Klasen, 1999, Murthi et al, 1995). Moreover, gender gaps in education and employment further reduce economic growth (Klasen and Lamann, 2009). Thus promoting female education and employment will help boost overall resources of the family plus the share controlled by women. Both would serve to improve women's and children's health.

Lastly, poor quality or often unavailable services are a major barrier for effective health systems in many developing countries. Often clinics are not staffed, staff morale is low, opening hours are not kept, medicines are unavailable. The problems are deep-seated and not only relate to a lack of resources, but also often a lack of accountability of the health system providers to its users as well as poor incentives for providers (World Bank, 2004).

4 Approaches to improving health conditions

Given the health conditions identified, a natural reaction would be to try to address these using direct medical interventions. In the case of maternal and child health, one would naturally think of acute obstetric care facilities, comprehensive prenatal

and post-natal care as well as nutrition interventions, immunization programs, and oral rehydration. While all of these programs are proven to effectively address the targeted medical condition, they only address part of the wider problems of poor health and poor health systems in developing countries. Often the health problems are more related to socioeconomic than health issues, and improved health does not necessarily have to be mainly about improved health services. Lastly, existence of health services does not guarantee their effective use.

As a result, identifying the most appropriate interventions to improve maternal and child health is not straight-forward. It first requires a country-specific analysis of the key constraints to better health. Are the main health problems related to poverty and inability to secure adequate nutrition and shelter? To poor sanitary conditions? Are the poor sanitary conditions related to a lack of clean water and adequate sanitation or poor hygienic practices? Is poor health related to a lack of health services or poor quality of available services? In a second step, one can then identify priority interventions which can range from conditional cash transfer programs to the provision of clean water, changing the structures of accountability in the health care system, to the design of direct interventions such as nutrition supplements or immunization programs. Possible interventions of governments and donor agencies can take place on community, household and individual level. For example, community interventions can focus on improved water and sanitation supply. Water, sanitation and hygiene practices can have an impact on health and economic outcomes. However, community level water interventions have been found not as effective as are household level interventions. The provision of a clean public water point does not necessarily lead to the consumption of clean water at the point of use as water gets contaminated during transport and storage (Fewtrell et al, 2005; Wright et al 2004). More effective are point of use interventions as storage containers or chlorination (Schipper et al, 2011; Wright et al. 2004).

Other possible health interventions can be combined with conditional cash transfer (CCT) programs. Households receive financial support if certain conditions are met. One example is the Mexican PROGRESA program. Here households receive a cash transfer of 20-30% of household income every 2 months if children are immunized and get nutrition monitoring; pregnant and lactating women visit clinics; and all family members participate in meetings on health, hygiene and nutrition regularly. There is evidence that health outcomes can be improved in cause of CCT programs. Morbidity of children younger than 3 years is reported to be lower if households participate in the program. Also anemia in children age 12-48 months was found to be less likely due to participation. No effect was found for the anthropometric measure of stunting (Gertler, 2004).

In short, improving health can be the results of a large variety of interventions. Which ones should receive priority is a complex question and will likely depend on local conditions.

5 Conclusion

Health and economic outcomes are closely related and affect each other. Better health can produce better economic outcomes and more money brings more investment in health services, especially if more money is given in the hands of mothers. Given this intricate linkage, there are many avenues to break the vicious cycle of poverty and poor health. They range from direct interventions to address a particular health problem to much wider socioeconomic interventions to combat poverty or improve access to nutrition and clean water. Much research remains to be done to determine the precise priority in different country and local settings.

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6 Cross-cultural bioethics as an interdisciplinary approach

Julia Inthorn

1 Health – universally valued?

Health is recognised as a valuable good throughout the world. From an individual standpoint, being healthy serves as a basis to pursue individual goals. When we are sick, our possibilities to work, to care for ourselves or a family, and simply to do what we want are limited. We cannot move properly, are quickly tired, or feel overwhelmed by pain. Therefore, health as a value is closely related to other values that can be pursued much easier when we feel fit and healthy. From the point of view of the state, health is part of human resources, with public health as a necessary condition for a prospering state. A healthy population can be more productive and prospering and needs less support. The value of health seems to be universally shared and can be seen as a shared starting point of cross-cultural bioethics. At the same time, cultural differences play a vital role when it comes to the understanding of illness and disease, the role of the patient, and health care systems. Migration brings together people with different cultural backgrounds who meet as professionals and patients in hospitals; globalisation enables a quick transfer of knowledge and technologies between health care systems. We find Ayurvedic Medicine in London, clients from all over the world in a beauty clinic in Taiwan, and transfer patients to specialists all over the world. Though health can be seen as universally valued, the understanding of health differs between those cultural contexts.

2 Cultural and social dimension of health

In order to understand what makes health so valuable, it is necessary to take a step back and ask what is meant when we talk about health, illness and disease. The WHO provides one of the most cited and at the same time most controversial definitions of health. It defines health as "a state of complete physical, mental, and social well-being and not merely the absence of disease or infirmity." (WHO 2006, 1) Health, understood in this way, is seen as a multidimensional phenomenon. Physical and mental aspects are combined with social dimensions of well-being. Only well-being in all three dimensions classifies as health in this understanding. Even a person who is free of medical conditions or of pain might not count as healthy if the person is socially isolated, discriminated against, or cannot pursue his or her goals. Health defined as the complete well-being turns the concept of health into an ideal, meaning that only very few people - if any - classify as healthy. In this understanding minor changes in physical or mental conditions as well as other conditions like losing one's job might lead to loss of health. Health is thus integrated into a multi-causal scheme of influences that combines classical medical circumstances like infections, vaccinations and health treatment with questions of social security, access to water or education.

This leads to the question of responsibility for health. If health is so hard to achieve, the question arises how much effort a state or a community must make to ensure the health of people and which aspects of health are part of an individual's self-responsibility. The definition doesn't give a clear answer to the question of responsibility. This can be seen as an advantage as well as a disadvantage of the definition. The definition opens up the perspective of multiple influences on health and thus makes it possible to identify various different causes of health problems. Problems can be approached under the perspective and legitimisation of health as an aim. Not only questions of health care but also questions of nutrition, housing, social participation or safety can be discussed under the perspective of health. Because of the generally acknowledged value of health, tasks can be prioritised that might otherwise be regarded as less important. On the other hand, the apparent broadness of this definition makes it impossible to approach all problems simultaneously. Various institutions and individuals share the responsibility for the health of one person. A working security system, trust in partnerships, a healthy environment, health care access, food security and access to drinking water are only a few factors to be addressed under the perspective of health. Since health is influenced by various factors it becomes very difficult to address those responsible for ill health in a particular case or to deduce political strategies for the improvement of health from the WHO-definition of health.

From an intercultural perspective, this openness of the definition can be seen as an advantage as well. It recognizes different priorities within the various dimensions of health in different local settings. Thus, WHO's broad definition of health encompasses culturally different understandings of health without singling out one

special perspective. For example, the idea of illness as inflicted upon someone by ancestors because of an individual's failure to partake in religious rituals, a stroke, and Ayurvedic ideas of balance can be accommodated without difficulties by the WHO definition. Thus the WHO description of health can be used as a starting point for intercultural dialogue on health issues (Inthorn at al. 2009, 17). At the same time concrete, culture specific understandings of health need to be taken into account in intercultural dialogue.

3 Health, illness and disease

Understanding health as an ideal or aim, like suggested by the WHO definition, rather than a condition, puts a focus on the desirability of health. The WHO definition already entails that health is valuable by linking it to the well-being of a person. This very open-ended concept of health can be further analysed by looking at the opposing concepts of illness and disease. The WHO definition of health leaves it open as to who is to define whether a person is healthy. Talking about well-being can imply that the individual and his or her subjective view is essential to understand if a person is healthy. But of course a medical diagnosis can also contribute to this question. The subjective understanding of lack of health is usually referred to as illness while the perspective of medical professionals on medical conditions is referred to as disease. We all know from experience that illness and disease are not necessarily the same. A person can feel well and at the same time have an undiscovered tumour, or a person can feel sick without a medical condition. In most languages we find terms indicating such conditions like being heart broken. Wikman et al. (2005) show for the Swedish population that illness, disease, and sickness absence from work have to be seen as representing different realities (Wikman 2005: 452). There is only a very loose relation between these three concepts. The difference between illness, disease and sickness absence is neither gradually nor can it be simplified as three different descriptions of one single objective state because the empirically found overlap between them is only very small. Wikman et al. give empirical evidence that there is an irreducible difference between illness and disease that needs to be carefully accessed if we want to get a better understanding of outcome variables of health care linked to the quality of life.

The difference of health and disease is also relevant for intercultural questions of medicine and bioethics. Medical professionals world-wide seek to define the difference between health and disease by diagnosis based on scientific methods. Their understanding of disease is largely influenced or even based upon a Western model of medicine which understands disease as the malfunctioning of organs or the disturbance of body systems. This concept of disease is often seen as universal while the concept of illness represents culturally different notions. "Most non-Western cultures tend to perceive illness in a much broader and far less tangible manner. Illness is often viewed as being linked to social, spiritual, and environmen-

tal determinants" (Bowman 2004: 665). As Bowman points out the difference between a concept of disease that comes along with Western medicine and illness is even broader in non-Western cultures than it already is in Western cultures. Whereas disease needs to be understood within a framework of medical professional knowledge, illness can only be analysed within a cultural and social framework.

4 Intercultural competencies as professional standard

In the interaction of healthcare professionals and patients, both dimensions of being unwell, i.e. disease and illness play an important role. While the patient talks about his or her state in terms of illness by using lay-expressions, professionals need to understand the disease-dimension of the patient's state. Communication between professionals and patients usually takes place within a shared cultural setting that makes it easier for professionals to translate the descriptions and narratives of illness, pain or being unwell into a professional understanding of disease. Due to globalisation and migration processes, this shared cultural context cannot be taken for granted anymore. People from different cultural backgrounds come together in hospitals as patients as well as professionals and need to be aware of this problem. Intercultural misunderstandings may have unwanted consequences for the outcome of health care; they might lead to misdiagnosis, lack of compliance, or simply add to the misery of a patient.

This reality has been recognized as a problem by different parties. Hospitals have begun to address this issue by implementing tools like a 'migrant friendly hospital' (MFH Project group 2004). Sensitivity towards cultural as well as religious differences is growing and special needs of patients with regard to religion or culture are met by the offer of religious services, special food, or interpreters. Health care professionals have begun to include intercultural issues into education and, by doing so, raise sensitivity for the special needs of all patients – not only migrants – but patients in general. Cultural sensitivity implies to take cultural differences seriously but at the same time to avoid new stereotypes. E.g. just because someone is Roman Catholic doesn't necessarily mean the person wants a vegetarian dish on a Friday or is happy to be visited by a priest.

Leininger defines cultural sensitivity as a professional attitude for the field of nursing. The author explains: Trans-cultural nursing is "a formal area of study and practice which takes into account the specific values, beliefs and ways of life of people of diverse and similar cultures with the goal to use this knowledge in creative ways to provide culturally congruent care." (Leininger 1994: 209) As Leininger points out a culture-sensitive approach needs to take values and often religious beliefs into account. Hallenback and Goldstein strengthen this point further and move this aspect into the centre of their reflection. The authors argue for the need for cultural competence of healthcare workers because of significant different val-

ues in intercultural settings (Hallenbeck/Goldstein 1999: 28). Cultural differences need to be understood and made understood in order to be able to react specifically. Therefore, cultural competence starts with the ability to explain as well as to listen to explanations about cultural, religious, and social characteristics. This concerns not only the understanding of health and disease but also values and the idea of a good life and life quality. Cultural competence in practice means the ability to communicate and understand differences on those levels. One very prominent example of culture-sensitive communication can be seen in the problem of the different importance of truth-telling between doctor and patient in different contexts. In Western contexts it is thought to be essential to give full information to a patient about his or her condition. In other contexts, offering information about a bad diagnosis can be seen as too much for the patient who should not be distressed by bad news. A culture-sensitive approach cannot take any of these positions for granted but needs to find out the individual need for information of a patient.

This example shows that cultural competence cannot be acquired like technical skills, or applied like a gold standard. Since values and a person's cultural background are individual, a culture-sensitive approach has its basis in good communication and aims at mutual understanding of needs and differences. But cultural competence exceeds good communication skills: Being open for the explanation of cultural or social differences also implies self-reflection about one's own culture. By pointing at differences, the contingency of what is seen as normal within one's own culture needs to be understood. Besides explaining differences there is also a need for mutual respect within conversations between different culturally motivated standpoints. Especially culturally embedded values need to be taken seriously. The dialogue of values might however lead to conflicts: A consensus between conflicting positions cannot always be found and room for tolerance and dissenting positions needs to be negotiated in a professional setting. Knowing that intercultural conflicts may not always be avoidable, Pinto and Upshur suggest humility as well as introspection as principles in intercultural relations (2009: 7ff.). These attitudes strengthen the idea of tolerance further. Applying the principle of humility helps to avoid to see one's own perspective as more important or better than the other, and to accept the position of a learning person who still needs to understand more about a different position. Introspection helps to clarify one's own position and to reflect on the values and reasons for one's standpoint that is often simply taken for granted.

Intercultural sensitivity and competence is needed in personal encounters between health care professionals and patients but also within research groups, for example, in multi-centre trails. The mutual understanding of viewpoints, values and concepts of health, illness and disease helps professionals in multinational teams to combine forces for the benefit of patients. Within multinational tails, not only a culture-sensitive approach is necessary but differences in health care systems also need to be taken into account.

5 Cross-country medical research and intercultural ethics

Research ethics, a part of medical ethics, studies the normative questions that arise when new pharmaceuticals or techniques are tested in patients. Evidence based medicine asks for large numbers so that studies provide statistically valid data. This is often realised by doing multi-centre tails in different countries, where cross-cultural aspects need to be considered. Similar questions arise when products and knowledge from one part of the world is tested in another part of the world, like it is often the case in HIV/AIDS research. Most countries have developed ethical standards and regulations for this type of research. "Ethical standards vary significantly between cultures as a result of differences for instance in history, religion, ethnicity, economic situation and traditions"(Aagaard-Hansen et al. 2004: 117). The difference in ethical standards is not only a question of culture. Some are simply stricter, or less strict, than others. Aagaard-Hansen et al. (2004) closely investigated the already existing variety of codes of ethics for medical research. Since the existing variety of codes is quite large, it is, especially in cross-cultural trails, often difficult to know which code to apply for a particular trial. The authors suggest as a rule at least to comply with the ethical standards of the researcher's home country and the country of research.

Besides the local ethical standards, the four bioethical principles established by Beauchamp and Childress (1994) can serve as heuristics to get a better idea of where ethical problems might occur in intercultural contexts. Within this framework, four cross-cultural challenges for research outside the home country can be identified:

Patient Autonomy: To ensure patient autonomy in clinical trails in a Western context, usually an informed consent is sought from the patients. Patients are provided with the necessary information about what a trail is about, possible risks and benefits, and then decide for themselves whether to participate or not. While there already is a broad discussion about how to ensure and empower autonomous decisions, and how to deal with non-competent patients, the concept of informed consent might give rise to new difficulties in varying cultural contexts. Fagan (2004) for example points out that letting people act according to their religious or cultural beliefs may imply a constraint of their autonomy. Another example is the problem of informed consent with women and children in cultural contexts with mainly male dominated family structures. Here the question arises how the tradition can be respected and at the same time the informed consent be given by the person participating whose autonomy is thereby strengthened.

Non-maleficience: Following the Non-maleficience principle, the idea of avoiding harm has to be translated into different cultural contexts. Besides the risk assessment that should be part of any trail, special respect needs to be paid to the vulnerability of special groups as well as power relations. Participating in a trail can bring benefits to a person like general access to health care services that, in some countries, cannot be accessed otherwise. This might lead to uncritically agreeing to par-

ticipate in a trail because the person doesn't want to loose the hereto connected benefits. This might be especially the case with mothers trying to provide for their children.

Beneficience: Taking part in a trail should be beneficial for those participating. Thus, the structure and funding of the trail have to take into account that some health care systems might not provide for needs that occur within or under the circumstances of the research. Funding for unforeseeable events needs to be factored in and the team has to be able to provide support, or by co-operating with other institutions, refer a person to other supporting authorities.

Justice: Multi-centre trails might take place in areas where health care services are provided at a lower level than in the researcher's country. Therefore, considerations of ethical obligations based on the idea of justice are needed for the time when the research has been completed. The subsequent withdrawal of health care provided throughout the research might lead to disappointment within the research area or study population. The study population might think that it is not just to be used for research without continuous care for their health, and thus being treated perhaps differently from participants in other countries. Considerations have to be made as how to help bridge this gap in the provision of health care. This might be done by ensuring that health care is provided for the trail-relevant disease afterwards, that people benefit from the results in the long run, and maybe equipment or know how be transferred through the research (see also Aagaard-Hansen et al. 2004: 118).

As briefly sketched above the discussion of the four principles can provide examples why multi-centre trails as well as trails in different cultural settings create new intercultural problems. Besides intercultural questions in doctor-patient relationships, the structure and effectiveness of existing health care systems has to be taken into account. Likewise, questions of justice and the benefits provided by the research for the participants and their region need to be addressed.

6 Shortcomings of Western bioethics

Intercultural and crosscultural bioethics try to make visible that ethical considerations are culture relative and cannot automatically be seen as universal. Since the development of bioethics is strongly connected to Western medicine, at the moment, Western approaches of bioethics are dominant within the crosscultural bioethical discourse. This might lead to problems and shortcomings. Bowman describes several limits to the application of (Western) bioethical theory within an intercultural context (Bowman 2004). First, he points out that cultural and psychosocial issues are often only described as limitations of decisions within ethical theory. Without taking a closer look at the lifeworld situation, the description of the influence of culture on decision making processes might be oversimplified. Cultural issues are not seen as a framework for decisions and ethical problems but cap-

tured as one of many variables influencing a decision. This description is unable to encompass how decisions are always embedded within a cultural framework and how within this framework decisions are shaped.

Second, Bowman shows that there is a discrepancy between a mainly secular focus within bioethics and a world that for the greater part is non-secular. At present, no-secular arguments aren't heard within the bioethical discourse. Western bioethics does not address the worldviews of religious agents, moral obligations motivated by religion, and religious concepts of death and dying. This point is further stressed by Hedayat in his comparison between Western and Islamic concepts of autonomy in cases of elective abortions. Though Hedayat points out many similarities, he comes to the conclusion that a universal standpoint is not possible in this question. The author criticises Western bioethics in this regard: "What is problematic are the declarations from a numerically small but disproportionately influential group of secular thinkers using nomenclature such as universal, where large sections of the world adhere to theocentric ethics, including many Christians and Jews in Western countries." (Hedayat 2007: 20)

Bowman (2004) points out that there are also methodological shortcomings of Western bioethics. Western bioethics focuses on dichotomies and not on equilibrium. A typical example is the Western dichotomous distinction between health and disease, whereas in other contexts a person can be considered healthy and ill at the same time. As already mentioned above, the Western focus on autonomy and truth telling can also not be regarded as a cross-culturally shared viewpoint. Marshall and Koenig (2004) mention another methodological problem of Western bioethics. The researches detect a reductionist approach in biomedicine that predominantly focuses on mechanical models of the human body. Because of the close relation of Western medicine and Western bioethics, Western bioethics has adopted this reductionist mechanical approach.

Even when bioethics is encompassing cultural factors, these are often oversimplified. The concepts of culture and social identity used in bioethics often lack sophistication (Marshall/Koenig 2004: 259). Cultural comparisons tend to focus on major differences such as family centred versus individual centred approaches, making differences very appealing by stressing opposite values. The complexity of culture is reduced to simple opposites. A thorough understanding of the context is often left to anthropologists but goes far beyond the idea of culture in bioethics. Therefore, Macer demands: "We really need to have in-depth cross-cultural dialogue and study rather than defining one ethics as Asian and one as not. The interesting point is at what point do you call something distinctly 'Japanese' or 'Asian' or 'British'."(Macer 1999: 293) This means to be sensitive not to reduce cultural differences, and to carefully differentiate between cultural and social factors in order to avoid cultural stereotypes.

7 Cross-cultural bioethics as an interdisciplinary approach

The brief overview above has shown that social, religious, and cultural factors should play an important role in addressing bioethical issues in cross-cultural contexts. As a discipline, cross-cultural bioethics renders a contribution hereto by providing a platform for interdisciplinary intercultural research. Interdisciplinary work in bioethics, first, needs to understand medical practise. The analysis of core concepts like health, illness, and disease can be a first step to gain a better understanding of cultural differences in health care practice and the influence of cultural and social factors on health. Working together with health care professionals from various disciplines and backgrounds gives an insight into current new developments and new ethical issues that are raised by medical research across cultures.

In order to provide information for cultural sensitive communication between patients and health care professionals cross-cultural bioethics needs a solid empirical basis. Culture-sensitive descriptions of an understanding of health and illness and cultural patterns of the social role of a patient can be accessed in an interdisciplinary approach between bioethics and social sciences combining concept analysis and empirical research. "Stronger ties between bioethics and the social sciences are also likely to lead to more fruitful explorations of the relationship between cultural models and modes of moral deliberation." (Turner 2005: 306) As Turner points out, cross-cultural understanding also aims at the level of values and norms. Cross-cultural understanding can start with the description of values related to medical decision making and the decision making processes itself. Values may have their foundation in secular as well as religious worldviews. A thorough understanding of norms and values in relation to concepts like health and disease, on the one hand, and medical practise and decision making, on the other hand, builds the framework for cross-cultural approaches in bioethics. An interdisciplinary approach can help to get a richer understanding of how concepts of health and disease, medical practise and norms come together in decision making processes or ethical dilemma situations. In co-operation with other disciplines, like religious studies or economics, different factors related to health, health seeking behaviour and health care can be analysed in depth.

The expansion of knowledge proves helpful for medical practise as well as for research. A thorough understanding of different cultural practises can help to improve intercultural sensitivity for the effective training of professionals. Another reason to have a closer look at culture is that "the concept of culture serves as a reminder of local variations in understanding of health, illness, suffering, and death." (Turner 2005: 308) Integrating the notion of culture into research leads to a more thorough look at what can count as contingent and what can be seen as shared or even universal. Sensitivity for cultural differences within and between cultures helps to overcome simplistic concepts of culture. This may also serve as a framework to initiate discussions on shared values between cultures and the question of universally shared norms.

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7 The role of plant health for human health

Elke Pawelzik

1 Introduction

Healthy plants products are essential factors for human health. In many developing countries people suffer from limited access to food and especially to healthy food. Climatic changes and variability as well as population growth may aggravate the problems of food insecurity and consumption of contaminated food.

Plant health is mainly determined by the resistance against fungal and bacterial diseases as well as by adequate plant nutrition and water supply. The development of fungi and bacteria on plants interfere their growth and development and may lead to lower yield and lower quality of the harvested products. Some of the fungal species are able to produce mycotoxins which may cause adverse effects on human and animal health (Bhat and Vashanti, 1999). The WHO estimates that worldwide approximately 1.5 billion episodes of diarrhea occur each year and about 70% of them have been caused by biologically contaminated food (Unnevehr, 2003). Also, the FAO estimates a worldwide loss of about one billion tons of foodstuff per year resulting from mycotoxin contamination (Salay, 2003).

In Africa, mycotoxins constitute the second greatest hazard after food-borne bacteria for the safety of food (Bankole and Adebanjo, 2003). However, in opposite to developed countries, in developing countries mycotoxins have not been strong considered in relation to human health effects. The reasons for that are incompletely studied but some of them are stated in a previous published article: first, incomplete knowledge of mycotoxins and their effects on human health and inadequate communication of the known risks in regions with high contamination

risks; second, relative low attention to measures to reduce mycotoxin contamination compared to vaccination programmes; third, insufficient consideration of control mechanisms for mycotoxin contamination at different steps in the pre- and post-harvest period; fourth, in communities that produce and consume their own food occurs the highest burden with mycotoxins and therefore, general regulations to control are mostly not effective; fifth, the mycotoxin contamination is an issue concerning agriculture, health and economics (Wild and Gong, 2010).

2 Mycotoxins in plant products

Mycotoxins are secondary metabolites mainly produced by fungi as *Aspergillus, Penicillium* and *Fusarium* spp. (Wagacha and Muthomi, 2008). They contaminate agricultural products in the field during growing and in the post-harvest period, e.g. during storage, during and after processing. Factors affecting the occurrence of mycotoxins can be grouped into climatic, agricultural and food production, and socio-economic. At first, one of the most important factors for mycotoxin contamination is the sensitivity of the genotype against fungal contamination. Climatic conditions facilitating the fungal development and thus the mycotoxin production, include high temperatures and high humidity, unseasonal rains and flash floods. Soil types, insect activity and poor harvesting practices are important factors of the agricultural production for the likelihood of contamination (Wagacha and Muthomi, 2008; Cole et al., 1995). During post-harvest period again high humidity but also improper drying methods and storage conditions will facilitate fungal growth (Wagacha and Muthomi, 2008). Poor education level especially in the rural areas of developing countries and lack of skilled human resources are important socio-economic factors (Bankole and Adebanjo, 2003).
Aflatoxin, fumonisin, deoxynivalenol (DON), ochratoxin A (OTA) and zearalenon (ZEA) are worldwide accepted as the most important agricultural mycotoxins (Shephard, 2008). The consumption of contaminated food leads to adverse human health effects. Several diseases are caused by mycotoxins (Table 1). These diseases can lead to reduced life expectancy and loss of productivity, whereby 40% of this loss is caused by diseases exacerbated by aflatoxins (Miller, 1996).

Table 1: Some human diseases in which mycotoxins are involved (Bryden, 2007)

Disease	Source of mycotoxin	Fungus
Akakabio-byo	Wheat, barley, oats, rice	*Fusarium* spp.
Alimentary toxic aleukia	Cereal grains (toxic bread)	*Fusarium* spp.
Balkan nephropathy	Cereal grains	*Penicillium* spp.
Cardiac beriberi	Rice	*Aspergillus* spp., *Penicillium* spp.
Hepatocarcinoma	Cereal grains, peanuts	*Aspergillus flavus, A. parasiticus*
Kwashiorkor	Cereal grains	*Aspergillus flavus, A. parasiticus*
Neural tube defects	Maize	*Fusarium verticillioides, F. proliferatum*
Oesophageal tumors	Corn	*Fusarium verticillioides, F. proliferatum*
Onyalai	Millet	*Phoma sorghina*
Reye's syndrome	Cereal grains (grain dust)	*Aspergillus*
Stachybotryotoxicosis	Cereal grains (grain dust)	*Stachybotrys atra*

In the regions of sub-Saharan Africa, the inhabitants are mainly exposed to high levels of aflatoxins and fumonisins through their daily consumption of maize, groundnuts and other plant products (Table 2).

Table 2: Food commodities and aflatoxin contamination in Africa: examples from the literature (summarized by Wagacha and Muthomi, 2008)

Country	Commodity	Frequency of aflatoxin positive samples	Contamination rate/concentration
Botswana	Raw peanut	78% contained aflatoxins	Concentration: 12 – 329 mg/kg
Nigeria	Preharvest maize Dried yam chips	A. flavus isolated from 65% of samples	Total aflatoxins in positive samples: 3 – 138 mg/kg Mean concentration of aflatoxin B1: 27.1 μg/kg
Senegal	Peanut oil	Aflatoxin B1 in over 85% of samples	Mean contents about 40 μg/kg
Kenya	Maize	Samples from local market Samples from government warehouses, 350 maize products	Up to 46,400 g/kgp Up to 1800 μg/kg

For comparison, the Kenyan regulatory limit for aflatoxins in food is at 20μg/kg (Wagacha and Muthomi, 2008), whereas the EU maximum value amounts for total aflatoxins in nuts and cereals is 4.0 μg/kg (EC, 2006). According to a World Bank study, these strict European standards, the strictest in standard worldwide (Wu, 2006), cost African countries about 670 million US dollars each year in export losses (Wilson and Otsuki, 2003).

Aflatoxins occur mainly in maize and groundnuts whereas fumonisins are almost found in maize (Bankole et al., 2006). Limited surveys indicate the presence of OTA, DON and ZEA but in Africa they are less widespread than aflatoxins and fumonisins (Bankole et al., 2006).

The current knowledge about diseases associated with exposure to aflatoxins and fumonisins is summarized in Table 3.

Table 3: Disease associations with exposure to aflatoxins and fumonisins (Wild and Gong, 2010)

	Aflatoxins	**Fumonisins**
Main plant contaminates	Cereals, maize, groundnuts, tree nuts, some spices	Maize
International Agency for Research on Cancer classification	Natural occuring mixtures of aflatoxins: group 1 Aflatoxin M1: group 2B	Toxins from *F. moniliforme*, fumonisin B1, B2 and fusarin C: group 2B; Fumonisin B1: group 2B
Main tumor sites reported in animals	Liver	Liver and kidney
Other main adverse effects in animals	Hepatotoxicity, growth impairment, immune suppression	Equine leukoencephalomalacia, pulmonary oedema in pigs, hepatotoxicity and nephrotoxocity
Main tumor sites reported in humans	Liver	Oesophagus (?)*, liver (?)
Other main adverse effects in humans	Aflatoxicosis, cirrhosis (?), growth impairment (?), immune suppression (?)	*Aspergillus flavus, A. parasiticus*
Main plant contaminates	Cereal grains (grain dust)	*Stachybotrys atra*

*(?) the relationship is not established

To the present, the evidence about diseases caused by mycotoxins in developing countries is not very strong because of lack of data collection and assessment and limitation in the number and diversity of studied regions. However, some epidemiological studies of human populations, e.g. in Africa, exposed to contaminated

foods with aflatoxins revealed a relationship between a high incidence of liver cancer and dietary intake of aflatoxins (MERCK, 2006). Especially, if people are infected with hepatitis B and C, consumption of aflatoxin contaminated food rises the risk of liver cancer by more than ten-fold compared to either infection alone (Turner et al., 2003). Other studies suppose an interaction between permanent mycotoxin exposure and malnutrition, immune-suppression, affected growth and diseases, e.g. malaria and HIV/AIDS (Gong et al., 2003, 2004).

3 Mycotoxin control and prevention strategies

Besides the direct health risks, economic losses in the present and implications for next generations are serious. Meanwhile, many developing countries realized the importance of reducing mycotoxin contamination because of long-term health benefits to the local population and to international trade advantages. However, it needs enormous efforts to establish long-term strategies for mycotoxin control and prevention which include the following measures: prevention of exposure to mycotoxins, decontamination and constant surveillance and monitoring of fungi in contaminated food and feed stuff (Wagacha and Muthomi, 2008). Prevention of exposure to mycotoxins to the greatest possible extend can be achieved by different measures over all steps of the food production chain, e.g. in the agricultural production, at harvest, during storage, transportation, marketing and processing as well as by legislation (Milićević, 2009, Wagacha and Muthomi, 2008, Williams et al., 2004). Measures of good agricultural practice include chemical control (application of fungicides), early harvesting, rapid and adequate drying to ensure storability, physical treatments (e.g. sorting and dehulling of maize), sanitation, insect management and cultural practices, e.g. crop rotation, management of irrigation and fertilization (Wagacha and Muthomi, 2008). Methods of decontamination after harvest are known but from the current knowledge, the application seems to be not very realistic because of high costs and possible side effects (Wagacha and Muthomi, 2008). Breeding for resistance is recognized as one of the most promising long-term strategies in mycotoxin threat in Africa. So far, only few maize cultivars have adequate levels of resistance to fungi producing mycotoxins (Munkvold, 2003).

Many of the environmental conditions cannot be controlled and therefore, surveillance of susceptible crops will be of greatest importance. But, depending on the mycotoxin producing fungi, pre- and/or post-harvest conditions have to be controlled. Fuminosins producing Fusarium spp. infect the maize plant during growing in the field and thus control of fumonisins requires special attention to pre-harvest practices and to effects of food processing (Humpf and Voss, 2004). However, aflatoxins are produced during the post-harvest period if the environmental conditions facilitate fungal growth and subsequently mycotoxin formation (Wild and Hall, 2000). Therefore, an understanding of the plant/fungus interaction is necessary to develop prevention strategies for reduction of human exposure to

mycotoxins (Wild and Gong, 2010). Finally, to ensure that food and feed commodities are harvested correctly, dried sufficiently and stored appropriately (Wagucha and Muthomi, 2008), the countries have to strengthen their surveillance and awareness as well as the education of all actors in the food production chain and the consumer e.g. via governmental and non-governmental organizations and media.

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8 Inter-disciplinary health approaches for poverty alleviation: Control of neglected zoonoses in developing countries

Anna L. Okello and Susan C. Welburn

1 Introduction: "One Health"[1] in a globalised 21st century

In just 200 years, the earth's population has increased by five billion people: this incessant rise is placing significant strain on the world's natural resources (Gibbs 2005). In order to cater for rapidly rising human populations, the last few decades have witnessed a change in use of ecosystem services, particularly in developing countries, amid a rapidly globalised world. Former Norwegian Prime Minister and Director of the WHO, Dr. Gro Harlem Brundtland, stated "In the modern world, bacteria and viruses travel almost as fast as money. With globalization, a single microbial sea washes over all humankind. There are no health sanctuaries" (Brundtland, 2001). With such a plethora of information about the threats of emerging disease, particularly stemming from animal reservoirs, there seems a strong argument for implementation of interdisciplinary or "One Health" approaches to global health, zoonoses in particular. It is perhaps not so much acceptance of the con-

[1] For example definitions, please refer to:
http://www.eeas.europa.eu/health/pandemic_readiness/index_en.htm,
or http://www.avma.org/onehealth/

cept, but agreement upon the political and financial aspects of implementation of interdisciplinary strategies that requires further refinement (Okello et al 2011).

2 Linking zoonotic disease to poverty alleviation strategies

2.1 The Millennium Development Goals and "other diseases"

In 2000, the United Nations Millennium Summit agreed upon the eight Millennium Development Goals (MDGs) developed to provide a "policy framework for interventions and advocacy for improved health" (Molyneux, 2008). The sixth goal "to combat HIV/AIDS, malaria, *and other diseases*" has led to large scale financial interventions aimed to address the issues of infectious disease and their contribution to poverty; these *other diseases* are known as the "Neglected Tropical Diseases" (NTDs). Within these NTDs lie a sub-group of disease which have been formally recognised as "Neglected Zoonotic Diseases" (NZDs) under WHO's NTD programme and include: anthrax, bovine tuberculosis, brucellosis, cysticerosis/neurocysticercosis, cystic echinococcus, rabies and human african trypanosimiasis (HAT) (WHO, 2009c).

Neglected Zoonotic Diseases are common in developing and middle income countries throughout the world, particularly in rural areas where conditions for their transmission and perpetuation are ideal. Poverty, reliance on livestock for income or food, and the close proximity in which animals and people live together in the developing world are all factors which favour the spread of zoonotic disease (Okello et al 2011, WHO 2009). Besides affecting the health of people in these poorest communities, livestock productivity losses or death as a result of zoonotic disease places an even greater strain on those whose livelihoods depend upon them. Although such conditions also favour the development of emerging zoonotic diseases such as avian influenza and SARS, it is endemic diseases which fall into the category of NTDs and are officially recognised by the WHO as diseases of the poor (WHO 2009).

2.2 Neglected zoonoses and maternal/child health

There is acknowledgement that further research is required into effects of zoonotic diseases on maternal and child health (Welburn, 2011). Women and children, being amongst the most vulnerable groups of society, potentially bear the highest burden of neglected zoonoses, due to both extrinsic (food preparation, milking livestock) and intrinsic (decreased immunological capacity of pregnant women and young children) risk factors being increased in these societal groups. Rabies for example, kills over 55 000 people a year, with children under 15 years accounting for the highest affected (WHO 2010). In developing countries, 99% of the reservoir occurs in local dog populations, as such canine vaccination programmes have the

potential to save over 22 000 children a year. More generally speaking, neglected zoonoses potentially contribute to a number of symptomatic illnesses which account for over 70% of child deaths in developing countries, including diarrhoea and respiratory illnesses (WHO 2010). In terms of maternal health, it has been estimated that over 50% of pregnant women in developing countries suffer from iron deficiency anaemia (Ndibazza et al, 2010), of which various NZDs such as brucellosis and zoonotic tapeworms could potentially contribute. A lot more interdisciplinary research is required to truly assess the burden of NZDs specifically on maternal and child health; however positive correlations may further link benefits of NZD control to poverty alleviation through contribution to MDG 4 (reduce child mortality), MDG 5 (improve maternal health), and others (MDGs 1, 2, 3) surrounding poverty eradication, gender equality and improved access to education (Welburn, 2011).

2.3 Prioritising integrated disease control for developing countries

Integrated interventions for the control of neglected diseases have been described as the "'low hanging fruit' of disease control interventions: cost effective, efficacious, reduce prevalence, are pro-poor and easy to implement" (Molyneux, 2008). It has been argued that prioritisation for disease control should be based around such "cost effectiveness" rather than tools such as the Disability Adjusted Life Year (DALY) (Canning 2006, Maudlin et al 2009). Many feel the DALY calculation is not an applicable tool for neglected disease, zoonoses in particular (Maudlin et al 2009), as "hidden" morbidities (including anaemia, diarrhoea, loss of work and education) associated with NTDs are uncounted for (Canning, 2006).

The other concern for the lack of investment into the Neglected Tropical Diseases, or more specifically the Neglected Zoonotic Diseases subset, is that for many of these diseases, the "burden" is either unknown, or under-estimated, often due to difficulty in diagnosis, or under-reporting (WHO, 2006). Maudlin *et al* states, "Many zoonotic diseases are notoriously difficult to diagnose as they are often confused with other diseases; for example, where malaria is present, fevers owing to brucellosis may be misdiagnosed." (Maudlin *et al* 2009). This point was reiterated in a Ugandan study where community members described drinking raw milk (a risk factor for brucellosis) as a cause of malaria (Okello et al 2011). As a result of under-reporting and misdiagnosis, it has been widely accepted that the burden of endemic zoonotic disease in poor communities is under-represented, resulting in "serious consequences in terms of funding for both research and control initiatives" (Maudlin *et al* 2009). The system of prioritisation for control and investment which has been adopted under the MDGs and various other significant funding bodies such as the Bill and Melinda Gates Foundation has, despite its logic, seen by some as "not universally accepted as being either fair or sensible" (Maudlin *et al* 2009) and could be an explanation as to why NZDs are left out of major control programmes and funding for Research and Development.

There has been some progress to date addressing such recommendations in the years since they were made. In 2008, WHO published their eight year "Global Plan to combat Neglected Tropical Diseases", in which the link between neglected diseases, poverty and the Millennium Development Goals was acknowledged (WHO, 2007). Innovation, multi-sectoral integrated approaches and a "focus on populations and interventions rather than specific diseases", (possibly as a direct result of papers published by Canning, Maudlin, Molyneux and others citing the cost effectiveness of interventions aimed at clusters of disease) were a strong component of the strategic vision (WHO, 2007). In 2005, the UK Commission for Africa recommended that the Neglected Tropical Diseases received specific funding as a group, however some feel the recommendations have been "slow to take effect" with the "big three" still receiving the majority of the world's attention (Molyneux, 2008).

In her keynote speech at the 2007 Nairobi meeting on neglected zoonotic diseases, Esther Schelling described the difficulties faced by developing countries in controlling zoonotic diseases, citing "dispersed smallholder livestock systems, predominance of informal markets and limited capacity and resources to deliver services" as challenges (WHO, 2007). The need for a One Health approach for the surveillance and control of zoonotic disease in developing countries was reiterated, encouraging participants to envisage the future research agenda as "interdisciplinary, participatory and integrated with prevention and control needs" (WHO, 2007).

There is therefore undeniable logic for the control of zoonotic disease in developing countries in order to improve the health of people living in developing countries, improve the health and subsequent productivity of their livestock, and increase food security and safety. There is also acknowledgement that despite addressing these "neglected" zoonoses of particular concern in certain communities, the capacity for detection of emerging zoonoses will also be increased with community awareness and participation in surveillance networks. Institutional support for the control of neglected zoonoses is growing; several publications have identified the growing widespread support for their control emulated in this summary "by simultaneously saving lives and securing livelihoods, the control of neglected zoonotic diseases offers a real and highly cost-effective opportunity for alleviating poverty, especially in remote rural communities and marginalized peri-urban communities" (WHO, 2009).

3 Raising the international profile of neglected zoonotic diseases

3.1 Geneva, September 2005: "The control of neglected zoonoses: A route to poverty alleviation"

This meeting was held in 2005 by WHO in conjunction with the Department for International Development Animal Health Programme (DFID-AHP). Until this point, there had been a substantial amount of focus by the international community on emerging zoonotic diseases, and to a lesser degree Neglected Tropical Diseases, however this meeting was the first to focus international attention on the Neglected Zoonotic Diseases as a separate entity. The main objective of the meeting – "to bring together groups that would not ordinarily meet to address a common problem of interest" (WHO, 2006) - was very much in keeping with the One Health concept. Seven endemic diseases were chosen at this meeting as a "target group" upon which to base initial control efforts, these were: anthrax, bovine tuberculosis, brucellosis, cysticercosis, cystic echinococcus, rabies and zoonotic trypanosomiasis (WHO, 2006).

This meeting really set the stage for the ongoing dialogue on the topic of neglected zoonotic disease which has been occurring up to this point. The reasons for why the poor suffer disproportionately from zoonotic disease, reasons for under-diagnosis and the associated "neglect" on the international stage, and recommendations for further research and collaborative efforts were all topics discussed at this inaugural meeting.

The growing evidence for the advantages of joint human-animal health systems in the field of the diagnosis, prevention and control of neglected zoonotic diseases was considered tantamount to the successful control of neglected zoonoses, leading to an overarching recommendation to "work towards the concept of 'One Health'" (WHO, 2006).

3.2 Nairobi, November 2007: "Integrated control of neglected zoonoses in africa: Applying the "One Health" concept"

This meeting was organised as a timely follow-up to the inaugural 2005 meeting on neglected zoonoses. Besides the WHO, the meeting connected a range of additional stakeholders, including the European Commission (EU), Danish Centre for Health Research and Development (DBL), International Livestock Research Institute (ILRI), the Food and Agriculture Organisation of the United Nations (FAO), The World Organisation for Animal Health (OIE) and the African Union (AU).

There was a large attendance of about ninety people, including not only public health and veterinary public health specialists but researchers and representatives from international and regional organisations (WHO, 2009). The overall objective of the meeting was to develop a strategic framework for the control of Neglected Zoonotic Diseases, in keeping with the actions points which arose from the 2005 meeting and included points surrounding intersectoral collaboration, improvement of diagnostic and surveillance capacity and foster research and advocacy.

In her keynote speech which opened the meeting, Esther Schelling proposed a "One Health" approach for the control of neglected zoonotic diseases, recommending this perspective would "enhance detection and control of zoonoses by intersectoral surveillance and communication, by contingency planning with all line ministries, and by providing novel cost-effective trans-sectoral options for zoonoses control in low income countries"(WHO, 2009c). She urged participants to consider the "untapped potential of new institutional and operations models" for the provision of joint health services in developing countries, and outlined ways in which international advocacy efforts could promote the One Health concept in order to raise the profile of neglected zoonotic diseases in the future (WHO, 2009).

Recommendations were made for action plans at the global, regional and national-levels to assess the burden of neglected zoonotic diseases in Africa; thus providing the framework for future control. It was recommended that a scientific advisory committee be formed to work as the "driving force" behind these recommendations, and that recent high profile initiatives such as the international response to avian influenza, and to a growing degree the neglected tropical diseases, be considered as advocacy platforms for "combating NZDs" (WHO 2009)

3.3 Integrated Control of Neglected Zoonoses (ICONZ) 2009-2013

This is a seventh framework project funded by the European Commission and managed by the University of Edinburgh, which began in 2009. It involves the collaboration of 22 European and African universities and research institutes working on clusters of zoonotic diseases in case studies in seven African countries; Morocco, Mali, Nigeria, Uganda, Tanzania, Mozambique and Zambia. This is the first large collaborative project of this nature in the field of neglected zoonotic diseases, and it is hoped that the understanding of diagnostics, burden of disease and intervention options for their control will be much improved as a result of the case studies. This information will fill vital knowledge "gaps" which currently exist on the burden of NZDs, providing a strong support basis with which to undertake advocacy and policy activities at the international, regional and national levels in developing countries.

4 Current political and institutional challenges of implementing interdisciplinary research for zoonoses control in developing countries

In order for the prevalence of neglected zoonotic diseases to be truly defined, in such a way that political and institutional support can be given to develop comprehensive diagnostic and intervention tools for their control, human and veterinary authorities would benefit from working together in developing countries to implement surveillance and reporting of cases of these diseases. However, the realities of practically implementing such a strategy are difficult, given the institutional and administrative factors which exist in most developing countries. This issue has been acknowledged by the FAO/OIE Strategic Framework for One Health (FAO 2008), despite the focus of this report really being to address emerging infectious disease such as avian influenza, rather than the endemic zoonoses. However the principles remain the same, and there are positive indications that platforms set up under the HPAI control and surveillance program may lead to long term intersectoral collaboration for other zoonotic diseases such as rabies and brucellosis (AO, Personal Communication, 2010).

Major constraints in many developing countries to the prioritisation of zoonotic disease control include human resources for surveillance and control, finances, and discrepancies within government structure such as decentralisation which means that often national or regional surveillance and control programmes are difficult to undertake on the ground (Okello et al, 2011, FAO, 2008). It is felt that government and research institutions, along with animal and human health systems (including those in the private sector) all require strengthening if disease control is to without long term subsidies from the international community. Additionally, the level of advocacy and public awareness to the prevention and control of zoonotic disease is important to ensure that community behaviour change occurs for the long term prevention and control. The strengthening of animal and human health systems is a pivotal component of the successful control of zoonotic disease in developing countries.

An additional challenge for implementation of One Health and functioning biosecurity and animal health systems in developing countries is the smallholder farming system which dominates the majority of rural settings, particularly in Africa (FAO, 2008). Access to public health and veterinary services is poor, with many of the free government services providing a lifeline to these communities and their animals disbanded after the introduction of structural adjustment in the 1990's. Due to poor sanitation, close living arrangements between humans and animals, and often intense farming practices as a result of diminishing land, infectious diseases are often well-established in humans and animals, or in the case of zoonoses, both (Okello et al 2011). Enhancement of biosecurity and surveillance mechanisms is necessary for the long term sustainable control of infectious disease in poor communities. However, cost, tradition, lack of income diversity and lack of alterna-

tives to current practices are often cited as reasons why surveillance does not occur, coupled with a lack of incentive for the smallholder farmer who may only own a handful of animals, owing to less market share compared to those farmers with commercial establishments, where uniform disease control measures may be beneficial (Okello et al, 2011, FAO, 2008).

5 Integration: What does it mean and how can it be applied in the context of One Health and neglected zoonoses?

Despite much effort to strengthen surveillance systems and control programmes for zoonotic diseases worldwide, especially for potential global pandemics such as avian influenza, there is wide acknowledgement that still more work is required. Many experts are calling for further "integration" within academia, governmental and private sector stakeholders involved with zoonotic disease control, and reviews of undergraduate and graduate curriculae in both medical and veterinary schools to raise awareness and promote greater understanding of the "One Health" concept.

Due to the many varied disciplines covered by the One Health concept, speaking of an integrated approach could be taken to mean many different things, and this is usually the case, depending on the mandate of the organisation promoting it. There are many different forms of integration which could be promoted in interventions for both the prevention and control of zoonotic disease, including inter-disciplinary, inter-organisational and inter-governmental. A comprehensive definition of integration refers to the "creation of linkages among existing programs to improve the delivery of health interventions given existing commitments and resources" (Grépin & Reich, 2008).

5.1 Types of programmatic integration which can occur with zoonotic disease control

Integration as a concept has certainly been promoted in the field of Neglected Tropical Disease Programmes; single interventions such as Mass Drug Administration (MDA) against a number of co-existing infections including lymphatic filariasis, soil transmitted Helminthiasis and schistosomiasis has been cited as a "natural entry point" for integrated public health programmes (Lammie *et al*, 2006). The concept has been further supported by a variety of high profile funding grants from organisations such as the Bill and Melinda Gates Foundation and the United States Agency for International Development (USAID). However, there is concern that understanding of the basic concept of integration may be lacking, and that many organisations show "limited experience in implementing integration and even less experience in conducting systemic analysis of these experiences" (Grépin & Reich, 2008).

Grepin and Reich proposed an "integration framework" which helps differentiate different types of integration which could occur in public health programmes and follows the concept of integration as domain, level or degree. They stipulate three questions which can be asked to ascertain the possibilities for integration, set out in this much simplified version of the framework (summarised from Grépin & Reich, 2008):

Table 1: Summarised version of the "Integration Framework" from Grépin & Reich, 2008

i) **Domain**: ***What is being integrated?*** Does the recommended integration refer to a specific activity, policy process or organisational structure within the given programme? ii) **Level:** ***Where is integration occurring?*** Is it at the global, regional, national or local level? iii) **Degree:** ***How is integration occurring?*** Is it through co-operation (programmes working together), collaboration (working together and sharing of resources) or consolidation (one part of a programme completely taken over by another).

Under this framework, any disease control programme or project which is being described as an "integrated" programme should be able to pinpoint the type of integration which is occurring. Some examples include:

a) Joint community training sessions for zoonotic disease prevention: Collaboration in the activity domain at the local level
b) Surveillance of multiple diseases by one epidemiological unit: Consolidation in the organisational domain at the national level
c) FAO/WHO/OIE strategic framework for the implementation of One Health (FAO 2008): Co-operation in the policy domain at the global level

A nice "real life" example of integration - co-operation at the regional level in the organisational domain - is the development of Integrated National Action Plans (INAPs) for the control of avian influenza in Sub-Saharan Africa. This co-operation is between the African Partnership for Livestock Development, Poverty Alleviation and Sustainable Growth Initiative (ALive) and the Global Framework for Progressive Control of Transboundary Animal Diseases (GF-TAD) and promotes regional co-operation of technical experts and donors committed to the prevention and control of avian influenza in the region (FAO, 2008).

5.2 Inter-disciplinary Research and Teaching Programmes

Some authors call for more investment and incentives for research in biomedical and comparative medicine, amongst fears that this type of research is "losing its appeal as a career" for veterinarians and physicians (Kahn, 2006). There are around 25% less research physicians in the United States compared with 20 years ago, with a similar picture in the veterinary profession (Kahn, 2006). The reasons for this in both fields include lack of mentorship and research opportunities, emphasis on clinical care, and a requirement to make money in order to pay off educational debt (Kahn, 2006). Another author calls for the promotion of inter-disciplinary science and closer attention paid to "ecology not economy" (Gibbs, 2005). In order to promote and sustain interest in comparative medicine research, there have been recommendations to change the way research funding is set up; for example promote "joint funding streams from human, animal and environmental health sectors to support integrated public health programmes" (Pappaioanou, 2010), and the prioritisation of research grants to teams promoting professional collaboration and inter-disciplinary research projects (Kahn, 2006). The AMVA is however a little more optimistic, citing the changes in the direction of teaching over the last five years which have improved linkages between public health and veterinary schools; "today, more than half of US veterinary colleges have formal dual Doctor of Veterinary Medicine (DVM/VMD)/Master of Public Health (MPH) degree programs" (AMVA, 2008).

6 Conclusion

In conclusion, a common appreciation for the concept of integration, and what type(s) of integration could be carried out at what level, is useful for those involved in the development of zoonotic disease control programmes, particularly in resource-poor regions. Grepin and Reich support the "need to accelerate the implementation of integrated NTD control activities, but they also must be evaluated in a systematic manner" (Grépin & Reich, 2008).

Despite the perceived difficulties of application of interdisciplinary approaches in developing countries, there are positives. This was recognised over a decade ago, when the focus of the 1999 FAO/OIE/WHO Veterinary Public Health conference in Teramo was particularly on Countries in Transmission (CIT[2]) and Developing Countries[3] in order to reach a wider audience. There was acknowledgement that despite Veterinary Public Health definitions and priorities were "more limited

[2] "Countries whose economies used to be centrally planned by the government but are now changing to market-based economies" (FAO, 1999)

[3] Based on the World Bank glossary, a DC is defined as low (64 countries) and middle (93 countries) income countries in which most people have a lower standard of living with access to fewer goods and services than do most people in high income countries (FAO, 1999)

compared to those in developed countries", the "opportunities for the collaboration of veterinary and human health activities were recognised as existing across all countries, and are not confined to specific regions, nor do they respect international borders, and they may extend across ethnic and political divides" (FAO, 2003).

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9 Arbovirus infections in cattle

Claus-Peter Czerny, Eva Schröer-Merker, Jessica Olbrich, Ulrike Diesterbeck

1 Introduction

Arboviruses are zoonotic viruses transmitted by hematophagous arthropods (*ar*thropod-*bo*rne viruses) and constitute the largest group of biological viruses that infect vertebrates (Sang et al., 2006). With about 400 species they can be found in a number of virus families and play an important role especially in tropical regions. This taxonomically wide-ranging group comprises almost exclusively viruses whose genome is present as ribonucleic acid (Weaver, 2006). About 50 % of the arboviruses isolated from vectors originate from mosquitoes and 25 % from ticks. However, it has to be considered that more investigations in this regard were done on mosquitoes than on ticks. In most agricultural systems, ruminants are widespread and exist in large numbers (Purse et al., 2005). The FAO (2008) specifies the number of cattle (including buffaloes) held worldwide in 2006 with more than 1.5 billion animals. In particular, regarding the progressive processes of globalization and climate change, which cause extensive consequences for the international transportation of animals as well as for local climate conditions, it is suspected that endemic areas of infectious diseases will continue to spread. Arboviruses are very climate sensitive (Koeijer et al., 2007; Patz et al., 2005). It is important to identify arbovirus infections worldwide and investigate their ways of transmission to establish efficient surveillance strategies.

2 Vectors

Vectors are living carriers of infectious particles. In tropical and sub-tropical countries often arthropods transmit germs to vertebrates (Thrusfield, 2005). There are two types of vectors, mechanical and biological vectors. In case of mechanical vectors, the infectious agent is transmitted mechanically from, e.g., fleas or lice to the vertebrate host. That means that the virus does not replicate inside the vector. In case of biological vectors, the pathogen undergoes a necessary stage of development and multiplication (Kuno and Chang, 2005). To initialize an infection cycle various conditions must be met. First, a susceptible vector needs to incorporate sufficient virus during its blood meal from a viremic host, so that its infection threshold is exceeded (Purse et al., 2005; Thrusfield, 2005). Then the vector has to survive the extrinsic incubation period until the next blood meal, which it has to take from a susceptible host. All hematophagous arthropods produce saliva containing anticoagulants, which they insert into the wound during the blood sucking process. There is a big number of poikilothermic and homothermic organisms, which are vectors for different pathogens such as sandflys, lice or rodents. Vector-borne diseases of ruminants primarily include those, which are attributable to midges (mosquitoes, biting midges, gnats) and ticks as vectors. As poikilothermic organisms they are very dependent on the ambient temperature. Little empirical research has been carried out regarding the relationships between ticks and their hosts as well as regarding their contact with humans, habitat-fragmentation, and health risks (Estrada-Peña et al., 2007). In addition, the sole isolation of viruses does not allow for conclusions of a vector function (Whitehouse, 2004). In many cases, as for the numerous species of ticks that are associated with the Crimean-Congo Haemorrhagic Fever (CCHF), there is no clear proof of the vector competency. The Bovine Ephemeral Fever (BEF), for example, does not appear over wide areas in enzootic countries leading to the indirect conclusion that this is due to climatic boundaries of the vectors (St. George, 1990). However, it is also easily conceivable that climatic boundaries of virus replication or the interaction between virus and vector are the reason for the limited appearance of, e.g., BEF. This emphasizes the complexity of the epidemiology of arboviruses. The fact that within the same time frame various arboviruses can be transmitted to a population by a single vector species, illustrates the risk of misinterpretations regarding the evaluation of the epidemiological situation. In addition, new vectors have been discovered, as in the case of Bluetongue Virus (BTV) in Europe, so that it has to be assumed that for other arboviruses, too, all possible vectors haven't been identified yet. Moreover, through the transport of livestock, zoo animals or non-animal goods, vectors can colonize new habitats. During the last ~230 years, at least 11 arthropod species had been introduced solely to the USA and firmly established,

another 10 are seen as potential risk for introduction (Little, 2008). Furthermore, vectors often function as competent transmitters for more than one disease what emphasizes again the complexity of epidemiology of arboviruses. Most vectors have a wide host spectrum enabling in principle arbovirus transmission to a number of susceptible species. The Rift Valley Fever Virus (RVFV) has been isolated from 30 species of six genera of *Culicidae*. But it is important to note that in case for some vectors only mechanical transmission has been proven. Because the suspected mechanical transmission paths by arthopods are not clarified by today, Lumpy Skin Disease Virus (LSDV) and Bovine Malignant Catarrhal Fever Virus (BMCFV) will not be discussed in detail here. Both viruses contain DNA as genetic information and are apart from "classic" arboviruses. Lumpy skin disease is caused by a poxvirus and is mainly enzootic in Africa where it has major economic effects. The bovine malignant catarrhal fever is a worldwide sporadically occurring herpes virus infection with high lethality.

3 Classification of arboviruses

Due to the vector-dependent transmission there are typical differences between the transmission process of arboviruses and those of contagiously transmitted viruses, especially a high dependency on weather conditions and climate (Koeijer et al., 2007). Furthermore, they are mostly promiscuous, rapidly replicating pathogens, which are transmitted by fast multiplying and ubiquitously occurring vectors (Purse et al., 2005). Some of the mentioned diseases are of international importance. For instance, Bluetongue Disease, Rift Valley Fever, and Lumpy Skin Disease were recorded by the World Organisation for Animal Health (OIE: "Organisation Mondiale de la Santé Animale") as "List-A"-diseases, while the Bovine Malignant Catarrhal Fever was recorded as "List-B"-disease (OIE Handistatus II). Since 2005, the OIE publishes continuously notifiable diseases. The genetic material of the majority of the pathogens described in the following consists of ribonucleic acid (RNA). Replication errors, such as base exchanges, insertions and deletions are common evolution mechanisms in RNA-viruses (Sall et al., 1999). In segmented RNA, partly also entire segments are exchanged implying the use of live vaccine to face the risk of returning to virulence. The risk of the unintentional circulation of life vaccines in the field has already been described (Sailleau et al., 2005). The examined arboviruses can be divided into two groups according to their vectors, comprising arboviruses transmitted by midges (Table 1) and arboviruses transmitted by ticks as main vector (Table 2).

Table 1: Arbovirus infections of cattle transmitted by midges

Disease	Virus taxonomy	Transmission	Hosts	Distribution
Bluetongue Disease	Reoviridae, Orbivirus, BTV, 25 Serotypes, dsRNA 10 Segments	Culicoides spp., Aedes spp., *Melophagus ovinus*	Ruminants	Worldwide
Rift Valley Fever	Bunyaviridae, Phlebovirus, RVFV, -ssRNA, 3 Segments	Aedes, Culex, Phlebotomus	Ruminants, Humans	Africa, East-, West-, Sub-Sahara, Jemen, Madagascar; Saudi Arabia,
Akabane Disease	Bunyaviridae, Bunyavirus, Simbu-Group, AKAV, -ssRNA, 3 Segments	Culicoides spp., *Aedes vexans, Culex triyaeniorhynchus*	Ruminants: Cattle, Sheep, Goats	Israel, Turkey; Middle East, Africa, South-East Asia, Japan, Taiwan, Australia
Ephemeral Fever	Rhabdoviridae, Ephemerovirus, BEFV, +ssRNA	Culicoides spp.	Exclusively Cattle	Africa, Asiam Australia

Table 2: Arbovirus infections of cattle transmitted by ticks

Disease	Virus taxonomy	Transmission	Hosts	Distribution
Krim-Kongo-Fever	Bunyaviridae, Nairovirus, CCHFV, -ssRNA, 3 Segments	Hyalomma spp., *Haemaphysalis punctata*, Rhipicephalus spp., *Dermacentor marginatus, (Ixodes ricinus)*	Mammalians, Humans, Cattle, Goats	Europe, Turkey, Africa, Asia, India, („Emerging Disease“)
Kyasanur Forrest Fever	Flaviviridae, Flavivirus, KFDV, +ssRNA	*R. appendiculatus, Haemaphysalis spinigera*	Cattle, Humans Monkeys	Saudi Arabia India, 1957 after forrest clearings; China
Dugbe Virus	Bunyaviridae, Nairovirus, -ssRNA, 3 Segments	Amblyomma spp., *Rhicpicephalus pulchellus, Hyalomma marginatum rufipes*	Cattle, Sheep, Humans, Vertebrates	Arid areas in Africa
Kupe Virus	Bunyaviridae, Nairovirus, -ssRNA 3 Segments	*Amblyomma gemma, Rhicpicephalus pulchellus*	Cattle	Kenya (Nairobi), recently discovered

-/+ssRNA = negative/positive-sense single standed RNA; dsRNA = double stranded RNA

3.1 Bluetongue disease

Pathogen. The bluetongue virus (BTV) belongs to the genus *Orbivirus* of the family *Reoviridae* and can be considered as a prototype for this genus (Dungu et al., 2004; Roy, 1992). Among others the viruses causing African horse sickness and the epizootic haemorrhagic disease of deers belong to this genus (Roy, 1992). Even though the pathogen was not known at the beginning of the 20th century, a vector-dependent transmission was already assumed and its similarity to the African horse sickness was emphasized (Bruce, 1905). The virion consists of three protein layers and has an outer diameter of 100 nanometers (nm), while the inner double-layered capsid has a diameter of 60 nm. The capsid contains seven virus-proteins (VP) and the double-stranded RNA (dsRNA) can be found in 10 segments inside the virion. Furthermore, four non-structural proteins (NS) are encoded. The non-enveloped virus particles are relatively resistant to solvents such as ether and chloroform but very sensitive to high temperatures and low pH-values. The virus is acid labile and stable from pH 6.4 to pH 8.0. So far, 24 serotypes have been known and recently a new one called *Toggenburg Orbivirus* has been discovered (Hoffmann et al., 2008). While the VP7 is serogroup-specific, the VP2 represents the serotype-determining protein (Roy, 1992). On the basis of genetic analyses of segment 2, which codes VP2, it was possible to identify 10 evolutionary lines within the 24 serotypes known until 2004, the so-called nucleotypes (Maan et al., 2004, 2007). They are defined by a nucleotide sequence difference of <35 % in segment 2. In addition, on the basis of the same segment, two topotypes were identified enabling the allocation of the strain of a serotype to an Eastern or Western region of origin. This high genetic diversity can be explained by point mutations ('genetic drift') and by the exchange of entire segments between different serotypes ('genetic shift') (Saegerman et al., 2007). For BTV, segment exchange was detected in a Holstein bull 20 years ago (Stott et al., 1987). In case of a coinfection with two serotypes, for example, there are already 1,024 (210) possibilities for an exchange of the 10 segments (Dungu et al., 2004). Moreover, even within particular serotypes there is a great diversity with respect to virulence and pathogenicity that are influenced by both the geographic origin as well as the amount of passages in cell cultures (Kirkland and Hawkes, 2004).

Bluetongue disease was first described by Hutcheon as "fever of epizootic catarrh" in 1880/81 (cited from Goltz, 1978). The term "bluetongue" was introduced later and describes the cyanotic change of the tongue in seriously ill sheep (MacLachlan, 2004). The first epizootic outbreak in cattle took place in South Africa in 1933 (Goltz, 1978). Up to the 1940s, the disease was regarded to be spatially limited to the African region in the South of the Sahara. The first documented epizootic outbreak outside the continent took place in Cyprus in 1943 and affected sheep (MacLachlan, 2004). Subsequently, the South of the United States, the Middle East, Asia, and Southern Europe were hit. Originally limited to subtropical regions, BTV has been established in various serotypes in large parts of Europe

since 1998 and has caused there the greatest documented outbreak of all to date by killing 1.8 millions of animals (Maan et al., 2007; Meyer et al., 2009). After Europe had been considered as free of the disease since 1979 (with few exceptions), BT occurred at first on four Greek islands (Sailleau et al., 2005). Subsequently, the Mediterranean region was hit. In the Western Mediterranean region, the serotypes 1, 2, 4, and 16 of African origin occurred and were mainly transmitted by *Culcoides imicola* (Saegerman et al., 2008). In Eastern Mediterranean countries outbreaks of the BTV-serotypes 1, 4, 9, and 16 were documented, which originated from the Near, Middle and Far East. They were transmitted by additional vector species. In August 2006, BTV first occurred in Northern Europe, where it was regarded as emerging disease (OIE, 2006). In Northern Europe the serotypes 8 and 6 have occured. In the United States, BT has been officially recognized since 1952 (Kirkland and Hawkes, 2004). From January 2005 to the end of 2008, BT had been reported to the OIE from more than 40 states from all five continents (WAHID Interface, 2009). Apart from direct impacts, BT causes high economic losses due to necessary trade restrictions (Maan et al., 2007; OIE, 2008).

Epizootiology and epidemiology. Meanwhile, BT is an ubiquitously occurring, infectious, non-contagious virus disease of ruminants that especially in sheep can lead to pronounced clinical symptoms (Conraths et al., 2009; Maan et al., 2007; Saegerman et al., 2008). African sheep breeds are resistant or have a mild course of infection (Dungu et al., 2004). In cattle, goats or some wild ruminants often mild or inapparent infections occur (Conraths et al., 2009; Dungu et al., 2004), while in cattle even prolonged viremia appears (Singer et al., 2001) and, they are therefore regarded as reservoir. The mild course of the infection and the prolonged viremia possibly indicate a stronger adaptation of the virus to cattle than to sheep (Takamatsu et al., 2003). Moreover, various carnivore species were tested seropositive probably by oral intake of meat infected by the virus (Murray et al., 1999). BT is not transmissible to humans. The virus is transmitted by gnats of the genus *Culicoides* that consists of 1,260 species of which around 30 are competent vectors of diverse orbiviruses (Saegerman et al., 2007 and 2008). Purse et al. (2005) referred to 1,400 *Culicoides* species of which <1 % had been infected by BTV-vectors – with the addition that so far only few species had been examined in this context. In addition to the original vector *Culicoides imicola*, gnats of the goups *C. obsoletus*, C. *pulicaris*, and *C. dewulfi* appeared in Europe (Koeijer et al., 2007; Saegerman et al., 2008). Also, species of *Aedes* as well as the ectoparasitic sheep ked (*Melophagus ovinus*) can transmit the disease. In these "non-vector" species, the vector competence is induced by temperature (Purse et al., 2005). Life expectancy of adult gnats is stated differently ranging from less than ten days (Takamatsu et al., 2007) to on average three weeks under favorable conditions (Koeijer et al., 2007). Nevertheless, the authors point out that a BTV-infection can reduce a vector's life expectancy. There is not any evidence for transovarial transmission (Takamatsu et al., 2003). To minimize flying time, gnats live in proximity to its hosts (Koeijer et al., 2007). They brood in a variety of humid microhabitats like, e.g., dung heaps, drainage

pipes or irrigation canals that can be found on most utilized agricultural areas (Purse et al., 2005). The development of *Culicoides* starts at a threshold value of 8 °C to 10 °C, while ideal temperature for population development is between 25 °C and 30 °C. After the intake of infected blood, vectors become infectious as soon as the virus has been replicated inside the gnats after it has reached the salivary glands (OIE, 2008; Wilson et al., 2008). Then the virus is transmitted by the saliva during the blood sucking process and the vector remains permanently infectious. The probability of completion of the transmission cycle is seen as relatively low for individual vectors, which, however, can be compensated by a high vector density and favorable weather conditions (Purse et al., 2005). The occurrence of new diseases, therefore, correlates with the vector prevalence and reaches its peak, for example, in Germany between September and October (Conraths et al., 2009). In climatically mild regions of Africa, transmission can take place constantly (Dungu et al., 2004). There are many details regarding the interaction between virus and vector, which still have to be clarified in order to reach a better understanding of BT epidemiology (Wilson et al., 2009). It is assumed that some BTV strains are able to infect the fetus via the placenta. For instance, a four-week-old calf of a BTV-positive dam was tested positive, too (Niedbalske, 2009) and in addition, BTV1-RNA was detected in liver and heart of a lama fetus (Meyer et al., 2009). The horizontal spread via semen is discussed, too. An Australian study with laboratory and field virus strains as well as with young and old bulls showed that primarily laboratory-adapted strains could be found in the excreted semen of bulls (Kirkland et al., 2004). This could be of particular interest when using live vaccines, the virus, however, was only excreted during or directly after viremia. For the geographic expansion of the BTV-area, various ways have been presented. The transportation of animal products like semen, the migration of wild and domesticated ruminants, infected *Culicoides*, which reach new areas on animals or plants by flying actively or being passively carried by the wind or in planes. Also new vector species, and the inapparent infection of cattle contribute to this. Moreover, for a permanent establishment of the BTV in Northern Europe, its overwinter survival is of major importance (Saegerman et al., 2008; Takamatsu et al., 2003; Wilson et al., 2008). It is assumed that the virus can hibernate inside an adult vector, can be reintroduced annually, persists inside an unknown vector or host species, is transmitted mechanically by living or dead vectors or is resistant due to other mechanisms in classical hosts. The persistent infection in bovine and ovine γ/δ T-cells *in vitro* is well known (Takamatsu et al., 2003). Furthermore, the virus is able to persist inside the vector in low titers at temperatures of <10 °C for 35 days and is subsequently able to replicate at higher temperatures (Purse et al., 2005). Also horizontal transmission paths like transovarial, transplacental, by semen or oral transmission (intake of the placenta after calving) are discussed to form the basis of the persistence of BTV during symptom-free periods (Wilson et al., 2008). BTV transmission by semen is observed only in a part of infected bulls excreting the virus during viremia. Often old animals are shedding discontinuously and with visible impurity of

the semen by blood (Kirkland and Hawkes, 2004; Kirkland et al., 2004). Serological studies in endemic areas mostly show high incidences of up to >80 % (Karaoglu et al., 2007). Purse et al. (2005) identified temperature and humidity as the two most important extrinsic variables for BTV transmission. BT transmission ways are more diverse and are not limited to the purely vector-borne transmission of a classical arbovirus.

Control and combat. There exist mobility and trade restrictions that should avoid the occurrence of new foci of infection. However, they are of limited use during the vector season (Conraths et al., 2009). Also models for local risk prediction depending on weather and vector density are currently under development, e.g., in the Netherlands (Koeijer et al., 2007). Two essential instruments for BT control are active immunization as well as the avoidance of contact between vertebrate and vector (Dungu et al., 2004). In 2008, vaccination was carried out across the whole area of Germany reducing the total number of new cases from 59,097 in 2007 to 1,070 within one year (Conraths et al., 2009). The new cases registered in 2008 in the German federal states of Lower Saxony and Baden-Württemberg can be attributed mostly to a later start of the immunization campaign caused by a lack of vaccine availability. Nevertheless, a complete eradication of BT in enzootic regions is considered as impossible and can be explained by the wide spreading of the virus and competent vectors as well as by the broad spectrum of hosts and the variety of serotypes (Dungu et al., 2004). In addition, the disease often occurs only sporadically in endemic areas like, e.g., Israel, where only two to four cases are reported annually despite the presence of serotypes 2, 4, 6, 10, 15, and 16 (Brenner et al., 2008). Furthermore, in endemic areas like Africa, extensive vaccination is hardly conceivable because autochthon sheep breeds are relatively resistant to BT, which therefore often is not perceived as a problem (Dungu et al., 2004). Costs also contribute to a reluctance regarding vaccination. But also industrial nations in part refrain deliberately from control measures. In the USA, for example, there is no routine monitoring of BT and only few laboratories carry out virus isolation or even typing. The principal control measure in the USA is vector control. Mobility restrictions of other countries are there considered as non-tariff trade barriers (Wilson et al., 2009). In Central and South America only little information is available on BTV making an exact assessment of the epidemiological situation impossible.

3.2 Rift Valley Fever

Pathogen. The disease was first described as "hepatitis" causing heavy losses in sheep in the Rift Valley (Kenya) in 1930/31 (Gerdes, 2004). Today it is referred to as "Rift Valley fever" (RVF) being one of the first known arbovirus species (Chaniotis, 2003). The virus (RVFV) belongs to the genus *Phlebovirus* in the family of *Bunyaviridae* and is a typical representative of that genus, which also includes the Toscana virus. The latter is a human pathogenic virus that is transmitted by sand-

flys *(Phlebotominae*) and is endemic in the Mediterranean region (Collao et al., 2009). The family includes another four genera, of which three are associated with arthropods. These are the genus *Orthobunyavirus*, to which the Akabane virus is assigned to, as well as the genus *Nairovirus*, which comprises the Crimean Congo haemorrhagic fever virus, the Dugbe virus, and the Kupe virus. Another genus is *Hantavirus*, a group transmitted by *Rodentia* that also gains in importance in Europe. The genus *Tospovirus* infects plants (Gerdes, 2004). This broad spectrum of hosts is a special feature of that family. The viral envelope carries short glycoprotein spikes, the viral core contains three segments of negative-sense single stranded RNA (-ssRNA) and has a diameter of up to 120 nm. The RNA segments are classified according to their size ranging from L (large), through M (medium) to S (small), whereby the latter has ambisense RNA and determines the degree of virulence (Callao et al., 2009; Davies and Martin, 2003). The RNA segments encode four virus proteins (VP) and two non-structural proteins (NS). The virus is sensitive and can be inactivated by degreasing solvents or a pH-value of <6 (OIE, 2008). Sequence analyses show a close relationship between the individual RVFV strains but also geographic differences. After examining all the three segments of the 33 strains there were identified seven virus lines, which could be classified geographically (Bird et al., 2007). Tolerance for mutations is low and the strains examined have a common recent origin dated between 1880 and 1890. As for other RNA viruses also for the RVFV "genetic shift" was described (Sall et al., 1999). The first large outbreaks of the disease were registered in 1930/31 in the Rift Valley (Kenya), in 1950/51 in South Africa, from 1951-53, 1961-63, and 1967/68 in Kenya again, in 1973/74 in Egypt and Kenya, in 1987/88 in Mauretania and Senegal, in 1991 in Madagascar, in 1993/94 in Egypt as well as in 1997/98 in the Horn of Africa. In 1998, once more there was an epizooty in Mauretania (Nabeth et al., 2001). In 2000, the disease occurred for the first time outside of Africa in Saudi Arabia and Yemen (Sall et al., 1998, Davies and Martin, 2003; Davies et al., 1985; Gerdes, 2004; Madani et al., 2003). In 2006/07, there was again an outbreak of the disease in East Kenya (CDC, 2007). In April 2008, Madagascar reported another occurrence of the disease to the OIE "World Animal Health Information System" (OIE WAHID, 2008). Between January 2005 and December 2008, the RVF had been reported by 14 states of which only three (namely Madagascar, from 2005 to the end of 2008, Yemen from 2005-2008, and Saudi Arabia in 2007/08) were not situated on the African continent (WAHID Interface, 2009).

Epizootiology and epidemiology. The RVFV is an enzootically and epizootically occurring pathogen of domesticated ruminants. It is also able to infect a large number of other vertebrates as well as humans (Gerdes, 2004). Thus, it can be classified as a zoonosis. Cattle and sheep are the most important amplification hosts (Sall et al., 1998). Since the Rift Valley fever occurred in Egypt in 1977, the epidemiology has shifted the emphasis from "veterinary/animal epidemics" to "people epidemics". This is explained by a relatively large population of susceptible people in contrast

to a relatively small population of susceptible animals (OIE, 2008). The outbreak in 1997/98 resulted in one of the biggest RVF epidemics with 89,000 affected people and 250 fatalities in Kenya and Somalia (Gerdes, 2004). This made RVF to one of the most serious zoonotic problems in Africa (Davies and Martin, 2003). Also the first description of RVF reports high numbers of causality in cattle and even more in sheep. There have been large outbreaks in cattle in Sambia and Zimbabwe, whereas autochthon breeds normally do not show any symptoms and only go through a short viremic phase. Poultry and birds are regarded as non-susceptible. In larger outbreaks, there are many re-infections within eight to 16 weeks, before infection rates decrease. In semi-arid to arid conditions the epidemic curve has been completed after 16 to 20 weeks, even though in humid areas, sporadic occurrences are possible during a period of up to two years. Epizootics have a cyclic course with long inter-epizootic intervals of five to 30 years, in which the virus either persists in an endemic cycle with an unknown host or it circulates on a small scale between livestock and mosquitoes (*Culicidae*) (Gerdes, 2004). These cycles correspond to periods with an above average amount of rainfalls following on long dry periods, thus they are shorter in semi-arid regions than in arid regions (Davies et al., 1985). The virus is transmitted by mosquitoes of the genus *Aedes*, which find ideal breeding conditions in flooded areas because they oviposit in the bottom of temporary water-bearing cavities, the so-called "dambos". Thus the occurrence of the disease is neither annually nor seasonally distributed, but has to do with the presence of water. Depending on the region, outbreaks of RVF had different causes. In the connection with heavy rainfalls in South and East Africa, in the vicinity of irrigated areas in dry Northern and Western countries of the African continent as well as after the construction of big reservoir dams in Egypt, Senegal, and Mauretania. The exact correlation between RVF epizooties and precipitations was investigated by Davies et al. (1985). Not short and heavy rainfalls are decisive but those which also have an above average persistence. More than 30 RVF-transmitting mosquito species of six genera are known (Davies and Martin, 2003; Martin et al., 2008). Apart from the genus *Aedes*, these also include the genera *Culex, Anopheles, Eretmapodites*, and *Mansonia* as biological vectors as well as *Culicoides, Simulium, Stomoxys, Glossina, Tabanidae*, and some tick species as mechanical vectors (Davies and Martin, 2003; Gerdes, 2004). Ticks, however, are considered as non-significant vectors (Mellor and Leake, 2000). Moreover, *Glossina* spp., better known as tsetse fly, play an important role as vector of the human sleeping sickness. Diallo et al. (2000) estimated the infection rate of *Culex poicilipes* in Mauretania to 0.37 $\pm$ 0.06 %. For a complete list of all to date identified as well as potential mosquito vectors please refer to Pfeiffer et al. (2005). This publication also indicates the distribution of known and potential vectors in the European Union (EU) and its neighboring states. The RVFV can also be transmitted transovarially and sexually in particular between some *Aedes* members of the Neomelaniconium group. As a result, it is possible that a generation hatched out after flooding is able to infect animals directly. The infected mosquito eggs can survive several years of drought

(Martin et al., 2008). Then additional mosquito species follow as secondary vectors (Gerdes, 2004). Humans are often infected through the contact with livestock, which, in turn, are infected by zoophilic mosquitoes. In urban areas, transmission often occurs directly by anthropophilic mosquitoes. Furthermore, human infections occur contagiously in slaughterhouses, in laboratories without accurate precaution, and possibly through aerosols and raw untreated milk. Contagious transmission between animals, however, seems to be rare, despite virus presence in secretions. For the most part, the virus circulates cryptically and can only be observed by means of antibody detection or in sporadically occurring human cases (Davies and Martin, 2003). These hypotheses of an endemic, cryptic, enzootic or even sylvatic cycle (in ruminants) are supported by phylogenetic investigations. The latter found only a low genetic diversity in temporarily separated isolates (Sall et al., 1998). In case of a given mutation rate, a high genetic diversity implies a relatively large effective virus population. Thus, here cycles with low viral activity are involved. These endemic/enzootic cycles, however, are still unclear (Martin et al., 2008). A possible way of the geographic spreading of the virus is the transport and trade of viremic animals (Gerdes, 2004). Shoemaker et al. (2002) assigned Saudi Arabian isolates to the East-West-Africa-group of RVF viruses, with which they seemed to be nearly identical. The antibody prevalence in humans working in the sector of livestock farming and processing was indicated with 14.5 % and reached 29.6 % in the Egypt population in 1977/78 (Gerdes, 2004). Antibodies could be detected during the cryptic circulation of RVF in two to 15 % of livestock (Davies and Martin, 2003). The transmission cycle of RVFV is complex and has not been clarified completely. Moreover, vector diversity is higher than those of the majority of the rest of arboviruses (Mellor and Leake, 2000).

Control and combat. Many African countries have not considered RVF as dangerous for livestock farming because autochthon breeds generally do not show clinical symptoms, even though high numbers of causality have been registered in local breeds during disease outbreaks in West Africa and Egypt (Gerdes, 2004). Furthermore, the low perception of RVF as a potential zoonotic problem in these countries led to an insufficient control of the occurrence of the virus (Davies and Martin, 2003). The Food and Agriculture Organization (FAO) published a guidebook for developing an emergency plan for RVF (Geering et al., 2002). Monitoring measures are, e.g., keeping of sentinel herds or early warning systems based on remote sensing. On the contrary, control measures include primarily trade restrictions, vector control by larvicides, and vaccinations (Gerdes, 2004). Both toxins (e.g., of *Bacillus thuringiensis*) and hormonal inhibitors like the chitin-inhibitor methopren can be used as larvicides. Moreover, sentinel herds enhance the generation of important epidemiologic basic information that would improve the understanding of RVFV during inter-epidemic periods (Davies and Martin, 2003). Early studies regarding forecasts of possible RVF-epizooties are focused on Kenya because many important data about outbreaks and precipitation were gathered there

over many years, so that a good level of basic knowledge existed. Early warning systems are of major importance to carry out emergency vaccinations in time and thus to limit the extent of an epizooty. Pastoralists are affected the most by trade restrictions, which stay in effect over several years, and by direct causalities, which hit them hard as they live almost exclusively on livestock farming. On the Horn of Africa, many people live completely on the sale of male sheep and goats for to Mecca religious holidays. As RVF is a human pathogen, the distribution of mosquito nets, increasing the awareness of the population, and informing the public health services in case of impending epizooties or epidemics is recommended.

3.3 Akabane disease

Pathogen. The Akabane Virus (AKAV) belongs to the family of *Bunyaviridae* and to the genus of *Orthobunyavirus*, within which it is part of the Simbu serogroup (Tsuda et al., 2004; Yoshida and Tsuda, 1998). The disease caused by AKAV in neonatal calves is referred to as Arthrogryposis-Hydranencephaly-Syndrome (AHS) (Uchida et al., 2000). *Orthobunyavirus* is divided into 48 serogroups that include viruses, which are enveloped, spherical or pleomorphic particles with a diameter of 80 to 110 nm. AKAV is the best investigated virus of this genus (OIE, 2008). The genome contains three segments of negative-sense single stranded RNA (-ssRNA) (Yang et al., 2008b). The segments are referred to as L, M, and S (Akashi et al., 1997), analogously to other viruses of that family. The S segment encodes one non-structural protein (NS) and the nucleocapsid-protein (NC), which is the antigen for the complement fixation test (CFT). Another NS and two glycoproteins are encoded by the M segment. The L segment encodes the L protein, which acts as RNA-polymerase (Kono et al., 2008). A study focusing on the antigenic differences between 63 strains, groups the virus into five lines that were temporally and spatially mostly consistent among each other (Yoshida and Tsuda, 1998). In addition, it was found that there are seven neutralizing epitopes on the glycoprotein G1, which are differently variable and conserved. Akashi et al. (1997) analyzed the sequence of the S segment phylogenetically that encodes the nucleocapsid-protein and found three clusters for 23 strains. These groups were defined more by spatial than by temporal proximity. Kono et al. (2008) came to similar results but identified only four phylogenetic clusters.

At least since 1931, AHS has occurred in North Australia and since 1949, it has appeared in Japan. Furthermore, it can also be caused by other Simbu viruses (St. George et al., 1998). The AKAV was first isolated in Japan in 1959 followed by Australia and Africa in 1972 (OIE, 2008). During the infection periods of the years 1972/73 and 1973/74 in Japan, epizooties occurred (Kurogi et al., 1977). Hitherto, this has been the largest outbreak of the disease and there are estimates of more than 42,000 affected calves (Kono et al., 2008). In 1984, there was another outbreak in Japan during which the Iriki-strain was isolated (Miyazato et al., 1989). In June/July 1992, the virus was first isolated in Taiwan (Liao et al., 1996). In July

1998, there was a large outbreak in many parts of Japan (Uchida et al., 2000) and in 2000/01 there was an outbreak of Akabane disease in Korea (Lim et al., 2007). In February 2002, Akabane disease was detected serologically in Israel, after AHS had occurred in 1969/70 (Brenner et al., 2004; Brenner et al., 2008). Tsuda et al. (2004) reported a continuous epizooty of several years in the South of Japan. Bryant et al. (2005) first detected the virus in Vietnam. In 2006, there was another large outbreak of the disease in the South of Japan (Kono et al., 2008). In addition, Akabane disease occurred in the Middle East, Kenya, South Africa and on Cyprus.

Epizootiology and epidemiology. The activity of the virus correlates with those of the vectors and starts in Japan during the summer months in July and August (Noda et al., 2001; Uchida et al., 2000). The infection of cows leads in pregnant animals to abortion or intra-uterine fetal infection (Noda et al., 2001). There are no breeds, which are highlighted as especially susceptible. However, if breeds are indicated, infections of Holstein Friesian and Japanese black cattle as well as of their hybrids are reported (Horikita et al. 2005; Kurogi et al., 1977; Uchida et al.; 2000). One line of the Japanese black cattle is market internationally as so-called "Kobe cattle". Kono et al. (2008) did not find any correlation between the breeds or gender and an AKAV-infection, however, 77.8 % of 180 animals were aged less than 24 months. Furthermore, antibodies were found in sheep, goats, horses, buffaloes, pigs, camels, and in many wild animals from the South of Africa (Lim et al., 2007; OIE, 2008; Yang et al., 2008b). The AHS, however, has been described only for cattle, sheep, and goats (Kirkland, 2008). Antibodies in the dam protect against fetal infection, thus epizooties sometimes occur with a few years interruption (OIE, 2008). Initial serological investigations in cattle in Indonesia revealed 80.0 % AKAV-positive sera out of 90 sera examined (Miura et al., 1982). Investigations of pigs in Korea showed that an AKAV-incidence of 37.4 % in 230 sera examined (Lim et al., 2007). In addition, co-infections with other arboviruses occurred relatively frequently: Akabane disease and Ephemeral fever 25.5 %; Akabane and Chuzan virus 3.5 %; Akabane and Aino virus 1.2 %. In similar studies, 5.5 % out of 804 sera of goats and 3.8 % out of 497 sera of horses showed AKAV-antibodies with low titers (Yang et al., 2008a, b). In Turkey, west of the Bosporus, AKAV was detected in cattle sera (Karaoglu et al., 2007). The first viruses isolations were successful from pools of *Culicoides* (OIE, 2008). *Culicoides oxystoma* is a known vector in Japan, *Culicoides milnei* and *Culicoides imicola* are known in Africa, and *Culicoides brevitarsis* and *Culicoides wadei* are known in Australia (Kirkland, 2008). In Vietnam, the virus was detected in mosquitoes such as *Culex tritaeniorhynchus*, *Ochlerotatus* spp., *Anopheles vagus*, and the subgroup *Culex vishnui* (Bryant et al., 2005). Moreover, in Kenya the virus was isolated from *Anopheles funestus*, while in Japan it was isolated from *Aedes vexans* and *Culex tritaeniorhynchus* (Kirkland, 2008). For some vectors, however, the confirmation of a biological transmission is still missing. There are no indications that Akabane disease is a zoonosis (Bryant et al., 2005).

Control and combat. Vaccinations can be used for control, e.g., before transporting susceptible animals to endemic areas (Kirkland, 2008). In order to prevent the occurrence of congenital symptoms, susceptible animals should only be transported to endemic areas when they are not pregnant or when the vectors are not active. Measures for vector control, such as repellents or the treatment of breeding grounds, are regarded as ineffective because of too short notice.

3.4 Ephemeral Fever

Pathogen. The Bovine Ephemeral Fever (BEF; also referred to as "Three-day sickness", "Bovine enzootic fever", "Dengue fever of cattle", "Lazy man's disease" or "Stiffsiekte") is caused by the Bovine Ephemeral Fever Virus (BEFV) of the genus *Ephemerovirus* of the family *Rhabdoviridae* (Della-Porta and Brown, 1979; Hsieh et al., 2005; St. George, 1990; Walker et al., 1991; Hamblin, 2008). There is only one serotype. Isolates, however, can be assigned to different subtypes within this serotype. The virulence of individual strains has a large range. Another five serologically similar viruses were isolated from the blood of clinically healthy cattle, whereas three are considered as non-pathogenic, for one strain bovine pathogenicity is still unclear and the Puchong virus can cause a BEF-similar disease. Virus particles are bullet shaped, enveloped with a length of on average 145 nm and a diameter of 70 nm with not completely parallel sides as well as an inner capsid (Holmes and Doherty, 1970). Five structural proteins are encoded by the negative-sense single stranded RNA (–ssRNA) including a surface protein G (Hsieh et al., 2005) and a non-structural protein (NS) (Hamblin, 2008). Walker et al. (1991) found another protein with an unsolved function, which was detected in infected cells but not in virions. Viruses of the family *Rhabdoviridae* contain a non-segmented genome. The virus is sensitive to degreasing solvents and can be inactivated at pH-values of <5 or >10 (St. George, 1990). Phylogenetic investigations showed low substitution rates indicating a slow development of the virus (Hsieh et al., 2005). BEF was first described in South Africa in 1906, even though it is known that it had appeared earlier. The disease was mentioned by Schweinfurth in 1867 and recognized in 1895 in Egypt (St. George, 1998). In 1909, there was an outbreak in Egypt (St. George, 1990), in 1937 and 1967 epizooties appeared in Japan and Australia. In 1966, the virus was first isolated by Van der Westhuizen in Onderstepoort, South Africa (St. George, 1990). In China BEF-symptoms have already been reported as from 1949, however, the virus was first isolated in 1976 (reviewed by Zheng et al., 2009). During the recent 60 years, there have been many outbreaks in 25 Chinese provinces. In Taiwan the virus first occurred epizootically in 1967, after that, there were another three epizooties in 1983/84, 1989/90, and 1996 as well as three larger outbreaks in 1999, 2001 and 2002 (Hsieh et al., 2005). In Saudi Arabia, outbreaks are assumed to have taken place in 1980 and 1990/91 as they were diagnosed due to the symptoms described. Another epizooty in that country occurred in 1996 (Abu-Elzein et al., 2006).

Epizootiology and epidemiology. The BEF is a disease of cattle and water buffaloes and has an acute course (Walker et al., 1991), while, aside from insects, the BEFV has been isolated only from cattle (St. George, 1990). In buffaloes the course of the disease is milder than in cattle (Hamblin, 2008). There is not any reliable information about the differences in the susceptibility between European breeds and Zebu cattle. However, symptoms are more pronounced in fat animals than in other groups and calves seem to be infected more rarely as well as less severely (St. George, 1990). In contrast, antibodies were detected in diverse species, inter alia in different deer species such as African buffaloes (*Syncercus kaffer*), waterbucks (*Kobus ellipsiprymnus*), blue wildebeests (*Connochaettes taurinus*), and red hartebeests (*Alcelaphus buselaphus*). Furthermore, there is a report about neutralizing antibodies in goats as well as about low antibody titres in kudu, scimitar-horned oryx, eland, impala, giraffe, and topi (Hamblin, 2008). These animals can constitute a large natural reservoir. In other species – sheep, mice, dogs and cats – viremia or symptoms were generated experimentally. Rats and rabbits produced antibodies in this way but no measurable viremia. So far, epizooties have occurred in China, Japan, Australia, Egypt, and South Africa (St. George, 1990). In China, the inter-epizootic periods have become shorter during the last 20 years. Therefore, epizooties only occur every three to five years, in a South-Eastern province of the country every one to two years (Zheng et al., 2009). According to reports from Taiwan and Australia, the epizootic intervals have become shorter, too (Hsieh et al., 2005; St. George, 1990). The epidemiologic development of BEF-epizooties in Australia has led to an approximation of the course of the disease to tropical regions (St. George, 1990). First, rapidly spreading epizooties occurred every 20 years, but since 1967 every two to three years and only locally with highly variable incidence. The rate of spread of individual epizooties varies considerably. In Australia, a period of six weeks to two years was indicated for a distance of 3,000 km. The direction of propagation of epizooties is in general away from the equator. Already at the beginning of the last century, a vector-borne transmission of the disease was assumed. To date, an unambiguous function of insects as biological vectors has not been proven (Hamblin, 2008; St. George, 1990). Some species of the genera *Culicoides*, *Anopheles*, and *Culex* are known as vectors (Wang et al., 2001). The virus was isolated from *Culicoides* spp., *Culicoides brevitarsis*, two mosquito-genera, *Anopheles bancroftii* as well as from species of *Culicine* (St. George, 1990). As a persistent infection of cattle is not expected, it is assumed that the virus persists inside the vectors. Contagious transmission does not occur, nor is there any evidence for horizontal transmission (Hamblin, 2008). With regard to a new infection, it has not been clarified whether the BEFV is directly injected into blood circulation or reaches the latter via the lymph (St. George, 1990). However, BEF could be only generated experimentally by an intravenous inoculation and the virus cannot be detected in the lymph during the early viremic phase. Thus, mosquitoes are currently favored as vectors (Hamblin, 2008). The geographic distribution of BEF, however, exceeds those of the so far identified vectors. BEF occurs along rivers

like the Nile during summer or during the rainy season, while epizooties are normally stopped by cold spells. From a geographic point of view, BEF can be found in a large number of habitats. In tropical to tempered, humid to arid regions as well as in regions at sea level and in highlands. The prevailing wind direction and the weather conditions are considered as important factors for the spread of BEF beyond oceans possibly by birds, bats or insects. An investigation of 230 pig sera for arboviruses in Korea revealed an incidence of 15.7 % for Ephemeral fever as well as co-infections with the Chuzan virus (2.8 %) (Lim et al., 2007). In similar studies in five provinces of the European part of Turkey, 8.04 % of 557 bovine sera were tested positive. In that case, results were ranging between 2.5 % and 15.3 % (Karaoglu et al., 2007). Earlier serological investigations in Indonesia revealed 78.9 % positive samples of 99 bovine sera (Miura et al., 1982).

Control and combat. For animal prophylaxis, maternal protection by vaccination is well suited. Low antibody titers caused by closely related viruses have to be taken into account as possible serological interference factors in control programs (St. George, 1990). Due to a lack of data, currently it is hardly possible to develop vector control programs. Nevertheless, insect-proof housing is worth consideration in case of valuable livestock (Hamblin, 2008). Due to the barriers, even eradication or limitation of BEF is not possible, although it seems to have been eradicated in New Guinea since 1956 (St. George, 1998).

3.5 Crimean-Congo Hemorrhagic Fever

Pathogen. The Crimean-Congo Hemorrhagic Fever (CCHF) was first described in the Crimean in 1944 (Al-Tikriti et al., 1981). The virus was first isolated in the Democratic Republic of the Congo (at that time Belgian Congo) in 1956 (Aidaros, 2003). The clinical picture, however, had been known years before in the Central Asian republics of the former Soviet Union and possibly already in the 12th century (Whitehouse, 2004). To date, the CCHF virus (CCHFV) has been the most closely examined virus of the genus *Nairovirus* of the family *Bunyaviridae* (Crabtree et al., 2009). It contains three individually encapsulated negative-sense single stranded RNA segments (–ssRNA) (Tonbak et al., 2006). Re-assortment was particularly detected for the M segment but there are also some indications for the L and S segments. In addition, there is some evidence for the re-assortment of short gene fragments of the S segment (Deyde et al., 2006). In 1979, CCHF was first diagnosed in Iraq (Al-Tikriti et al., 1981). Since several years, CCHF has been an emerging disease in Turkey (Estrada-Peña et al., 2007). Nearly 100 % of the cases occurred in Northeastern Anatolia. In 2008, however, a mild case of a Greek CCHFV strain that had been considered as non-virulent was identified in the Balkan region near Istanbul (Midilli et al., 2009). The CCHFV strains that occured near the Black Sea were phylogenetically closely related to those from Kosovo, Bulgaria and Southern Russia (Tonbak et al., 2006). High homologies have also

been observed between the strains from South and West Africa as well as between those from Iraq and China (Deyde et al., 2006). There is only limited serological evidence for the presence of CCHFV in France, Portugal, India, and Egypt (Whitehouse, 2004).

Epizootiology and epidemiology. CCHF is a zoonosis that is widespread in the Mediterranean area (Chaniotis, 2003). It is attributed to the hemorrhagic fevers (Tonbak et al., 2006). Beside cattle also sheep, goats, rabbits, birds, and rodents function as reservoir (Chaniotis, 2003). For domestic ruminants, the viremic stage lasts for about one week from infection (Aidaros, 2003). Furthermore, other domestic animals, ostriches, and mosquitoes can be infected. Human infections are often caused by tick bites, contact with body fluids or with tissue of infected livestock or contact with CCHF patients in the acute phase (Estrada-Peña et al., 2007; Yapar et al., 2005). Nosocomial outbreaks in humans can occur through the contact with infected blood and secretions but also veterinarians and slaughterhouse staff are exposed to a higher risk (Aidaros, 2003). The virus is normally transmitted by ticks requiring three hosts. CCHF was isolated from two *Argasidae* (soft tick) species and seven different genera of *Ixodidae* (sheep tick) (Whitehouse, 2004). Among others, *Rhipicephalus bursa* is known as vector. The virus can be transmitted especially by *Hyalomma marginatum marginatum* that is widespread in Eurasia and South Africa and remains infected during all development stages (Aidaros, 2003). In a tick study in Turkey, the virus was detected in *Hyalomma marginatum marginatum* and *Rhipicephalus bursa* of cattle and goats. In addition, *Haemaphysalis punctata* and *Ixodes ricinus* are regarded as source of infection in Europe. Transovarial transmission occurs with a high efficiency (Deyde et al., 2006) and also sexual transmission was detected in ticks (Aidaros, 2003). However, small vertebrate hosts are considered as the most important source of infection for ticks in instars (Aidaros, 2003; Nabeth et al., 2004). Ticks are not only regarded as vectors but also as reservoir for the virus (Tonbak et al., 2006). Large outbreaks are associated with an abrupt increase in the population of ticks (Aidaros, 2003). This, in turn, can be attributed to appropriate environmental conditions such as dense ground vegetation and a high amount of intermediate hosts for nymphs. Causally, these developments can often be attributed to an extended movement of animals and humans, war or climatic changes. In Senegal a negative correlation between the sero-prevalence in sheep and precipitation was found (Wilson et al., 1990). The low amount of non-fatal human cases despite high sero-prevalences indicated that the real incidence is unknown. Immunoglobulins (IgG) were detected in 21.1 % of the humans and in 21 % of the sheep examined dependent on the region.

Control and combat. Due to its virulence and pathogenicity, CCHFV is regarded as a potential biological weapon of category C (Deyde et al., 2006; Whitehouse, 2004). Acaricides can be applied for combating ticks (Aidaros, 2003).

3.6 Kyasanur Forest Disease

Pathogen. The Kyasanur Forest Disease (KFD) is a febrile, biphasic disease of monkeys and humans (NIV, 2005). Cattle don't develop clinical symptoms. The spherical KFD virus (KFDV) is 45 nm in size, enveloped, and belongs to the family of *Flaviviridae*. Since 1955, the disease has been known in the Southwest of India. After comparing 48 KFDV isolates, it was concluded that the isolates from India, Saudi Arabia (Alkhurma virus) and China shared their last common ancestor around 1942 (Mehla et al., 2009). However, it should be added that the authors questioned the authenticity of the Chinese isolate due to its complete identity with the Indian reference strain isolated in 1957.

Epizootiology and epidemiology. In recent times, cattle are not assigned a role in virus circulation, except the fact that they serve as nutritional basis for replication of ticks (NIV, 2005). The reason for this is the low viremia. In addition, it is considered possible that cattle play a role as amplification host (Mehla et al., 2009). The ratio of clinical and subclinical infections of >50 % is high (Pandit, 1960). The disease mostly occurs between January and May, which corresponds to the activity of nymphs (NIV, 2005). KFD was discovered in forest regions in the Southwest of India in succession of a high mortality of two monkey species, Hanuman langurs (*Semnopithecus entellus*) and Indian bonnet monkeys (*Macaca radiata*) (NIV, 2005). Cattle in that region are often heavily infested by ticks of the genus *Haemaphysalis*. They offered the highest percentage of positively tested sera in comparison to other species (Pandit, 1960). In that study, however, only neutralizing antibodies were detected and no positive results were achived in hemagglutination inhibition tests (HIT) or complement fixation tests (CFT). Ticks of the genus *Haemaphysalis* are known as vectors, in particular *Haemaphysalis spinigera* that are considered as anthropophilic (NIV, 2005; Pandit, 1960). The virus has been isolated from 16 tick species, it is transstadially persistent and transovarial transmission has only been detected in *Ixodes petauristae* (NIV, 2005). For humans, an incubation period of two to seven days is indicated. Diagnosis normally is mainly based on clinical picture. In humans, clinical symptoms occur fulminantly including shivering, frontal headache, and high fever of >40 °C. Muscle pain, cough, vomiting, diarrhea, and photophobia last for 12 days or longer. There often is a relapse after one or two weeks, which lasts two to 12 days and partly leads to complications. The recovery phase is long. The number of human cases of the disease ranges from 40 to more than 1000 a year with a mortality of four to 15 %. A similar mortality has only been detected in two native monkey species (Panidt, 1960). For laboratory diagnostics and antibody detection HIT, neutralization tests (NT), and immunofluorescence tests (IFT) are available (NIV, 2005).

Control and combat. First attempts to develop a vaccine have been made in the 1950s (Pandit, 1960). Currently exists an inactivated vaccine, which stimulates the production of neutralizing antibodies in approximately 70 % of the vaccinated persons (NIV, 2005). Forest clearing leads to changes in the population of ticks and is regarded as a risk factor for outbreaks.

3.7 Dugbe Virus Infection

Pathogen. The Dugbe virus belongs to the genus *Nairovirus* of the family of *Bunyaviridae* (Gonzales et al., 1989). Like CCHFV, the Dugbe virus has been thoroughly investigated (Crabtree et al., 2009; Marriott and Nuttall, 1996). Among others, this is due to the fact that the Dugbe virus is less dangerous than the CCHFV and therefore has often been used for basic research in nairoviruses (Gonzales et al., 1989). The virions have a diameter of 90-100 nm (David-West and Porterfield, 1974) and cause only a slight cytopathic effect on pig kidney cells and diverse monkey cell lines. However, cytoplasmatic inclusions with basophils are detectable. The virus is inactivated by 0.1 % sodium deoxycholate (10 min at 37 °C) or 0.1 % trypsin (60 min at 37 °C). In solution the virus is inactivated at 4 °C or -20 °C after two months or at 37 °C after 12 hours. At pH-values of <3, the virus is instable but remains infectious up to a pH-value of 9. The Dugbe virus has been the first completely sequenced member of the nairoviruses (Marriott and Nuttall, 1996)

Epizootiology and epidemiology. The Dugbe virus was first isolated in Dugbe, Ibadan in Nigeria in 1964, afterwards, further isolates were obtained in other African states such as Senegal, Uganda, Cameroon, Ethiopia, and Kenya (Beran, 1994). The virus has often been isolated from cattle but also from humans and once from a Gambian pouched rat (*Cricetomys gamianus*). The virus is regarded as a weak pathogen for humans and is associated with febrile diseases and thrombocytopenia (Sang et al., 2006). The Dugbe virus has been isolated from ticks of the genera *Amblyomma, Hyalomma, Ixodes, Rhipicephalus*, and *Boophilus* (Beran, 1994). In Kenya, it was isolated from the species *Amlyomma gemma*, *Amblyomma variegatum, Amblyomma lepidum*, and *Rhipicephalus pulchellus* (Sang et al., 2006) as well as from *Culicoides* and *Aedes aegypti* (Beran, 1994). Gonzales et al. (1989) found that adult *Amblyomma variegatum* replicate the virus more efficiently than nymphs which contradicted previous studies. They explained their findings with possible differences in the used tick species or virus strains. In addition, the virus was found in eggs of these tick species indicating a transovarial infection. Serological investigations in Nigeria revealed 29 % positive cattle out of 331 sera tested, 3.7 % positive goats and sheep out of 81 animals tested but no positive result in humans (Beran, 1994).
Control and combat. The virus is not attached much importance in terms of threat to human and animal health (Beran, 1994).

3.8 Kupe Virus Infection

To date this virus has only been subject to two publications (Sang et al., 2006; Crabtree et al., 2009), while the latter provided its first characterization. The Kupe virus is a newly identified virus, which was first isolated from a pool of the tick species *Amlyomma gemma* and *Rhipicephalus pulchellus* in 1999 (Sang et al., 2006). It is a species of the genus *Nairovirus* of the family *Bunyaviridae* and is closely related to the Dugbe virus (Crabtree et al., 2009). Like the other members of the genus, the enveloped virus has three segments of a negative-sense single stranded RNA (–ssRNA), which are designated according to their size with S, M, and L. The viral genome was completely sequenced. In cell cultures, the Kupe virus replicates faster than the Dugbe virus but then decreases faster in titre. None of both viruses replicates inside mosquito cells. With the exception of BHK-cells, cytopathic effects were at first observed after infection with Kupe virus and the total damage in the cell monolayers was higher for this virus, too. The analyses indicated that the L segment of Kupe virus could have been obtained by segment exchange with the Dugbe virus. Although the Kupe virus showed a higher virulence in cell culture experiments than the Dugbe virus, its possible pathogenesis in mammals is not known yet.

4 Transmission and surveillance of arboviruses

The various exotic bovine arboviruses constitute a diverse group of viruses, which have developed different survival mechanisms. While some of them are already of international relevancy, in case of the others there is the risk of a potential establishment especially in the European Union (EU). A permanent establishment, however, first of all requires their introduction into the European region through one of the many possible ways of transmission. To date, there hardly exists any information about the vector capacity of the European arthropods for the mentioned bovine arboviruses. However, it can be assumed that both viruses and vectors pass through mutual adaptation processes. Beside the urgently necessary expansion of the existing knowledge about arboviruses in cattle, the adaptation processes require its constant actualization. The latter is very important as neither vector capacity nor geographic boundaries of the range of arboviruses can be considered as fixed values. Here molecular biological methods can make an important contribution since comparisons of various virus isolates enable phylogenetic analyses. This makes it possible to clarify relations between geographically different strains as well as to understand long-term evolutionary processes. In order to expand and deepen the knowledge about arboviruses, inter-disciplinary wide-ranging

studies may be advisable. Moreover, only in this way it is possible to encounter the complexity of the disease. Factors that influence the distribution pattern of diseases are the level of population immunity, virus virulence, presence of vector species, relative transmission efficiencies of present vectors, vector habitat, geographic barriers, climatic conditions (St. George, 1990). With regard to the question in which ways a pathogen can reach its potentially new range next to the distribution patterns of diseases, also the fundamentals of the distribution are of considerable importance. This issue will explore trade, climatic conditions, socio-economic causes (land use, pasture shortage, ways of nomadic herds, trade of used tyres, rural exodus, drought, hunting bans), migratory birds and zoo animals. The observation of vectors and arboviruses is very important. Therefore, vector competence studies, on-site sampling as well as national and international institutions operating efficient databases must be established through special research programs. This also includes the development of parameters for early warning systems and remote sensing. Further development of prophylaxis conditions are also a main focus. They concentrate on modern protective vaccines and vaccination strategies, breeding and breed optimization, minimization of exposure, as well as vector control with direct control measures or indirect control measures such as habitat control.

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II. Health risks related to maternal and child mortality – examples from Africa and India

10 Maternal mortality: A consequence of a lack of reverence for life?

Martin Tamcke

1 Introduction

Since its introduction by Albert Schweitzer, the concept of reverence for life has been widely received and has left its religious or ideological context to enter a number of state constitutions, as for example in Germany[1]. Schweitzer saw the idea of taking the subject as a starting point captured in the simple formula: "Ich bin Leben, das leben will, inmitten von Leben, das leben will." [2] Schweitzer's approach tackles all those instances of apathy and the use of force that we have allowed to become parts of social life either deliberately or unconsciously. The difficult social standing of women and children in many, if not all, important societies around the globe represents a fundamental contradiction with the postulate of reverence for life. This becomes most evident where life is coming into existence and thus should be given the highest measure of reverence – both with respect to the life of the newborn child and to the life of the mother who grants and nourishes this life with her body.

Especially in this area, there certainly are slight differences in the progress on realizing reverence for life, but deficits are clearly noticeable worldwide. The Ger-

[1] Cf. Wilfried Härle, *„Ehrfurcht vor dem Leben." Darstellung, Analyse und Kritik eines ethischen Programms*, in: Marburger Jahrbuch Theologie IX: Leben, Marburg 1997, 53-81.

[2] Cf. Günter Altner, *Leben inmitten von Leben. Die Aktualität der Ethik Albert Schweitzers*, Stuttgart 2005.

man discussions about childrens' rights following a series of infant deaths by starvation due to a lack of parental care are no less frightening than the structural violence that Indian mothers and infants have to endure. The Institute for Ecumenical Studies at the Georg-August-Universität Göttingen has successfully integrated Schweitzer's concept into international cooperation. This was first achieved in the dialogue with our Muslim partners.[3] Here, the concept proved readily accessible to Muslims with an affinity to mysticism, who sought more open religious concepts. The result was a local, active and independent reception of Schweitzer's approach. [4] Subsequently, the concept was tested in the Indian context. [5] Here, too, it was immediately adopted, although further development and adjustment of the approach is still called for. [6] There has yet been no application of the concept on the specific problem of maternal and infant mortality. It is to be an integral part of our future endeavors.

2 The death of a mother

"No more. We have lost her." [7] These are the words author Abraham Verghese assigns to gynecologist Hema when, after a long medical battle following the complicated delivery of twins, she has to witness the death of a mother, with whom she had a particularly close relationship. The death that Verghese relates is not one of the frequent deaths of young mothers in India, but that of a nurse who had emigrated to Ethiopia. She is a catholic nun, but has her roots in the old Syrian Saint Thomas Christianity of India. Her conversion to Catholicism had been a blow to her family, alienated her permanently from her social and geographic origin (Cochin in the state of Kerala) and led her first to Madras, Tamil Nadu and finally via Yemen to Ethiopia. The many storylines of the novel turned it into a worldwide bestseller. It compassionately describes the fate of a patient as well as the medical interventions, highlighting the attitudes and behavior of the medical and nursing personnel. This is precisely the program that made Abraham Verghese not only an

[3] Martin Tamcke, *Bir Mistik Teolog Olarak Albert Schweitzer* (Transl. by Arst. Gör. Abdulmuttalip Baycar), in: Review of the Faculty of Theology, The University of Kahramanmaras Sütcü Imam 6.12, Kahramanmaras 2010, 137-146.

[4] Ece Neslihan Paköz, Research-Assistant of the Dean of the Faculty, wrote her final paper on Albert Schweitzer and for this purpose spent one year examining the texts at Göttingen.

[5] Martin Tamcke, *Albert Schweitzer. The Defender of Life and its Diverse Expression,* in: George Zachariah, Christian Witness in India Today. Challenges and Perspectives, Gurukul Journal of Theological Studies XXI, Chennai 2010, 71-78.

[6] Regarding the difficulties of the reception of Albert Schweitzer in India cf. Christoffer Grundmann, *Monolog oder Dialog? - Zu Albert Schweitzers Auseinandersetzung mit der indischen Geisteswelt*, in: W. E. Müller / M. Ecker (eds.), Religion und Verstehen - Albert Schweitzers Religionsverständnis und der interreligiöse Dialog, Beiträge zur Albert Schweitzer Forschung, Vol. 8, Frankfurt am Main et. al. 2001, 39-67.

[7] Abraham Verghese, *Cutting for Stone, New York 2009, 100*

exceptional littérateur but earned him considerable credit in academic circles. Verghese's dramatic tale of the struggle to save the life of the dying mother focuses not primarily on her, but instead presents it as the crisis of the aides around her.

According to the novel, medical expertise occasionally becomes useless because of human emotions, as for example in the case of a British clinician, who is at the same time the father of the twins and the representative of a postcolonial Indian view on the former colonists. Medical knowledge can be put to use mechanically in order to demonstrate one's ability to act, but at times it may be aware of its own futility from the outset. This is illustrated by the Indian doctor Hema, who keeps trying to save dying patients, although it already dawns upon her that she will not succeed. The ability to take care of patients may be undermined by human consternation (the senior nurse faints, because she feels so close to the dying mother), or it may turn into incompetence where book knowledge and active knowledge are disconnected (e.g. the trainee nurse, who fails to observe important parts of the treatment). In the face of this dramatic situation evolving around the dying mother, medical intervention itself becomes the main issue. The author closely examines its limitations and its questionability.

Human factors, however, which oscillate between interference and motivation for action, have their place only in a somewhat "unreal reality" aside from the medical interventions: the religious dimension. This dimension becomes accessible in all its facets, i.e. the mystic religiosity of an Indian nun (the dying mother), the atheism of a British man (the medically and ethically failing father), the religious rituals of the doctor in charge, who experiences her limitations not only as a medic and deeply suffers from the events. She calls upon her favorite god Shiva, hoping that he will transform the situation and save the day. In fact, everything is lost at this point and the appellation merely paves the way for a shift of attention from the deceased woman to the surviving infants. In his incapacity to grasp the events, the Brit calls for a god from whom he had long distanced himself. The nun, as far as it is discernable at that point, dies in religious acquiescence. Every heartbeat of her life is said to have been accompanied by divine actions. Always did she try to please God with her life. Following her passing away, an employee simply takes the rosary and conducts the rituals that are appropriate in this situation. The staff begins to chant the traditional dirges until they fill the entire hospital.

Hema's reaction, however, is to dance. Her answer to all this madness is the dance of Shiva, the imitation of his mask-like smile. She begins to sway and moves as though Shiva's six arms and legs were dancing to an internal tune. Hema stomps with her heels and bends her knees – for her, this is the dance that holds the world together and saves it from extinction. Through her movements she joins into the rhythm of all living things: "What to do except dance, dance, only dance…."[8]

[8] Ibid., 108

3 One Career, one program

Verghese knows exactly why and what he is writing. He transcribes the reality of his daily experience on the job into the fictional universe of a novel. His answer to the question of how medical schools and their professors should call attention to the deficits in nursing and the health care system is characteristic of his position: "It's a struggle […] but if you're going to do it, you're going to do it only by showing them the charm and the magic of being at the bedside. There is no passion and romance that you can illustrate to them in front of a computer, which is, where a lot of care takes place these days. The only way to excite students about medicine it to do it one by one, by them seeing you being the kind of physician that they'd like to be." [9] Even more explicit are his statements on the function and purpose of medicine in general. "It's naive to think facts alone will change things. If facts alone would change things, then we would all eat healthy and wouldn't smoke. Stories change things. Pain changes things. Suffering changes things. In many ways, that's what I'm saying is happening in medicine. If it's all about facts and numbers, it doesn't move patients. Medicine is an art and not a science. The science part is the numbers. But we can't abandon the art part. It's so important." [10] Elsewhere he states: "My desire to be a physician had a lot to do with that sense of medicine as a ministry of healing, not just a science. And not just a science and an art, but also a calling, also a ministry." [11] He intends to correct a mechanical perception of medical work, asserting, "You know, there are nuances to exam that no machine is going to give you." [12] In this context, religion obviously takes a significant role in correcting the tendency towards mechanization: "And I think when you're in medicine, you agonize over matters of faith." [13] Verghese ridicules the conduct of medical professionals, who have lost sight of the human dimension to their actions. "I joke but only half joke that if you show up in an American hospital missing a finger, no one will believe you until they get a CAT scan, MRI and orthopeadic consult." [14] For him, rituals are a natural part of the healing process, especially in the sense of transformation. "Rituals are about transformation. […] If we short-change the ritual by not being attentive, you are inputting into the computer while the patient's talking to you, you basically are destroying the opportunity fort he transformation. And what is the transformation? It's the sealing of the pa-

[9] Jessica Marcy, *Checking In With Dr. Abraham Verghese On The Inportance Of The Bedside Manner*, Interview 09/15/2009, http://www.kaiserhealthnews.org/Checking-In-With/verghese.aspx (accessed online 07.01.2011).

[10] Ibid.

[11] Fred de Sam Lazaro, *Religion & Ethics NewsWeekly. 07/16/2010 Abraham Verghese*, http://www.pbs.org/wnet/religionandethis/episodes/july-16-2010/abraham-verghese/ (accessed online 07.01.2011).

[12] Ibid.

[13] Ibid.

[14] Ibid.

tient-physician bond." [15] Verghese seeks to achieve "powerful effect[s] on patients" through empathy on the part of the medical professionals. [16] He came to hold these opinions not through his studies in medicine, but through his practical work in nursing care. [17]

Today, Abraham Verghese is Professor for the Theory and Practice of Medicine at Stanford University Medical School and Senior Associate Chair of the Department of Internal Medicine. He received his medical degree (MBBS) from Madras University in 1979, was a resident of Johnson City, Tennessee (affiliated with East Tennessee State University) from 1980 to 1983, a fellow at Boston University School of Medicine in 1983 (he worked at Boston City Hospital for two years, concentrating on the urban epidemic of HIV). In 1985, he obtained a post as Assistant Professor of Medicine (later tenured) in Johnson City, working with rural AIDS. In 1991 he accepted a position as Professor of Medicine and Chief of the Division of Infectious Diseases at Texas Tech Health Sciences Center in El Paso, Texas. He lived there for eleven years and was awarded the Grover E. Murray Distinguished Professorship of Medicine at the Texas Tech School of Medicine. He became the founding Director of the Center for Medical Humanities & Ethics at the University of Texas Health Science Center at San Antonio in 2002 and held the Joaquin Cigarroa Chair and the Marvin Forland Distinguished Professorship. In 2007, he was recruited for Stanford University School of Medicine (Theory and Practice of Medicine and Associate Chair of Internal Medicine). His main area of interest and his primary goal is to ensure respectful and attentive treatment of the patients. His family originally comes from the Indian state Kerala, his parents emigrated at first to Ethiopia to pursue their teaching professions.

4 Awareness for motherhood

Verghese's approach is presented here as one amongst other, similar models. Into his concept of attentiveness he integrates the religious ties of the patients as well as their rituals and treats these as constitutive elements of the process of treatment. One thing he only calls on the attending personnel to realize is the indispensability of all persons in the social network of an expectant mother, particularly where women deliver their children without gynecologic assistance. Against this backdrop, our institute decided to participate in the effort to establish an attitude of

[15] Ibid.

[16] Ibid.

[17] Cf. Powells.com Q&A, *Abraham Verghese*, http://www.powells.com/ink/abrahamverghese.html (accessed online 07.01.2011). "I would say it was being on orderly when my medical school education was interrupted. In the process of bathing patients, helping them get dressed, dealing with bedpans and all that, I began to see what it was the patient really went through in the 23 hours and 55 minutes of the day when the doctors were not around. I look back on that period as terribly important in teaching me humility about the doctor's role and the importance of the role of the nurses and nursing assistants."

attentiveness towards motherhood in India through accompaniment of the respective initiatives and scientific studies there. The intercultural orientation of the institute and our studies in the field of trans-culturality have the potential and the assignment to initiate reciprocal learning processes in the area of religion and culture, aiming at attentiveness towards motherhood, the particular requirements in India notwithstanding.

The programs already existing in India have accomplished major results. Nevertheless, models on the integration of religion and medicine are still underdeveloped. For this reason, our institute contributes to the planning of projects concerning "Awareness for Motherhood" and draws upon the experience with its own research on women in South Andhra as well as on its director's quarter-century of teaching activity at Indian universities. The international master's program in "Intercultural Theology" that is associated with the institute runs projects for example on the Dalits and regularly dispatches students to India for the conduction of on-site research, interviews and in order to arrive at a deeper understanding of the situation through participant observation. In cooperation with our Indian colleagues, a first outline for a project was devised, which will need further revision parallel to similar concepts designed for the African context. The following is quoted from an unpublished first draft that was developed together with our Indian partners.

"In most of the South Asian societies socio cultural and religious factors act as barriers for safe motherhood. Religious beliefs and practices, gender disparities and role expectations in the age of stratified families, apart from individual factors act as barriers to safe motherhood in case of Indian society. Though there are institutional similarities in India there are regional specificities which create disparities such as difference between fertility rates in North and South India, for example. Such disparities are found even within the state and because of historical and cultural background, accelerating change process becomes an issue. Research shows that impact of development indicators such as education or work may be effective some region but may not be so in another, due to cultural backgrounds. Hence it is necessary to examine how the social construction of concept of motherhood has taken shape in order to make an effective intervention."

The Indian researchers and the institute have also named provisional objectives for the undertaking. "The project will assess the factors related to social construction of motherhood in the selected two villages from two regions of Maharashtra and one urban slum area. It will assess the factors related to the social construction of motherhood. It will examine the positive or negative factors related to role expectations, knowledge and practices and emotional readiness/expectations by family, village, religious community and interest groups for marriage and motherhood. Related to these, it will find out possibilities for interventions to reduce maternal mortality and child morbidity. Three generational perception of motherhood (past present future) taking into consideration caste (tribals), religion (the

diverse traditions and possible cultural commonalities) and family background will be examined in the context of the village community. Is the perception changing? What generational conflicts exist? Against this backdrop, the transition of a girl to a wife and to motherhood will be traced in context of religious and socio cultural beliefs, practices of the village community. Perception of a daughter in law, of a would be mother and her role expectations, control of elders (especially the mother in law) and the woman's autonomy, her stresses, resilience and negotiations on the background of patriarchal family structure will be assessed in order to understand her accessing of health facilities, knowledge of reproductive health (of wife and husband), and general well being. Thirdly, the role of factors such as education, work participation or any other agents will be assessed to examine how barriers can be changed for possible interventions. The influence of conceptions of the world as well as overcome practices and rituals will be investigated by means of oral traditions, the diverse media, religious set ups and schoolbooks. We will additionally examine the extent to which socio religious factors create barriers or offer opportunities for a strengthening of health measures."

Students from our institute will dwell directly at the locations that are being investigated and will participate in the examinations as far as the situation allows it. As an outcome, the institute expects a growing awareness for the necessity of global action.

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11 Risk of maternal mortality: Indian scenario

Anjali Radkar

1 Introduction

At United Nations millennium summit, in September 2000, leaders of world's governments signed a declaration and committed themselves to a series of goals, namely Millennium Development Goals (MDGs). The goals are about eradication of poverty, imparting universal primary education, improvement in child and maternal mortality indicators, combating HIV / AIDS and ensuring environmental sustainable development. Fifth of the eight millennium goals addresses the issue of maternal health which states the reduction in maternal mortality ratio (MMR) by three quarters between 1990 and 2015 and achieve universal access to reproductive health by 2015. Midterm review indicated that maternal mortality is decreased by less than 1 percent per year between 1990 and 2005, which is far below the 5.5 percent annual improvement needed to reach the target (United Nations, 2008). MMR is one public health indicator which shows maximum variation between developed and developing countries. Every time woman in the developing countries becomes pregnant, her risk of dying is 200 times more than that of risk of woman in developed countries. Developing countries carry the burden of 99 percent of global maternal deaths. Thus the ultimate responsibility of reduction in MMR lies on developing world.

Maternal death is an outcome of chain of events and disadvantages throughout women's life (Motashaw, 1997). If everything goes well almost all theses deaths can be prevented. It is also observed over the years, where maternal mortality is high, deaths are rarely recorded and if they are, the cause of death is usually not reported

or misreported. Causes of maternal mortality are well established and are grouped as direct and indirect. Direct causes refer to those conditions or complications that arise during pregnancy like abortion, ectopic pregnancy, hypertensive disorders of pregnancy, ante partum and postpartum hemorrhage, obstructed labour and sepsis. Indirect causes are those problems which may be present even before pregnancy but are aggravated by pregnancy, which include heart disease, anemia, essential hypertension (high blood pressure of unknown origin), diabetes and certain other diseases of red blood cells. In fact the reasons of maternal death are multi-layered. Behind medical causes are logistic causes like not-so-efficient heath service delivery and lack of transport facilities and behind all this are social, cultural and political factors which together determine the status of women, their health, fertility and health seeking behaviour (WHO, 1991).

During early twentieth century in Mumbai high maternal mortality is attributed to practice of early marriage, inferior status of women and tradition-bound health practices (Ramana, 2007). In the case study of India by Choe and Chen (2006) determinants of maternal mortality are listed as knowledge of reproductive health, access to and utilization of reproductive as well as medical health care along with the socio-economic and cultural factors associated with knowledge and use of services. The determinants of maternal mortality as portrayed by Jejeebhoy (1997) include women's autonomy, role in decision making, mobility, control over economic and other resources, gender and power relations, household economic status, physical accessibility to health care services and quality of services.

1.1 Objectives

This study is designed to understand the levels of direct risk factors of maternal mortality in India. Specific objective of this work is to understand the lifetime risk of maternal death and the levels of various determinants of maternal mortality for India by socio-economic levels with special emphasis on the utilization of health services during pregnancy and childbirth. It also aims to look at biological risk factors of women to explore about share of high-risk pregnancies.

1.2 Data

For this study data on MMR comes from Sample Registration System (SRS) whereas for the determinants, it is from the National Family Health Survey – 3 (NFHS-3), conducted during 2005-06.

Sample Registration System gives the estimates of vital statistics since 1969 – 1970 on a regular basis. It is a dual record system. National Family Health Survey – 3 is conducted in India during 2005 – 2006. It was carried out in 35 states, covering 99 percent Indian population.

The sample of the NFHS – 3 consists of 109041 households with 124385 women in the childbearing ages - 15 to 49 years. Out of all the women, infor-

mation has been collected from 56438 the women who have given birth(s) in the reference period of 5 years. It includes the detailed data about their antenatal care (ANC), delivery and also about postnatal care, if any. It also gives information on biological characteristics of the woman. Since the data is collected from women about their births, it does not have data on actual maternal death, if at all it has occurred in the selected household.

Biological characteristics include age of the women at the time of birth and birth order. Health service delivery indicators are ANC – its individual components and complete ANC, institutional delivery or delivery attended by health personnel, check-up and pathological tests during pregnancy, awareness about pregnancy complications and what needs to be done then as well as postnatal care. The NFHS -3, gives information on the current pregnancy as well. Data on hemoglobin level and Body Mass Index (BMI) of pregnant women can portray their nutritional status during pregnancy which is a determinant of maternal and newborn health or even mortality

2 Results and discussion

2.1 Risk of maternal death

Every year India witnesses about 65000 – 70000 maternal deaths. Women here are 60 to 70 times more likely to die a maternal death than that of women in developed countries. Pregnancy related mortality and morbidity continues to take toll on lives of women and newborns. Considering such a huge gap in the indicators in developed and developing countries and importance of a life that can be saved, the MDG 5 is set.

In case of India, MMR was supposed to reach 200 by 2007 and should reach 109 by 2015. MDG 5 is important for India because 20 percent maternal deaths take place in India, which is the highest number for any single country. Unless Indian figures improve it is impossible for the World to achieve the goal. National Sample Survey (NSS) estimates are the indirect estimates whereas SRS estimates are based on the sample. In India all fertility and mortality indicators are computed by SRS. MMR, maternal mortality ratio, number of maternal deaths per 100000 live births is declining over the period but the pace is not as expected, if the goal is to be achieved.

Table 1 Maternal mortality ratio, India, 1957 – 2006

Year	Maternal Mortality Ratio (MMR)	Source
1957- 1960	1321	NSS*
1963 – 1964	1195	NSS*
1972 – 1976	853	SRS
1977- 1981	810	SRS
1982 -1986	580	SRS
1987 -1991	519	SRS
1992- 1996	440	SRS
1997 – 1998	398	SRS
1999 – 2001	327	SRS
2001- 2003	301	SRS
2004- 2006	254	SRS
2007- 2009	212	SRS

*Based on indirect time series estimates

India is one of the countries with high MMR though the recent estimates show sizeable decline from 1321 in 1957-1960 to 254 in 2004-2006 to 2012 in 2007-2009 (SRS, 2006, SRS 2009, SRS 2011). Initially decline was faster compared to recent period, which is in line with the fact that as the estimates reach lower levels, it is difficult to maintain the same pace to take it down further.

It is well documented that there are large disparities in the level of maternal mortality across states. Latest estimates of MMR, maternal mortality rates and life-time risk are presented for India, Empowered action Group (EAG) states and Assam together, southern states and other states. EAG states are demographically backward states. The reason for the grouping is to highlight the differentials. EAG states are lagging behind in reproductive and child health related indicators and Southern states are well ahead. Remaining states are in-between. Assam is combined with EAG states here because MMR of Assam is the highest in the country though it is not an EAG state.

As regards MMR, during 1999-2001 there was increase in southern and other states however EAG states showed the declining trend. Share of maternal deaths for EAG states is much more therefore India estimate also shows the declining tend. For all other time periods, in general both MMR and maternal mortality rate are declining for all the subgroups. Both these indicators are sizably more for EAG states and least for southern states.

Life-time risk is defined as the probability that at least one woman of reproductive age (15 to 49 years) will die due to childbirth or puerperium assuming that chance of death is uniformly distributed across the entire reproductive span and has been worked out using the formula Life time risk = 1 – (1 - Maternal Mortality Rate / 100000) [35]

Table 2 Maternal mortality ratio, maternal mortality rate and life-time risk for India and states subgroups, 1997 – 2009

Year	India	EAG states and Assam	Southern states	Other states
Maternal Mortality Ratio				
1997-1998	398	520	187	184
1999-2001	327	461	206	229
2001-2003	301	438	173	199
2004-2006	254	375	149	174
2007-2009	212	308	127	149
Maternal Mortality Rate				
1997-1998	34.8	63.4	13.9	18.2
1999-2001	31.2	57.8	15.3	19.2
2001-2003	27.4	52.4	12.3	15.8
2004-2006	20.7	40.9	9.3	12.7
2007-2009	16.3	31.2	7.5	10.2
Life-time Risk (in %)				
1997-1998	1.2	2.2	0.5	0.6
1999-2001	1.1	2.0	0.5	0.7
2001-2003	1.0	1.8	0.4	0.6
2004-2006	0.7	1.4	0.3	0.4
2007-2009	0.6	1.1	0.3	0.4

As life-time risk is the function of maternal mortality rate, it behaves similarly. Slowly the risk is going down. For southern and other group of states it has gone down but EAG states have to work more so that India figure would go down. The decline in the maternal mortality is also associated with decline in fertility (Bhat et al, 1995). It highlights the underlying fact that fertility decline of EAG states also needs attention. Once again it comes out that maternal mortality cannot be looked at in isolation.

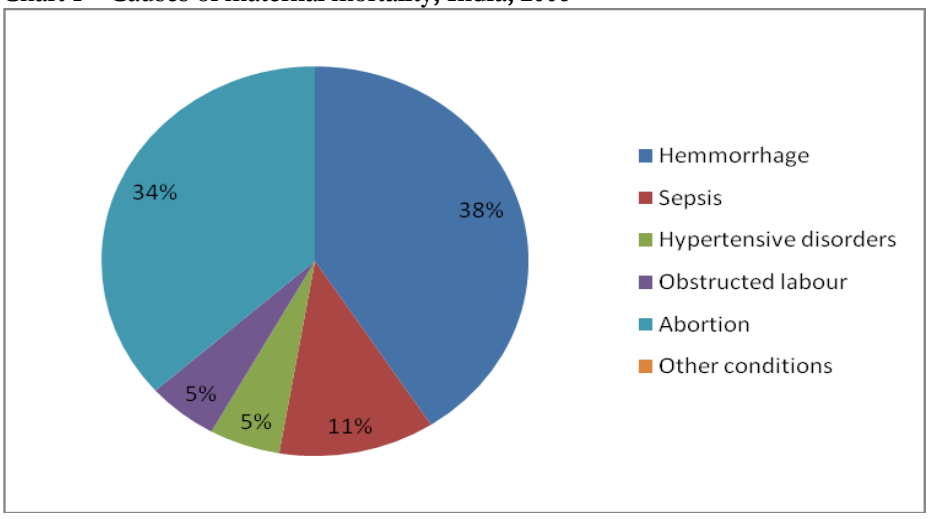
MMR 212 actually translates into huge figure of maternal deaths – over 55000 a year, considering, in India approximately 26 million births take place in a year.

Ratio of maternal deaths to live births measures the risk of dying as a result of given pregnancy. Thus MMR 212 means that woman's chance of dying each time when she becomes pregnant is 1 in 471. Her lifetime chance of maternal death depends on number of times she gets pregnant. Thus with the current TFR of 2.6, during lifetime, risk of maternal death is roughly 1 in 181 live births. Though the decline in MMR is visible, it still has to go long way as it still has not reached 200, MDG for 2007 and is very far from 109 by 2015. In order to reach the goal, precise identification of risk factors and its levels is necessary a step to plan the action strategies followed by its effective implementation.

2.2 Levels of determinants of maternal death

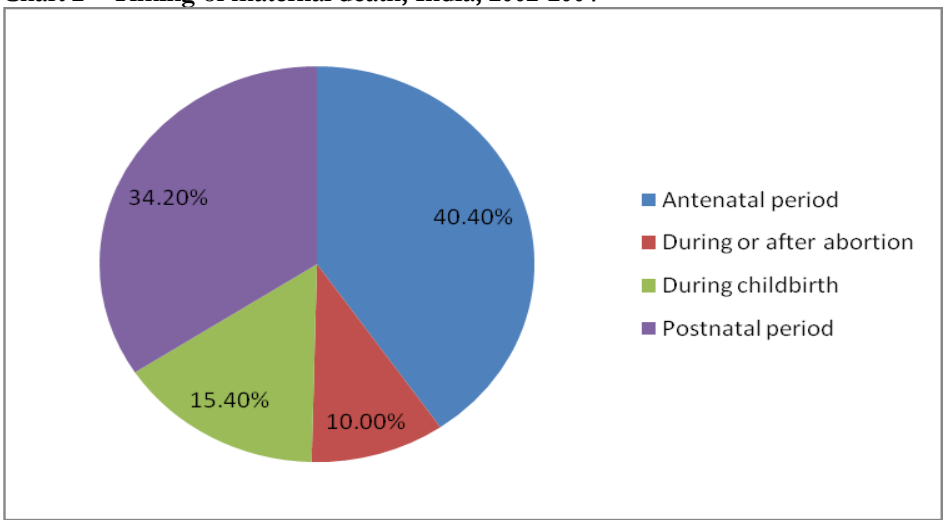
Share of causes of maternal mortality in India are hemorrhage 38 percent, sepsis 11 percent, hypertensive disorders and obstructed labour 5 percent each, abortion 8 percent and other conditions 34 percent (SRS, 2006). On this background, maternal deaths can be reduced if the women receive proper ANC and deliveries are institutional, attended by health personnel conducted in aseptic conditions.

Chart 1 – Causes of maternal mortality, India, 2006



Similarly distribution of maternal deaths in India by timing of death shows that 40.4 percent maternal deaths take place when woman is pregnant, 10 percent during or after abortion, 15.4 percent during childbirth and 34.2 percent after 6 weeks of childbirth or at the end of pregnancy (Radkar and Parasuraman, 2007). Antenatal and postnatal care would help reducing about three fourth of maternal deaths and other 25 percent by providing abortion and delivery care.

Chart 2 – Timing of maternal death, India, 2002-2004



As discussed before, among the major risk factors of maternal mortality are, utilization of health services before, during and after childbirth as well as the biological characteristics like age of the mother at the time of birth and birth order. Under reproductive and child health, apart from contraception a lot more emphasis has been given on all other aspects of safe sexual and reproductive practices. Reproductive health encompasses a range of health concerns including the ability to go safely through pregnancy and childbirth and have best chance of having a healthy infant and the right of access to appropriate health care services as well as access to safe and affordable abortion facilities. Abortion is an area where getting information in large sample surveys is difficult and in turn they are underreported. Whereas the data related to childbirth is comparatively easier to gather and is very useful as most of the maternal deaths are associated with births. The data would be analyzed by socio-economic characteristics of the women who have given birth in the reference period to capture the differentials. Among the socio-economic characteristics, place of residence gives an idea about the accessibility of the services as also modern values, standard of living index captures the overall living standards of the household and wealth index portrays the economic condition. Education of woman is for awareness, perception and modernity whereas caste variable gives an idea about the accessibility and overall vulnerability.

2.3 Differentials by socio-economic level

Table 3 portrays the extent of utilization of maternal health services as well as the share of births with selected biological parameters. Services include ANC and its components, whether the delivery is institutional or is attended by health personnel as also any postnatal care. To get clearer picture, based on the components of ANC, complete ANC is also presented. Complete ANC is defined as 3 Tetanus Toxoid (TT) injections, first antenatal visit in the first trimester, at least 3 visits and eating minimum 100 Iron and Folic Acid (IFA) tablets. If all this is followed, it is quite difficult to skip the complicated pregnancy and would definitely be referred for the delivery.

Among the components of the ANC, TT injections are taken for more than half the births, followed by more than 3 visits (36.5 percent), early first visit (30.8 percent) and then iron supplementation (10.7 percent). Extent of complete ANC is extremely low, just 7 percent. It is clear here that components of complete ANC individually are on lower side. Therefore combination of all is lower as expected. IFA consumption is making a dent on complete ANC, which is one of the major correlates of maternal health. After that 39 percent deliveries are institutional whereas 47 percent deliveries are attended by health personnel like doctor, nurse or trained birth attendant. Less than half the women avail the assistance from health personnel at the time of delivery. If something goes wrong then women have to bear the consequences in terms of morbidity / mortality then or during postnatal period. In connection with maternal mortality, 42 days after delivery also are important. Postnatal checkup might bring out the complications during this period. As expected when ANC is not complete, very few would avail the postnatal checkup. Postnatal visit is reported in case of only 13.5 percent births. Postnatal checkup would be useful to arrest maternal deaths caused by infections, sepsis. However, attention is not paid towards postnatal visits which would bring out these complaints to the notice of health personnel. Utilization of the maternal health services is undoubtedly poor here.

From maternal health point of view the births occurred in very young (i.e. below 20) and old (35 and more) age are considered to be risky. This study shows that three fourth of the births take place in the right ages where a quarter are still in the danger zone. Births in the younger ages are because of low age at marriage and after 35 means higher fertility. Higher fertility means more pregnancies and thus more risk of maternal death. Biologically, the first birth as well as the births of higher order i.e. birth order 4 and more are considered as risky, whereas births of order 2 and 3 are relatively safe. Here 43.3 births fall in the safer category. Share of 4 th or higher order births is over 26 percent. These births would affect maternal mortality statistics.

Table 3 Extent of utilization of health services and biological parameters of women by socio-economic characteristics, 2005-06

Socio-economic characteristics	TT injections	Number of visits	First visit in first trimester	IFA supplementation	Complete ANC	Institutional delivery	Del attended by health personnel	Post natal care	Age 21-34	Birth order 2 or 3
Place of residence										
Urban	64.2	55.5	47.2	17.7	14.4	67.5	73.5	15.5	80.3	45.7
Rural	50.0	30.1	25.3	8.3	5.0	28.9	37.5	13.1	72.8	42.4
Standard of living index										
Low	42.9	21.6	17.4	4.9	2.3	18.1	25.0	12.3	71.7	38.9
Medium	50.8	31.9	25.8	7.2	4.2	32.5	41.2	13.3	72.8	43.6
High	66.7	56.2	49.4	19.9	15.7	65.2	73.1	16.3	81.3	47.7
Not de jure resident	58.1	40.1	34.9	13.0	9.2	46.2	54.0	13.0	70.4	42.2
Wealth index										
Poorest	39.8	17.8	15.2	4.0	1.5	12.7	19.4	11.3	71.0	37.1
Poorer	47.7	25.5	20.3	5.3	2.7	23.5	31.8	11.9	70.8	42.3
Middle	55.1	37.9	30.4	9.0	5.5	39.3	49.0	16.6	71.7	45.4
Richer	62.3	49.3	41.3	14.3	10.4	57.9	67.2	16.1	78.4	47.8
Richest	74.5	69.3	62.7	28.6	23.9	83.8	88.8	16.4	86.9	47.2
Education of woman										
No education	42.3	20.4	16.9	3.9	1.7	18.4	26.1	11.1	73.3	39.0
Incomplete primary	55.9	38.0	28.7	9.1	5.5	36.4	45.0	16.4	69.1	50.5
Complete primary	58.2	38.8	30.7	9.1	5.6	38.6	48.2	13.3	70.1	48.0
Incomplete secondary	65.0	53.5	45.1	16.5	11.8	61.4	70.0	19.6	74.6	48.1
Complete secondary	73.8	67.5	60.4	26.4	22.0	78.7	84.6	19.9	87.9	43.7
Higher	80.1	77.0	74.2	39.2	34.3	92.2	95.7	14.2	94.3	43.2
Caste										
Scheduled caste	49.9	30.9	25.0	7.0	4.3	32.9	40.4	12.9	71.3	42.6
Scheduled tribe	42.2	27.6	22.3	7.4	3.4	17.8	25.5	19.2	71.5	39.9
Other backward class	53.4	34.8	30.0	10.4	7.5	37.7	46.6	11.6	74.8	43.5
Other	60.4	46.7	39.9	15.0	11.0	52.9	59.9	15.3	78.9	44.8
DK	56.1	53.1	40.3	11.2	8.2	53.8	64.3	14.8	71.4	43.9
Total	53.6	36.5	30.8	10.7	7.4	38.7	46.6	13.5	74.7	43.3

For all the socio-economic characteristics, the trend is clearly visible for every component of ANC, delivery practices and even postnatal care. Similar is the picture in case of biological parameters. Thus typically, women residing in rural areas having low living standards coming from backward castes and who are poor and illiterate are at the maximum of risk of maternal death.

2.4 Maternal care and health problems

Causes of maternal mortality include hemorrhage, sepsis, obstructed labour, hypertensive disorders, abortion, toxemia, eclampsia and other conditions. If along with the ANC certain other tests are conducted then the women suffering or at least showing the symptoms of the above conditions can certainly captured and can be

referred and treated. Similarly if women are aware of the pregnancy complications and what needs to be done in these conditions also can help reducing maternal deaths. Information as collected in the NFHS – 3, has been compiled in Table 4.

Table 4 Distribution of births by medical tests, ANC checkup and awareness about complications of mothers, 2005-2006

Tests, checkup and awareness during pregnancy	No.	Percent
During pregnancy - weighed	19356	34.3
During pregnancy - blood pressure taken	19532	34.6
During pregnancy – urine sample taken	17792	31.5
During pregnancy – blood sample taken	18212	32.3
During pregnancy given / bought iron tablets / syrup	25831	45.8
ANC – Abdomen checked	22061	39.1
ANC – Told expected due date	16539	29.3
ANC – Advised to deliver in the hospital	16180	28.7
ANC – Advised on pregnancy nutrition	20198	35.8
Told about pregnancy complications	7521	13.3
Told where to go for pregnancy complications	12588	22.3
Alerted to pregnancy complications Vaginal bleeding	5093	9.0
Alerted to pregnancy complications Convulsions	4714	8.4
Alerted to pregnancy complications Prolonged labour	6149	10.9

It is seen from Table 4 that only in about one-third of the births pathological tests are conducted and blood pressure measured whereas abdominal checkup has been conducted in 39 percent pregnancies. Iron supplementation is taken in 46 percent cases and nutritional awareness is created in 36 percent cases. When it comes to giving right information and alerting about the complications and danger signs of pregnancy, percentages suddenly drop. There seems to be no dialogue between health personnel and pregnant woman, which actually is necessary for woman to understand all this, especially if she is pregnant for the first time - which is risky, as well as she has no prior experience of childbirth.

If women suffer from some problems or if they observe some symptoms they must actually report it to the health personnel and get the clarification and treatment, whatever is required in the broader spectrum of maternal health. Because one can never understand whether these symptoms indicate something serious which need to be addressed immediately. It is also necessary to understand whether the safe delivery has been conducted or not as also whether the women had suffered after delivery. The data for such issues is complied in Table 5. It is by women who have specifically said 'yes' for the questions asked.

Table 5 Distribution of births by symptoms / health problems during pregnancy, care taken during childbirth and problems immediately after childbirth, 2005-2006

Health problems during pregnancy, care during childbirth and problems after childbirth	No.	Percent
During pregnancy		
Had difficulty with daylight vision	2497	4.4
Had difficulty with night vision	3527	6.2
Convulsions not from fever	4071	7.2
Leg, body or face swelling	9971	17.7
Excessive fatigue	18961	33.6
Vaginal bleeding	1742	3.1
During delivery		
Disposable delivery kit used	4800	8.5
Clean blade used to cut umbilical cord	21353	37.8
In first 2 months after birth		
Massive vaginal bleeding	4901	8.7
Very high fever	5352	9.5

During pregnancy about one-third reported to have excessive fatigue followed by swelling on legs, body or face (17.7 percent), convulsions (7.2 percent), night blindness (6.2 percent), difficulty with daylight vision (4.4 percent) and vaginal bleeding (3.1 percent). Any of these symptoms can lead to serious consequences, if ignored. During delivery it has been reported specifically that clean blade is used for 37.8 percent births and safe delivery kit used for 8.5 percent. In first two months after childbirth 9.5 percent women suffered from high fever and 8.7 percent from massive vaginal bleeding. These postnatal problems of women need to be addressed on a priority because they can turn to be fatal. Many a times, women get less importance after the childbirth as focus then shifts from woman to the child.

2.5 Reason for not using health facility for delivery

Service delivery is not very efficient which also is reflected in the utilization. Among the total births 61.3 percent are not conducted in health facility. To understand the view point of the users, information about the reasons of not delivering a child in the health facility is collected in the NFHS–3. In case of over 72 percent births the reason mentioned is 'not necessary' and in 6 percent cases it is 'not cus

tomary'. In about 6 percent cases family did not support for the institutional delivery. In all these cases there is a need to increase awareness of advantages of institutional delivery in terms of health of the mother and the newborn, especially in case of complications, in case emergency obstetric care is required.

Most other reasons talk about the problems in institutional delivery. Major one among them is the associated costs (26.2 percent) followed by facility is far and there is no transport available (11 percent). Others include the functioning / timings of the facility (3.4 percent), unavailability of female doctor (1.1 percent) and the trust about the system (2.6 percent). These are the ground realities in utilization of services need to be addressed when one really wants to reduce maternal mortality.

Table 6 Distribution of not institutional births by reason of not delivering in the health facility, 2005-2006

Reason for not delivering in the health facility	No.	Percent *
Cost too much	6066	26.2
Facility not open	788	3.4
Too far / No transport	2550	11.0
Don't trust facility	613	2.6
No female provider	264	1.1
Husband/family did not want	1371	5.9
Not necessary	16627	71.8
Not customary	1467	6.3
Other	726	3.1

* - Percentages will not add up to 100 because of multiple responses

2.6 Nutritional status in pregnancy

During the NFHS – 3, 6429 women (5.2 percent of women in reproductive ages) were pregnant. Among these 1631 were in first trimester (25.4 percent), 2470 in second trimester (38.4 percent) and 2328 were in third trimester (36.2 percent). Lesser number in first trimester could be attributed to poor registration rates in early pregnancy (Kapoor et al, 1996) or not being aware of the pregnancy. In Indian setup, there is also a culture that women do not reveal pregnancy in the initial stages, especially to outsiders.

Table 7 Percent distribution of pregnant women by stages of pregnancy and body mass index, India, 2005-2006

Stages of pregnancy	Underweight	Normal	Overweight	Obese	Total
First trimester	65.4	31.6	1.9	1.1	1559
Second trimester	44.1	50.9	3.8	1.2	2393
Third trimester	20.8	70.7	6.0	2.5	2206
Total	41.1	53.2	4.1	1.6	6158

Data on the BMI as provided in the NFHS – 3 has been analyzed and presented in Table 7 by the trimester of pregnancy. BMI categorization for pregnant women is different than that of the categorization for not pregnant women, considering the allowance for expected weight gain during pregnancy. As per the standards, BMI upto 19.8 is underweight, between 19.9 and 25.9 is normal, between 26 and 29 is overweight and above 29 is obese (Institute of Medicine, 1990). Among the 6429 pregnant women height and weight is measured for 6158 women (95.8 percent), of which, 2533 (41.1 percent) are underweight, 3269 (53.1 percent) normal, 255 overweight (4.1 percent) and 101 (1.6 percent) obese. Little over 50 percent pregnant women have normal BMI and the remaining are malnourished as per BMI classification. Of the malnourished, 41 percent are undernourished and only 6 percent are over-nourished. Table 7 shows proportionately more women in the category of underweight for first trimester. This is the early phase of pregnancy and weight gain during this trimester could usually be less compared to other two. It is also possible because the special BMI categories of pregnant women are applied; number of first trimester women falling under the underweight category is more. However, share of underweight women gradually goes down as pregnancy advances.

Table 8 - Percent distribution of pregnant women by stages of pregnancy and anemia status, India, 2005 – 2006

Stage of pregnancy	Anemia			No anemia	Total
	Severe	Moderate	Mild		
First trimester	1.8	20.6	23.1	54.5	1542
Second trimester	2.1	29.7	29.0	39.2	2346
Third trimester	2.7	38.8	24.3	34.2	2140
Total	2.2	30.8	25.8	41.2	6028

To assess the nutritional status other more reliable indicator is biochemical parameters. The NFHS – 3 provides blood hemoglobin levels, which is used here to explore the prevalence of anemia. It is seen that 55.2 percent of all women in the

ages 15 to 49 years are anemic, whereas, prevalence of anemia among pregnant women is 58.8 percent. Categorization as per WHO classification of anemia is as follows. Hemoglobin level below 7 g/dl is severe anemia, between 7 g/dl and 9.9 g/dl is moderate and between 10 g/dl and 11.9 g/dl is mild. Hemoglobin level above 12 g/dl is normal. It is seen that as pregnancy advances anemia increases. About 2/3 rd pregnant women are anemic in third trimester and in about 42 percent cases anemia is either severe or moderate. Risk is more for this group though not perceived so. How underweight and anemic women would sustain the pregnancy and give birth to the healthy child when they themselves are not healthy. If things go wrong, in case of hemorrhage, will they be able to survive maternal death?

3 Conclusions

Globally, more than half a million women die each year because of complications related to pregnancy and childbirth. About half the maternal deaths occur in sub-Saharan Africa alone and one third in South Asia. Causes of these deaths are hemorrhage -leading cause, sepsis, prolonged or obstructed labour, the hypertensive disorders of pregnancy, especially eclampsia, and complications of unsafe abortion. Goals for MMR for India are 109 by 2015 as set in MDGs and 100 by 2012 as in National Rural Health Mission (NRHM). According to the estimates by Murthy (2008) based on regression models, MMR 200 could be reached only by 2014-15 and 109 by 2024-25 if this pace prevails.

Maternal mortality is an important indicator of health of women and is also indicative of the performance of health care systems. Levels of maternal mortality often reflect the overall performance of a country's national health system - particularly during pregnancy, delivery and in the postnatal period. It has come out from this data set also that if maternal health care delivery is efficient maternal deaths would go down. Service delivery is also reflected in fertility through contraceptive use. More the unmet need more the unwanted births and thus higher risk of maternal deaths. In all the developing countries infant as well as maternal mortality is high and their determinants are also same. Decreasing the level of risk factors can control both maternal and infant mortality. Reduction in infant mortality would get reduction in fertility and reduction in fertility would get down maternal mortality.

Socio-economic status of women is strongly associated with maternal health. Thus increased awareness of components of maternal health and their utilization by women from the lower strata, would help reducing maternal deaths. Services should be provided typically to rural, poor, not educated women from backward castes of the society. Same is true with the states of India. Differentials in maternal mortality among the states are because of the differentials in development.

Apart from health care service delivery, biological variables like age of the mother at the time of birth and birth order also play important role in explaining

the risk of maternal death. Similar is the case with anemia level and BMI. To sustain the blood loss during and after childbirth woman should not be suffering from anemia. The situation is otherwise, as about 60 percent of women are anemic during pregnancy in India. This really goes against maternal health. Underweight as well as overweight women suffer from associated maternal health problems. They are undoubtedly risk factors of maternal health.

Maternal mortality also has its importance from child health point of view – in case of maternal death, life / health of the child is also at risk. Maternal deaths would go down for sure if the services during pregnancy and during and after childbirth improve. Every pregnancy has to be tracked, checkup along with pathological tests should be conducted and nutritional awareness should be created. Complications during pregnancy and childbirth are unforeseen and can happen any time. Therefore its awareness, right perception and knowledge about necessary action to be taken then should be made universal as every life – of both mother and child - is valuable.

4 The way forward

Recognizing the importance of Health in the process of economic and social development and improving the quality of life of our citizens, Government of India resolved to launch the NRHM to carry out necessary architectural correction in the basic health care delivery system. The Goal of the Mission is to improve the availability of and access to quality healthcare by people, especially for those residing in rural areas, the poor, women and children. It has made an impact in 5 years with the innovations like *Janani Suraksha Yojana* (JSY) – cash incentives for poor and backward caste women and Appointment of ASHA for 1000 population. These initiatives would certainly improve maternal health scenario in India. Both morbidity and mortality would go down but such data is not available as yet.

Historical evidence of developed countries suggests that significant decline in maternal mortality has been coincided with use of antibiotics, blood transfusion and management of hypertensive disorders of pregnancy. India still lacks in these interventions during pregnancy and childbirth. Undoubtedly a major factor which determines the pregnant women's risk of death is the lack of access to well-equipped health care services.

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12 Neonatal infection in resource-limited countries

Mercy J. Newman, Christabel C. Enweronu-Laryae and Nicholas T.K.D. Dayie

Infections are a major cause of neonatal morbidity and mortality in low resource countries especially in sub-Saharan Africa. In this chapter we present an overview of neonatal infections and discuss challenges for interdisciplinary research.

1 Introduction

It is estimated that over three quarters of the global population live in the low and middle income countries in Africa, Asia and Latin America and the other one quarter of the population live in the industrialized countries. There are major differences between the two groups, including wide differences in economic status and also maternal and child mortality rates. For example, World Health Organization (WHO) estimates maternal mortality ratio as 900 per 100,000 live births in sub-Saharan Africa, about 100 times the ratio of the resource-rich countries which is 9 per 100,000 live births (WHO, 2005).

Neonatal mortality is defined as the number of babies dying in the neonatal period (first 28 days of life) per 1000 live births. In Europe it is 11 per 1000, while in Africa it is estimated to be 44 per 1000 live births (Seale et al, 2009). Neonatal mortality is about 34% in Asia and 17% in Latin America. There are wide variations between countries in these regions as well as within the countries (Vergnano et al, 2005). For example in Africa neonatal mortality ranges from 11% in South Africa to 68% in Liberia (Costello et al, 2001). Table 1 shows the contribution of the majors causes of neonatal deaths in different regions.

In countries with high neonatal mortality, approximately 34% of all neonatal death are due to infections including diarrhea and pneumonia (Lawn et al, 2005, Lawn et al, 2008). Three-quarters of these infections occur within 7 days of birth. These early infections in newborns are closely related to maternal infections especially when there is inadequate perinatal care. In resource-limited countries, there are several gaps in the continuum of care of pregnant women. These gaps may be in antenatal care, delivery and postnatal care and may be related to socio-economic factors, lack of health facility or unskilled health care personnel. These gaps in the continuum of care adversely affect newborns and impact on early identification or appropriate treatment of early neonatal infections.

Many newborns delivered in Asia and sub-Saharan Africa are not born in health facilities. Poor hygienic practices during the delivery process and traditional practices with regards to birth and care of the newborn increase the risk of infection in newborns delivered at home. In a study by Penfold et al on home delivery: women reported that only half of the attendants washed their hands with soap and water. The cord may be cut with unsterilized razor blade and tied with a piece of cloth, substances may be put on the cord to help healing (Penfold et al, 2010). All these factors could adversely affect the baby.

Table 1[a] Causes of neonatal mortality in geographical regions.

	Africa	Eastern-ern-Mediter-ranean	Southeast Asia	Europe	Americas	Western Pacific
Infections (%)	34	31	33	11	15	8
Preterm complications (%)	28	31	26	34	37	29
Birth asphyxia (%)	28	22	20	15	15	27
Congenital abnormalities (%)	7	11	4	21	19	10
Other (%)	3	4	17	19	15	27

[a] Extracted from Black RE et all, Lancet 2010; 275:1969-87

2 Aetiology of neonatal infection

Sepsis in neonates may be classified into three groups; congenital, early-onset and late-onset. Each group may have specific causative organisms. They could also be classified as viral, bacterial, fungal and others including congenital malaria. Although sepsis can occur in any infant, it is more commonly associated with prolonged rupture of membranes, maternal infection and pre-term newborns.

3 Congenital infections

Congenital infections are very closely associated with maternal infection during pregnancy. TORCH is an acronym for a group of infections with a recognized pattern of clinical manifestations that could be acquired during pregnancy with devastating consequences for the infant. These are toxoplasmosis, rubella, cytomegalovirus (CMV) and Herpes simplex. In addition other infections like syphilis, varicella zoster, parvovirus, malaria, and HIV are also important especially in Africa.

A study in the Gambia found 14% of babies infected with CMV, although 87% of the mothers were antibody positive (Bello et al, 1991). In malaria endemic areas, up to one quarter of newborns may have parasitaemia. Fischer et al found 7% of newborns had congenital malaria (Fischer, 1997).

4 Early-onset sepsis (EOS)

Few studies differentiate between early and late-onset infections (Vergnano et al, 2005), but differentiation is important since early onset neonatal infection is more likely to be due to vertically transmitted infection from the mother (Penfold et al, 2010). Risk factors for EOS are prematurity, premature rupture of membranes, chorioamnionitis, low birth weight and difficulties at delivery (e.g. obstructed labour). Some of the risk factors for early onset neonatal bacterial sepsis in sub-Saharan Africa are probably similar to those described in resource-rich settings, but in low-income countries the problem may be more complex since other factors like HIV, maternal undernutrition and placental malaria come into play (Seale et al, 2009).There is paucity of published data on the etiology of early-onset disease in resource-limited countries due to lack of reliable microbiological data (Lawn et al, 2005). Available data are often from single tertiary health facilities and these cannot be extrapolated to the general population.

5 Late-onset infections

The source of late-onset infection is either nosocomial or community acquired; it usually presents as septicaemia, pneumonia or meningitis. Clinical features of septicaemia and meningitis may often overlap. These infections are due to common hospital organisms like coagulase negative staphylococci, Enterobacteria, viruses and fungi. Infections are common in babies with central lines and may be associated with prematurity, mechanical ventilation and admission to intensive care units. Community infection is associated with poor hygiene, poor cord care, and bottle feeding .The microorganisms vary in the different studies. Most reports on blood stream infections are mainly from individual health facilities and therefore cannot be accepted as national statistics. Table 2 shows common causative organisms from different countries.

Table 2

Country	Type of study	Duration of study (months)	Positive blood cultures (n)	Early onset (%)	Mortality (%)	Late onset (%)	Mortality (%)	Most common isolates
Nigeria[1]	Prospective surveillance	11 (1994-1995)	62	47	8	53	5	Staphylococcus aureus, Pseudomonas
Kenya[2]	Prospective/ retrospective	6 (1997–1998)	121	30	4	30	10	Klebsiella, Citrobacter
The Gambia, Guinea, Philippines, Ethiopia[3]	Multicentre (prospective surveillance)	24 (1990–1993)	167 (84 in newborns)	30	n/a	70	n/a	Staph aureus, Streptococcus pyogenes, Escherica coli
India	Prospective surveillance	24 (1995–1996)	131	23	4	77	10	Klebsiella, Enterobacter, E. faecalis

6 Infection control

Overcrowding is a common feature of newborn units in low-resource countries. This is mostly because few health facilities provide basic skills and equipment for the care of newborns. Cross infection is common because inadequate facilities for hand hygiene and shortage of staff. A few cases of outbreak of infection had been reported from intensive care units in Africa. In Ghana an outbreak of infection due to multidrug resistant Salmonella occurred in the neonatal intensive care unit (NICU) at a time when the ward was overcrowded with babies and cots were practically touching each other (Newman, 1996).

The price of overcrowding in a neonatal facility is nosocomial infection because of the breakdown of standard operating procedure and quality control that result from overcrowding. It had been estimated that about 85% of all NICU surfaces will grow nosocomial pathogens (Chandrashekar et al, 1997). A South Korean study reported that cumulative incidence rates were 30.3 and they also had 44.6 infections per 100 admitted neonates (Jeong et al, 2006). An environmental study to determine the types of microorganisms in a NICU in Ghana showed that gram negative organisms known to cause nosocomial infection including Eschericia coli and Pseudomonas aeruginosa were found in the environment and on equipment in the ward (Newman, 2002).

Although implementing infection control activities is challenging in developing countries because of the limited resources, they are nevertheless important for safety of patients and ultimately save resources. Hand hygiene is the simplest and most effective measure for prevention of hospital infection; sometimes compliance may be very low. In a study in Accra, Ghana, compliance to hand hygiene procedures occurred in only 12.2% of high risk contacts (Asare et al, 2009). In addition to washing hands before and between handling babies it should also be done after handling any potentially contaminated objects like pens and telephones. Lack of time, understaffing and overcrowding are some of the reasons why health care staff may not comply with hand hygiene procedures.

7 Laboratory services

There is shortage of well equipped laboratories and skilled biomedical scientists in resource-limited countries. Some university hospitals and large private hospitals in capital cities may have well equipped laboratories. The laboratories in smaller regional and district hospitals may have the capacity for general chemistry, haematology and microbiology. Those in rural settings lack these facilities (Okeke et al, 2006). Automation in chemistry and haematology makes it relatively easier to process specimens, but performing culture, identification and sensitivity tests for bacteria may sometimes present problems due to shortage of good quality reagents and sensitivity discs. Equipment for the anaerobic culture may not be available even in the best equipped laboratories. Even when all requirements are available,

lack of trained technical staff and the inability of staff to use standardized techniques, is another hurdle to be surmounted before appropriate results can be produced. These challenges make it difficult to determine accurate local susceptibility patterns of common infective agents. Without this information, it is difficult to select the most appropriate drug for empirical treatment. Therefore selection of antimicrobial agent for empirical treatment is not evidence-based.

In Ghana, for majority of patients in the rural areas, the nearest laboratory may only perform blood smears for malaria, haemoglobin levels for anaemia and stool microscopy for parasites. When culture and sensitivity is required, patients have to be referred to regional hospitals. This may cause some delays and sometimes patients may be too poor to make the journey.

8 Antibiotic susceptibility

It is well known that selective pressure from antimicrobial drug use leads to development of resistant strains. The WHO in 2001, developed a global strategy for containment of antimicrobial resistance (WHO, 2001). The interventions include creating a national task force, developing indicators to monitor and evaluate the impact of antimicrobial resistance and designing reference microbiological facilities that would coordinate effective surveillance of antimicrobial resistance among common pathogens. Unfortunately, most low resource countries have not implemented these recommendations.

To collect specimens, culture, identify and do sensitivity tests before treatment is almost impossible for most neonatal infections in low resource countries. Empirical treatment with broad spectrum antibiotics is common practice. Therefore, even susceptible infections may be treated with broad spectrum and more expensive drugs. In addition, there is patient pressure for antimicrobial prescriptions for even non-bacterial diseases. Finally, control of access to drugs is so weak that patients can buy drugs from pharmacies and drug stores without prescriptions, further aggravating the problem of multiple drug resistance. In a nation-wide study from Ghana, (Newman et al, 2011) reported that, the presence of multidrug resistance was widespread among different types of bacteria including strains of common infective agents like Staphylococcus aureus, Salmonella species, Escherichia coli and Streptococcus species.

9 Management of neonatal infections

Tests for investigation of infection in neonates include surface swabs, white cell count, culture of body fluids including blood, cerebrospinal fluid, and urine. Other tests are radiological investigations and other biomarkers of infection. The use of surface swab is not as important as it used to be. Some recent studies had conclud-

ed that surface swab microbiology contributes little if anything to postnatal management (Zbinden et al, 2011)

In well resourced countries neonatal sepsis is usually investigated but in developing countries early detection of infection is challenging. Sometimes parents and inexperienced health care providers may miss subtle signs of infection such as irritability, lethargy, and temperature instability (Ganatra et al, 2010). Delay in early diagnosis may also occur because families may be reluctant to seek care outside the home in the early neonatal period because of local custom or superstition.

The majority of neonatal infections are unlikely to be investigated. As suggested by Newton, when the aetiological agent is not known, it can be assumed that gram negative organisms are likely to be the causative agent in hospital and gram positives are likely in the community, this assumption can be used to tailor empirical treatment to site of infections (Newton, 2007). Scarce data from community sources poses a challenge for community-based treatment guidelines (Thaver et al, 2009).

10 Challenges to reducing the burden of neonatal infections

It is not new knowledge that infections are the single most important contributor to the high morbidity and mortality of newborns in Africa and other low-resource regions. However, there remain major perennial challenges in preventing, diagnosing and treating neonatal infections. Socio-cultural factors and inefficient health systems in these countries further complicates the situation. In this section we attempt to highlight these challenges and make suggestions for interdisciplinary research.

11 Prevention of neonatal infections

Prevention of infections in the newborn should be the goal. Though this may not always be possible, comprehensive continuum of care for maternal and newborn services could significantly reduce the burden of neonatal infections and other causes of neonatal mortality (Bhutta et al 2005, Darmstadt et al 2005). A comprehensive continuum of care intervention requires a health system that would provide essential facilities and logistics including continued health education for health care workers, mothers and the community at large. Though such programs do not presently exist in most of sub-Saharan Africa it has the potential to significantly reduce congenitally acquired neonatal infections, improve antenatal uptake of tetanus vaccination and prevent infestations like malaria (Osrin et al 2004).

Implementing good hygienic practices in newborn nurseries and at birth irrespective of where the birth occurs remains a challenge. Such quality care is not only dependent on the availability of water, soap, gloves and clean equipment but also requires change in the attitude of health care workers to hand hygiene

(O'Boyle et al 2001, Maue S et al 2004). Promoting use of alcohol-based hand rub is a plausible option (Wisniewski et al 2007) but there are cost implications that may affect sustainability of the intervention in low-resource communities.

Exclusive breast feeding reduces neonatal infections (Løland et al 2007). This effect is not only due to the anti-infective properties of human milk but it also reduces the exposure of the newborn to feco-orally transmitted pathogens. Promoting exclusive breast feeding in affluent and rural communities remains a challenge (Gilmour et al 2009, Burns et al 2010). Unfortunately, rural communities usually lack clean water and adequate sewage disposal systems such that newborns are exposed to high risks of infection when given water to drink.

Changing traditional and cultural beliefs and practices pertaining to childbirth and the newborn is somewhat a herculean task. Changing community attitudes to these beliefs and practices will increase facility-based births, promote early referral of sick newborns and reduce traditional practices that put newborns at risk of infection (Thairu et al 2008, Agrawal et al 2006).

12 Diagnosis of infection in the newborn

Newborns are unable to mount adequate immunological response to infection; therefore early diagnosis of neonatal infections is a crucial step to reducing the burden of neonatal mortality. Early recognition that something is amiss in the newborn is a skill that is lacking in the community and among frontline health care workers (Choi et al 2010, Brousseau et al 2006). There are no pathognomic clinical signs for neonatal infection. Though fever is a significant sign, a common cause of low grade fever during temperature assessment in outpatient departments in African newborns is overwrapping with layers of clothing.

There has been extensive research on early markers of neonatal infection in developed countries (Ng et al 2010, Vouloumanou et al 2011, Popowski et al 2011). However, many health facilities in rural and even urban settings in Africa do not have the capacity to do basic laboratory investigations. Clinical recognition of illness in the newborn remains a vital tool for diagnosis in these settings. Algorithms for identification of illness in the newborn are needed (Mullany et al 2006, Bang et al 2005, World Health Organization 2003). The effectiveness of these clinical tools in sub-Saharan Africa rural settings needs evaluation and if found to have significant predictive value the use of these tools should be scaled up. Innovative ways to diagnose infection in newborns in low-resource settings are urgently needed.

13 Treatment of neonatal infections

Evidence-based choices for antimicrobial drug use in specific geographical locations at all times would be ideal. Appropriate use of antimicrobial drugs requires good knowledge of local flora and drug susceptibility. Unfortunately, choices for antimicrobial use in many low-resource countries are based on data from large tertiary health facilities in that country or developed countries. Few studies have examined the aetiology and drug susceptibility of pathogens causing neonatal infections in rural settings (Zaidi et al 2009).

Effective treatment of neonatal infections requires quality drugs that are available and affordable at all levels of health care delivery including rural populations. Few drugs meet these criteria. Even though gentamicin, ampicilin and penicillin are widely available and affordable and have been recommended by the World Health Organization, many bacterial pathogens are now resistant to these drugs (Thaver et al 2009, Darmstadt et al 2009). Also, these drugs are given parenterally such that skills required for their administration may be lacking at the point of need in the community. The bioavailability of orally administered antimicrobials in the newborn is uncertain and requires more research (Darmstadt et al 2009).

14 Health systems and the neonatal health

The World Health Organization defines a good health system as one that "delivers quality services to all people, when and where they need them...provides a robust financing mechanism; a well-trained and adequately paid workforce; reliable information on which to base decisions and policies; well maintained facilities and logistics to deliver quality medicines and technologies" (WHO 2010). Such a system defends the population against what threatens its health and protects them against the financial consequences of ill-health. It also provides equitable access to health services and involves the community in decision making. Health systems in Africa are woefully deficient in meeting these criteria. Where good systems exist newborn health services are not usually given the priority it deserves.

15 Interdisciplinary research

The mystery of tradition, spirituality and science intertwine neonatal health in Africa. While this remains a significant underlying factor for the slow progress in improving newborn health in Africa it is also a goldmine for interdisciplinary research.

If social scientists could improve our understanding of cultural beliefs and practices about pregnancy, childbirth and neonatal illness, implementation scien-

tists and policy researchers would be able to come out with interventions that best suit a community. Research into methods of teaching and the curriculum for front-line health care workers especially at the primary level of care is needed. Medical education researchers could work with social scientists and psychologists to design training programs that enable health care workers to apply knowledge to practice with the right attitude to newborn care.
A seamless link between community and facility health services for maternal and newborn health in the context of continuum of care is urgently needed. Public health researchers need to work with all stakeholders to make this a reality. Research into this area of public health delivery is urgently needed to guide policy.

Laboratory scientists, the pharmaceutical industry and clinicians need to find simple, cheap and sensitive markers of neonatal infection that can be used in rural settings to identify affected newborns before they develop overwhelming sepsis. Safer simpler effective ways of delivering antimicrobial drugs that are bioavailable without the use of parenteral injections in rural settings are needed.

16 Conclusion

Neonatal infections are a major threat to achieving the fourth MDG by 2015 in low-resource countries. Even though complex factors underlie this disease, concerted efforts by all involved in the formulation and delivery of health care can overcome this challenge if we work in tandem.

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13 Reducing child and maternal undernutrition in the context of food security programmes – ongoing activities of FAO

Hartwig de Haen

1 Introduction

In spite of much progress in economic development in many parts of the world, child and maternal undernutrition still take a terrible toll on societies of many developing countries.

I will first briefly recall the quantitative order of magnitude of the global problems. I will then provide some information about current international efforts, mainly within the United Nations system, to reduce hunger and malnutrition among children and mothers. My focus will be on actions taken in the broader context of programmes that seek to achieve food security. I will specifically refer to initiatives involving the Food and Agriculture Organization (FAO) of the United Nations. I am grateful to my former colleague, Ms. Ellen Mühlhoff in FAO's Nutrition and Consumer Protection Division, for relevant information, in particular about current programmes of FAO in the field of nutrition. [1]

[1] For more information about FAO's Nutrition and Consumer Protection programmes see: http://www.fao.org/food/human-nutrition/en/

2 Food security and nutrition situation

Regarding the extent of hunger and malnutrition in the world, available indicators give us orders of magnitude, but we do not know with a high degree of accuracy how many people are suffering, who they are, where they live and what the specific expressions and causes of their nutrition problems are. Indeed, measurement and assessment is an area requiring more research[2]. Fortunately, the anthropometric measurements of nutritional status of children and mothers are relatively more reliable than some of the other indicators.

Notwithstanding the need to improve the indicators, we can summarize the current state of food and nutrition insecurity as follows:

- Many developing countries are currently experiencing a *nutrition transition*. Lifestyles are becoming more urban and sedentary with foods and drinks being more energy-dense and diets containing more processed foods, sugars, fats and animal products. The result is a *triple burden of malnutrition*[3] : one part of the population is still chronically undernourished; many suffer from deficits of specific nutrients, in particular micro nutrients, whereas others are overweight.
- According to available estimates, *close to one billion people are chronically undernourished*. Their regular food intake does not cover the food energy required for an active and healthy life.
- Almost *13 million children are born annually with low birth weight*, due to poor maternal nutrition.
- *Micronutrient malnutrition* or "hidden hunger" affects over 30% of the world population[4] . The consequences in term of diseases are serious. Just to mention some: *Iron deficiency* is affecting between 40 and 50% of pregnant women and preschool children in developing countries, causing retarded physical and cognitive development of children and 20 percent of all maternal deaths. An estimated 250 - 500 000 children become blind every year due to *vitamin A deficiency*. About 15% of people in developing countries lack adequate *iodine*, causing various degrees of mental impairment.
- On average, more than *12000 children die every day* from weakness or diseases, which they would most likely survive if they were better nourished.

[2] A recent publication by colleagues from two Departments at the University of Göttingen (respectively de Haen and Qaim, Agricultural Economics and Rural Development, and Klasen, Economics) provides an overview and evaluation of relevant indicators: H. de Haen, Klasen, S. and Qaim, M.: What do we really know? Metrics for food insecurity and undernutrition. *Food Policy* Vol.-36 (2011) pp. 760-769

[3] Per Pinstrup Anderson, Understanding the Interactions between Agriculture and Health. IFPRI 2020 panel discussion, Washington October 2010

[4] WHO, http://www.who.int/nutrition/topics/vad/en/

- Two thirds of the world's population is reported to live in countries where overweight and obesity kills more people than underweight[5]. According to WHO, *nearly 43 million children under five were overweight in 2010*[6]. Overweight is the result of a combination of consumption of more highly refined and energy dense foods and lack of physical activity. It is associated with various non-communicable diseases. These numbers underline the need to fight undernourishment as well as overweight and obesity.

What is so alarming is the fact, that poor foetal growth and child stunting can have an irreversible impact and perpetuate poverty if they are not addressed in early phases of life. They reduce young people's physical and mental capacity which in turn impact negatively on health status and life-long income earning potential. Moreover, undernutrition passes from one generation to the next as maternal undernutrition increases the risk of intrauterine growth restriction and low birth weight as a life-long handicap.

Unless decisive remedy action is taken, the *number of hungry people may be growing* further in the foreseeable future.

3 Joining forces to protect and improve nutrition

FAO promotes food-based approaches to reducing undernutrition and micronutrient deficiencies as part of broader strategies towards sustainable food and nutrition security. [7]

Although food and nutrition problems are complex and action to overcome them cannot be limited to agriculture alone, the sector plays a fundamental role in their solution. This is so for two reasons: firstly, adequate food from domestic sources is essential for good nutrition and, secondly, the food and agriculture sector is the main source of employment and livelihood for the majority of the poor and undernourished worldwide. While urbanization is advancing more than two thirds of the poor are still rural people.

According to the World Food Summit of 1996, food security exists when all people, at all times, have physical and economic access to sufficient, safe and nutritious food to meet their dietary needs and food preferences for an active and healthy life. This definition depicts the entry points for nutrition interventions which may be any of the following four pillars of food security:

[5] *Ricardo Uauy, Measures of Overnutrition/Obesity*. Paper presented at workshop on Measuring Food Insecurity and Assessing the Sustainability of Global Food Systems, organized by the national Academies, Washington, 15-16 February 2011

[6] World Health Organization, Obesity and overweight, Fact sheet N°311, March 2011

1 *Supply of food*: examples include diversification of farming systems, home gardens, bio-fortification of plant varieties with special micro-nutrients such as Vitamin A and post-harvest loss reduction.
2 *Access to food*: examples range from general measures to reduce poverty to very specific ones such as school feeding.
3 *Stability of access*: examples include any actions that help to have a stable income flow or entitlements to food assistance.
4 *Intra-household utilization of food*: examples range from nutrition education to improving clean water supplies and household hygiene

Very often, under- and malnutrition are not only a consequence of poverty, but also its major cause. Accordingly, FAO emphasizes the importance of *twin-track strategies* which comprise, on the one hand, longer-term investment in sustainable productivity growth benefiting in particular the smallholders in rural areas, and, on the other hand, social safety nets which ensure that even in times of particular food scarcity, the neediest, including especially elderly poor, children and their mothers, are given immediate access to essential food and basic social services, including health, water and sanitation.

Together with WHO, FAO also has programmes to help countries enhance *food safety and quality along the food chain* and thus reduce the still heavy burden of food borne disease. There are *two basic approaches* through which the nutrition of mothers and children can be improved: one consists of general programmes that seek to improve the food security of all population groups; the other is a set of programmes targeted specifically on mothers and children.

Generally, under- and malnutrition must be addressed through integrated food and nutrition security, public health and social protection approaches, as acknowledged by the *UN Standing Committee on Nutrition* at its High-level meeting in November 2009. The SCN calls for Government institutions, UN agencies, NGOs and CSOs to join efforts at regional, national and local level.

It is in this spirit that FAO is an active partner in a number of *recent initiatives* addressing very specifically nutrition problems, including maternal and child nutrition. These might be of special interest to the Göttingen International Health Network being launched today. Let me briefly list a few:

1. *The REACH Initiative (Renewed Efforts Against Child Hunger)* has been endorsed in 2008 by FAO, WHO, UNICEF and WFP. REACH facilitates joint action at country level to reduce under-five child malnutrition in the context of MDG1. FAO is currently involved in 24 UN Joint Programmes (UNJPs) for the thematic window Children, Nutrition and Food Security. These are funded by the UNDP/ Spain Fund for the Achievement of the Millennium Development Goals.

2. *FAO also contributes to the Scaling-Up Nutrition (SUN) movement*, a collaborative process including governments, academia, research institutions, civil society, the private sector, UN organizations and the World Bank. SUN addresses the continuing high levels of under-nutrition and the uneven progress towards the *MDGs*. The SUN roadmap provides practical guidelines for joint action to be adapted on a country-by-country basis.

3. *International Conference on Nutrition – 20 years later (ICN+20)*. To give new impetus to political action and commitment to ending hunger and malnutrition, FAO and WHO have decided to jointly convene a second International Conference on Nutrition, twenty years after the first ICN was held in 1992. The ICN+20, to be held in Rome in 2012 will review progress in efforts to address global nutrition problems, identify emerging challenges, recommend actions and mobilize the political will and resources necessary for achieving the nutrition-related MDGs.

4. A programme funded by Germany aims to improve dietary intakes and nutritional status of infants and young children through improved food security and complementary feeding counselling. One important set of activities under this programme are *"Trials of Improved Practices"* (TIPs).

5. *TIPS* stands for feeding recommendations that have been developed and tested through a *participatory research process*, which uses several quick, interactive information-gathering methods with family members, especially mothers and other key people. FAO has been using it to promote improved complementary feeding in Afghanistan, Cambodia, Laos and Zambia. Families learn how to enrich young children's diets using locally available nutrient-dense foods. To date, the results suggest that families are very interested. However, they also face major constraints of seasonal food scarcity and lack of affordable sources of micronutrient-rich foods.

6. The German Ministry of Food, Agriculture and Consumer Protection (BMELV) is funding a three year research project to study the *impact of joint food security and complementary feeding interventions* for children, 6-23 months of age, in two countries, Malawi and a country to be chosen in Asia. The objectives are to improve our understanding of combining behaviour change communication with crop and dietary diversification and learn under which conditions improved complementary feeding practices will be sustained over time. The research is being undertaken through a partnership with the Institute of Nutritional Sciences, University of Giessen, and a national research institution.

There are many initiatives currently focusing on what has been termed the *"1000 day window"*. The period from early pregnancy through to the first two years of life

of a child (or the 1000 day window) is a critical period for interventions to reduce and prevent undernutrition and micronutrient deficiencies. At the same time there is increased attention to the linkages between agriculture, health and nutrition.

It would be an exciting and helpful research effort to document the effectiveness of such approaches which combine food security and nutrition interventions.

To conclude, taking action against child and maternal undernutrition is not only a moral imperative and not only an obligation of governments in the framework of the human right to food. As tolerating hunger and malnutrition has enormous economic costs, investment in improved nutrition and food security can be highly profitable. I wish you all possible success for the GIHN.

14 Global policies and local implementation: maternal mortality in rural India

Kim Gutschow and Padma Dolma

1 The burden of maternal mortality

Pregnancy or childbirth remains a leading cause of death, disease, or disability for women of reproductive age across the developing world (WHO 2010; Gill, Pande and Malhotra 2007). In fact, the fifth Millennium Development Goal (MDG)—whose stated goal is to "improve maternal health" by reducing maternal mortality and providing universal access to reproductive health—is now regarded as the most off-target of the eight Millennium Development Goals (Graham 2009). Every year, global pregnancies result in over 10 million maternal disabilities, 368,000 maternal deaths, 46 million abortions, 2.6 million stillbirths, and 3.8 million neonatal deaths (WHO 2010; Lawn et al 2009, 2011). Many of these deaths can be collectively prevented with basic care around pregnancy and childbirth. India, our focus below, provides an excellent vantage point for studying these intertwined deaths as it accounts formore maternal deaths (63,000), more neonatal deaths (1.1 million), and more births (27 million) than any other nation in the world (WHO 2010; Lawn et al. 2009).

These deaths are not without economic costs. Conservative estimates suggest that global maternal and neonatal mortality alone results in $15 billion in lost productivity each year (Gill, Pande, and Malhotra 2007). Despite these costs, a lack of political and financial will around maternal and neonatal mortality remains. The 4.3 million mothers and newborns that die each year far outnumber the number of

people who die from HIV alone (2.9 million) or TB and malaria combined (1.7 million and 1.3 million respectively). Yet global assistance still lags for maternal and neonatal health, which was $1.2 billion in 2006 compared with the $10 billion allotted for HIV/AIDS in 2007 (Shiffman and Smith 2007). Repeated calls to prioritize maternal health have led to suggestions that The Global Fund to Fight AIDS, TB and Malaria should include maternal and neonatal health under its rubric (Horton 2010, Costello 2005). After repeated concern about lack of progress on MDG 5, the Secretary General of the United Nations proudly announced a pledge of over $40 billion towards the Global Strategy for Women's and Children's Health in September 2010.

The twists and turns of what was first known as the Safe Motherhood Initiative (SMI) and later branded as Making Pregnancy Safer (MPS) have been summarized elsewhere (AbouZahr 2003; Shiffman and Smith 2007). The SMI was founded when three major multilateral aid organizations—the World Bank, the World Health Organization (WHO), and the United Nations Fund for Population Activities (UNFPA)—met in 1987 with the stated goal of reducing maternal mortality. This focus on maternal conditions arose after a landmark essay (Rosenfield and Maine, 1985) subtitled "Where is the M in MCH?" had argued that the focus on child health in MCH initiatives had come at the cost of women's and maternal health. Yet progress would remain out of reach for some time due to the challenges of bringing different agendas——mother versus child, community-based versus clinical care, and primary health versus vertical programs—and different agencies under one initiative (Lawn et al. 2006; Starrs 2006; McCoy et al. 2010). By 2005, donors sought to combine funding by merging the SMI with other initiatives to create The Partnership for Maternal, Newborn & Child Health (PMNCH). The PMNCH strategically linked maternal survival with newborn and child survival in order to better promote the linked MDGs 4 and 5 (McCoy et al. 2010).[1]

2 Recent shifts in policy

Maternal health policy has undergone a considerable shift in recent years towards privileging strategic adaptation to local context over global policies and solutions. As a key editorial (Costello et al. 2006: 1477) in the *Lancet's* Maternal Survival Series warned: "We are concerned about the one-size fits-all core strategy and believe the policies need to be context-specific." Another essay summing up maternal health policy noted without irony that policies should not be copied from one

[1] The PMNCH was launched in 2005 to supercede three partnerships: (1) the Partnership for Safe Motherhood and Newborn Health hosted by the WHO, (2) the Healthy Newborn Partnership hosted by Save the Children, and (3) the Child Survival Partnership hosted by UNICEF. The first partnership itself grew out of the Safe Motherhood Interagency Group, which was comprised of the three founding agencies of the SMI—the WHO, the World Bank, and the UNFPA—along with UNICEF, UNDP, the Population Council, and the International Planned Parenthood Foundation (IPPF).

country to the next because, "the devil is in the detail" and "context matters" (Penn-Kekana et al. 2007: 34). A key essay on the eve of the twenty-year anniversary of the founding of the SMI summarizing decades of research on maternal mortality called for a renewed emphasis on implementation and context rather than a continued focus on global causes or solutions:

> "Implementation of maternal health services on the ground has been woefully neglected in the global safe motherhood community.... We are not advocating a single universal approach to implementation, but neither are we suggesting that every situation is so unique that it has to start from scratch. *In short, we know what to do, but how to do it varies by context.* Understanding context entails an appreciation of the relation between supply and demand within the district level health system—ie, the continuum from home or community, up through health posts and health centres, to the first referral level facility" (Freedman et al. 2007: 1384, my emphasis).

The tack from „what to do" to „how to do it" shifts concern from broad causes and solutions towards local strategies of prevention and treatment. However, the focus on supply and demand still emphasizes the reductionist views of economists and policy makers that frequently shortchange the role of culture, power, and agency. In short, the language of efficacy can elide the complex intersection of power, gender, culture, and social hierarchy that are central to critical medical anthropology (Pfeiffer and Nichter 2008; Inhorn 2006, 2007). Yet there are signs that policy makers and researchers are recognizing the role of quality and agency in determing access to obstetric care.

> "Ensuring the availability of a package of effective intrapartum interventions in health facilities does not guarantee an effect on maternal mortality, which is contingent on uptake by the target population, the quality of implementation, and the avoidance of harm introduction" (Campbell and Graham 2006: 1292).

Campbell and Graham critically isolate the uptake of services to quality of services and avoidance of harm, while others (Thaddeus and Maine 1994) have shown the importance of transport, costs, and other social barriers to uptake. Quality of care has emerged as a key concern that must be balanced against the over-whelming drive to increase coverage. As Graham and Varghese (2011: 378, citing Godlee 2009) recently argued, "the global insanity—continuing over and over again to deliver poor-quality health services for women and children and yet expecting results…" must give way to sustained efforts to provide high quality care, namely care that is "effective, safe, and a good experience for the patient". The emphasis on quality of care draws on growing evidence that a significant fraction of maternal deaths are caused by clinical delays, omissions, and failures.

> "Confidential enquiries into maternal deaths in a diverse range of countries, together with find-ings from clinical audits, suggest that the proportion of which substandard care played a substantial role is often more than a third. (Ronsmans and Graham 2006: 1196).

The emphasis on quality of care is linked to the overwhelming push towards increasing skilled attendance at birth across the globe. While institutional deliveries may appear to fulfill one core safe motherhood strategy—access to skilled intra partum care—they only do so if the staff, the clinics, and the protocols at such institutions actually deliver emergency obstetric care (Gabrysch et al. 2011). Safe motherhood policies have had to account for both high risk and low risk pregnancies. After years of privileging either low risk or high-risk pregnancies/deliveries—often at the expense of the other—it is now recognized that most deliveries and pregnancies fall along a risk continuum that can change in sudden and unpredictable ways. Most importantly, it is difficult to predict which pregnancies will wind up as a high risk or low risk delivery. Although antenatal care does correlate with improved neonatal and maternal outcomes, studies have yet to show direct causal links between antenatal care and reductions in maternal mortality (Maine and Rosenfield 1999, Miller et. al. 2003).

3 India and the JSY scheme

The JSY scheme in India offers important lessons for the global attempt to increase institutional deliveries within the home-to-hospital continuum of care. Launched in 2005 with World Bank funding, India's Janani Suraksha Yojana (JSY) scheme is the largest conditional cash transfer program in the world in terms of beneficiaries. At a cost of roughly $134 million (15.4 billion Rupees) in 2009-10, the schema currently pays women in LPS (low performing states) like Jammu & Kashmir (our focus below) 1400 rupees per institutional delivery and 500 rupees for home births. The scheme also provides 600 rupees for the Accredited Social Health Activist (ASHA) who is supposed to accompany women to the hospital for delivery, 250 rupees to pay for emergency transport, and 1500 rupees to pay for an emergency cesarean if there are no free government services for cesareans. Plagued initially by bureaucratic inefficiencies and confusion over who qualified for the schema, the schema soon dropped the stipulation that women have a marriage certificate, a BPL (below poverty line) certificate, and be below 19 years of age. Yet it continues to be underused across India. By 2009, less than 10% of eligible women benefitted in states that have high maternal mortality ratios such as Uttar Pradesh and Jharkhand (Lim et al 2010).

While the JSY program did achieve an increase in institutional deliveries across India, persistent worries remained about the lack of medical staff, supplies, and quality of care at government institutions (Jeffery and Jeffery 2010; Das, Rao, and

Hagopian 2010; Lahariya 2009). By including births in rural clinics or sub-centers in the definition of 'institutional deliveries', the JSY schema is paying women to deliver in a notoriously unreliable set of clinics at the bottom of India's rural health care system. There is a serious danger in shifting births to clinics and hospitals that are underequipped to handle an increase in deliveries or emergencies (Jeffery and Jeffery 2010; Lahariya 2009). A recent study argued that if many obstetric wards in India are overwhelmed with two or more patients per bed, it is unclear how increasing deliveries will improve maternal outcomes or quality of obstetric care (Lahariya, 2009: 16). The JSY scheme has been correlated with improvements in perinatal and neonatal outcomes yet shows no correlation with improved maternal outcomes (Lim et al. 2010).

These studies indicate that the very institutions where women are sent may lack timely or integrated basic or comprehensive emergency obstetric care.[2] If applied in a timely and integrated fashion, basic or comprehensive emergency obstetric care can treat all of the major causes of maternal mortality in India which are: hemorrhage (29.6%) anemia (19%), sepsis (16%), obstructed labor and ruptured uterus (9.5%), abortions (8.9%), and eclampsia (8.3%).[3] The timing of interventions is critical, as the median time from onset to death of an untreated hemorrhage is just six hours (Costello et. al 2006). Moreover, a single complication–such as post-partum hemorrhage–may require a combination of interventions, such as oxytocin to increase contractions and stanch the blood flow, removal of placenta and uterine products to limit source of bleeding, blood transfusion to make up the lost blood, and finally surgical hysterectomy if all else fails. Jeffery et al. (2007: 175) starkly note that "government institutions in Uttar Pradesh are currently incapable of accommodating routine deliveries, leave aside dealing with complications that require emergency care". [4] The same study reports that one fifth of all community health centers in Uttar Pradesh were found to have even 60% of the equipment needed for handling basic obstetric emergency care and only a third of such centers had 60% of the medical staff required. Other studies have argued that the lack of timely transport or referral schemes constitute gross violations of obstetric care and human rights (Jeffery and Jeffery 2008, 2010; George 2007; Gutschow 2010).

[2] Basic emergency obstetric care (BEOC) comprises six signal functions—parenteral antibiotics, parenteral anti-convulsants, parenteral oxytocin, manual vacuum aspiration, manual removal of retained placenta, and instrumental vaginal delivery (forceps or vacuum), while Comprehensive emergency obstetric care (CEOC) adds two more—cesarean sections and blood transfusion or blood products.

[3] Rawal (2003) cites the major causes of maternal mortality recorded by the the Registrar General of India using the Sample Registration System (SRS). The Federation of Obstetric and Gynaecology Societies of India (FOGSI) finds a rather different breakdown of causes: anemia, eclampsia, sepsis, hemorrhage, and abortion in declining order.

4 Jeffery et al. (2007) also found inappropriate levels of injectable oxytocin use for the intrapartum period, without sufficient attention to the dangerous sequelae of such use. Compare Van Hollen (2003) and Jeffery, Jeffery, and Lyon's earlier analyses of the shifting medicalization of birth in Tamil Nadu and North India (1989).

These anthropological critiques imply that the JSY schema may be doing little or nothing to reduce maternal deaths in some parts of India.

4 The JSY in context: Ladakh

Slightly smaller than Norway, but home to only 270,000 people, Ladakh consists of two districts, Leh and Kargil. Each district has one government hospital based in the central towns, Leh and Kargil, from which the districts draw their names. These two hospitals currently provide the only comprehensive emergency obstetric care in the region. Yet many of community level health clinics and subcenters lack several measures of basic emergency obstetric care. While the auxilliary nurse midwives (ANM), who attend most of the home and clinic deliveries, can provide basic intrapartum care including injectable antibiotics and oxytocin, they often lack the instruments or the skills to perform manual vacuum aspiration, instrumental deliveries, and other signal functions of basic emergency obstetric care. In short, many rural clinics and midwives in Ladakh are ill prepared to save the mothers and neonates who suffer life-threatening complications. This is significant given the obstacles to accessing hospitals or clinics in this remote, rural Himalayan region. Many valleys lack access to the hospital except on foot for six months every winter when passes are blocked and emergency helicopter services are unreliable. Women who live in remote parts of Ladakh, who are due to deliver between November and May, must make the decision (and have the financial resources) to leave their homes months before their due date if they wish to deliver at a hospital.

This essay draws on fieldwork concentrated between 1994-2002 and 2006-2011 at Leh hospital and in rural parts of Kargil district. Besides collaborating with the two chief obstetricians of Leh hospital since 1994, Gutschow has conducted extensive interviews with the nurses, nurse-midwives, and medical assistants who provide institutional and home-based antepartum and intrapartum care across Ladakh. Between 1994 and 2011, Gutschow interviewed more than 200 women in Ladakh and a range of tradi-tional 'experts' who deliver traditional healing in Ladakh including practitioners of Tibetan medicine, monks, nuns, and oracles about reproductive and maternal health (Gutschow 2004, 2006, 2010).

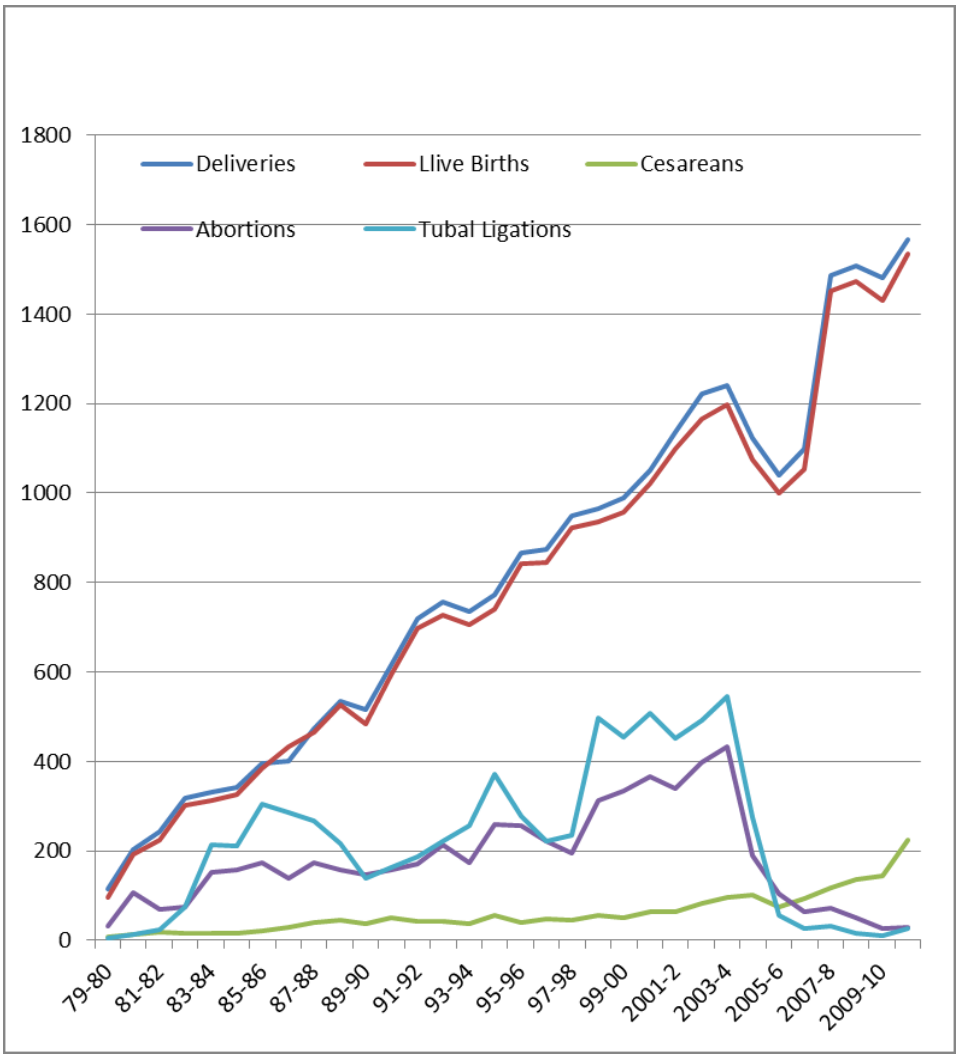

Figure 1: 30 Years of data from Leh's Government Hospital: 1979-2010. Kim Gutschow or Padma Dolma collected this data from hospital records in 1995, 1999, 2006, 2007, 2009, and 2011.

This chart shows a steady rise of deliveries, live births, and cesareans as well as the more variegated rise and fall of family planning services at the Leh government hospital over the last 3 decades. The shift of birth from home to hospital in Ladakh long precedes the introduction of the JSY scheme into Ladakh in 2006 and outpaces the trend towards institutional birth across India. By 1995, while almost half of all deliveries in Leh district were facility-based, only 20% of all births in India were institutional (Wiley 2002). By 2007, 74 % of all deliveries in Leh district but only 45.5 % of the deliveries in Kargil district were facility-based, even as the all-India rate of institutional deliveries remained less than 50% (Pathak et al 2010). [5] What distinguishes Leh hospital from Kargil hospital has been the service of two obstetricians, aunt and niece who have dedicated their lives to providing quality obstetric care over the past three decades (Gutschow 2010). The different rates of institutional deliveries at Leh and Kargil hospitals imply that women prefer the quality of obstetric care at Leh hospital, which is born out by our interviews with patients at Leh hospital. Other studies indicate that rural women in India prefer home births to poor quality of care at institutions (Pathak et al. 2010; Jeffery and Jeffery 2008, 2010). Other major factors contributing to the rise in institutional deliveries in Ladakh as in the rest of India include the greater value placed on each birth in a context of lowered fertility and improved income, education, access, and transport facilities (Gutschow 2010, Chawla 2006, Van Hollen 2003, Pinto 2008, Jeffery, Jeffery, and Lyon 1989).

The perceived quality of care at Leh hospital is born out by maternal outcomes as well. Maternal mortality ratios (MMR) fell precipitously at Leh Hospital in the last 3 decades, from 746/100,000 in 1988 to 96/100,000 in 2006. There are no good statistics on neonatal and perinatal mortality at the Leh hospital, but the still-birth rate ranged between 38 and 41/1000 between 2004 and 2007. In recent years, the MMR at Leh hospital was roughly half that found in the nearby but remote subdistrict of Zangskar and less than half that found in a government hospital in the state of Kerala, noted for its maternal health outcomes. [6] Observations and interviews in the labor and delivery wards at Leh hospital in the past 15 years confirm that most medical staff are able to provide evidence-based and quality obstetric care in timely fashion.

Yet these indications of quality of care starkly contrast with the notable decline in both abortions and tubal ligations at Leh hospital after 2003. When Dr. Lahdol, who served as the Chief Obstetrician at Leh hospital from its founding in 1979, retired in 2003, the provision of family planning services at Leh hospital took a hit

[5] The rates of institutional deliveries and skilled attendance at birth are quoted from the Leh District Health Plan (Government of India 2007b: 49) and Kargil District Health Plan (Government of India 2007a: 48). The report elsewhere mistakes the institutional delivery rate from pregnancies not live births; I have ignored those rates.

[6] The MMR recorded at Leh hospital between 2005 and 2007 (93.5/100,000) was less than half that found in rural Zangskar between 2006 and 2009 (225/100,000). The Leh hospital's MMR was less than half that found at a teaching hospital in Trivandarum (215/100,000) and a fraction of that recorded at a teaching hospital in Allahabad (3778/100,000) (Purandare (2007).

from which it is yet to recover. Although Dr. Lahdol was awarded a Padma Shri, one of the highest civilian honors in India, her concerted efforts on behalf of maternal and reproductive health earned her increasing attacks by right wing religious and political groups. Since her retirement, the attacks on family planning have not abated and the number of abortions has continued to decline. After nearly three decades of steady gains, the number of abortions reported in 2010-11 had sunk to a level not seen since 1979-80, even as the number of births increased fifteen-fold. This restriction on safe abortion services leaves women little choice but to travel days to reach a private hospital or clinic that in the nearby cities of Jammu, Srinagar, or risk an unregulated abortion in a private clinic. It is important to recall that abortion is one of the five leading causes of maternal mortality in India. Significantly, the JSY program seems to have had little impact on the provision of abortions in Ladakh, one of signal functions of basic emergency obstetric care.

The quality of care found at Leh hospital stands in contrast to the sub-standard care delivered across many rural centers. Currently, many of the block level clinics or community health centers in Kargil lack the basic functions of emergency obstetric care on a 24/7 basis. Official documents outlining district level provision of healthcare are littered with phrases such as: 'capacity building in Emergency Obstetric Care", "all CHC [community health centers] to be developed as FRU's [first responder units]", and "PHC to be developed as 24x7 facilities" (Government of India, 2007b: 44). Yet even five years after the JSY has been introduced, these same centers were still found to be closed at night or staff unavailable on a 24x7 basis. As such, women are being lured to deliver in facilities with limited or unavailable emergency obstetric care. This is born out by the following admission in the Kargil District Health Plan's section on maternal health: "The community does not have enough confidence in the government facilities since the personnel are not always available and also adequate infrastructure, equipment, and drugs [sic]." (Government of India, 2007a: 49). The Padum Community Health Center (CHC) still lacks a functioning operation theater and an anesthesiologist despite spending millions of rupees in upgrading the facility to a CHC. In short, despite the best intentions, the JSY scheme has not provided the emergency obstetric care required to sustain reductions in maternal and neonatal mortality.

5 Conclusions

While it may be true that many home births in India lack access to skilled or emergency obstetric care, it does not necessarily follow that institutional births necessarily involve access to emergency obstetric care. Further research is needed to evaluate whether the JSY scheme is improving maternal and neonatal outcomes across India and whether hospitals, clinics, and staff can provide the quality emergency obstetric care they claim to. The experience in India and Ladakh suggests a degree of caution towards the inexorable push to institutionalize birth. Currently,

there simply are not enough facilities to accommodate India's 27 million annual births. As Anthony Costello (2006: 1477) wrote in the Lancet's Maternal Survival Series:

> "Intrapartum care based in health centers is appropriate for all as a longer-term strategy, but it might not be the best option for reducing maternal mortality in all contexts in the shorter term. In many communities with high maternal mortality this strategy is simply not achievable with current resources and infrastructure."

A health center strategy is only the 'best option' for reducing maternal mortality if one can guarantee the quality of obstetric care in those centers. It is unclear that the push towards institutionalizing birth across India and the globe has yet to fully account for quality of care or skill of health care providers at the relevant facilities. Until women are guaranteed quality and respectful care, they will continue to choose home births over institutional births (Campbell and Graham 2006). Until then, one needs more qualitative and systematic studies comparing quality of care across the continuum of care from home to hospital or those comparing low risk home and hospital births in low resource settings. Similar studies in high re-source settings comparing low risk home and hospital deliveries have shown lower rates of maternal interventions and similar rates of neonatal mortality and morbidity (Janssen et al. 2009, De Jonge et al. 2009, Johnson and Daviss 2005). Clearly, efforts to improve quality of care (Graham and Varghese 2011) must coexist with the ongoing efforts to institutionalize birth if we are to see progress in maternal and neonatal outcomes in India. There is a need to measure both the quality and quantity of obstetric care if the 5th MDG is to be met in time in India as elsewhere across the globe.

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15 Research as a tool to tackle maternal health problems in resource-poor settings

Azucena Bardají

1 Background

Improving the health of the most vulnerable populations continues to represent a huge global health challenge. Maternal and children mortality and morbidity rates remain unacceptably high in the developing world.

Decrease of children and maternal mortality, and attainment of universal access to reproductive health are key objectives of the Millennium Development Goals (MDGs).[1] Despite some progress, global efforts to adequately address reproductive, maternal and perinatal health problems have been revealed to be insufficient and often fragmented, particularly in improving maternal mortality and morbidity (MDG5).[2, 3]

Annually, approximately 8 million women suffer from pregnancy-related complications, of which nearly half a million die.[4] Everyday, 1000 maternal deaths occur worldwide, most of them (99%) in developing countries where the maternal mortality ratio (MMR), number of maternal deaths per 1000 live births, is up to 100 times higher than in developed countries.[5] In 2008, around 20 developing countries held MMRs higher than 1000 per 100.000 live births, and more than 50% of all maternal deaths were concentrated in just six countries; India, Nigeria, Pakistan, Afghanistan, Ethiopia, and the Democratic Republic of the Congo.[6]

The United Nations annual statement of progress on the MDGs released on 23rd June 2010 showed that the rate of drop was short of the 5% annual reduction needed to reach the target under MDG5, for diminishing maternal mortality rates

by three quarters between 1990 and 2015.[7] It has been suggested that a reason why MDG4 and MDG5 will not be reached according to latest projections is that the current global aid structure for reproductive, maternal, newborn and child health is not structured in a way that optimally allows mobilization of financing and rapid scale-up.[8]

In fact, maternal health has been a neglected area in many ways, not only in financing. Often, when it has been tackled, this has occurred through a children's health approach, both in terms of policy making, advocacy and research. An example is that pregnant women have been excluded systematically from clinical trials due to security concerns. Similarly, issues regarding women's health have become a highly politicized topic, with the subsequent slow advancement on effective maternal health policies.

2 Emerging and increasing focus on maternal health

On the grounds of the slow steps forward being seen on key global health challenges, maternal health issues have begun to increase awareness and to attract international attention. It has become a top priority. Civil society, academia and researchers, global leaders, the United Nations, private foundations and health care professionals are joining efforts in making a difference towards an improvement of women's health and put it on top of the global agenda.[8]

In the last years initiatives such as the Partnership for Maternal, Newborn and Child Health (PMNCH), the IMMPACT project (a global research initiative for the evaluation of safe motherhood intervention strategies), the Centre for Maternal, Reproductive and Child Health (MARCH), Women Deliver, or the International Health Partnership (IHP) among others, are providing higher visibility to health needs in developing countries with focus on the most vulnerable. This culminated in the Global Strategy of United Nations Secretary General Global Strategy (August 2010) that set out the key areas where action is urgently required to enhance financing, strengthen policy and improve service delivery for MDGs 4 and 5 to trigger a decisive move to improve the health of women and children. Another major converging platform is the H4+, that brings together World Health Organization (WHO), the Joint United Nations Programme on HIV/AIDS (UNAIDS), UNFPA, UNICEF, and the World Bank, which is also a promising initiative.[8]

3 The role of research to improve the health of the most in need

Women and their children are those that principally concentrate the unacceptably effects of the vicious cycle of poverty and disease in developing settings. Biomedical research in developing countries represents a challenge at the same time that an enormous opportunity to make a difference about the health of the most in need.

In many occasions decisions about women's health are determined by policy makers based on merely political agendas, but not data-informed. Public health policies on maternal health will also affect undeniably their offsprings and need to be evidence-driven. It is crucial making available clear data to highlight why it makes sense to spend in the health of women. Research on maternal health problems needs to be one of the priorities of the international community since women are the cornerstone for the social and economic development of low-income countries.

In the last decade, academic and research centres have strengthened a network of north-south or south-south partnerships that have promoted excellence through multidisciplinary, translational and cross-cutting research with the aim to improve global health. In this picture, capacity building through training of local health leaders has been a main cornerstone in their missions.

An example of this it is the Manhiça Health Research Centre (CISM) in Southern Mozambique that was created to promote and conduct biomedical research in priority health areas.[9] The improvement of maternal health is one of the priorities of the CISM research agenda. Some of its contributions have been the investigation of the impact of malaria during pregnancy on maternal and infant health, of new drugs for intermittent preventive treatment during pregnancy, the impact of maternal HIV infection on infant health and mechanisms involved in the mother-to-child-transmission of the HIV infection, and the understanding of the causes of maternal deaths.

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Figure 1: Clinical evaluation of a new born at Manhiça District Hospital, Mozambique

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Figure 2: Evaluation of a blood smear for malaria parasitaemia determina- tion in the laboratory of the Manhiça Health Research Cen tre (CISM), Mozambique

4 Priority areas on maternal health research

Pointing out the priorities on maternal health research requires mapping of the foremost health problems affecting those most at risk, and identifying the knowledge gaps and evidence needed in areas critical to reducing maternal and newborn mortality and morbidity.

Research agenda on maternal health should include the understanding of the causes and mechanisms of diseases affecting pregnant women and their newborns, the evaluation of efficacious treatments, as well as of effective preventive strategies, and through an interdisciplinary approach.

Some areas that can be envisaged as priorities in maternal health research are the following:

- *Maternal mortality*. Understanding the specific causes of maternal deaths in the most affected areas can provide genuine data that may contribute to the prioritization of public health strategies to reduce the unacceptably high rates of maternal deaths in the sub-Saharan region, and achieve one the key MDGs.[10] This may include identifying the constraints of available resources of information on the aetiology of maternal deaths as verbal, autopsies, clinical records or necropsies. It is also necessary to ascertain and measure the determinants of maternal mortality such as health care access barriers, the quality of care in the delivery of preventive and curative interventions and the economic costs and affordability of maternal health care.

- *Perinatal and neonatal mortality*. Lowering child mortality increasingly depends on tackling perinatal and neonatal mortality. Reducing neonatal deaths requires knowing its causes.[11]. Establishing the causes of perinatal and neonatal mortality is crucial to ascertain the prioritization of specific interventions and approaches. This also should include the identification of the available sources of information on the burden and determination of the causes of deaths, to evaluate the impact of vertical transmission of non-HIV sexually transmitted infections and to measure the determinants of perinatal and neonatal survival, health care access barriers and economic costs associated with neonatal care. Similarly, it is necessary to assess the impact of point-of-care testing during pregnancy to reduce infant survival and maternal morbidity.

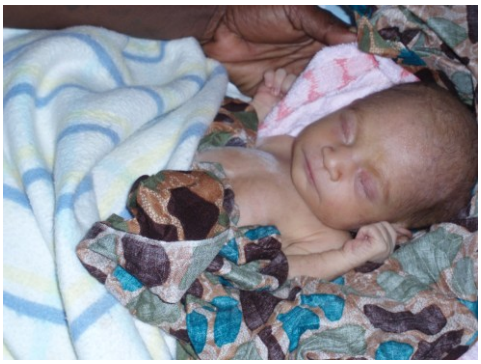

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Figure 3: A low birth weight baby born at the maternity of a district hospital in Madang, Papua New Guinea

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Figure 4: A pregnant woman is invited to participate in a study aimed to assess the burden of P.vivax malaria during pregnancy in Bikaner, Rajasthan, India

- *Maternal morbidity*. Annually hundreds of thousands of women suffer from pregnancy-related complications and diseases. To establish the major causes of maternal morbidity is key information in order to optimize resources for antenatal care and minimize its impact on infants and mother's health. Other areas that deserve attention is to identify best practices to introduce maternal care interventions and integrating them into existing maternal health programmes, and to determine the economic impact of maternal morbidity at community, national and regional level.

  In many parts of Southern Africa, more than 30% of pregnant women attending the antenatal clinics are infected with HIV.[12] This makes HIV infection one of the most common and important complications of pregnancy in these settings. To investigate the impact of HIV/AIDS epidemic on maternal health, birth outcomes and infant survival constitutes one of the cornerstones in research agendas. Similarly, it is crucial to understand the mechanisms involved, and the most efficacious and effective strategies to prevent the mother-to-child transmission of HIV infection.

  Malaria during pregnancy is associated with maternal and foetal morbidity and mortality through its contribution to maternal anaemia, low birth weight and prematurity.[13, 14] In high transmission malaria endemic areas, as sub-Saharan Africa prevention of malaria during pregnancy is a public health priority. Some of the key research areas may include 1) the understanding of the burden and impact, and the pathophysiological mechanisms of malaria during pregnancy and its contribution to maternal and infant mortality and morbidity,

both in high and low transmission settings, and 2) the assessment and development of new strategies on malaria control in pregnant women. In addition, the evaluation of the cost-effectiveness of malaria control tools during pregnancy is necessary to facilitate in the decision-making process.

- *Sexual and reproductive health*. Closely related to maternal health, women´s health issues that deserve major attention are the 1) evaluation of the burden and impact of sexually transmitted infections in young adolescents and adult women, 2) to identify best practices to reinforce adolescent sexual health for equitable and responsible relationships, 3) to evaluate the access barriers to reproductive health services, 4) to assess the epidemiology of human papillomavirus infection (HPV) and to identify best practices for delivery, prevention, screening and treatment interventions, 5) to evaluate the integration into reproductive health care programs of chronic diseases affecting women also in developing countries as breast cancer and cervix cancer, and 6) investigate the impact of violence against women, pregnant and non-pregnant, on women´s health.

- *Health systems strengthening and implementation*. A major question for the success of maternal health interventions is to ascertain the role of social determinants in the use of health systems, such as the barriers to access to health care and association with poor health outcomes, and the economic factors related to poor delivery of health care. Also it is crucial 1) to understand the links between poverty, vulnerability and gender inequality, 2) to assess the role of women in the health care system (from providers of care, to power professional health positions), and 3) the financing mechanisms for reproductive, maternal and neonatal health delivery.

5 The need for a prioritized research agenda: The role of academia and research institutions

When it comes to maternal health, and the same applies to women´s health, research efforts have been set up, more often than desired, without much coordination, leading to fragmentation of resources, redundancy of evidence and consequently to having a lesser impact.

If research agendas on maternal health at country, regional and international level are not guided by a common scheme, the limited available resources will be inadequately distributed. A common strategy will enable to inform policy makers and donors on assigning and investing specific responses more successfully and equitably to improve maternal health. This highlights the need for a coordinated and prioritized research agenda in areas critical to reducing maternal morbidity and mortality and accelerating access to reproductive health.

On the ground of the current situation on women's and children's health,[3] the United Nations Secretary General, revitalized the international community pledges by launching the Global Strategy at the MDG Summit in 2010. Within this strategy it was stated the role that research and academic institutions are expected to play, and these were asked to deliver a prioritized and coordinated agenda, promote increased budget allocation for research and dedicate efforts on building capacity at research institutes in low and middle income countries.

Thus, the role of academia should be to facilitate a multi-disciplinary, participative and inclusive process towards the delivery of a global agenda on the basis of the advantages and opportunities that joint efforts and collaborative networks can provide.

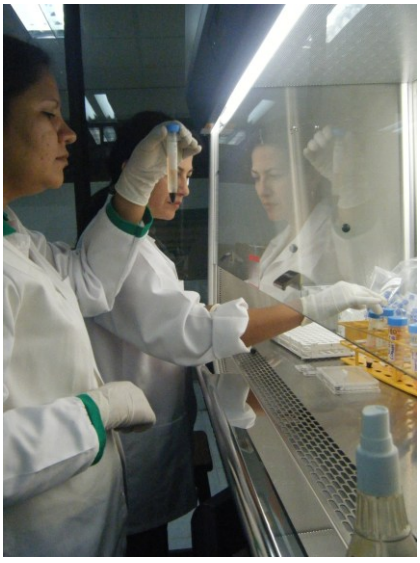

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Figure 5: Colombian researchers processing samples collected from pregnant women infected with malaria for immunological assays

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Figure 6: Engaging global leaders on women´s health. Plenary session at 7th European Congress on Tropical Medicine & International Health, Oct 2011, Barcelona, Spain

6 Conclusions

In the 21st century, we are probably the first generation with the sufficient tools and knowledge to overcome main inequities in health and wealth. However, maternal health still holds a wide range of unconquered challenges being some of the most representative the lesser advances on main outcomes such as maternal survival or universal access to reproductive care.

Public health measures need to be evidence-driven and biomedical research represents a huge opportunity to have an effect on improving maternal health in developing countries. Pointing out the priorities on maternal health research requires the mapping of the foremost health problems, identifying the knowledge gaps and evidence needed, and political commitment and investing from donors on specific and coordinated responses. Lastly, the academia, through the set up of collaborative networks, has a key role in the leadership of these efforts.

Acknowledgements
I would like to thank colleagues from CRESIB-ISGlobal, Clara Menéndez, Magda Robert and Nuria Casamitjana for their leadership in maternal health through research, advocacy and training, that it did help and inspired the conception of this chapter.

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16 The agriculture and health program of the International Institute of Tropical Agriculture (IITA), a CGIAR institution in Africa

Victor M. Manyong., Bussie Maziya-Dixon, Ranajit Bandyopadhyay and Rousseau Djouaka

Abstract
The agriculture and health program of the International Institute of Tropical Agriculture (IITA) is one of the eight research for development (R4D) programs implemented by IITA in the humid and sub-humid tropics of sub Saharan Africa. The overall goal of this program is to improve diets, health, and productivity through research in micronutrients content, food toxins, nutrient patterns and science-based evidence policy advocacy.

This paper explains the rationale of this program, the main objectives, key research areas and expected outputs. It also briefly presents examples of highlights from implementing R4D activities on key research areas.

1 Introduction

Agriculture can play a major role for the health of African people, not only by providing food for sufficient macro-nutrition (calorie sufficiency), but also by providing food that reduces micro- nutrient deficits and enhances health of specifically vulnerable groups like women and children.

The global hunger index for 2008 (*von* Grebner et al. 2008) shows a large majority of countries in sub-Saharan Africa in either alarming (hunger index of 20.0 to 29.9) or extremely alarming (hunger index of equal or more than 30.0) situations. Globally, 35 to 55 percent of all childhood deaths are related to malnutrition, which affects roughly one third of all children in developing countries (Lancet 2008). With the recent food and financial crises, an estimated 1.02 billion people, the highest number since 1970, suffer from hunger (FAO 2009). According to official statistics, about half of the Sub-Saharan African population suffers from iron deficiency (Harvest Plus 2007), mostly women and children, and more than five percent of Africans are at risk from Vitamin A deficiencies and resulting blindness, again most of them children, with one third of children under the age of five affected (Harvest Plus 2007). Zinc deficiency affects presumably two thirds of the African population, resulting in stunting and morbidity (Harvest Plus 2007).

Recent estimates suggest that vitamin A and zinc deficiencies in young children contribute significantly to the global burden of diseases, and between 4-6% of all under-five deaths. Iron deficiency also leads to 115,000 maternal deaths or 2.4 million disability adjusted life years (DALYs) (Black et al. 2008). There is increasing evidence that other deficiencies in micronutrients such as riboflavin, calcium, and vitamin B_{12} are also widespread and resulting in poor health outcomes among vulnerable populations (Dewey and Brown 2003; McLean et al. 2008). Heavy reliance on monotonous plant-based diets and the lack of access to diverse diets are primarily responsible for the widespread micronutrient deficiencies affecting poor populations in developing countries.

Many regions of the world, including sub-Saharan Africa, continue to be overburdened by nutritional and nutrition-related health problems, most of which can be traced to insufficient intake of micro-nutrients (vitamin A, iron and zinc in particular), and in recent years – over- consumption of energy-rich, often cheap, foods leading to increased incidence of chronic diseases, particularly in urban areas. But malnutrition occurs also in many families that are not poor – because people do not always know what food or feeding practices are best for their children or themselves, and because people cannot easily tell when their children are becoming malnourished, since faltering growth rates and micronutrient deficiencies are not usually visible to the untrained eye.

At an immediate level, an individual becomes malnourished because of inadequate or in appropriate dietary intake ill health or both. These two factors often interact in a negative synergy. Illness reduces appetite and increases nutrient requirements, while inadequate intake of food (quantity or quality) makes the body susceptible to illness. Underlying this vicious cycle are household or community deficits in food security, inadequate access to health and environmental services, and household childcare behaviors and practices. These underlying factors often summarized as "food, health and care also interact, and they too are under pinned by more basic causes relating to the amount, control, and use of resources and capacity in societies.

In many African countries, rates of hunger and under nutrition are increasing. The importance of this issue is reflected in the Millennium Development Goals (MDGs) established by the United Nations General Assembly at its Millennium Summit. Indicators for meeting the target of reducing hunger are stated in terms of under nutrition and inadequate food consumption – reducing the prevalence of underweight children, and reducing the proportion of the population below the minimum level of dietary energy consumption. Under nutrition have multiple causes, both direct - including food consumption, care and health, and indirect - such as agricultural production, employment opportunities, women's status, and service delivery systems. Thus, cross-sectoral and inter-institutional collaborations are essential to addressing this complex problem, and must involve all relevant players, women as well as men.

Good nutrition underpins progress towards each of the first six MDGs – The evidence suggest that good nutrition status reduces poverty by boosting productivity throughout the life cycle and across generations (Goal 1), that it leads to improved educational outcomes (Goal 2), that dealing with malnutrition typically empowers women (Goal 3), that malnutrition is associated with about 60% of all child mortality (Goal 5) and that good nutrition status slows the onset of AIDS in HIV – positive individuals, increases malaria survival rates (Goal 6) and lowers the risk of diet related chronic diseases (Goals 1, 4 and 6).

At the policy implementation level, there is poor awareness on the link between agriculture, nutrition, health and gender. Policy makers appear not to be fully aware of the gender division of labor, the gendered distribution of and access to resources as they relate to food security and malnutrition. Consequently, there is still much to be done in improving the policy advocacy and community based program to improve the nutritional status of women and children.

Dietary consequences of socio-cultural and economic changes across all developing countries contribute to many of the health problems faced especially by the poor. Unfavorable changes in food habits of both urban and rural households and over-dependence on a few staple food crops have resulted in lack of diversity in diets, micronutrient malnutrition and an exceptional increase in diet-related chronic diseases. It is well acknowledged that the nutritional quality of foods in developing countries depends on the diversity within the traditional food systems. Agricultural biodiversity provides an important safety net to resource-poor communities and engenders food and nutritional security for poor households. Diversity in a community's food supply contributes to the dietary diversification that can in turn contribute to ongoing efforts at addressing under nutrition and diet-related chronic diseases.

Food and food fortification is another important entry point to mitigating malnutrition, as it is more cost-effective than medication, e.g. in the case of iron-deficiency, where food bio-fortification costs are at less than 10 percent of medication/supplementation, and reaches vulnerable groups more efficiently than medical supplements (Harvest Plus 2007).

Apart from imbalanced diets in terms of macro- and micro-nutrition, there is the important issue of food safety, and related issues of health as well as regional and global trade. One of the most prominent problems is the one of mycotoxins, in particular aflatoxins. Aflatoxins are potent human carcinogens and have great acute toxicity causing death. It is also reported to be associated with stunting in children and suppression of immune system. The extent of aflatoxin contamination is high in food and feed in sub-Saharan Africa. The population is exposed to unacceptable aflatoxin levels throughout their lives including prenatal exposure of the fetus and the consequences have been largely ignored. (Bhat and Vasanthi 2003). Recent outbreaks of acute aflatoxicosis in Eastern Kenya, underline the urgency of the problem.

Aflatoxin contamination in particular of groundnuts but also maize imposes a barrier to domestic, regional and international trade. The 2004 Kenya case of aflatoxins in maize and subsequent ban of maize imports from neighboring Uganda gives an example of regional trade restrictions, whereas in 2010 the Kenyan government declared 2.3 million bags of maize as non-tradable in the domestic market due to unacceptable levels of aflatoxin contamination. The largest number of rejections reported in European Union's Rapid Alert System for Food and Feed (RASFF) are for aflatoxins (European Commission, 2011). In 2010, none of the aflatoxin-related rejections were from Africa. It is unclear if lack of rejection from sub-Saharan Africa is related to reduced agriculture trade between Africa and EU for aflatoxin-sensitive crops.

Apart from the negative effects of some food characteristics in Africa, there are also potentials for new food markets that are related to health implications, recently referred to as 'nutri-business". One of these that came up in the nineties is the idea of "functional food", for example flavonoid rich food that is said to prevent heart diseases, or gluten-free food components. This could open up new markets for African products, given that quality standards are met.

IITA is one of the 15 international agricultural research centers of the CGIAR group. The IITA mission is to increase agricultural production, food security and income in the tropics, especially sub-Saharan Africa. IITA activities are clustered under eight programmes. One of these programs is on agriculture and health. This program operates at the interface of the two sectors as agriculture is essential to good nutrition and health and good health is an outcome and major input into agriculture.

2 Agriculture and health program at IITA

There are basically three components of the Agriculture and Health programs: screening and breeding for biofortification, food safety, as well as HIV/AIDS and malaria impacts on agricultural productivity. The former two components were integrated in the breeding programs up to 2006, whereas the latter two compo-

nents were a part of the social sciences program. In early 2006, the program was created to allow for better monitoring and evaluation of the respective activities, but also to create a research field that could prove as an innovation platform to go into until then under-explored issues of food and agriculture.

The program pursuits three main objectives as follows:

- To improve nutrition quality, in particular by seeking ways of providing a higher diversity and density of micronutrients in human diets, as well as by reducing food toxins
- To increase the knowledge on nutrition patterns and distribution of food and nutrients within social systems, in particular with respect to human nutrition across social strata and gender
- To research ways to overcome labor force bottlenecks in farms and households affected by HIV/AIDS or malaria or Buruli ulcer through appropriate technologies

The expected outputs are:

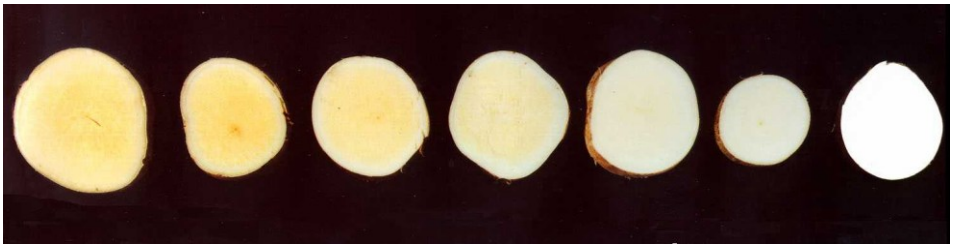
- Varieties with enhanced nutritional quality and reduced anti-nutritional factors and toxic substances;
- Diets of nutritionally disadvantaged populations and human health improved, and market opportunities increased;
- Health risks from mycotoxins reduced;
- Impact studies, advocacy and policy dialogue for better health

2.1 Key research areas undertaken at IITA

Key Research area 1: Characterization and development of varieties with enhanced nutritional quality and reduced anti-nutritional factors and toxic substances

This key research area is basically on the characterization and development of crop varieties germplasm for micronuntrients (vitamins, minerals), as well as macronutrients (protein, energy etc.), while at the same time countering anti-nutritional factors such as trypsin inhibitors and toxic contents of crops. The main target crops are maize (Picture 1), cassava (Picture 2), and banana/plantain. In 2011, Nigeria has officially released the first biofortified cassava varieties.

Picture 1: New orange maize rich in Vitamin A



Picture 2: Range of cassava varieties from deep yellow rich in Vitamin A and white poor in Vitamin A

Key research area 2: Strategies to enhance the diets of nutritionally disadvantaged populations, improve human health and increase market opportunities

This research area focuses on the downstream aspects of food and nutrition. Key elements are research on reduced anti-nutritional compounds in processed foods; enhanced bioavailability of nutrients in processed foods and on increased diet diversity through food-to-food fortification. For example we used cost effective *in vitro* methods to demonstrate that the bio-accessibility of β-carotene (BC) in boiled cassava from various cultivars is highly correlated with its content. We also investi-

gated three traditional styles of preparation by fermentation and roasting and the potential to differentially affect both retention and bio-accessibility of BC. The calculated retinol activity equivalence per 100 g dry weight was 272 and 255 for boiled cassava and fufu, respectively, but only 131 for gari due to loss during preparation.

The ability of high-β-carotene cassava to prevent vitamin A deficiency has not been determined. In our research we found that biofortified cassava adequately maintained vitamin A status and was as efficacious as β-carotene supplementation.

Key research area 3: Food safety to reduce health risks

This research area addresses issues related to food safety and occupational hazards. Key research areas are on increased food safety, reduced factors negatively affecting bio-availability, reduced toxic substances in food (such as mycotoxins – Picture 3), and judicious pesticide use and reduction of related risks (food, feed safety and occupational hazard).

Picture 3: Groundnut kernels (left) and maize grain (right) infested by *Aspergillus flavus* fungus

IITA in collaboration with USDA and University of Arizona has developed Aflasafe, a biological control technology to reduce toxic strains of aflatoxins in the fields (Picture 4).

Picture 4: A farmer holding a box of Aflasafe

Key research area 4: Impact on human health, advocacy and policy advice

This research area focuses on determining the impact of agricultural developments on human health, including nutrition and food safety (e.g. Figure 1 for reducing malaria in agro-ecosystems). Results from this research area should help to better justify and focus research in the project, and also allow for better communication with the public, including donors and policy makers to increase the project's profile and investor awareness. Another important issue is the targeting of particularly vulnerable groups.

We have recently launched an agro-eco-health system thinking initiative for controlling malaria and Buruli ulcer in wet agro-ecosystems (Picture 5). The initiative is a trans-disciplinary and multi-country program which brings together scientists with diversified backgrounds (agronomists, epidemiologist, clinicians, socio-economists, and biologists, environmentalists) and focuses on the analysis of linkages between poor agricultural practices and the emergence of human diseases. This initiative is also focused on the identification of environmentally sound and cost effective innovations for preventing and controlling Buruli ulcer and malaria in wet agro-ecosystems.

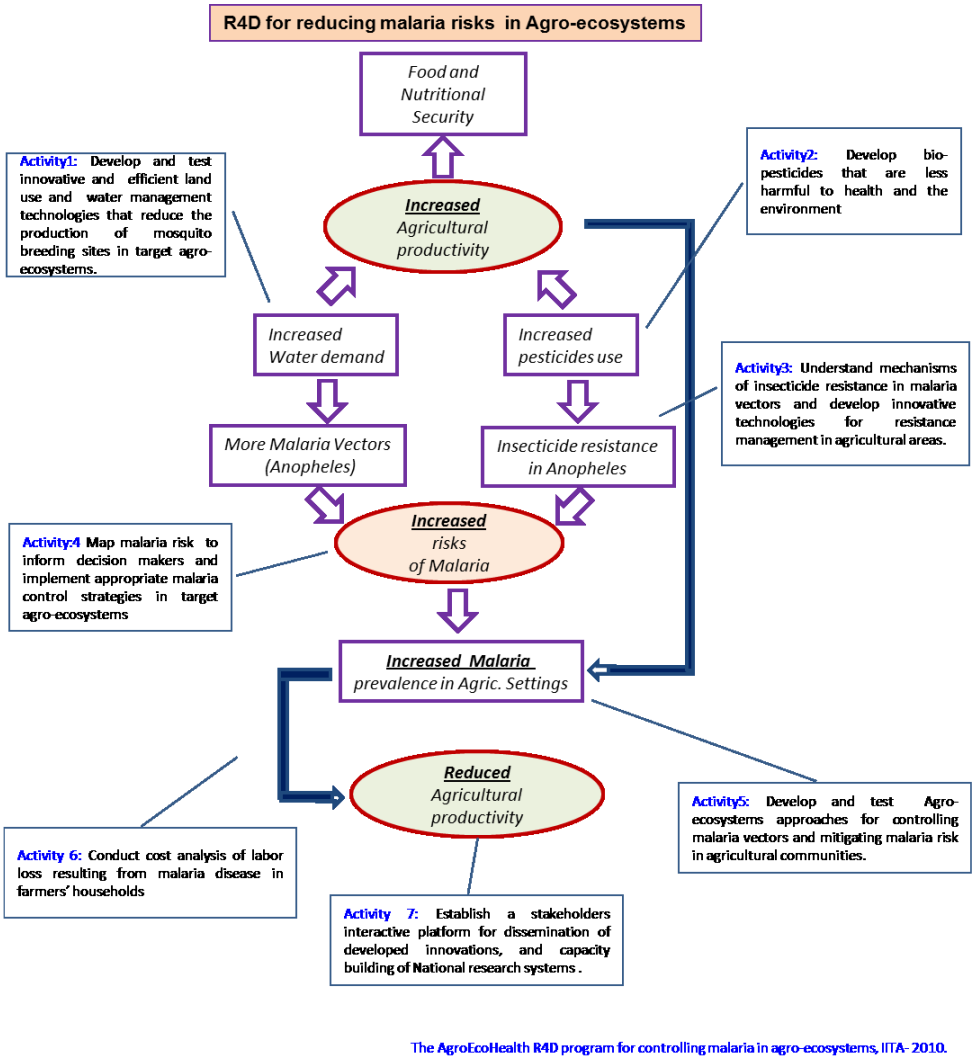


Figure 1: Impact pathways for Research for Development (R4D) Strategies for Reducing Malaria in agro-ecosystems.

Picture 5: Agro-eco health platform for sustainable agricultural productivity in West Africa.

3 Partnership

Partnership is particularly important as IITA as such does not have the capacity to work on all the issues related to agricultural and health so that such research fields have to be covered by partner institutions.

IITA has been working in partnerships with universities such as Vienna University of Technology (Austria), University of Arizona (USA), University of Thies (Senegal) (in aflatoxin research) and University of Leeds, UK (Faculty of Medicine and Africa College: epidemiology on bioavailability of nutrients and tools for impact); government organizations in the north and the south such as USDA-ARS in aflatoxin research (Determination of Aflatoxin-Resistance and Marker Identification in IITA Maize Breeding Materials, and aflatoxin biocontrol research), research institutes such as KARI (Kenya), INERA (Burkina Faso) and DPV (Senegal) for aflatoxin research, and PRONANUT for nutrition studies in DRC; CG centers (e.g. CIAT) and African ARIs provide technologies like germplasm (e.g. CRBP Cameroon) and services (e.g. University of Zambia), WHO Geneva for Buruli ulcer in wet agroecosystems, and University of Gottingen Health International health network (GHIN). Other important partnerships are with bureaus of standard, drug and health agencies, as well as the related ministries.

Acknowledgement
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III. Specific initiatives and research topics under the vision of GIHN

17 Aspergillosis : a major challenge for public health

Bharat Singh, Gainda L. Sharma, Seema Singh, Utz Reichard, Michael Oellerich, Dharam P. Bhadoria and Abdul R. Asif

1 Introduction

Aspergillus species are common pathogens that cause a wide spectrum of diseases in the host (Pfaller et al, 2004). Among the genus *Aspergillus*, four species are found to be most pathogenic in humans: *Aspergillus fumigatus, Aspergillus flavus, Aspergillus niger* and *Aspergillus terreus*. Particularly, A. *fumigatus* is prominent and in fact, reported to be responsible for more than 90 % of *Aspergillus* induced infections. This marked predominance of *A. fumigatus* in clinical samples is also reflected by its environmental preponderance over other pathogenic *Aspergillus' species* (Latge, 1999). In addition, the incidence of A. *fumigatus* induced infections has increased to an alarming rate in the past decades (Abad et al, 2010). Such an increase in the prevalence of aspergillosis has been attributed to the growing number of transplant recipients, neutropenic individuals, allergic patients and those treated with corticosteroids, or other immunosuppressive drugs (Denning, 1998). Despite a better understanding of pathology and epidemiology of *Aspergillus* induced infections, there are persisting diagnostic limitations (Sarfati et al, 2006).

2 A. fumigatus as a pathogenic mould for humans

A. *fumigatus* sporulates abundantly to release large numbers of tiny conidia (2-3 μm in size) into the environment. Once the conidia are released into the air, their small size renders them buoyant and keeps them as airborne microparticles, both indoors and outdoors (Latge, 1999). Since the conidial production of A. *fumigatus* is highly prolific, the human respiratory tract always remains at risk of acquiring *Aspergillus* infection (Latge, 2001). Environmental surveys have indicated that all humans inhale at least several hundred conidia of A. *fumigatus* every day (Chazalet et al, 1998). In upper airways, conidia may cause respiratory discomfort due to contact irritation and allergic responses. A pictorial presentation of A. *fumigatus* asexual life cycle in the environment including the infection of a human host, leading to the development of an invasive disease is shown in Figure 1. A. *fumigatus* is able to establish infections in various organs like lungs, paranasal sinuses, brain, skin, heart, eyes etc. However, the lungs are the prime target due to uptake of conidia by inhalation via the internasal route. The characterization of A. *fumigatus* infections is based on the site of infection and extent of mycelial colonization, which are influenced by the immune system of the host (Taylor et al, 2009). Generally, a hyperactive immune system leads to allergic manifestations, whereas individuals with an impaired immune system develop invasive forms of the disease. However, the immunocompetent host may also acquire an infection (Latge, 2001). "Invasive aspergillosis" (IA) is considered to be the most devastating form of the disease, which may develop in any part of the body by dissemination of A. *fumigatus* species, frequently present in severely immunocompromised patients (Steinbach et al, 2003).

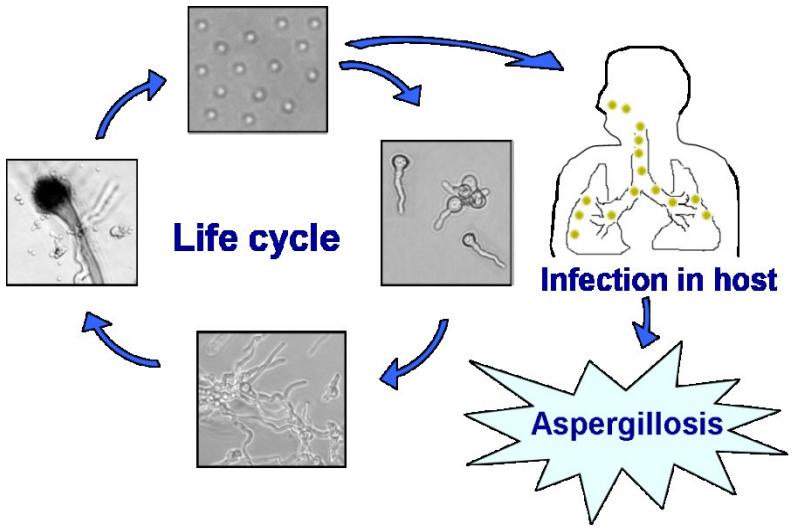

Figure 1: Asexual life cycle of A. fumigatus showing infection of the human host by conidia leading to development of a disease.

3 Allergic aspergillosis

The initial allergic responses of the host to A. *fumigatus* are accountable for the development of four distinct and clinically recognizable forms of hypersensitivity disorders of the respiratory tract i.e., allergic bronchopulmonary aspergillosis (ABPA), allergic *Aspergillus* sinusitis, IgE-mediated asthma, and hypersensitivity pneumonitis (Shah and Panjabi, 2002). In atopic individuals with diseases of altered lung function, such as asthma and cystic fibrosis, A. *fumigatus* can cause ABPA, which is a hypersensitive response to fungal components. It is the most severe allergic pulmonary complication caused by *Aspergillus* species. The first cases of ABPA were reported in England by Hinson et al (1952) and in the USA by Patterson and Golbert (1968). In India, the first three cases of ABPA were identified by Shah (1971). The clinical course of ABPA is known to range from mild asthma to fatal destruction of lungs with bronchiectasis and fibrosis (Rosenberg et al, 1977). Several attempts have been made to determine the prevalence of ABPA, but the lack of uniform diagnostic criteria and standardized tests represent a challange(Bedi and Bedi, 2007). *Aspergillus* hypersensitivity (AH) is characterized by the presence of an immediate type hypersensitivity reaction to A. *fumigatus* antigens and is the first step in the development of ABPA (Patterson and Golbert, 1968). Agarwal et al (2009) reported ABPA a prevalence of 27.2% in their study of 564 asthmatics in North India. The overlapping clinical features of ABPA with other

respiratory disorders mainly with tuberculosis, quite often leads to its misdiagnosis which is the main reason for considering ABPA as less important as it truly is.

The factors considered to be important with respect to high incidence of ABPA in the Indian subcontinent are (i) high prevalence of tuberculosis (TB) and (ii) radiological similarity between ABPA and TB. Therefore, most patients are erroneously diagnosed with TB and keep on receiving anti-tuberculosis treatment (ATT) over long periods. Studies have indicated that ABPA was misdiagnosed as TB in as many as 17-50% of cases (Bedi, 1994 and Behera et al 1994). The symptoms of ABPA are quite nonspecific and an overlap of its clinical and radiological features has been reported (Delhaes et al, 2010 and Agarwal et al, 2008). In addition, corticosteroids are easily available as over the counter drugs in India (without a physician's prescription), leading to a gross misuse in asthmatics and increases the risk of *Aspergillus* infection. In the absence of a widespread availability of mycoserological tests and computer tomography (CT) scans these conditions of ABPA get masked and is only diagnosed at its late stages (iv).

4 Aspergilloma and chronic pulmonary aspergillosis (CPA)

Aspergilloma, generally referred to as "fungus ball," may be formed due to repeated exposure to conidia and targets preexisting lung cavities, such as the healed and non-healed lesions, or cavities in tuberculosis, sarcodiosis, or other bullous lung disorders and chronically obstructed paranasal sinuses (Addrizzo-Harris et al, 1997). In the early 1950s, aspergilloma was considered as the classical form of aspergillosis. In the current scenario 10-15% of patients with cavitating lung diseases may develop this syndrome (Latgé 1999).

CPA is described as a slightly different condition than aspergilloma, due to slow progression of infection by damaging the lung tissues, which may result in fibrosis and inflammation., The global prevalence of CPA, together with aspergilloma, estimated over a 5 year period in countries exceeding a population of more than 50 million was reported in 2005 by Denning et al (2011). The 5-year (2005-2010) estimated prevalence of CPR per 100 000 population was 23.1 in India and 0.6 in England (Denning et al, 2011).

5 Invasive aspergillosis (IA)

The occurrence of IA is usually observed in settings of immunocompromised states, but rarely found in immunocompetent hosts (Karim et al, 1997). Indeed, IA has become a leading cause of deaths, mainly among patients suffering from hematological disorders. Within this group for example, the incidence of IA ranges between 7.9% to 11% (Pappas et al, 2010). IA also occurs in patients with nonhematogenous underlying conditions; increasingly reported in AIDS patients (1 to 12%) (Nash et al.1997) and has been a common infectious complication (25% to 40%)

of chronic granulomatous diseases (Denning et al, 1998). Despite the remarkable advancement in the field of diagnostic medicine, the diagnosis of IA remains difficult even today, especially in its early stages. A definitive diagnosis of IA requires histopathological demonstration of mycelial growth in tissues. This is not possible in most patients, due to the serious nature of underlying conditions which often contraindicate tissue biopsy. Thus, IA is mostly diagnosed only during postmortem autopsy (Groll et al, 1996). The mortality rate in IA is high, generally greater than 50%, which may reach upto 95% in certain cases (Maschmeyer et al, 2007). Due to the difficulty in diagnosis and rapid progression (1 to 2 weeks from onset to death), clinicians have no choice but to treat patients with suspected IA empirically rather than waiting for the diagnosis to be established. Moreover, waiting until diagnosis is confirmed will subject the patients to a greater risk of untreatable IA, since the fungal burden might reach a level too high for antifungal therapy.

6 Chemotherapy for aspergillosis

The various agents available for treating Aspergillus infections include

a. Polyenes: Amphotericin B.
b. Azoles: Voriconazole, Itraconazole, Posaconazole.
c. Echinocandins: Caspofungin, Anidulafungin Micafungin.

Amphotericin B is one of the polyene groups of antibiotics produced by several species of *Streptomyces* (Hamilton-Miller, 1973). Amphotericin B and other polyenes bind to sterol in plasma membranes, thereby leading to alterations in the membrane permeability and cell lysis (Kinsky, 1970). It has the broadest spectrum of antifungal activity, but severe side effects. Particularly nephrotoxicity following amphotericin B usage is very common. To increase the efficacy and reduce the toxicity, several newer formulations of amphotericin B have been developed; the most promising approach involved the modification of the physical state of amphotericin B in different formulations with lipids. The examples of such formulations include amphotericin B-lipid complex, amphotericin B colloidal dispersion and liposomal amphotericin B (Clark et al, 1991, Coukell et al, 1998 and Lopez-Berestein, 1987). Azoles are synthetic derivatives of imidazole and have a wide range of antifungal activity. Particularly, voriconazole, itraconazole and posaconazole have been found to act against *Aspergillus*. Currently, voriconazole is the drug of choice for invasive IA. The echinocandins are a newer class of antifungal agents with caspofungin, anidulafungin and micafungin exerting activity against *Aspergillus*. Caspofungin, posaconazole and AmB are considered second line agents for treatment of IA. In addition, a combination therapy is increasingly used in IA (Herbrecht et al, 2002). The rationale for combination therapy is that different classes of drugs act on targets of different pathways.

The antifungal agents are also used to treat allergic aspergillosis with the rationale that by reducing the fungal load, less antigenic stimulation will take place and hence a reduced inflammatory response as observed in ABPA. However, the treatment of ABPA with most fungicidals has been found to provide very low efficacy only (Malo, 2003). Therefore, glucocorticoids remain the mainstay of treatment for ABPA. But even in addition to glucocorticoids, the patient often requires treatment for long periods, there are high relapse rates on withdrawl and a state of steroid dependence is developed quite frequently (Agarwal et al, 2006).

Itraconazole has been used as a corticosteroid-sparing agent in patients on long-term oral prednisolone treatment (Leon and Craig, 1999). An Indian study by Rai et al (2004) demonstrated that itraconazole improved symptoms, lung function, and the radiologic picture in patients of ABPA. A decline in exacerbation rates was seen in patients as well. It was also inferred from the Cochrane database review that itraconazole in addition to modifying the immunological activation associated with ABPA, improved clinical outcome (Wark et al, 2004). Therefore, it is suggested that until further results are available from large multicentre randomized clinical trials, the use of itraconazole should be restricted as a steroid-sparing agent to only those clinical settings where steroids are contraindicated or have intolerable side effects. The beneficial effect of antifungal agents in treating aspergilloma has not been indicated and so far it always requires surgical excision.

7 Clinical diagnosis

This issue has been haunting clinicians since the recognition of the disease as a distinct entity and even today there is no single test available, which can establish the diagnosis of ABPA. The diagnosis of ABPA usually relies on a set of criteria. Following criteria take clinical, radiological and serological features into account (Rosenberg et al, 1977).

Major criteria:

- Asthma
- Presence of transient pulmonary infiltrates (fleeting shadows)
- Immediate cutaneous reactivity to A. *fumigatus*
- Elevated total serum IgE
- Precipitating antibodies against A. *fumigatus*
- Peripheral blood eosinophilia
- Elevated serum IgE and IgG specific to A. *fumigatus*
- Central/proximal bronchiectasis with normal tapering of distal bronchi

Minor criteria:
- Expectoration of golden brownish sputum plugs
- Positive sputum culture for *Aspergillus* species
- Late (Arthus-type) skin reactivity to A. *fumigatus*

8 Serodiagnosis

The diagnosis of A. *fumigatus* infections has been based on the clinical features, and on *in vivo* (skin prick test and intradermal test) and *in vitro* tests (radioallergosorbent test, enzyme linked immunosorbent assay ELISA and Western blot). Sensitization of hosts with allergens of A. *fumigatus* may induce elevated levels of total serum IgE and *Aspergillus* specific IgE and/or IgG antibodies. Many of these molecules have been shown to be useful in the serodiagnosis (Sarfati et al, 2006). The detection of total IgE and *Aspergillus* specific IgE and/or IgG antibodies in sera has been considered to be important immunodiagnostic criteria for ABPA (Kurup, 2006) and IA (Reiss, 2000 and Stynen et al, 1995). However, still there is a lack of antigenic standardization between laboratories, because of the use of local antigen preparations (de Oliveira et al, 2007). The crude extracts used at different centers for sero diagnosis are not comparable in their protein composition, due to use of different strains (Steringer et al, 1987) and even batch-to-batch variations of same strains have been quite common (Vailes et al, 2001). The fungal extracts mainly produced from mycelial cells and/or spores may differ in their protein pattern (Paris et al, 1990). On the other hand, growth conditions, protein extraction methods and storage conditions are critical with respect to the quantity and existence of individual allergens in fungal preparations (Horner et al, 1995, Ferreira et al, 2004). In this context use of recombinant protein provides an alternative which is worth to explore.

9 Recombinants proteins of A. fumigatus

A large number of immunoreactive allergens/antigens of A. *fumigatus* have been identified (Crameri 1998, Vailes, 2001, and Crameri et al, 2006) and a brief description of A. *fumigatus* allergens is summarized by Abad et al (2010) and is shown in Table 1.

Table 1. Brief description of the *A. fumigatus* allergens

S. No.	Allergen name	Protein name	Function	Pathogenesis related activity
1	Asp f1	Restrictocin, Ribonuclease Mitogillin	Ribotoxin	Protein biosynthesis inhibition, Cytotoxin, Apoptosis, Type 1 hypersensitivity
2	Asp f2	ASPND1	Fibrinogen binding protein	Adhesion, Type 1 hypersensitivity
3	Asp f3	Peroxisomal protein, Thioredoxin reductase, PMP20, Putative peroxiredoxin	Peroximal membrane protein	Type 1 hypersensitivity
4	Asp f4	Hypothetical protein		Type 1 hypersensitivity
5	Asp f5	Metalloprotease	Protein degradation (collagen and elastin)	Tissue destruction/invasion, Type 1 hypersensitivity
6	Asp f6	Mn superoxide dismutase	O_2^- degradation	ROS protection, Type 1 hypersensitivity, Autoimmunity,
7	Asp f7	Secreted and cytoplasmic proteins		Type 1 hypersensitivity
8	Asp f8	Ribosomal protein P2	Protein synthesis (elongation step)	Type 1 hypersensitivity, Autoimmunity
9	Asp f9	Cell wall glucanase, Crf1	Cell wall assembly	Type 1 hypersensitivity
10	Asp f10	Aspartic protease	Protein degradation (collagen)	Tissue destruction/invasion, Type 1 hypersensitivity
11	Asp f11	PPIase, Peptidyl-prolyl cis-trans isomerase, rotamase	Peptide synthesis chaperone and cell signaling	Type 1 hypersensitivity, Autoimmunity
12	Asp f12	Heat shock protein P90, 65 kDa IgE-binding protein	Chaperone	Chaperone activity and protein transport in growth at 37 °C, Stress response during inflammation, Type 1 hypersensitivity, Autoimmunity

S. No.	Allergen name	Protein name	Function	Pathogenesis related activity
13	Asp f13	Alkaline serine protease, Alkaline proteinase; ALP, Elastase	Protein degradation (elastin, collagen, fibrinogenand casein)	Tissue destruction/invasion, Type 1 hypersensitivity
14	Asp f15	Homologue of Asp f 13	Protein degradation (elastin, collagen, fibrinogenand casein)	Tissue destruction/invasion, Type 1 hypersensitivity
15	Asp f16	43kDa protein Asp f 9 homolog	Putative glycosylhydrolase	Type 1 hypersensitivity
16	Asp f17	Hypothetical protein	Cell wall galactomannan protein	Adhesion Type 1 hypersensitivity
17	Asp f18	Vacuolar serine protease	Protein degradation	Tissue destruction/invasion, Type 1 hypersensitivity
18	Asp f22	Enolase	Glucose metabolism	Type 1 hypersensitivity
19	Asp f23	Ribosomal protein L3	Protein synthesis	Type 1 hypersensitivity
20	Asp f 27	Cyclophilin	Peptide synthesis Chaperone Cell signal function	Tissue destruction/invasion, Type 1 hypersensitivity
21	Asp f 28	Thioredoxin	Protein disulphide reductase	Type 1 hypersensitivity
22	Asp f 29	Thioredoxin	Protein disulphide reductase	Not known
23	Asp f 34	PhiA cell wall protein	Cell wall protein	Not known

Adapted from Abad et al (2010)

In addition to the allergens of A. *fumigatus*, a large number of potential virulence factors are described in the literature (Abad et al, 2010). Some of these molecules have been shown to be useful in the serodiagnosis (Sarfati et al, 2006). However, there exists a lack of antigenic standardization between laboratories, because of the use of local antigen preparations (de Oliveira et al, 2007). This frequently results in variability of such antigenic preparations and thus, in a limited sensitivity and specificity resulting in limited usefulness in uniformly detecting A. *fumigatus* infections

(Sharma and Sarma, 1993). The diagnosis of ABPA still remains difficult, due to an overlap of its clinical and radiological features with cystic fibrosis (Delhaes et al, 2010). It is also often misdiagnosed as tuberculosis, because of similar symptoms and therefore, treated incorrectly (Agarwal et al, 2008). In fact, a cross reactivity due to sharing of common antigenic epitopes of A. *fumigatus* allergens with other fungal and bacterial allergens renders it difficult to use all A. *fumigatus* allergens for diagnostic purposes (Crameri et al, 2009). In the absence of ideal antigenic preparation the crude antigenic fractions of A. fumigatus are commonly used for diagnosis of ABPA. Several biotech companies offer tests based on the crude antigens of A. *fumigatus*. The ELISA and radioimmunoassay based on the few recombinant allergens (rAsp f1-f4 and rAsp f6) of A. *fumigatus* have also been used commercially for diagnosis of allergic aspergillosis (Kurup et al, 2006, and Knutsen et al 2004). The use of recombinant allergens, however, has been limited to the IgE detection only (Sarfati et al, 2006). Therefore, more effort is required to produce the recombinant antigens, which should provide more standardized diagnostic tests.

Global efforts are made to identify antigenic preparations of A. *fumigatus* with therapeutic potential (a details see, Ito et al, 2006, Ito et al, 2009 and Montagnoli et al, 2006). Most studies carried out so far on vaccination, have been limited to experimental animals only and not even a single protein has yet been identified to develop immunoprotection in humans. Therefore, more A. *fumigatus* proteins from the crude fractions of A. *fumigatus* are needed to be screened from conidial, secreted and cytosolic fractions to identifiy the potential immunotherapeutic molecules.

10 Identification of new molecules and their possible use in diagnosis and therapy

The release of 29.4 megabase genome has reported the presence of 9,926 genes in A. *fumigatus* (Nierman et al, 2005). The products of many of these genes have not yet been identified and only just predicted. The recent update in a public resource for genomic data of various *Aspergillus* species provided an array, The Central *Aspergillus* Resource (CADRE) of online tools for searching and visualizing features of the significant fungal genus to understand the pathogenic components of A. *fumigatus* (Mabey Gilsenan et al, 2011). The *Aspergillus* genome database (AspGD) has now completed a comprehensive review of the entire published literature on A. *fumigatus* and multispecies information. The AspGD facilitates comparative genomics by providing a full-featured genomics viewer, as well as matched and standardized sets of genomic information for the sequenced species of *Aspergillius* (Arnaud et al, 2011). This information could be considered as a tool for identification of molecules which are not yet known. But their sequences have been identified in A. *fumigatus* genome which might play crucial role in the development of *Aspergillus* induced allergic and invasive disorders. A review of literature has shown that out of the known allergens of A. *fumigatus*, a single molecule may not be suffi-

cient for universal use in the diagnosis of ABPA at initial stages of infection (Kurup, 2005). Thus the less explored cytosolic antigenic fraction in combination with secreted molecules may form a panel of potential key determinants for the selection of universally reacting molecules for wider application, as well as for early and more specific diagnosis of A. *fumigatus* induced disorders. A recent report discussed the comparison of conventional diagnostic criteria, which included detection of anti-A. *fumigatus* IgE, IgG, precipitins and IgE against recombinant A. *fumigatus* allergens and/or detection of thymus and activation regulated chemokine to diagnose ABPA in CF patients (Delhaes et al, 2010). Investigators used the cDNA library screening approach in order to improve available diagnostic tools, but selecting the right protein target using cDNA screening has proven to be difficult (Glaser et al, 2009 and Glaser et al, 2008). Recent advances in technologies introduced microarray-based allergen chip diagnosis that made it possible to detect IgE against a multiple number of allergens in small amounts of serum (Ott et al, 2008). Though this approach appeared to be very promising, it still requires evaluation and optimization (Schneider et al, 2006). In fact cloning and expression of all antigens/allergens of A. *fumigatus* to elucidate their biological functions is not feasible. Therefore dependence on available, less useful few recombinants may continue for some time.

First reports on the proteomics based identification of A. *fumigatus* molecules have appeared only in the last decade (Bruneau et al 2001). The possible reason for such delay was unavailability of the proteomic based information on A. *fumigatus*, difficulty in sample preparation from its fractions (cell wall, secreted, cytosolic and mycelial) and poor separation of fungal proteins by two dimensional gel electrophoresis (2DE) (Kniemeyer et al 2008). In a recent report Vodisch et al (2009) generated a proteome map of A. *fumigatus* from cytosolic and mitochondrial fractions. Teutschbein et al (2010) identified proteins from dormant conidia to provide complete profiling of A. *fumigatus* conidial fraction. Gautam et al (2007) identified a panel of secreted antigens as potential allergens of A. *fumigatus* by IgE reactivity with sera of ABPA patients. Kumar et al (2011) also identified secreted antigens of A. *fumigatus* by immunoreactivity with ABPA patients and hyper reactive animal sera. A detailed account of vaccine candidates from cell wall-associated (Asif et al, 2006) and immunoprotective molecules from cytosolic fraction (Asif et al, 2010) has been reported by our group. A comprehensive identification of potential allergens/immunogens from secreted and cytosolic fractions of A. *fumigatus* on the basis of IgG and IgE reactivity with sera of ABPA patients was carried out and identified 101 molecules (Singh et al, 2010a and 2010b), including 35 secreted and 66 cytosolic allergens/immunogens. These identified panels of immunoreactive molecules could be promising in developing a chip assay and diagnostic peptides for better management of A. *fumigatus* induced infections.

11 Conclusion

Aspergillosis is a complex disorder, which is difficult to treat and various limitations remain associated with the use of existing allergens/immunogens of A. *fumigatus* as diagnostic and therapeutic molecules. The recent developments in the high throughput techniques, such as immunoproteomics, have introduced hundreds of new antigenic proteins, few of which are already characterized for diagnostic utility, but are found to be of limited use. Hence selection of newly identified antigenic/immuogenic proteins for recombinant production and their detailed characterization for their immunological properties will be promising in diagnosis and desensitization therapies of aspergillosis.

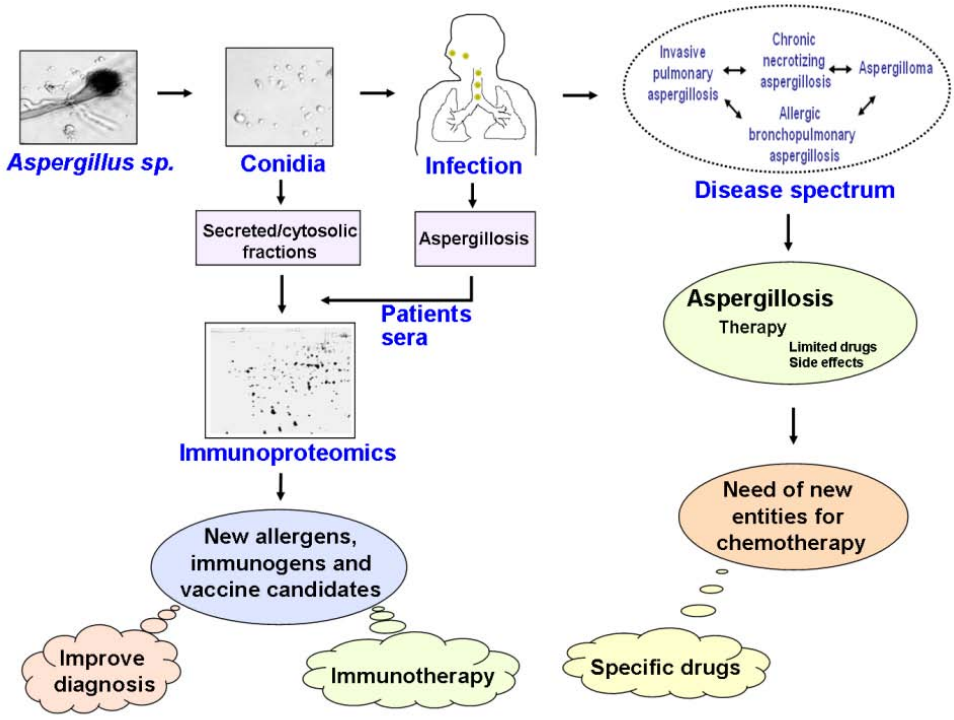

Figure 2: Approaches for identification of diagnostic and therapeutic molecules for better management of Aspergillus induced infections.

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18 IGHEP – a partnership on health education between Indonesian and German universities

Ichsan, Marut Tangwattanachuleeporn, Abu Tholib Aman, M. Nasrum Massi, Mohamad Yani, Syrhul, Christiane Hennecke, Natalie Diffloth, Uwe Groß and IGHEP members

1 Introduction

In late 2004, the coastal areas of many countries situated along the Indian Ocean were devastated by a tsunami. Located near the epicenter of the causative earthquake, the Aceh province in northern Sumatra/Indonesia suffered most. In Banda Aceh alone, the capital of that province, more than 250,000 fatalities or missed people were counted. Amongst these were numerous students and lecturers from the local universities.

2 The first step – a partnership between two universities

Shortly after the tsunami catastrophy, the Georg-August-University Göttingen initiated a *Fact-Finding-Mission* composed of three representatives from the Faculties of Medicine, Agriculture, and Forestry. In early 2005, this group evaluated the possibilities of a partnership with the Syiah Kuala University (UNSYIAH) in Banda Aceh. As one result, a *Memorandum of Understanding* between the Medical Faculty of UNSYIAH (UNSYIAH-MED) and the University Medical Center Göttingen (UMG) was signed. A first summer school was organized in 2006 in Banda Aceh. This outlined the themes for which further academic and educational support from

UMG and its German partners could be provided to UNSYIAH-MED. At that time, neither a Department of Infectious Diseases, nor Tropical Medicine, nor an isolation ward for highly contagious infections were available at UNSYIAH-MED. Likewise, no Master's or PhD program could be offered to the medical students in Banda Aceh. Instead, all medical students were offered a four-year Bachelor program that was followed by a two-year period of clinical practice in order to become a physician.

As a consequence, the major aims of the Göttingen-Banda Aceh partnership were to develop educational programs on infectious diseases and tropical medicine and to guide the process of implementing an interdisciplinary Master's program on Molecular Tropical Medicine at UNSYIAH — one that would allow the university's students to obtain a Master's degree, which is a prerequisite for applying for PhD study programs in Germany and elsewhere.

Starting in 2007, the German Academic Exchange Service supported the partnership financially through its Physicians Program. By this means, regular summer schools and workshops on the management of defined infectious diseases were held on an annual basis (Fig. 1).

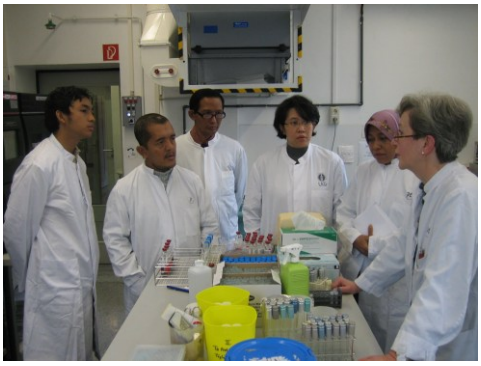

Figure 1: Courses on microscopy (H. Fleischmann, 2009) and tuberculosis (O. Zimmermann, 2009) in Göttingen

Training units on specific subjects related to infectious diseases have been conducted in Göttingen and Banda Aceh – covering laboratory-related topics such as cultivation of bacteria and polymerase chain reaction (PCR) (Fig. 2), but also clinically related techniques such as ophthalmology, ultrasound and laparoscopy (Fig. 3).


Figure 2: Practical teaching in cultivation of bacteria (M. and O. Bader, 2008) and in PCR (J. I. Dasti, 2008) in Banda Aceh.

E-learning modules on (i) basic molecular biology and (ii) applied molecular biology related to specific tropical infectious diseases were developed. In addition, Indonesian faculty members were able to join UMG in order to obtain their Master's or PhD degrees. Reciprocally, via medical rotations in Banda Aceh, German medical students have been able to take advantage of the opportunities offered by UNSYIAH-MED to learn more about practical aspects of tropical infectious diseases.


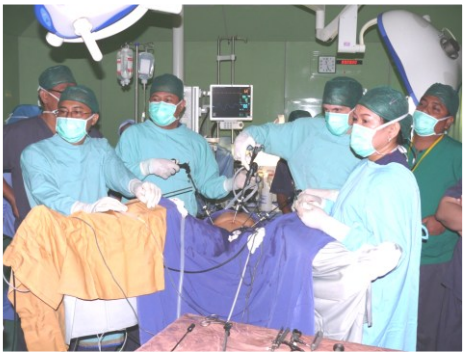

Figure 3: Training units on ultrasound (H. Sudeck, 2008) and endoscopy (A. Guenthert, 2010) in Banda Aceh.

Another accomplishment was the establishment of a Department for Tropical Medicine as well as an isolation ward – especially for patients with suspected bird flu – in the New Hospital RSUD Dr. Zainoel Abidin. This hospital was constructed in the post-tsunami era through the financial support of the Federal Republic of Germany. Since its founding, it has served as the teaching hospital of UNSYIAH-

MED. Finally, the partnership supported the development of a road map foreseeing the implementation of the above-mentioned Master's program on Molecular Tropical Medicine at UNSYIAH.

3 The second step – the establishment of the Indonesian German Health Education Partnership (IGHEP)

By opening the summer schools to lecturers and participants from other universities, the original partnership between UNSYIAH-MED and UMG matured into a network of more than 15 Indonesian and eight German biomedical institutions (Fig. 4).

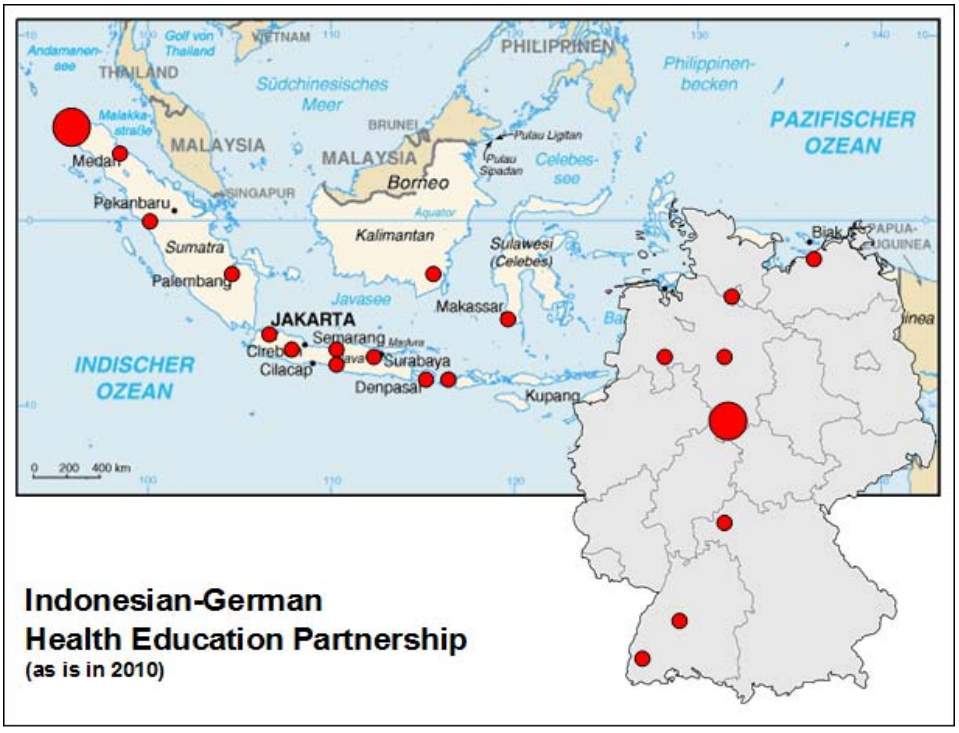

Figure 4: The Indonesian-German Health Education Partnership (IGHEP) as is in 2010.

Starting in 2010, a migrating summer school was established that took place in Banda Aceh and Yogyakarta/Indonesia. In addition, this network decided to designate itself the "Indonesian German Health Education Partnership, IGHEP" and to create its own website (http://ighep.wordpress.com) in order to establish a clear

organizational identity and platform for communicating and sharing information among stakeholders.

Having established a bi-national medical network, a focus had to be decided upon for medical themes that had a high socio-medical impact. Apart from infectious diseases, (which in densely populated tropical countries represent a major factor in morbidity and mortality), infant and maternal health was determined as an issue playing a critical role.

Indeed, in 2000 the member states of the United Nations agreed upon the Millennium Development Goals (MDG). The MDG hopes to attain specific goals by 2015, among them MDG 4 and 5, which are still far from achieving their desired targets. While MDG 4 hopes to reduce the under-five mortality rate by two-thirds between the years 1990 and 2015, MDG 5 aims to improve maternal health and reduce maternal mortality by three-quarters by 2015.

Improving health care, food production and basic economic conditions are key goals in international development. IGHEP is committed to addressing the improvement of maternal-child health in Indonesia through an integrated approach that brings together medicine and natural science, as well as social and economic science, under one roof.

Table 1: Data by country for MDG 4

	1990	**(2003-) 2008**	**Goal 2015**
Germany	9	4	3
Indonesia	91	41	30

Table 2: Data by country for MDG 5

	1990	**2003-2008**	**Goal 2015**
Germany	22	8	5
Indonesia	650	230	165

Data source: www.unicef.org/infobycountry and www.mdgmonitor.org

Although Indonesia is on track regarding MDG 4 and 5 (Table 1 and 2), when compared with the situation in Germany, mother-child health in Indonesia leaves considerable room for improvement. It is expected that broad variation exists for the conditions and basic indicators of maternal-child health within the different regions of Indonesia. Therefore, including participants from the major Indonesian islands in the Indonesian-German Health Education Partnership allows us to address geographic differences regarding maternal-child health within a territory as broad as Indonesia.

Causes of maternal and child morbidity and mortality in countries such as Indonesia are complex, but are highly dependent upon access to and quality of medical care, as well as upon specific environmental conditions. Most important is access to fresh potable water and to safe, high quality food. Medical study programs are

often limited to addressing health issues as such, but neglect issues indirectly associated with health. For these reasons, the Indonesian-German Health Education Partnership intends, through discussion and collaboration, to elaborate interdisciplinary approaches for improving health by implementing strategies that combine medicine, veterinary sciences, agricultural and forest sciences, geography, and theology, as well as social and economic sciences. Through this interdisciplinary approach, the close interconnection of the health-associated MDGs 4 and 5, along with MDG 1 on nutrition, MDG 3 on gender equality, MDG 6 on AIDS/HIV, tuberculosis and malaria, and MDG 7 on environmental sustainability, will be taken into account.

Based upon our initial partnership program which had a focus on infectious diseases, the Indonesian-German Health Education Partnership aims to concentrate its future programs on infectious diseases that are relevant for maternal and child health — especially under tropical conditions such as those found in Indonesia, including for example malaria, dengue fever, HIV/AIDS, tuberculosis, typhoid fever, and STDs. Since issues such as (i) access and quality of medical care, and (ii) access to and risk assessment of drinking water and nutrition are relevant to the development of these diseases, we believe a multidisciplinary, biomedical approach will be appropriate for developing adequate problem-solving strategies — ones that include an assessment of the impact of socioeconomic, ethnic and gender issues on the respective diseases.

In order to facilitate this multidisciplinary approach, members of the UMG and its local partners, the Faculties for Agricultural and Forest Sciences, Geography, Social and Economic Sciences, as well as of the Faculties of Biology and Theology of the University of Göttingen have established the Göttingen International Health Network. Together with its partners from other German and Indonesian institutions, this network aims to substantially contribute to the development of interdisciplinary strategies on ways to improve health within the above-mentioned context.

Following the summer schools in Banda Aceh (2006, 2007, 2008, and 2010), Göttingen (2009), and Yogyakarta (2010), the DAAD supported a second round of partnership within its program PAGEL (Partnerschaften für den Gesundheitssektor in Entwicklungsländern; Partnerships for the Health Sector in Developing Countries). In line with this broadened program, the first summer school was organized within the context of the Indonesian-German Health Education Partnership in Makassar/Sulawesi in 2011. More than 130 participants presented and discussed issues related to maternal-child health. The presentations compiled information on the following subjects:

- the epidemiology of infections affecting maternal-child health under tropical conditions in Indonesia (e.g. malaria, dengue fever, HIV/AIDS, tuberculosis, typhoid fever)
- the epidemiology of pregnancy-related infections that occur worldwide (e.g., group B streptococci infection, listeriosis, CMV, toxoplasmosis)

- potential risk factors that are of relevance to the above-mentioned diseases
- presently employed measures and strategies for improving health, access to quality nutrition and to clean drinking water
- veterinary medicine and agriculture within the context of the overall health of the ecosystem (human health, animal health, and plant health) and also related to infections influencing maternal-child health
- the impact of gender, economic and religious issues on the above-mentioned diseases.

In addition to presentations, and laboratory courses, case records were discussed in small groups and medical consultations were provided during ward rounds. Joint research projects with a focus on maternal-child health were initiated and a mycology-related network of young scientists including the nomination of Young ISHAM' representative for Southeast Asia was established during this first IGHEP summer school.

Taking a long view, the Indonesian-German Health Education Partnership has a broad and diverse catalog of aims. Among them is to highlight the most prevalent infectious diseases affecting maternal and child health in different regions of Indonesia. In this context, potential risk factors influencing maternal and child morbidity and mortality should be discussed, and the impact of gender, economic and religious issues on health should be evaluated. Here it is also important to identify needs and knowledge gaps, especially when it comes (i) to tools and methods for adequate diagnosis of disease and (ii) to risk assessment regarding water and food, including methods of molecular biology. The group's goals also include the discussion of possible integrated and sustainable strategies for the prevention and management of infectious diseases of mothers and their children.

On a structural level and over the long run, the Indonesian German Health Education Partnership should be stabilized and extended organizationally. This should include the funding of a network of biomedical alumni from German universities across Indonesia. Further, regional support should be augmented through the strengthening of subject-focused local networks — thereby leveraging benefits for stakeholders on different levels in research, education, society, business and politics. Together, this will increase awareness of and willingness to improve maternal-child health in Indonesia.

4 IGHEP members

Indonesia:
E. Amalia (Palembang), A. T. Aman (Yogyakarta), R. Amtarina (Riau), N. M. Andalas (Banda Aceh), N. A. Audah (Kalimantan), Azwar (Banda Aceh), A. Budianti (Jakarta), S. M. T. Chalid (Makassar), Chrysanti (Bandung), H. Dimiati (Banda Aceh), I. B. N. P. Dwija (Denpasar), D. B. Febriani (Makassar), Franciscus (Me-

dan), M. Gaffar (Makassar), P. Hadi (Semarang), I. Hafizah (Kendari), I. Handayani (Makassar), R. Hapsari (Semarang), Hasmiwiati (Padang), Z. Hayati (Banda Aceh), M. Hendrayana (Bali), Ichsan (Banda Aceh), R. Indah (Banda Aceh), I. Iqbalawati (Banda Aceh), A. Indrayati (Bandung), K. F. Jamil (Banda Aceh), F. Jamal (Banda Aceh), F. Juliantina (Yogyakarta), M. J. Kurnia (Banda Aceh), D. C. Lestari (Jakarta), T. Mahdi (Banda Aceh), M. Masri (Makassar), M. N. Massi (Makassar), Mulyadi (Banda Aceh), H. Munirwansyah (Banda Aceh), A. K. Ningrum (Jakarta), H. Nirwati (Yogyakarta), L. Nurbati (Mataram), Nurfadly (Medan), P. B. Purnomo (Surabaya), A. E. Putra (Padang), Rahmiati (Banjarmasin), L. P. Riski (Yogyakarta), Rusmunandar (Banda Aceh), R. Sadeli (Bandung), L. Salawati (Banda Aceh), L. Saptawati (Solo), E. N. Sholikhah (Yogyakarta), M. P. L. Suriana (Denpasar), I. K. Swastika (Denpasar), Syrhul (Banda Aceh), B. Wahydin (Makassar), S. Widad (Yogyakarta), A. D. W. Widodo (Surabaya), M. A. Wijayanti (Yogyakarta), Yadi (Samarinda), D. Yahwardiah (Medan), A. Yaman (Banda Aceh), M. Yani (Banda Aceh), Y. Zenia (Riau), Zubir (Lhokseumawe)

Germany, Switzerland:
M. Bader (Göttingen), O. Bader (Göttingen), G. Braus (Göttingen), T. Buhl (Göttingen), J. I. Dasti (Göttingen), N. Diffloth (Freiburg), J. Dreesman (Hannover), T. Fleige (Göttingen), M. Grade (Quakenbrück), U. Groß (Göttingen), A. Günthert (Bern/CH), M. Hufnagel (Freiburg), G. Jahn (Tübingen), M. Kirchner (Hannover), R. Kuehne (Göttingen), M. Loebermann (Rostock), A. Malik (Göttingen), A. Müller (Würzburg, J. Petersen (Göttingen), E. Reisinger (Rostock), C. Schroeder (Göttingen), F. Schwab (Bern/CH), N. von Steinbüchel (Göttingen), A. Stich (Würzburg), H. Sudeck (Hamburg), M. Tangwattanachuleeporn (Göttingen), J. Wienands (Gottingen)

Acknowledgment
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19 Usefulness of microbiological laboratories in a rural African setting

Uwe Groß, Marco Schulze, August Stich and Ortrud Zimmermann

1 Introduction

Infectious diseases account for a major proportion of morbidity and mortality in African patients. According to a WHO estimate for 2008, infectious and parasitic diseases including respiratory infections are responsible for more than one fifth of worldwide deaths but in Africa for even more than 50 % of all deaths (WHO, 2008). Especially invasive bacterial infections may be an underappreciated cause of death (Petti et al. 2006).

A limited number of diagnostic tests like blood films for malaria, microscopy of stool samples and urine for detecting parasites and worm eggs, microscopy of acid-fast stained sputum smears for TB diagnosis as well as rapid tests for diagnosing HIV infection and syphilis are available in most African hospitals (Bates and Maitland, 2006). In contrast, facilities to perform bacteriology are restricted only to larger hospitals or university health institutions in most countries of sub-Saharan Africa. Indeed, laboratory services are one of the most neglected areas of health care provision in sub-Saharan Africa and are disproportionately affected by (i) staff shortages, (ii) low enthusiasm, (iii) poor communications, (iv) lack of training, and (v) inadequate equipment that all have an influence on those involved in delivering health care in African countries under resource-poor conditions (Bates and Maitland, 2006). In line with this grievance is the fact that only relatively little funding has been allocated to build laboratory capability in contrast to disease prevention and provision of care (Petti et al., 2006). It is therefore not surprising that the vast

majority of small hospitals especially in rural and resource-poor settings lack appropriate laboratory facilities and skills in bacteriological diagnosis (Okeke, 2006). The situation is even worse when it comes to the diagnosis of fungal infections.

Based on these limitations in laboratory diagnosis, valid epidemiological data on most infectious diseases other than malaria, tuberculosis, syphilis and HIV/AIDS are rarely available for Africa, and even those might not be reliable. In fact, it is widely accepted that febrile episodes are usually classified as malaria but are in reality often the result of systemic bacterial infections. Treatment guidelines for infectious diseases in Africa either rely on so-called historical data or expert opinions, single case-based criteria, data derived from European or US American studies, or just do not exist. Consequently, without proper epidemiological baseline information and reliable diagnostic tools, treatment of infectious diseases might be inadequate resulting in a high burden of morbidity and mortality and the emergence of antibiotic resistances (Okeke, 2006; Petti et al., 2006).

For these reasons and starting as a pilot project in the year 2000, the University Medical Center Göttingen together with the Medical Mission Institute Würzburg established laboratories for microbiological diagnosis in missionary hospitals in rural settings of Ghana which since then run continuously and provide service at adequate standard. Here, we describe the implementation process and discuss the necessity for appropriate microbiological diagnosis under resource-poor settings.

2 Establishing microbiological laboratories

2.1 Prerequisites

Motivation for laboratory staff depends on several aspects, amongst them (i) self-confidence in her/his own knowledge and technical skills, (ii) an adequately equipped and maintained laboratory, (iii) appreciation of their work by the physicians, and (iv) an appropriate salary.

For these reasons, prerequisites to establish a microbiological laboratory were defined by us as follows:

- sufficient expertise of the laboratory staff in basic and advanced laboratory techniques (e.g. biochemistry, serology, microscopy, parasitology);
- existing and good communication structures between physicians and laboratory staff;
- an interest of both, physicians and laboratory staff, to participate in the comprehensive training courses;
- a well-functioning general laboratory for clinical chemistry, haematology, blood-transfusion, HIV and syphilis serology, and parasitology;

- two air-conditioned rooms (one for use as media kitchen, the other for culture and differentiation techniques, as well as for sensitivity tests; Fig. 1). If possible, solar energy supply in connection with a storage battery should be considered for the air condition and electronic equipment.
- laboratory glassware and equipment (including pressure cooker as autoclave, incubator, hot oven for sterilization, water bath and microscope). The costs for hardware were about 15.000-18.000 €. In addition, a refrigerator with freezer department should be bought in the given country. Description of electronic equipment should be available in English, French, or the language that is officially been spoken in the given country. Routine maintenance and spare parts should be available for all equipment.
- reagents for culture media and differentiation. The starting costs for these were about 5.000 €.
- laboratory glassware and especially the reagents should be available in the given country to assure independence of the laboratory which is key for sustainability of the diagnostic methodologies that were selected for the implementation process.

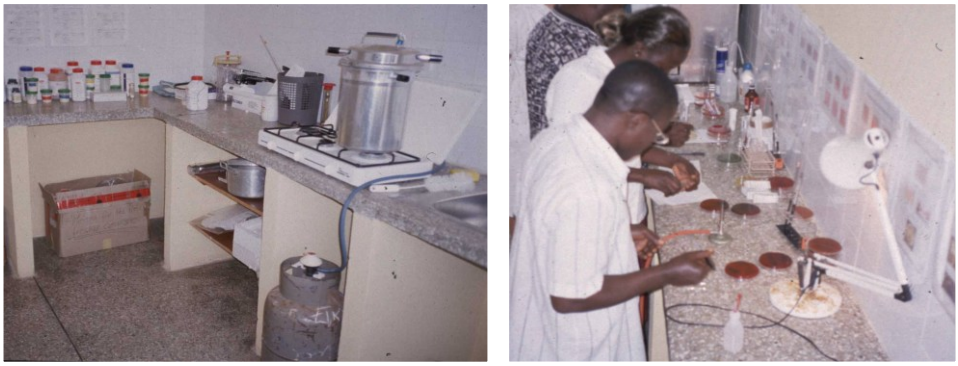


Figure 1: Microbiological laboratory in Eikwe; media kitchen (left) and training course in the main laboratory room (right).

In Ghana, the three Catholic Mission hospitals in Assin Foso, Eikwe and Nkawkaw met these criteria and were therefore selected for the implementation of microbiology. At these hospitals, a basic bacteriological laboratory was established and three training courses were conducted on standardized operational procedures (SOPs) to ensure an inexpensive and appropriate diagnostic program of high quality even in resource-poor settings.

In addition to the training courses, the leading laboratory technician together with the financial administrator was instructed on how to properly calculate the costs for microbiological diagnosis and how to charge the patients for this diagnostic service. This strategy also helped to reconsider the salary scheme for those labora-

tory personnel who showed outstanding engagement in implementing innovative diagnostics of infectious diseases.

2.2 Overview of the implementation concept

Basic understanding of (i) the principles of infectious diseases, (ii) clinical presentations of the most prevalent infectious diseases, (iii) adequate selection of specimens to be taken, and (iv) pathogen distribution in regards to defined diseases had to be imparted to physicians and lab personnel. Therefore, these pre-analytical aspects of infectious diseases were taught and discussed in joint courses allowing also a team building process between physicians with a special interest in infectious diseases and the laboratory personnel. In the African situation, where the number of physicians is often limited, and depending on the clinical presentation, the sampling of specimen was delegated to the lab technicians in defined cases. Therefore, these joint courses also included ward rounds in order to demonstrate adequate specimen sampling and to demonstrate the significance of microbiological diagnosis to both, the physicians and the lab personnel.

In addition, separate courses were given (i) for lab personnel on analytical aspects, e.g. diagnostic methods, quality control measures and how to write the lab report, and (ii) for physicians on post-analytical aspects, such as the rational use of antibiotics and the development of antimicrobial resistance.

The entire implementation of appropriate microbiology took two courses (first year = basic medical microbiology and analytical methods; second year = applied and clinical microbiology) and was completed by a third course in which the lab personnel was taught on how to train other lab members as well as personnel from laboratories of other hospitals. Each course lasted around 4 weeks and was given by a physician specialized in "microbiology, virology and epidemiology of infectious diseases" and a technician with special expertise in medical microbiology. Upon successfully passing the theoretical and practical examination, the participants received a certificate.

2.3 Analytical procedures

Microbiological diagnosis was restricted to life-threatening or highly prevalent infections, such as blood-stream infections, meningitis or wound infections. This also had the advantage of not interfering significantly with the existing workload of the laboratory staff, because they should also continue to perform clinical chemistry and other laboratory techniques at high quality.

In order to keep costs low, no ready-made test kits were used. Instead, the implementation of in-house tests for the identification of bacteria was favored and the media were prepared locally in the laboratory. Media preparation was always done during day-light times and in a room with closed windows (air condition!) in order to minimize the risk of contamination by flying or crawling insects. For in-

ternal quality control, all agar plates were incubated overnight at 37°C in order to exclude contamination prior inoculation.

The following flow chart and table demonstrate the algorithms that were used to investigate *blood-stream infections* (Fig. 2) and to identify bacteria belonging either to the normal flora or to the most prevalent pathogens (Table 1). The applied basic bacteriological tests guaranteed that laboratory personnel with even lesser qualifications could easily be trained as supporting staff.

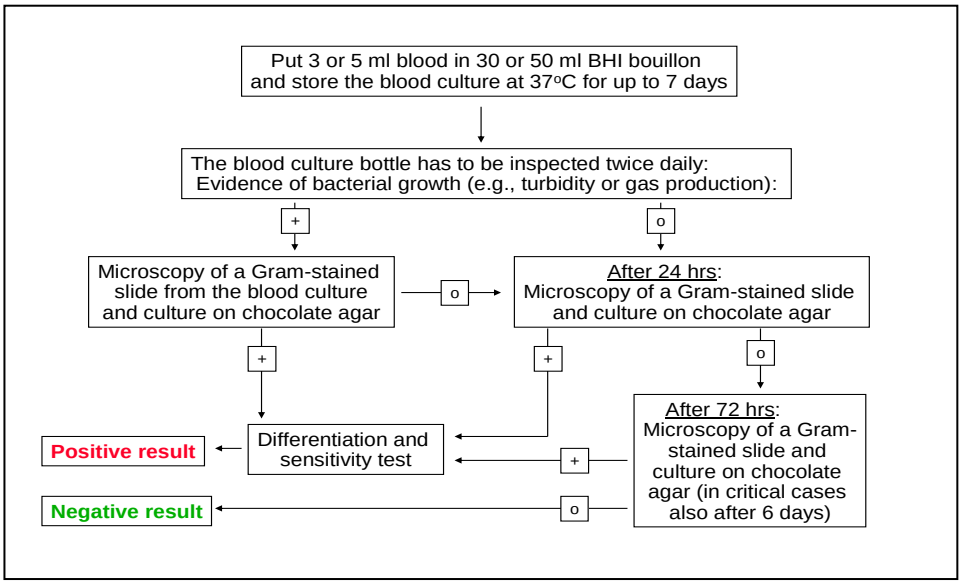


Figure 2: Algorithm for diagnosing blood-stream infections

Microscopy was done from all pre-incubated blood cultures and sediments of CSF. Depending on the microscopic result, a first report could be given to the physician in charge (see box below). That, however, had to be subsequently confirmed by the results from culture and differentiation assays.

Gram:	+ cocci in clusters	-> suspect of *Staphylococcus aureus* / *S. epidermidis*
	+ cocci in chains	-> suspect of streptococci / enterococci
	+ diplococci	-> suspect of pneumococci
	- diplococci	-> suspect of meningococci
	- rods	-> suspect of *Salmonella* Typhi, *E. coli* and others
	- rods, pleomorphic	-> suspect of *Haemophilus influenzae*

Table 1: Algorithms for bacterial differentiations in a resource-poor setting (for cost effectiveness, the microscopic diagnosis of blood culture or CSF guides the selection of subsequent agar plates; in indeterminate cases, both blood agar and McConkey agar should be used, see Table 2):

Chocolate agar	Microscopy (Gram stain)	->	Blood agar	McConkey	Differentiation tests	Result
grey colonies	- rods	->	not done (n.d.)	lactose -	oxidase - biochemical differentiation serotyping*	*Salmonella enterica*
grey colonies	- rods	->	n.d.	lactose +/-	oxidase - biochemical differentiation	Enterobacteriaceae other than Salmonella
golden colonies	+ cocci	->	golden colonies with hemolysis	n.d.	catalase + coagulase +	*Staphylococcus aureus*
white colonies	+ cocci	->	white colonies w/o hemolysis	n.d.	catalase + coagulase -	Coagulase-negative staphylococci (CNS)
flat grey colonies	- rods	->	silver - shadowed surface, aromatic smell	evtl. pigment formation	oxidase + surface growth on Kligler	*Pseudomonas spp.*
grey colonies	- diplococci	->	n.d.	n.d.	oxidase +	Meningococci
grey colonies	+ cocci in chains	->	ß hemolysis	n.d.	catalase - latex agglutination A bacitracin sensitive	*Streptococcus pyogenes*
grey colonies	+ diplococci	->	α hemolysis	n.d.	catalase - optochin sensitive	Pneumococci
grey colonies	+ cocci in chains	->	α, ß, or γ hemolysis	n.d.	latex agglutination D bile esculin + NaCl 6.5%+	Enterococci
flat grey colonies	- rods, pleomorphic	->	use *S. aureus* as wet nurse for satellite phenomenon	no growth	X-, V-, XV+	*Haemophilus influenzae*

Microbiological diagnosis of meningitis was performed from cerebrospinal fluid (CSF). Following centrifugation, the sediment was used for microscopy and culture on chocolate agar. In some cases, we observed that meningococci could not be cultivated on chocolate agar plates, when these were prepared from blood derived from human donors. Further investigations showed that inhibitory substances, most likely antibiotics, were present in the blood. Therefore, blood for preparing media plates should be drawn from sheep, which are inexpensive and should be kept for this purpose on the hospital ground or laboratory ward.

For diagnosing wound infections, swabs were taken from the suspected anatomical site and cultivated on blood agar and McConkey agar plates for at least 2 days.

In general, chocolate agar allows growth of nearly all facultative anaerobe and aerobe bacteria including meningococci and *Haemophilus influenzae* as well as fungi. The same bacteria (excluding meningococci and *Haemophilus influenza* w/o wet nurse bacteria) and fungi grow on blood agar. However, blood agar has the advantage that - if present - the type of hemolysis can be used for diagnostic purposes. Finally, McConkey agar was used as a selective media for gram-negative rods, allowing also the differentiation in lactose-positive and negative bacteria.

Biochemical differentiation of enterobacteriaceae was achieved using an in-house biochemical differentiation system that consisted of five tubes: Kligler agar (glucose, gas formation, lactose and H_2S formation), glucose bouillon, citrate, urea, and MIO (motility, indole, ornithine). If the biochemical differentiation test revealed the species *Salmonella enterica* or *Shigella spp.*, subsequent serotyping was performed using defined antisera (Table 2).

Table 2: Serotyping scheme of *Salmonella enterica* and *Shigella spp.*

	A-67	B	09	Vi		ShigI	ShigII
S. Typhimurium	+	+	o	o			
S. Enteritidis	+	o	+	o			
S. Typhi (most strains)	+	o	+/o	+			
S. Paratyphi A	+	o	o	o			
S. Paratyphi B	+	+	o	o			
S. Paratyphi C	+	o	o	+/o			
Citrobacter freundii	(+)	o	o	o			
Proteus vulgaris	(+)	(+)					
Shigella flexneri/S. sonnei						+	o
Shigella dysenteriae						o	+

2.4 External quality control

A key element of the implementation of microbiological diagnosis was the commitment of the laboratories to participate in regular external quality controls that were provided biannually by the Institute of Medical Microbiology of the University Medical Center Göttingen. These quality controls consisted of three bacterial (or yeast) species. The laboratories had to identify the correct bacteria (or had to give Candida in case of yeasts) and had to achieve the correct sensitivity test results in order to receive their certificate (Fig. 3). Our strategy to begin the pilot phase with three hospitals assured that in case that one of the participating laboratory failed twice, one of the other two laboratories could be available for refresher courses in microbiology.

Figure 3: Certificates for successful participation in external quality controls on display in one of the laboratories.

3 Microbiological investigations and results

In order to motivate the participating physicians and laboratory staff, minor epidemiological projects were initiated. These were also used to evaluate the analytical performance of the laboratories.

3.1 Bacterial colonization of the nasal mucosa

The first event of bacterial infection is the colonization of the mucosa or skin. In order to evaluate the potential risk of infection, the colonization of the nasal mucosa was investigated. For this, swabs from the nasal mucosa of 200 individuals present at the outpatient area of the St. Martin de Porres Hospital in Eikwe/Ghana were analyzed for the most prevalent bacterial species. As a comparator, 101 individuals were analyzed, who were present at a meeting of the Medical Mission Institute in Würzburg/Germany. Significant differences in the colonization of the nasal mucosa between Ghanaen and German individuals were obvious (Table 3). Whereas *Staphylococcus aureus* and CNS were found in both study populations at similar ratios, the nasal mucosa of Ghanaen individuals was significantly more often colonized with nonfermenting bacteria (including *Pseudomonas spp.*) and Enterobacteriaceae (Groß and Seeba, unpublished).

At the time the swabs were taken (2001/2002), chloramphenicol was widely used in Ghana but not in Germany anymore. In contrast, the chinolon ciprofloxacin was already available in Germany but not in Ghana at that time. As expected, the ratio of chloramphenicol-resistant enterobacteriaceae that were found on the nasal mucosa was significantly higher in Ghana than in Germany (62% versus 5%), whereas the ratio of ciprofloxacin-resistant CNS was significantly higher in Germany when compared to Ghana (20% versus 5%) (Groß and Seeba, unpublished).

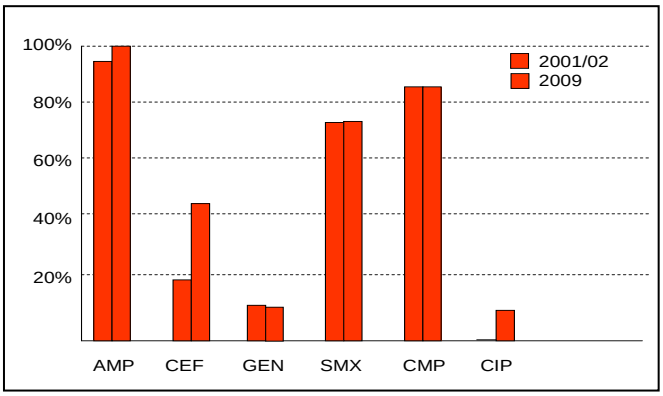
Table 3: Colonization of the nasal mucosa in German and Ghanaen individuals

Bacterial species	Individuals from **Ghana** (n = 200)	Individuals from **Germany** (n = 101)
Coagulase-negative staphylococci (CNS)	49.0% (98)	49.5% (50)
Staphylococcus aureus	17.0% (34)	15.8% (16)
Pseudomonas spp., other nonfermenters	11.5% (23) 28.5% (57)	1.0% (1) 14.9% (15)
Enterobacter spp., other Enterobacteriaceae	15.5% (31) 20.0% (40)	1.0% (1) 4.0% (4)

3.2 Blood-stream infections

The results obtained from the nasal swabs suggested that the spectrum of bacteria that colonize mucosal surfaces might have a direct impact of invasive infections. Indeed, own data from a subsequent investigation of blood cultures indicated that the ratio of Gram-negative rods causing bacterial blood-stream infection is higher in African than in German patients (37-55% versus 20-40%).

Similar to the situation of bacteria that were cultivated from the nasal mucosa, a high ratio of chloramphenicol resistance was also found in those bacteria that were isolated in Ghana in 2001/2002 from blood cultures (Zimmermann et al., 2005). Following the introduction of the chinolon ciprofloxacin in 2004 and an increased use of cefuroxime in Ghana, the rate of chloramphenicol-resistant bacteria causing blood-stream infections in 2009 did not change significantly (Groß et al., 2011). However, significantly more bacteria causing blood-stream infections were found to be resistant against cefuroxime or ciprofloxacine at this time (Fig. 4).



Abbreviations:
AMP = ampicillin,
CEF = cefuroxime,
GEN = gentamicin,
SMX=trimethoprim
-sulfamethoxazole,
CMP = chloramphenicol,
CIP = ciprofloxacin

Figure 4: Resistance rates of bacteria causing blood-stream infections in patients from the participating hospitals in 2001/02 versus 2009.

3.3 Wound infections

In contrast to Germany, wound infections are widespread in rural African settings. The reasons for this are obvious, e.g.: (i) low standard of personal hygiene, (ii) high-risk activities such as using the bush knife without protection, (iii) reduced health-seeking behaviour, and (iv) in many cases, the so-called traditional healer or herbalists is the first person to be contacted and who might provide inadequate primary care (Fig. 5). Although Enterobacteriaceae were again found to dominate in these infections, other pathogens such as *Staphylococcus aureus* or *Streptococcus pyogenes* could also be found frequently.

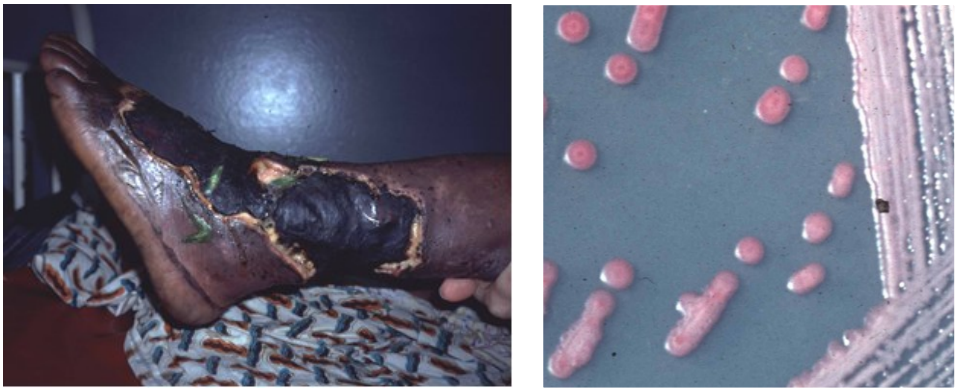


Figure 5: Infection of a large wound that was initially treated by a traditional healer with herbs and other plants as well as tar-like materials (left). Microbiological diagnosis revealed massive growth of *Klebsiella spp.* (right).

3.4 Impact of the establishment of microbiological diagnosis

Statistical data of the three pilot hospitals clearly showed positive developments since microbiological laboratories were established: (i) mortality numbers were reduced, (ii) the average hospital length of stay was significantly shortened, and (iii) the costs of antibiotics were considerably diminished. Figure 6 shows the mortality numbers in one of the hospital. Here, the average length of stay also decreased from 5.8 days in 1998 to 3.5 days in 2007.

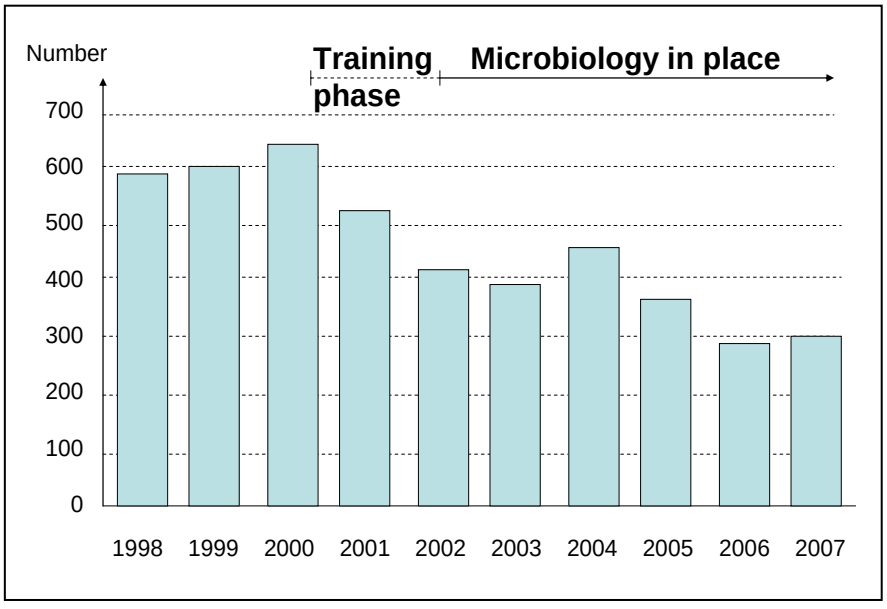


Figure 6: Data on patient mortality in one of the participating hospitals

4 Discussion

Starting as a pilot project in the year 2000, we established microbiological laboratories in three Catholic Mission hospitals in Ghana. Using the achieved laboratory competence, we analyzed the spectrum of bacteria that colonize the nasal mucosa and we performed an epidemiological survey on bacterial blood-stream infections. Thereby and in comparison to German individuals, we found a significantly higher ratio of Gram-negative rods on the nasal mucosa and in blood cultures of individuals and patients in Ghana. In line with this observation is also the finding of a previous study showing that Enterobacteriaceae contribute to a large extend to bacterial blood-stream infections in Ghana (Marks et al., 2010). Likewise, Enterobacteriaceae also dominated in Nigerian patients who suffered from septicemia (Adeyemi et al., 2010). This is in contrast to the situation in The Gambia, where grampositive cocci, especially pneumococci and *Staphylococcus aureus*, were identified as the major causes of bacterial blood-stream infections (Hill et al., 2007).

Although the distribution of pathogens that cause blood-stream infections might differ between the studies that were performed in sub-Saharan Africa, all of them confirm an alarming trend of increasing antimicrobial resistance, especially against first-line antibiotics, such as chloramphenicol that still is widely in use in sub-Saharan Africa (Adeyemi et al., 2010; Hill et al., 2007; Mandomando et al., 2010; Marks et al., 2010; Moyo et al., 2010), indicating the need to re-evaluate the current treatment guidelines. A similar trend has also been shown for bacteria isolated from other clinical materials (Yismaw et al., 2010) as well as from CSF of patients who suffered from meningitis. Here, like in Germany, *Haemophilus influenzae*, pneumococci, and meningococci are most prevalent in the respective patients in sub-Saharan Africa (Laganju et al., 2008; Roca et al., 2009).

Even in sub-Saharan Africa, microbiological diagnosis must not focus on blood-stream infections and meningitis alone. In most of the respective countries, wound infections are more prevalent than in Europe making it necessary to also monitor pathogen distribution and antimicrobial resistance rates in these cases. Again, a recent study on wound infections performed in Nigeria confirmed our findings and showed that more Gram-negative rods were isolated than any other bacterial groups (Ojo et al., 2010).

So far, most studies on epidemiology of infectious diseases caused by bacteria that have been performed in sub-Saharan Africa were from larger hospitals, mostly from university hospitals. The epidemiological situation in urban areas might differ significantly from the one in rural areas. Our program of establishing microbiological laboratories in Catholic Mission hospitals in Ghana showed that this kind of diagnosis can even be used for epidemiological studies in a resource-poor setting in rural areas. Through these, more representative data on pathogen distribution and antimicrobial resistance rates can be obtained than when only focusing on data that were obtained from a few or even a single national hospital. We therefore suggest to establishing microbiological diagnosis even in smaller hospitals in order to ob-

tain valid data that might help policy makers to re-evaluate their strategies on how to manage infectious diseases and allow them to adapt regional or national treatment guidelines.

The observation that since 2000/2001 mortality rates and the average length of stay significantly decreased in the hospitals that participated in our program indicates that the establishment of human capacity building in microbiological diagnostics in district hospitals in resource-poor settings has a positive impact on health and socioeconomics. We therefore conclude that the implementation of microbiological diagnostics in concert with regular biannual quality control measures is a valuable instrument to improve health conditions even in rural and resource-poor settings.

Finally, gaining robust data on the epidemiology of infectious diseases will help decision makers to establish strategies on how to prevent the relevant infectious diseases. Given the facts that typhoid fever was highly prevalent in our bloodstream infection study and is a water-borne disease, improvement of water canalization and sanitation systems in line with adequate educational programs are meaningful and effective control instruments (Fig. 7).

Figure 7: Improvement of water canalization and sanitation systems in the small city Assin Foso.

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20 Rapid diagnostics for resource-poor settings

Manfred Weidmann and Frank T. Hufert

1 Advances of infectious disease diagnostics and current state of the art

In the developed world laboratory diagnosis of infectious agents has developed rapidly. In serology methods experienced a leap forward with the introduction of monoclonal antibodies and the enzyme linked immunosorbant assay (ELISA), which partly lead to automation of serological testing in big commercial or governmental diagnostic centres. The cytometric bead array (CBA) is the latest development and its fluid phase kinetics produce even more clear-cut results but has not yet reached the diagnostic laboratory.

Western blots have passed through 3 generations to the currently available line assays and first steps towards chip based protein arrays. Lateral flow dipsticks are a parallel development, which combines the advantages of western blots with chromatography allowing for very short assay times which has opened the way for point-of-care testing (POC).

Similarly the arrival of b-DNA, PCR and real time PCR boosted the accuracy of molecular diagnosis of infectious agents also driving high throughput solutions in centralised diagnostic laboratories[1]. The combination of the PCR technique with microfluidic lab-on-a-chip platforms,[2] microarrays[3] or more recently oil emersion droplet systems[4] may pave the way for the next step of this development. Microarrays seemed a promising approach for diagnostics but have not met the expected hopes as only amplification-microarrays (PCR, MLPA ect.[5-7]) manage to perform in the sensitivity range required. Truly diagnostic microarrays have not yet made it

to the market and there are few publications. More recently a flurry of developments for isothermal amplification with real time fluorescent monitoring offers the possibility to use smaller affordable benchtop devices and even simpler microfluidic lab-on-a-chip solutions than for PCR[8].

2 The potential of point-of-care diagnostics

In contrast to this shiny new world of modern diagnostic laboratories the situation in developing countries is drab and complicated due to a mix of missing basic infrastructure, training and experience. In fact transferring the current state of the art diagnostics to this setting would be too costly and probably fraught with failure at many levels right from the start. So how could the possibilities of the new methods be used to meet the requirements of diagnostics in resource poor settings?

In the developed world current diagnostic laboratories depend on delicate instruments, well trained staff, a stable supply of electricity and a reliable cold chain for reagents. Here point-of-care (POC) testing could help to optimize diagnostics at the GPs office or at centralized laboratories by improving the turn around time for results, and is perceived as a means towards a personalized medicine strategy, providing specialized point-of-care tests (POCT) all day all week.

In developing countries the low amount of benchtop gadgetry available, too tends to be centralised but is therefore less accessible and the capacity on site is usually overwhelmed by the amount of sample input.

The situation is additionally aggravated by the conditions of sample transport, which needs to be paid for, organised (or rather improvised) to cover long distances, leading to improper transport conditions (cooling, UV exposure) and eventually unreliable results due the state the samples are in when finally subjected to testing. Backflow of results is often very late leading to patients lost to follow-up.

In summary, whereas point-of-care diagnostics in the developed world is conceived as a new market for economically sound diagnostic concepts in the increasingly expensive health care systems, point-of-care diagnostics in the developing world could basically help to supply affordable accurate medical treatment to a much bigger population than hitherto possible[9-11].

3 Introduction of first generation POCT

Due to the lack of available timely diagnostics and out of sheer necessity a policy of syndromic treatment has prevailed e.g. for malaria, tuberculosis and other diseases during the last decades. This however has lead to widespread overtreatment, which is a waste of resources, causes morbidity and mortality e.g. in patients treated for malaria instead for bacterial infections, and in the case of antibiotics and anti-malarials is conducive to the generation of resistances.

The first wave of POCT introduced in the last decade basically consisted of immunological assays like agglutination assays, optical immunoassays, lateral flow assays. Many turned out to be less sensitive and specific than laboratory based assays. A good example in the developed world are the POC antigen detection assays for Influenza A virus which show very poor performance[12].

In the developing world many of the first wave immunological POCT showed low sensitivity and specificity. Nevertheless the wide spread use of POCT confirmed that for example most malaria treated children don't have malaria and actually suffer from bacterial infections causing high mortality due to inappropriate or no treatment[9, 13].

The first generation POCT also showed weaknesses in the stability of components and in handling and results were partly shown to depend on the handling skill of the operator [14]. This has lead to the impression that as a rule POCT might be less efficient and error prone when handled by non-laboratory staff.

Cost-effectiveness studies however indicate that the use of POCTs for a particular disease may indeed reduce costs in high prevalence areas by improving accurate treatment and reducing overtreatment whereas in low prevalence areas they may increase costs[10, 15]. The first lesson therefore is that POCT need to be adapted to the local health situation.

4 Specifications of next generation POCT

Successsful POCT need to be implemented in handheld or small mobile benchtop devices that have to be resistant to heat and humidity and are maximally driven by small batteries as currently used for mobile phones. Electrical wire taping to maintain mobile phone charge is a widespread skill.

The design of the sampling procedure needs to meet several requirements. Sampling time should be brief and feasible with minimal invasiveness (ideally a finger or earlobe prick), it should be biosafe to avoid infections and it should have an identification system allowing for sample identification and sample management.

Sample preparation i.e. concentration, purification and extraction of the infectious agent for nucleic acid or antigen assays, or separation of plasma and/or serum for serological assays should be integrated and require no extra skills from the operator.

In a two components approach with a disposable cartridge for sample preparation and assay biochemistry (less than 25$) plus handheld or portable reader for detection and reporting, widespread use by non specialized staff could be feasible and would obliterate the inefficiencies of few centralized laboratories as described above[11]. Disposable units would also contain potential infectious material and allow for biosafe waste treatment.

Small sample volumes however means that the detection methods need to be highly sensitive which points towards nucleic acid detection. The superiority of nucleic acid detection over serology has been described and discussed in many instances[16].

POCT need to be rapid not only because of economic constraints but essentially because of concerns of patient care. Due to regionally very poor medical infrastructure people will travel or basically walk for very long distances in search for medical help for children, themselves or relatives. Good medical anamnesis and reliable rapid tests offer the possibility to suspect, confirm and possibly treat infectious disease on the same day, literally before the patients walk home again. Decision time for treatment is also critical since many patients in developing countries present themselves in an advanced stage of disease and in life threatening sepsis the critical time window for appropriate treatment may be as small as 6 hours. Speed is also imperative for viral diseases since the peak of viraemia may be on the downswing at the time of presentation and only just detectable by nucleic acid or antigen assays.

Ideally POC system should be able to perform syndromic multiplexing since it would help to reduce costs by addressing differentials. Finally an automatic reporting system for more sophisticated sample management and epidemiological surveillance and analysis at a centralised base could be possible via mobile phone technology.

All of this has already been laid down in the ASSURED criteria (Affordable, Sensitive, Specific, User-friendly, Rapid, Equipment free, Delivered to those in need) which are the current specification lead for POCT[17].

The necessity for such a concept has been demonstrated by the first wave of serological POCT which due to their lack of sensitivity and specificity actually have created suspicion concerning their accuracy and consequently reduced trust in obtained results. One of the measures taken by the WHO to solve this situation was the creation of the Diagnostic Expert Evaluation Panel at the WHO-TDR (DEEP). Here evaluation results of POCT can be reviewed and recommendations on additional validation offered to POCT developers. Unfortunately currently the continued funding of DEEP is unclear and it can be only hoped that this very important review board will be maintained.

The next generation devices need to be more easy and cheaper to implement and maintain while providing the same level of accuracy and reproducibility, sensitivity and specificity required for a diagnostic assay. Only the introduction of well-evaluated POCT into the health care setting of developing countries would basically jump the current level of instrumentation and infrastructure common in the laboratories of the developed world[9, 11].

Finally these devices could also help to increase the level of identification and monitoring of several sexually transmitted and blood borne diseases if useable by visiting doctors to facilitate home testing.

Simply publically going to a certain laboratory which is known e.g. to perform Hepatitis B testing may cause social isolation since cultural and religious and / or ethical concepts are quite disparate from the practices in the developed world.

5 Minaturising molecular diagnostic assays

Since the introduction of molecular diagnostics ample proof of its sensitivity and specificity has been generated. Indeed partly molecular diagnostics are deemed superior to bacterial culture techniques or serological diagnostics[16, 18, 19]. Some authors have even opted for entirely eliminating the old methods to streamline centralised laboratories for molecular diagnostics [1, 20, 21].

In particular PCR has been very successful and therefore many approaches to miniaturisation have tried to include PCR in micro total analysis system (μTAS), micro–electro-mechanical-system (MEMS) and lab on a chip (LOC) platforms.

On-chip PCR by using either electrophoresis, hybridisation (microarray), fluorescence or electrochemical readout, have been explored. The challenges encountered are the choice of low cost thermoplastic polymeric materials used for fabrication such as polymethlymethacrylate (PMMA), polystyrene (PS), polycarbonate (PC), cyclic olefin copolymer (COC) and the inert and non-toxic polydimethylsiloxane (PDMS), which is also thermal stable and has very good optical characteristics. Apart from soft lithography (PDMA), injection molding, lot embossing, laser ablation (PMMA, PC), and blister packaging technology using thin films have been used[22].

In all cases however a major obstacle is the increase of the surface to volume ratio inherent in the miniaturisation of cavities, leading to unspecific adsorption and depletion of enzymes from the reaction mixture and subsequent loss of reaction efficiency, and to impediment of actuation of the fluids in the microdevices. Therefore a lot of attention and detail is paid to structuring and coating the surface of the channels and chambers in the micro devices.

The three temperature cycles needed for PCR demand quite some engineering and are either provided by heating reaction chambers or by meandering the reaction volume in a continuous flow through fixed temperature fields. Use of microfabricated thin film heaters, metal blocks or peltier elements for direct heating have achieved impressive results with very fast cycling. Infrared, laser or microwave assisted indirect heating may be slower but might make less elaborately engineered devices possible. The combination with the latest developments of droplet based PCR seem promising.

The flurry of activity in this field has however not yet provided a complete integrated device dealing with all steps from sample entry to test result. Bulky accessory devices to maintain actuation via gas or mechanics are in many cases still far from the disposable cartridge and battery driven handheld or mobile benchtop device.

Altenative several isothermal amplification methods that have been developed in the recent decade include T7 promotor driven amplifcations (TMA, NASBA, SPIA) strand displacement methods (SDA, LAMP, SmartAmp), helicase dependent amplification (HDA), recombinase polymerase amplification (RPA) and several rolling circle amplification (RCA) methods[23-27].

Most fluorescent formats for isothermal amplification use non-specific intercalating fluorophores or fluorescent primers (LAMP, SDA, HDA, RCA). For specific detection probe formats have been developed for NASBA, RCA, HDA, and RCA[28-32].

In contrast to PCR the reaction kinetics of these methods are not marred by ramping rates as ramping is not necessary which in turn makes minaturisation more easy from the engineering side than for PCR since rapid heating and cooling is simply not required. The only constraints given are the enzyme activity rates and indeed some of the isothermal methods show very fast reaction kinetics of below 10 minutes run time down to the limit of sensitivity. Miniaturisation efforts for NASBA, LAMP, HDA, SDA, RCA and RPA have recently been reviewed[8]. In principle the low temperature isothermal method such as SDA, NASBA, RCA and RPA show an advantage for minaturisation as they need much less energy input and are therefore much better candidates for battery driven handheld devices than high temperature isothermal reactions (LAMP, SmartAmp, HDA).

At present there are only few real 'sample in – result out' systems and hardly any have reached clinical evaluation. An interesting approach is the use of centrifugational LabDisks as described for RPA[33]. This type of cartridge could come close to the requirements for simple benchtop devices formulated above if sample preparation were included. It would come closest to a lab on a cartridge in contrast to the majority of systems for miniaturized molecular assays currently developed which have aptly been described as 'chip in lab' rather than 'lab on chip' platforms[8].

The current efforts for the development of POCT system need to be considered in the light of feasibility and sensibility. The developments have reached a stage were real 'sample in – result out' systems applicable in the clinical setting are beginning to look feasible in the upcoming decade, however POCT systems will only be successful in both the industrialised and the developing world if the assays implemented reflect the health needs or in another word make sense. The key words are differential diagnostics and syndromic assay panels.

Indeed the most pressing needs for diagnostics in the developing world have been identified for prenatal care, HIV, sexually transmitted diseases and neglected tropical diseases[9, 11]. As pointed out previously POCT could also help to improve diagnostics in the developed world and this is particularly the case for respiratory tract infections. A recent Dutch study shows that current laboratory based PCR diagnostics for respiratory diseases are of no avail as to clinical outcome whether there is immediate or delayed reporting of results to the GP [34]. This strongly indicates that if at all, molecular diagnostic POCTs need to be possible on site at the

presentation of the patient in order to reduce overprescription of antibiotics. In contrast, in developing countries POCT for respiratory infections would make indicated antibiotic treatment at all possible.

However developed platforms need to be flexible as distinct panels e.g for encephalitis causing agents may be needed for Europe, Asia, Africa or the two Americas due to the regional occurrence pattern of the agents implied.

6 Conclusion

Improving health will help economies of developing countries to pick up speed[35],[36]. One way of improving health is to provide infectious disease diagnostics to a larger population by jumping the current state of laboratory techniques and providing them in next generation POCT devices into a basically non-existing laboratory infrastructure lacking resources and trained staff.

The current speed of the development of POCT at all levels currently is still driven by a microsystem engineer's point of view with an emphasis on feasibility. Strategy and design of research consortia that assemble to develop platforms that may be eligible for marketing are all to often influenced by companies participating in these consortia which naturally have an eye on the profitable markets in the developed world where POCT are seen as a means to streamline and optimise current diagnostics.

The ASSURED criteria have however not been developed to mainly boost these developments but rather the development of POC diagnostics for a much larger market in the developing world. New POCT platforms will only be successful if they provide sensible concepts to answer diagnostic questions. Therefore development strategies and design of new POCT need to be developed in close partnership with clinicians from the developing world to improve acceptance and trust into and eventually the success of POCT.

Sensible syndromic or differential panels used on a large scale will help to levy the epidemiological data that are missing from many countries, therefore result data flow and analysis will develop into an important feature of POC testing.

Example of resource poor laboratories in a health station without electricity in South-East Senegal (left) and a better equipped laboratory of a primary health care centre in West India (right).

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21 Urinary tract infections in Tanzania: diagnosis, pathogens and susceptibility pattern

Stephen E. Mshana

1 Introduction

Tanzania is one of the sub-Saharan African countries most affected by bacterial infectious diseases. Communicable diseases dominate the pattern of overall morbidity and contribute to over 49% of the total burden of diseases [1]. Irrational drug use as well as the presence of counterfeit drugs on the local market has been shown to be the main factors in the emergence of multi drug resistance (MDR) bacteria. Worldwide, more than 50% of all medicines are prescribed, dispensed or sold inappropriately, and 50% of all patients fail to take them correctly [2]. As a consequence, the prevalence of antimicrobial resistances is an emerging threat, with resistances of up to 70-90% to original first-line antibiotics [2].

In Tanzania, high prevalence of nosocomial infections caused by *Klebsiella pneumonia*, *Escherichia coli* and *Staphylococcus aureus* has been reported in tertiary hospitals affecting many departments especially, Intensive Care Unit (ICU), post-operative, burned, and pediatric patients [3, 4, 5]. Studies in Tanzania have documented a high prevalence of ESBL in tertiary hospitals. Prevalence of ESBL at the Muhimbili National Hospital (MNH) is about 40% [6]. At the Bugando Medical Centre (BMC), prevalence is 25% for *Escherichia coli* and 50% for *Klebsiella pneumonia* [4].

The absence of a national survey for antibiotics resistance patterns in Tanzania and lack of routine culture to diagnose infections may underscore the magnitude of the multi drug resistant bacterial infections and its morbidity Tanzania. In this review

we present in summary the diagnosis, pathogens and susceptibility pattern of common isolates involved in urinary tract infection in Tanzania.

2 Epidemiology of urinary tract infections in Tanzania

Urinary tract infections with its diverse clinical syndrome and affected host groups, remains one of the most common but widely misunderstood and challenging infectious diseases encountered in clinical practice. Urinary tract infection (UTI) is a common and important clinical problem in most health facilities in Tanzania [1]. Urinary tract infections may complicate to renal scarring, hypertension and end stage renal diseases [7].

UTI is a common problem among children and pregnant women in Tanzania [3, 8, 9, 10]. Other special groups like diabetic women have been found to suffer UTI significantly [11]. In 1992 among 164 children with severe malnutrition UTI was the commonest infection [12]. Recently at Bugando Medical Centre the prevalence of UTI among febrile children has been found to be 39.7% [9], while at Makongoro clinic-Mwanza, the prevalence of UTI among febrile children is about 20.3% [10]. As describe in previous studies, in these two studies [9, 10] female children were significantly more affected than male children [7]. The prevalence of UTI among pregnant women in Tanzania varies from one region of the country to another; it was observed to be 13% among women attending Bugando Medical Centre Mwanza [8], while at Muhimbili National Hospital in Dar es Salaam the prevalence observed was 21% [3]. UTI is responsible for majority of infectious diseases seen at Bugando Medical Centre; out of 389 urine specimens processed between July and August 2008; 38.8% were found to have significant bacteriuria i.e. >105CFU/ml. Large proportion of infections occurred among children below 10 years [13]. Other special groups like diabetic women have been found to suffer from UTI significantly in Tanzania [11]. Asymptomatic bacteriuria has been observed in 13.4% of diabetic women in Dar es Salaam [11]. *Table 1*

Different factors have been found to be associated with UTI in children; prolonged fever, diarrhea, female sex and age below 2 years have been found to be risk factors of UTI in children [9]. Other parameters found to predict significant bacteriuria are positive nitrite test and positive white blood cells in urine [9, 13]. In pregnant women, no significant factors have been found to be associated with bacteriuria among pregnant women [3, 5]. In diabetic women, age above 50 years and glucosuria were significantly found to predict UTI, while level of education, blood glucose level and BMI were not associated with significant bacteriuria [11].

3 Sensitivity of urinalysis in the diagnosis of UTI in Tanzania

Urinalysis either microscopy or using dip stick is the commonest test used to diagnose UTI in Tanzania. Routine urine culture is done in few centers in Tanzania, mainly in referral hospitals, few regional hospitals and few private hospitals. The sensitivity of urinalysis in the diagnosis of UTI was found to range from 29.7 to 58% with specificity of 86-92% [8, 9, 11, 13]. This poses challenges in many settings in Tanzania were these methods are used to diagnose UTI. Large number of false negative children and pregnant women will lead to UTI associated complications among Tanzanian children and pregnant women.

4 Pathogens associated with UTI in Tanzania

Various pathogens have been found to be involved in UTI in Tanzania. In the study by Isaac et al 1992 [12], which involved malnourished children admitted at Muhimbili Hospital the common pathogen from urine was *Escherichia coli* followed by *Klebsiella pneumoniae*. In the same hospital between June 2003 to July 2004 *Escherichia coli* and *Klebsiella pneumoniae* contributed to 44.75% and 33.0% of the total 400 isolates obtained from urine specimens [16]. Among pregnant women between January 2007 and December 2009 at Muhimbili National hospital, *Escherichia coli* were the commonest pathogen causing significant bacteriuria in pregnant women, followed by *Klebsiella spp* [3].

Similar observations were observed in Bugando Medical Centre; between July and August 2008; of 151 pathogens isolated from urine specimens 60% were *Escherichia coli* followed by *Klebsiella pneumoniae* which contributed to 24%. Gram positive bacteria were found only in 4% of the total isolates [15]. At Bugando Medical Centre out of 36 isolates from 247 pregnant women 47.2% were *Escherichia coli*, followed by *Enterococcus spp* 8/36 [8]. *Escherichia coli* also was found to be the commonest isolate causing UTI in children at Bugando Medical centre; of 147 isolates 43.5% and 35.4% of isolates were *Escherichia coli* and *Klebsiella pneumoniae* respectively [9]. *Escherichia coli* (16/41) were also found to be the commonest isolates at Makongoro Clinic, in Mwanza city [10].

In summary, of 1241 isolates from urine specimens in Tanzania, *Escherichia coli* contributed 46.7% while *Klebsiella spp* contributed 31.1% o total isolates; therefore more than 77% of isolates from urine specimens are gram negative enteric bacteria. *Table 1*

5 Susceptibility of Escherichia coli and Klebsiella spp from urine specimens

There is an increase trend of these isolates to become resistant to commonly used antibiotics in Tanzania. In 1995-1996, 17.4% of *Escherichia coli* from Northern rural Tanzania were resistant to ampicillin [15]; in the same study 4.3% of *Escherichia coli* were resistant to nitrofurantoin. In 2003 at Muhimbili it was found that 92% (165/179) of *Escherichia coli* were resistant to ampicillin, similar resistance pattern was observed at Bugando Medical Centre whereby more than 92.7% of *Escherichia coli* isolates from urine specimens were found to be resistant to ampicillin [9]. The resistance of *Escherichia coli* to amoxicillin/clavulanate in Tanzania ranges from 37.5% among diabetic women in Muhimbili to more than 85% among children at Bugando Medical centre [9, 11]. In *Escherichia coli*, the rate of gentamicin resistance ranges from 6.9% at Muhimbili in 2003 to more than 44% in the same hospital in 2011 [11, 14]. At Bugando Medical Centre the gentamicin resistance ranges from 5.9% among pregnant women to 21.9% among febrile children [8, 9]. The resistance of *Escherichia coli* to SXT has been found to range from 50% in diabetic women to 97% among children from community at Ma-kongoro Clinic in Mwanza city. *Escherichia coli* were found to be more susceptible to ciprofloxacin with resistance rate between 8.1%-30.4% [9, 11]. At Bugando the rate of resistance of *Escherichia coli* to ceftriaxone was observed to range from 14% to 29.4% [8, 9] while at Muhimbili 50% of *Escherichia coli* from urine specimens were resistance to cefotaxime in 2008 [6]. In all studies higher resistance rates to common antibiotics were observed among *Klebsiella spp* isolates. *Table 2*

6 Conclusion

UTI is the commonest cause of fever among children and women in Tanzania and is caused by multi drug resistant *Escherichia coli* and *Klebsiella spp*. Due to low sensitivity of urinalysis in the diagnosis of UTI, urine culture should be routinely performed to diagnose UTI in febrile children and pregnant. Continuous surveillance of *Escherichia coli* and *Klebsiella spp* from urine specimens to monitor susceptibility pattern is urgently needed in Tanzania and other developing countries in Africa.

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Table 1: Common pathogens causing Urinary tract infection in Tanzania from 1992-2011

Years	Place	Population	Escherichia coli	Klebsiella sp	Staphylococcus aureus	Enterococcus spp	References
1992	Muhimbili	Malnourished children	*N	*N	*N	*N	**12**
2003-2004	Muhimbili	Adult and Children	179/400	132/400	15/400	-	**14**
2007-2009	Muhimbili	Pregnant women (200)	14/42	9/42	6/42	3/42	**3**
2010	Muhimbili	Adult and Children	138/270	132	NA	NA	**6**
1995-1996	Hydom Lutheran Hospital	Pregnant women (541)	27/107	4/107	2/107	15/107	**15**
2008	Bugando	Adult and Children (389)	91/151	37/151	2/151	4/151	**13**
2008	Bugando	Pregnant women (247)	17/36	2/36	-	8/36	**8**
2011	Bugando	Febrile Children (370)	64/147	52/147	4/147	8/147	**9**
2011	Makongoro clinic-Mwanza	Febrile children (231)	34/47	10/47	-	-	**10**
2011	Muhimbili	Diabetic women (300)	16/41	9/41	2/41	1/41	**11**

***Not shown**

Table 2: Resistance pattern of *Escherichia coli* and *Klebsiella spp* from Urine specimens to common antibiotics

Years	Place	Population	*AMP*	*SXT*	*AMC*	CN	CIP	F	CRO	CAZ	*Ref*
1992	Muhimbili	Malnourished children	*N								
2003-2004	Muhimbili	Adult and Children									
	Escherichia coli (179)		165 (92%)		95 (53%)	12(6.9%)	16(8.1%)	-	-	-	***14***
	Klebsiella sp										
2007-2009	Muhimbili	Pregnant women (200)									
	Escherichia coli										
	Klebsiella sp										
2010	Muhimbili	Adult and Children									
	Escherichia coli (138)		133(96%)	111(80%)	96 (70%)	53(38%)	42(30%)	31(23%)	70(51%)	68(50%)	***6***
	Klebsiella sp(132)		130 (98%)	107(83%)	103 (78%)	38 (28%)	25(19%)	24(18%)	87 (66%)	-	
1995-1996	Hydom Lutheran Hospital	Pregnant women (541)									
	Escherichia coli (23)		4 (17%)	-	-	-	-	1 (4.3%)	-	-	
2008	Bugando	Adult and Children (389)									***13***
	Escherichia coli (134)		ND	ND	ND	ND	ND	ND	ND	ND	

Table 2: Resistance pattern of *Escherichia coli* and *Klebsiella spp* from Urine specimens to common antibiotics

Year	*Place*	Popula-tion	AMP	SXT	AMC	CN	CIP	F	CRO	CAZ	*Ref*
	Klebsiella sp (52)		ND	ND	ND	ND	ND	ND	ND	ND	
2008	Bugando	Pregnant women (247)									***8***
	Escherichia coli (17)		9 (53%)	11 (64.7%)		1 (5.9%)		1 (5.9%)	5 (29%)		
	Klebsiella sp		100%	50%		50%		-	100%		
2011	Bugando	Febrile Children (370)									
	Escherichia coli (134)		131 (98%)	127 (95%)	117 (88%)	29 (23%)	16 (12%)	17 (13%)	19 (14%)	15 (11%)	***9***
	Klebsiella sp (52)		52 (100%)	49 (95.3%)	45 (86.5%)	20 (38.5%)	10 (19%)	11 (21%)	24 (460)	17 (33%)	
2011	Makongoro clinic-Mwanza	Febrile children (231)									***10***
	Escherichia coli (34)		34 (100%)	33 (97%)	29 (85%)	11 (32%)	3 (8.8%)		9 (26.5%)	5 (14.5%)	
	Klebsiella sp (10)										
2011	Muhimbili	Diabetic women (300)									***11***
	Escherichia coli (16)		11 (69%)	8 (50%)	6 (37%)	7 (44%)	2 (13%)	5 (31%)	3 (19%)	-	
	Klebsiella sp(9)		5(56%)	5 (56%)	1 (11%)	1 (11%)	4 (44%)	2 (22%)	3 (33%)	-	

Ampicillin (AMP), Sulphamethaxazole/Trimethoprim (SXT), Amoxicillin/clavulanate (AMC), Gentamicin (CN), Ciprofloxacin (CIP), Nitrofurantoin(F), Ceftriaxone (CRO), Ceftazidime (CAZ), Not done (ND)

22 Rapid screening and mapping of urinary schistosomiasis prevalence at the village scale in the Sourou Valley, Burkina Faso: Adapting the school-base questionnaire method

Issouf Traoré, Ali Sié, Boubacar Coulibaly, Maurice Yé, Daniel Karthe and Martin Kappas

Abstract

Urinary Schistosomiasis which is responsible for the largest proportion of schistosomiasis infection remains largely unstudied in Burkina Faso. This fieldwork was initiated to bridge the paucity of epidemiological data on urinary schistosomiasis and to set up a database with more recent cases at a fine local village by village scale for 29 villages in Sourou Valley. The school based questionnaire method was adapted to the academic research context to rapidly screen and map the prevalence of the disease in 22 primary schools all located in the Sourou Valley.

Results showed that the questionnaire approach was applicable to 79% of the villages (23/29), and the method was not extendable to 21% (6/29) of the villages. Reported blood in urine rates varied between 10.62% and 100%, with 30.14% as global prevalence rate for the 23 villages. Results also showed that boys reported more urinary schistosomiasis symptom than girls did: 33.83% vs. 26.33% (OR= 1.26, $p < 0.001$). Peaks of prevalence rates depended on children age (R2= 0.156, p= 0.162); 13 years for boys (42.70%), 9 for girls (30.67%) and 11 years for all ages (35.04%). The questionnaire sensitivity and specificity were 65% (95% CI= 44 – 86) and 55% (95% CI= 46 – 64) respectively.

Keywords
Urinary schistosomiasis/illness – prevalence determination – self-report questionnaire – primary schools – mapping – Sourou Valley – Burkina Faso.

1 Introduction

Compared to the rest of the world, the burden due to schistosomiasis (also bilharziasis) is an issue of growing public health concern in sub-Saharan Africa (SSA), where 97% of the globally 201.5 million infection cases were estimated to occur with about 150,000 deaths yearly (Engels et al., 2002, Van der Werf et al., 2003; Gryseels et al. 2006; Utzinger et al., 2009; Hotez & Kamath, 2009). Because of their adverse effects on child cognitive development, pregnancy outcome, and agricultural worker productivity, schistosomiasis together with other neglected tropical diseases (NTDs) represent a major reason why the "bottom 500 million" people in SSA cannot escape poverty (Hotez et al., 2008; Hotez & Kamath, 2009; Savioli et al., 2009).

Despite this alarming picture, insufficient resources have been allocated for research and control since schistosomiasis was firmly placed back on the international health agenda by the World Health Assembly Resolution 54.19 in 2001 (Utzinger et al., 2009; Savioli et al., 2009). Therefore, schistosomiasis (and many other NTDs) became the forgotten disease of forgotten people largely confined to the rural areas of the developing countries (Hotez, 2007; 2009; Hotez & kamath, 2009). As a consequence, urinary schistosomiasis which is responsible for the largest proportion of schistosomiasis infection remains largely unstudied and not well documented, particularly in Burkina Faso with more than 2 million reported haematuria cases associated with *Schistosoma haematobium* infections (Poda, 1996; Van der Werf et al., 2003; Garba et al., 2006; Koukounari et al., 2007; Schur et al., 2011).

While trying to study geographical determinants of human schistosomiasis transmission in Sourou Valley, Burkina Faso we encountered a scarcity of epidemiological data across the country in general and at the community by community level like in Sourou Valley in particular. Hence, this fieldwork was initiated to bridge the paucity of epidemiological data on urinary schistosomiasis and to set up a database with more recent data at a fine local village by village scale in Sourou Valley. For two reasons, past studies were found to be of little help. Parasitological studies had been carried out in a very limited number of villages (manly irrigation sites) located on the east bank of the Sourou River. Series of MDA with praziquantel done throughout those studies and by the national control program (PNLSc) have introduced changes in the disease prevalence in the local community (Poda et al., 2001; Poda et al., 2004; Poda et al., 2006; Koukounari et al., 2007; Touré et al,. 2008; Clements et al., 2008; Koukounari et al., 2011). The question

was how to fulfill this urinary schistosomiasis prevalence data gathering mission, village by village, in a context of very limited resources?

Numerous researchers were probably looking for a way to overcome the scarcity of schistosomiasis prevalence data, but we owe to Lengeler and colleagues, who were the firsts to work out an inexpensive and simple tool, a school-based questionnaire used to detect urinary schistosomiasis prevalence (Lengeler et al., 1991a, b). The questionnaire method is based on the reported blood in urine, since it is not a symptom of other common diseases in children. The health state of an individual is the resultant of a complex multifactor system and healthy/illness status is an eminently variable appreciation (Amat-Roze, 1998). The BU associated with *S. haematobium* is too habitual in endemic areas that it is easily perceived individually and collectively (Amat-Roze, 1998; Lengeler et al., 2002; Poda et al., 2006). This humanistic approach, in a health context, sees people as continually engaged in the construction of health/illness knowledge (Stainton, 1991, cited Gatrell, 2002, p. 32). Consequently the views of ordinary people, even referred to as "subjective" or "lay", have as much status as those of the health professionals (Gatrell, 2002). It has been well established that the presence of blood in urine is a reliable, indirect indicator of infection. The questionnaire method has been extensively replicated and successfully validated in different geographical settings throughout SSA such as in Cameroon, Côte d'Ivoire, Malawi, Nigeria, Congo, R.D. Congo, Tanzania, Zambia, and Zimbabwe (Ansell et al., 1997; Guyatt et al., 1999; Lengeler et al., 2002; Brooker et al., 2009). Indeed, the World Health Organization (WHO, 1995) recognized this approach as standard in rapid identification of schools with high prevalence for warranting mass drug administration (MDA) with praziquantel.

Primary schools are ideal for schistosomiasis prevalence rates determination for four reasons: 1) schools are accessible and receptive; 2) the highest prevalence levels of urinary schistosomiasis infection are found among school-age children; 3) data collected in this age range may be used to evaluate not only if schistosomiasis threatens the health of school-aged children, but also if there is need for intervention in the community as a whole; 4) children in intermediate grades (generally between ages 9–12) allow for the accompaniment of treatment impact over one to two years, before they leave school (Savioli et al., 2005, cited Koukounari et al., 2011, p. 11).

Initially designed for control strategy development purpose (WHO, 1995), the questionnaire approach has been used in the present study within a framework of academic research. Also, the questionnaire has been adapted to the particular situation of Sourou Valley and focuses on symptoms aiming to identify high-risk community, rather than infected individuals. Therefore outcomes of the present study have to be interpreted with caution.

2 Materials and methods

2.1 Study area

The present study was undertaken in the Sourou Valley, north-western Burkina Faso – a land-locked country. The study area is marked by a tropical savanna with an intercalation of two seasons, a long dry season and a contrasting short raining season (June-September). The daily temperatures vary between 11-45° C. The mean annual precipitation is 675mm (1980-2010). The Sourou Valley, home of anthropogenic and demographic changes, remains one of the most important wetlands in the country. Centered on the Sourou River (main water flow in the study area) that flows north to south (about 65 km) and becomes a tributary of Mouhoun River (the most important and permanent water flow in the country), the area meets potentialities for hydro-agricultural development, which first attempt dated roughly back to 1950s by the colonizers. The irrigation project took off veritably in 1984 through a radical hydrological modification. The natural flow of the Mouhoun River was modified using a canal that forced it to pour the totality of its water into the Sourou River. The back flow of the water from the Sourou into the Mouhoun was controlled using vanes installed near the confluence (GIRE, 2001; Bethemont et al., 2003; Legare, 2003). Once the water was sufficiently available for irrigation, series of hydro-agricultural development projects have been carried out. Following this development, the local government, via the Sourou Valley Management Authority (AMVS), had organized farmers' immigration. Irrigation projects have helped to give pieces of lands and resettled thousands of families recruited across the whole country (GIRE, 2001; Legare, 2003; Cissé, 1999). Fishing remains the principal professional activity for men in traditional villages, while growing irrigated rice and other garden products is the essential professional occupation in agricultural villages (Guièdougou, Débé, Niassan). The Sourou River, as well as irrigation canals and ponds are mostly used by women to accomplish domestic tasks and favour recreational swimming activities particularly among school-age children.

Administratively, Sourou Valley belongs to the region of Boucle du Mouhoun divided in six provinces: Balé, Banwa, Kossi, Mouhoun (the region capital), Sourou and Nayala (see Figure 1). Locally Sourou Valley is mainly shared by Kossi and Sourou provinces, and Nayala for a small piece. Each province is divided into urban and rural communes. At the communal level, five rural communes share the Sourou Valley: Barani (47,991 inhabitants) and Sono (7,317) on the western bank; Di (23,864), Lanfièra (18,817) and Gassan (37,873) on the eastern bank (INSD, 2009). Rural communes are composed of villages with or without school. School

(DEP, 2011). Primary school attendance net rate varied according to gender. Both boys and girls proportions are high in Sourou compared to Kossi at the provincial level.

Table 1: Schooling net rates (%) at the provincial, regional and national levels

	Schooling net rate (%)		
Level	**Boys**	**Girls**	**Total**
Kossi	**55**	**53.2**	**54.1**
Sourou	**71.2**	**68.2**	**69.7**
Boucle du Mouhoun Region	**63.4**	**61.1**	**62.3**
National	**65.1**	**60.9**	**63.1**

2.2 Schools sampling

Figure1 shows our area of interest (AOI) which encompasses 30 villages which were selected based on a distance criterion fixed to 6 km from the main water flow. A total of 23 primary schools are found within this AOI, but 22 located in 18 villages were investigated (see Table 2). Di, Guièdougou, Gouran and Niassan are localities with two separate schools each ("A" & "B") at the time of the survey. All classes in each school were enrolled (N= 89). A total of 6,918 pupils were sampled (51% boys and 49% girls). The overall sex ratio was 1 and the mean size per class room was 78 pupils. Each school is under the responsibility of a headteacher. The sampled schools belong to four primary education districts with each having an inspector as the head. Provincial directions of primary school of Kossi and Sourou occupy the upper level in the primary education structure at the provincial scale. Further high ranks in the administrative structure are the regional direction at the Boucle du Mouhoun Region level and the ministry at the national level.

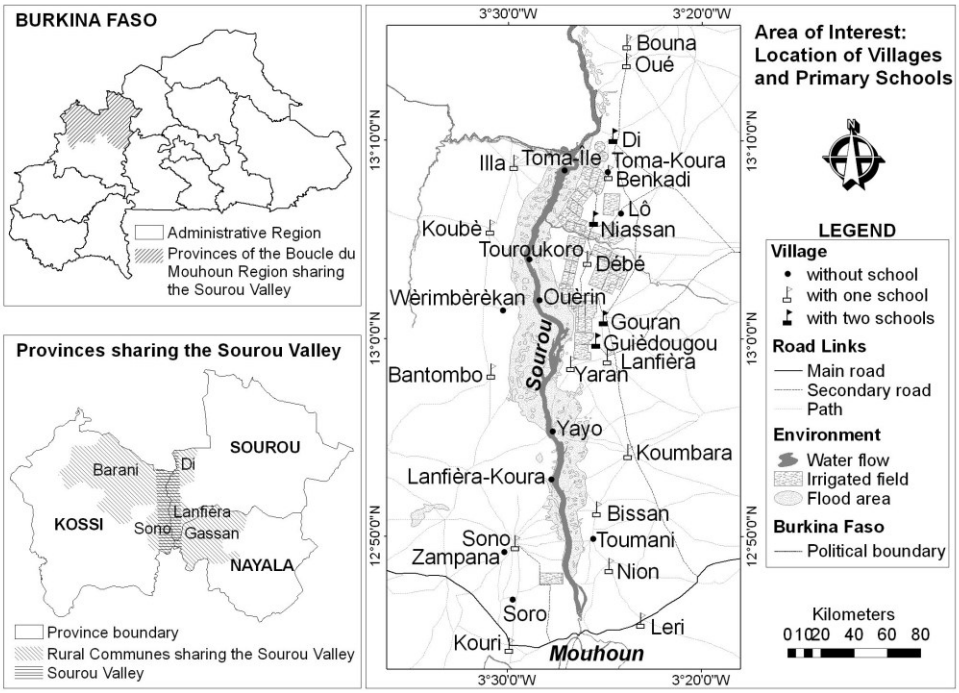

Figure 1: Map of the AOI showing villages and schools location

Table 2: Statistics data on sampled schools

Primary education district	Primary school	Number Class-rooms	Total pupils	Boys (%)	Girls (%)	Sex ratio (B/G)	Mean (Pupils/ Class-room
Barani	Illa	3	190	65	35	1.8	63
	Koubé	3	80	50	50	1.0	27
Total 1	2	6	270	60	40	1.5	45
Nouna IV	Bantombo	3	99	65	35	1.8	33
	Sono	6	366	44	56	0.8	61
	Kouri	4	213	44	56	0.8	53
Total 2	3	13	678	47	53	0.9	52
Di	Benkadi	6	344	49	51	1.0	57
	Bouna	1	85	55	45	1.2	85
	Débé	6	643	52	48	1.1	107
	Di "A"	6	694	50	50	1.0	116
	Di "B"	5	477	52	48	1.1	95
	Niassan "A"	6	633	52	48	1.1	106
	Niassan "B"	5	323	49	51	1.0	65
	Oué	3	334	49	51	1.0	111
Total 3	8	38	3533	51	49	1.0	93
Kassoum	Bissan	1	66	55	45	1.2	66
	Gouran "A"	6	476	45	55	0.8	79
	Gouran "B"	1	67	54	46	1.2	67
	Guièdougou "A"	6	793	56	44	1.3	132
	Guièdougou "B"	3	296	51	49	1.1	99
	Koumbara	3	206	44	56	0.8	69
	Lanfièra	6	242	55	45	1.2	40
	Nion	2	113	49	51	0.9	57
	Yaran	4	178	61	39	1.5	45
Total 4	9	32	2437	52	48	1.1	76
TOTAL 1+2+3+4	**22**	**89**	**6918**	**51**	**49**	**1.0**	**78**

Sources: SSCE/Kossi & Sourou, 2011

2.3 Data collection

– *Questionnaire survey*

Enough questionnaires and 89 posters were designed, printed and distributed to all schools at the beginning of April 2011. The questionnaire was designed in simple table and printed on white paper (A4 format). Teachers had to fill lines by writing down names of children one line per child. Additional individual data were indicated by column headers: sex, age, village of origin, quarter in the village and self-report status. Poster (see Figure 2) was artistically drawn on white paper (A3 format) and designed in three main parts:

- at the top: a school building with a teacher and late comer-pupils running, means that they are the targeted persons;
- at the middle: a pop-up that depicts the transmission route and shows school children (boys and girls) playing in a contaminated surface water, their often daily recreational activities after school;
- at the bottom: the hematuria symptom is displayed, two pupils (a boy and a girl), urinating with blood in their urines, and thinking about their activities after classes. This also shows that both sexes can contract the disease.

The questionnaires were administrated by teachers by interrogating children directly on their current urinary schistosomiasis status based on a daily recall-period in eight different days.
Day "0": the first time to present the poster to pupils. The teacher presented the poster pedagogically from top to bottom as follows: "That is our school (1), and those of you who like playing or swimming in surface water (2), run a risk to be infected by a disease which manifests by abnormal red urines sometimes accompanied with pains when urinating (3)". The hematuria symptom on the poster was made clear using the local meaning of the disease "Gnèguèni-Ouillé" (GO) which means red urine. After having explained the content of the poster, the teacher asked children if they have noticed such manifestations when urinating yesterday or today. Answers were then written down individually using the following codes:

0 = did not report any symptom; **1** = have reported BU or GO only; **2** = have reported only pains when urinating; **3** = have reported BU or Go and pains when urinating.

At the end of this session, i.e. Day "0", the teacher kindly asked children to observe their urines and pay more attention to the symptoms displayed on the posters. With two days interval between each session and for the remaining seven sessions, the children were only asked whether or not they have noticed changes in their disease status the day of the interrogation or the day before.

Figure 2: The poster accompanying the questionnaire

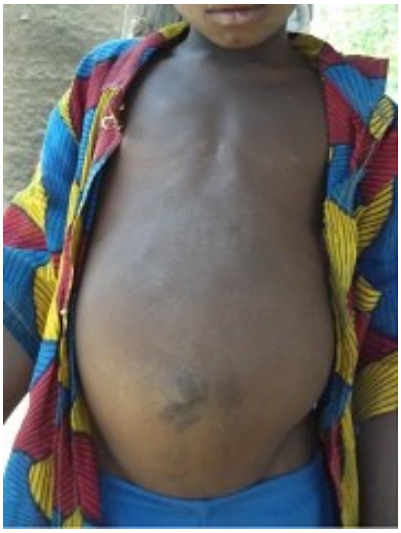

Figure 3: A seven year old school boy having reported GO

All questionnaires, correctly filled, were gathered at the end of April 2011. But the posters were given as present to all children of the classrooms; particularly those suffering from urinary schistosomiasis disorders (see Figure 3). Teachers were asked to hang up the poster on the classroom walls, so that it could each day remind the children of the danger. Schools coordinates (longitude and latitude) were obtained using a global positioning system (GPS Garmin 60CSx) device.

– *Parasitological survey*

Randomly, 124/847 subjects (~15%) were selected, with 60 having reported symptoms and 64 having not. Children's sampled urines for microscopy examinations were from the five primary schools, all located on the western bank of the river: Bantombo (N=20), Koubè (N=13), Kouri (N=12), Illa (N=54) and Sono (N=25). Because of partial-non-availability of lab technicians and their involvement in other routine studies and works, and the villages accessibility, remoteness from the laboratory (minimum distance = 50 km, maximum = 70 km), bad state of rural paths, the urine samples gathering was extended to four consecutive days (16-19 Mai 2011); so that samples could be collected and analyzed within the same day.

The first two days were dedicated to Koubè and Illa, the third day for Kouri and Sono and the fourth day for Bantombo. The field team included two lab technicians, one geographer and a driver. However, the team was supported on the field by teachers to facilitate data collection. Before collecting urine samples pupils were asked to do some physical activities to increase the chance of dropping eggs in their urines. Each child was given a wide-mouthed polythene bottle and asked to urinate into it. After urine collection, an individual code was written on the bottle. All urine samples were collected between 10-14 a.m., and kept at 4° C using cooler and ice-boxes. The urine samples were then brought to the laboratory located in Nouna health district hospital using a car (4x4). In the laboratory, urine samples were centrifuged to check for *S. haematobium* eggs under microscopy. Children whose urine contained one or more eggs were defined as infected; if no eggs were seen, children were defined as uninfected.

2.4 Legal and ethical aspects of the study

– *Ethical approval*

The full proposal of the present study was submitted to the local ethic committee (CLE) of the Nouna Health Research Centre (CRSN)/Ministry of Health. On the demand of the CLE's president, a meeting took place at CRSN conference room on March 29th, 2011 in order to present orally the proposal to the CLE members and to bring responses to their arising questions. After this meeting the study won the CLE approval (N°2011-04/RBMH/PKSS/CRSN/CLE-CRSN).

– *Legal authorization*

After having addressed to them an official letter requesting the permission to involve the schools in the study, authorizations was obtained from the two provincial directions of the primary education of Kossi and Sourou (N°2011-024/MEBA/RBMH/DREBA/DPEBA/KSS and N°2011-251/MEBA/RBMH/DREBA/DPEBA/SUR). Leri School was not investigated because we had no authorization from the provincial direction of Nayala since we could not travel to Toma, capital province of Nayala.

Information circulars were sent by the provincial directors to all district inspectors, town councils, school headteachers and presidents of the association of school children parents. The names of the investigated schools, the topic and objectives of the study, the references of the study principal investigator were clearly mentioned in the circulars. The school children were neither obligated to participate in the study nor to give an answer if the teacher asks them. In particular, pupils were free to provide urines samples or not.

2.5 Data analysis

All questionnaire data were digitalized using a Microsoft Access 2003 database. Pupils were identified by a unique code so that the data could be anonymously entered in the computer and still avoiding pseudo replications. Prevalence rates of reported BU or GO were calculated for each school and village following the WHO (1995) expression: Number of positive answers divided by number of children interviewed, multiplied by 100. For that answers 1, 2 and 3 of self-reported status were re-codified as having reported BU or GO, by attributing them the same code. In fact, it is not common for school-aged children to report having BU or pain when urinating without having urinary schistosomiasis (Brooker et al., 2009). Lengeler et al. (1991a) also concluded that pain in the lower abdomen and dysuria are others powerful predicators and that hematuria was not the only symptom perceived by children with urinary schistosomiasis. Further, children coming from villages of our AOI were selected to compute the prevalence rates at the village scale. The sensitivity and specificity of the questionnaire were calculated as formulated by Ansell et al. (1997): sensitivity: the number of infected children who reported BU or GO divided by the number of children who reported BU or GO plus the number of infected children who did not report BU or GO; specificity: the number of uninfected children who reported not having BU or GO divided by the number of uninfected children who reported not having BU or GO plus uninfected children who reported BU or GO. Villages were mapped in five groups using ArcGIS, version 9.3.

3 Results

3.1 Questionnaire survey participation level

Table 3 shows a global participation rate of 89%. The rates varied at the school level from 53 to 100%. At Gouran "A" School, the class 3 (with 93 children) was not investigated due to health problems of the teacher. Absence of children during the survey period or simple abandons were other reasons explaining the participation rate under 100%. Table 3 also shows that in 81% (18/22) of schools, participation rates above 90% were recorded.

Table 3: Distribution of the questionnaire respondents' rates per school

Schools	Total pupils	Total respondents	Participation rate (%)
Bantombo	99	99	100
Benkadi	344	324	94
Bissan	66	66	100
Bouna	85	83	98
Débé	643	492	77
Di "A"	694	671	97
Di "B"	477	459	96
Gouran "A"	476	252	53
Gouran "B"	67	64	96
Guièdougou "A"	793	746	94
Guièdougou "B"	296	214	72
Illa	190	180	95
Koubé	80	75	94
Koumbara	206	195	95
Kouri	213	199	93
Lanfièra	242	226	93
Niassan "A"	633	632	100
Niassan "B"	323	321	99
Nion	113	113	100
Oué	334	299	90
Sono	366	294	80
Yaran	178	172	97
Total	**6918**	**6176**	**89**

3.2 Constancy and frequency of reported BU or GO

Figure 4 shows the questionnaire administration session to session, the global number of children having reported BU or GO which had varied between 1,264 and 1,371 with 1,341 as mean value per session. The lowest reported cases of the day "0", is notable. There were progressive inputs, new cases detection with maximum numbers reached at the fifth session (day "4"). Based on the daily mean value, five sessions out of eight (62%) recorded reported cases above the mean value. Below mean value was only observed for day "2" and "5" and showed a slight output. Table 4 shows the variation of the frequency of reported BU or GO and the correspondent prevalence rates, when counting the minimum, maximum, or computing the mean or taking into account all children having reported at least one time BU or GO. According to these four numbers, global prevalence rates varied from 20.47 to 30.1%.

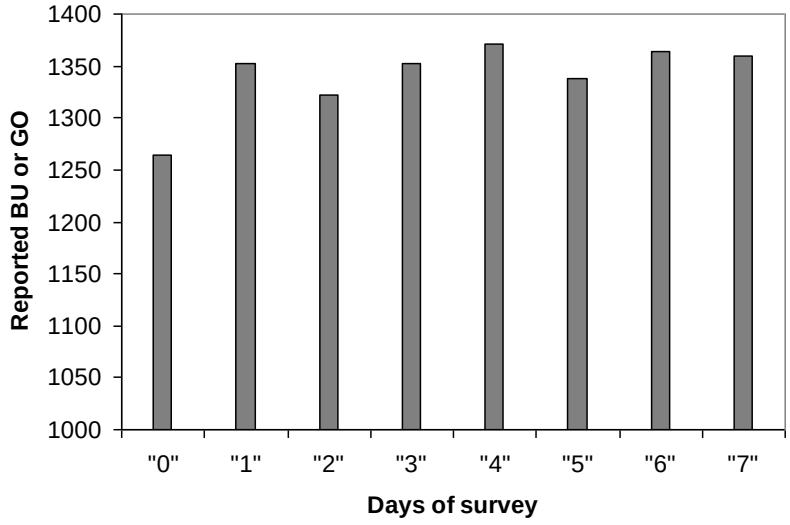

Figure 4: Total number of reported BU or GO cases per session

Table 4: Daily change of reported BU or GO per school after the daily minimum, maximum, mean and final cases (TR: Total Respondents, N: absolute number, P: corresponding prevalence)

		Frequency of reported BU or GO							
		Minimum		Maximum		Mean		Final cases	
Schools	**TR**	**N**	**P**	**N**	**P**	**N**	**P**	**N**	**P**
Bantombo	99	26	26.26	30	30.30	28	28.16	34	34.34
Benkadi	324	153	47.22	190	58.64	176	54.32	194	59.88
Bissan	66	5	7.58	10	15.15	7	10.61	15	22.73
Bouna	83	34	40.96	40	48.19	38	45.93	65	78.31
Débé	492	50	10.16	81	16.46	62	12.68	101	20.53
Di "A"	671	143	21.31	160	23.85	149	22.17	190	28.32
Di "B"	459	51	11.11	67	14.60	57	12.39	94	20.48
Gouran "A"	252	90	35.71	97	38.49	93	36.81	111	44.05
Gouran "B"	64	15	23.44	20	31.25	19	29.10	21	32.81
Guièdougou "A"	746	27	3.62	57	7.64	43	5.70	93	12.47
Guièdougou "B"	214	2	0.93	22	10.28	15	6.83	35	16.36
Illa	180	106	58.89	155	86.11	147	81.67	162	90.00
Koubè	75	4	5.33	10	13.33	7	9.33	11	14.67
Koumbara	195	20	10.26	44	22.56	26	13.33	49	25.13
Kouri	199	17	8.54	28	14.07	24	12.12	31	15.58
Lanfièra	226	17	7.52	31	13.72	23	10.07	39	17.26
Niassan "A"	632	107	16.93	152	24.05	143	22.63	172	27.22
Niassan "B"	321	59	18.38	81	25.23	68	21.03	96	29.91
Nion	113	2	1.77	10	8.85	5	4.54	12	10.62
Oué	299	125	41.81	135	45.15	130	43.35	176	58.86
Sono	294	12	4.08	54	18.37	27	9.06	67	22.79
Yaran	172	48	27.91	68	39.53	56	32.70	91	52.91
TOTAL	**6176**	**1264**	**20.47**	**1371**	**22,20**	**1341**	**21.70**	**1859**	**30.10**

3.3 Spatial homogeneity or heterogeneity of schools' sizes

13 out of 22 schools (59%) had a spatial homogeneous sample. All respondents were from the villages within which schools were located. Nine (41%) had a spatial heterogeneous sample; respondents formed a melting-pot of children coming from different villages. Figure 5 shows schools prevalence rates based on the final cases.

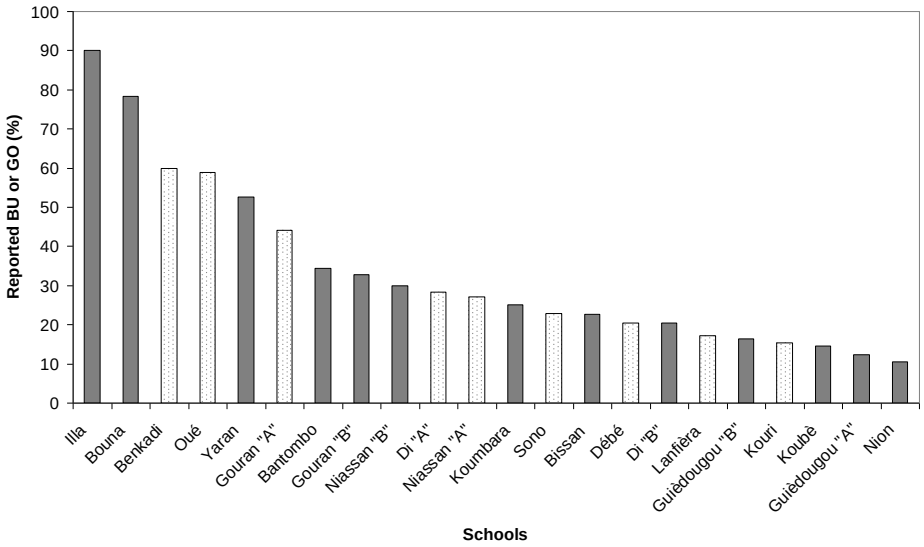

Figure 5: Distribution of schools after their final prevalence rates
(Black bars: spatial homogeneity; dotted bars: spatial heterogeneity)

3.4 Distribution of reported BU or GO per village

According to respondent's provenance, 99% of the children (6,144/6,176) were coming from 23 out of 29 villages within our AOI, (79% of the total villages). Among the 23 villages, 78% have schools and 21% (N=5) have pupils but there were no schools (figure 6). Over 99% of the participants that have reported BU or GO, dwelled in our AOI (1,855/1,859) with an overall prevalence of 30.14% (1855/6155). Figure 6, also shows that nine villages (39%) had reported BU or GO above the overall rate and the remaining 14 (61%) were below.

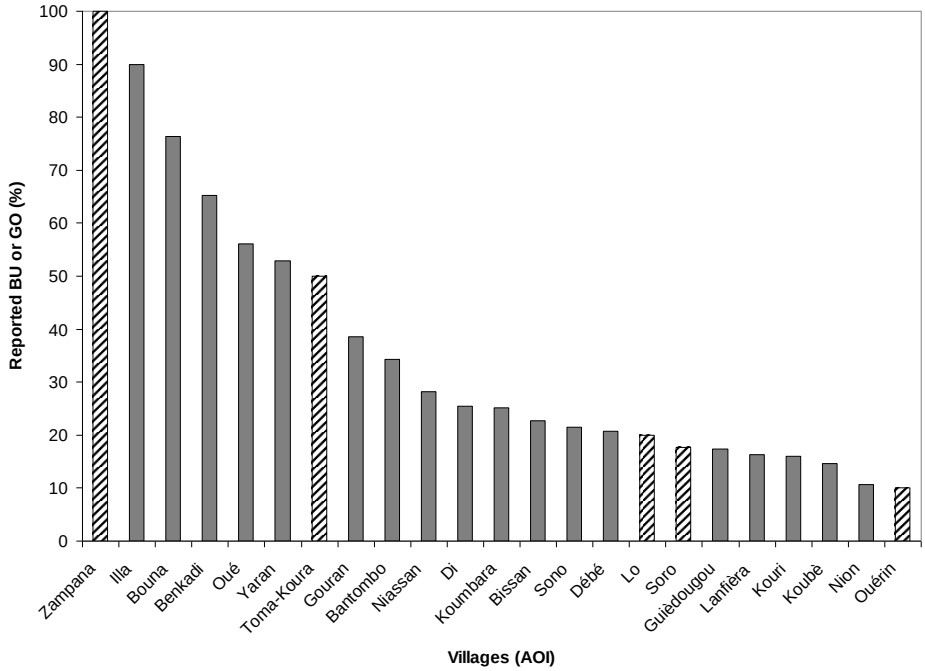

Figure 6: Distribution of total prevalence rates ranged descending per village (Black bars: villages having schools; hatched bars: villages without schools)

– *Relationship between children sex and frequency of reported BU or GO*

Among the AOI respondents, 3,169 were boys (51%) and 2,986 were girls (49%). The sex ratio varied extremely from 0.3 at Zampana to 2 at Illa, with overall sex ratio of 1.1. Globally, there were more BU or GO reported by children on the western bank than on the eastern one: 36.88% vs. 29.35% (OR = 1.26, $p < 0.001$). Figure 7 shows the unequal rate of reported BU or GO among boys and girls. We observed a big difference among boys, and according to the bank location. Contrary to the boys, girls reported rates that were similar (26.44% on the East and 26.18% on the West banks). On both banks reported rates were higher among

boys than girls. In addition, boys' proportions overtook the total rates (boys + Girls). The prevalence rates varied among boys and girls according to their permanent residence within the AOI. Table 5 shows that 16/23 villages (70% of villages) presented high proportion among boys while the contrary was observed in seven villages. In three villages from the seven, cases were reported only by girls (i.e., Lô, Ouèrin and Soro).

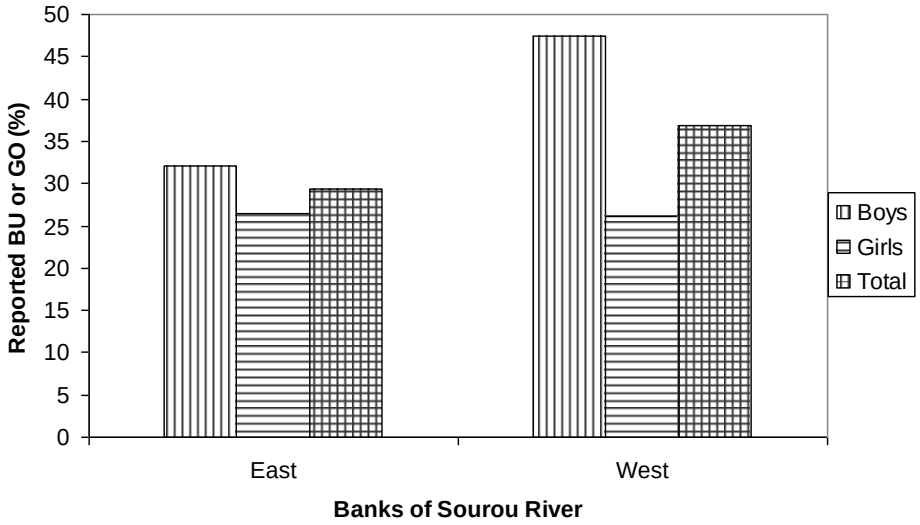

Figure 7: Distribution of prevalence rates by bank according to gender
(East = Sourou province, West = Kossi province)

Table 5: AOI: Spatial distribution of prevalence rates per village following the gender (TB: Total boys, RB: Reported cases Boys, PB: Prevalence Boys, TG: Total Girls, RG: Reported cases Girls, PG: Prevalence Girls, TT: Total boys + girls, RT: Reported cases Total, PT: Prevalence Total)

	Boys			Girls			Total (Boys + Girls)		
Villages	**TB**	**RB**	**PB (%)**	**TG**	**RG**	**PG (%)**	**TT**	**RT**	**PT (%)**
Bantombo	64	19	29.69	35	15	42.86	99	34	34.34
Benkadi	129	99	76.74	127	68	53.54	256	167	65.23
Bissan	36	7	19.44	30	8	26.67	66	15	22.73
Bouna	74	64	86.49	61	39	63.93	135	103	76.30
Débé	249	51	20.48	234	49	20.94	483	100	20.70
Di	587	173	29.47	587	126	21.47	1174	299	25.47
Gouran	85	35	41.18	107	39	36.45	192	74	38.54
Guièdougou	606	108	17.82	508	86	16.93	1114	194	17.41
Illa	120	110	91.67	60	52	86.67	180	162	90.00
Koubè	36	6	16.67	39	5	12.82	75	11	14.67
Koumbara	86	29	33.72	109	20	18.35	195	49	25.13
Kouri	68	19	27.94	101	8	7.92	169	27	15.98
Lanfièra	96	17	17.71	94	14	14.89	190	31	16.32
Lo	3	0	0.00	2	1	50.00	5	1	20.00
Niassan	477	156	32.70	469	111	23.67	946	267	28.22
Nion	55	6	10.91	58	6	10.34	113	12	10.62
Oué	125	75	60.00	123	64	52.03	248	139	56.05
Ouérin	6	0	0.00	4	1	25.00	10	1	10.00
Sono	135	37	27.41	144	23	15.97	279	60	21.51
Soro	5	0	0.00	12	3	25.00	17	3	17.65
Toma-Koura	11	6	54.55	11	5	45.45	22	11	50.00
Yaran	109	52	47.71	63	39	61.90	172	91	52.91
Zampana	1	1	100.00	3	3	100.00	4	4	100.00
TOTAL	**3163**	**1070**	**33.83**	**2981**	**785**	**26.33**	**6144**	**1855**	**30.19**

– *Relationship between child age and reported BU or GO*

The school children ages varies between 5 and 18 years (mean = 11.5). The 9-year-old children represented the majority of the pupils (1,047) while only one child was 18 years old.
Figure 8, shows the age-dependence on reported BU or GO rates (R^2= 0.156, p= 0.162). Among boys, the peak of 42.70% was reached at 13 year old (114/267). Among girls, the highest rate, 30.67%, was observed at 9 year old (146/476). For both boys and girls put together, the peak of 35.04% was reached at 11 year old (246/702). On the contrary, troughs of prevalence rates were observed among 6-year-old school children. From 17 years, prevalence rates decreased considerably. None of the boys have reported BPS or GO (0/4) and only 1/11 girls has reported urinary schistosomiasis symptoms.

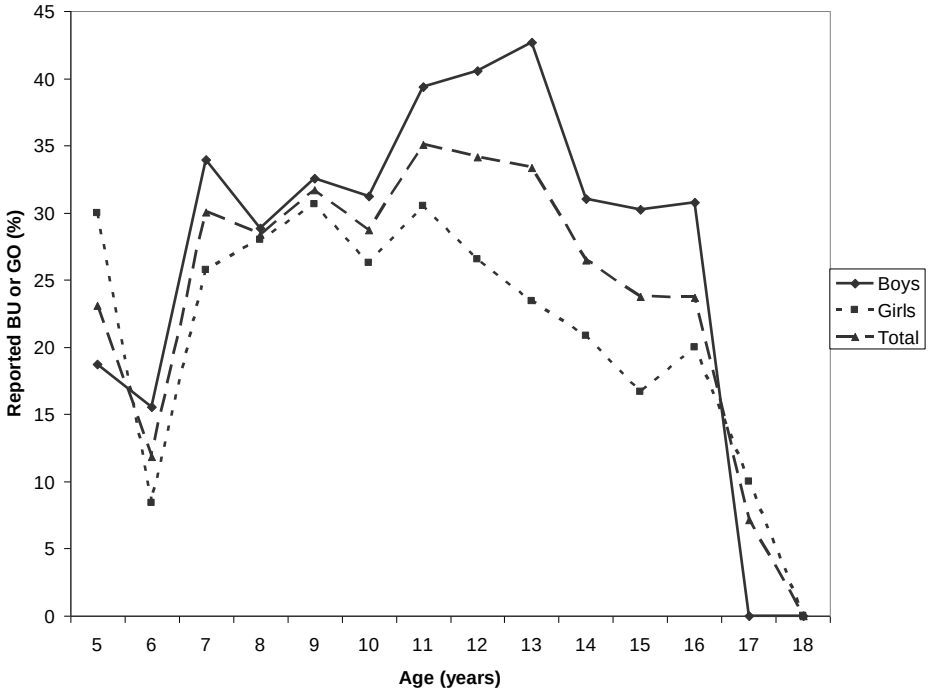

Figure 8: Distribution of prevalence rates per age after the gender

3.5 Accuracy between BU or GO and infection

Figure 9 shows the gap between self-reported and infection prevalence rates (Pearson r= -0.049, p= 0.937). At Bantombo School, the questionnaire approach underestimated the prevalence rate compared to the outcomes of the urine samples

check out, 34.34% reported BU or GO vs. 70% infected children. The opposite was observed at Illa and Koubè Schools, 90% vs. 5.56% and 14.64% vs. 0% respectively. However, the questionnaire approach gave a good approximate figure for the prevalence of infected children at Kouri School, 15.58% reported BU or GO vs. 16.67% infection. The reported BU or GO prevalence on this bank was over-estimated, i.e. 36.88% obtained with questionnaire vs. 16.13% obtained by parasitological examinations.

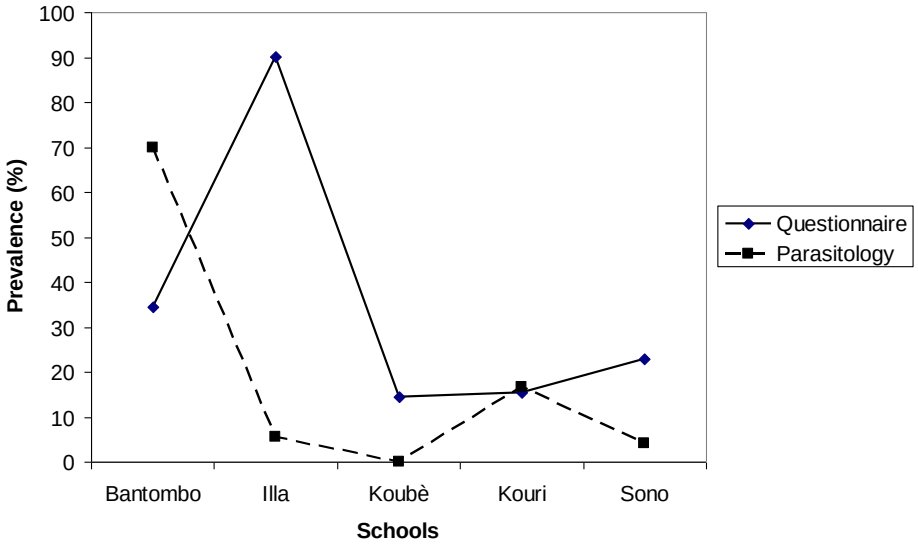

Figure 9: Comparison between questionnaire and parasitological outcomes for five schools

On the western bank of the Sourou River, parasitological examinations revealed that 21.7% (13/60) of children having reported BU or GO were infected. The sensitivity of the questionnaire on this bank was moderate 65% (13/20) (95% Confident Interval CI: 44 – 86). On the other hand, 89% (57/64) of children who did not report BU or GO were found uninfected. The specificity of the questionnaire was 55% (95% CI: 46 – 64). Among the rest 30% children that provided urine samples, 87% of them have reported BU or GO but were found uninfected and 13% of them were infected but they did not report having BU or GO.

3.6 Mapping reported BU or GO prevalence

Figure 10, maps five groups of villages. The first group, 38% (N= 11) has villages where the questionnaire method has screened less than 25% of symptomatic cases.

The second group, 17% (N= 5), represented villages in which symptomatic cases were reported from 25% to 49% by children. The third group of villages, 14% (N= 4), concerned those where reported BU or GO rates were between 50% and74%. The fourth group, 10% (N= 3), represented villages where the questionnaire has screened 75% and more of reported hematuria. The remaining 21% of villages (N= 6) for which the questionnaire method was not applicable represented the fifth group (no data).

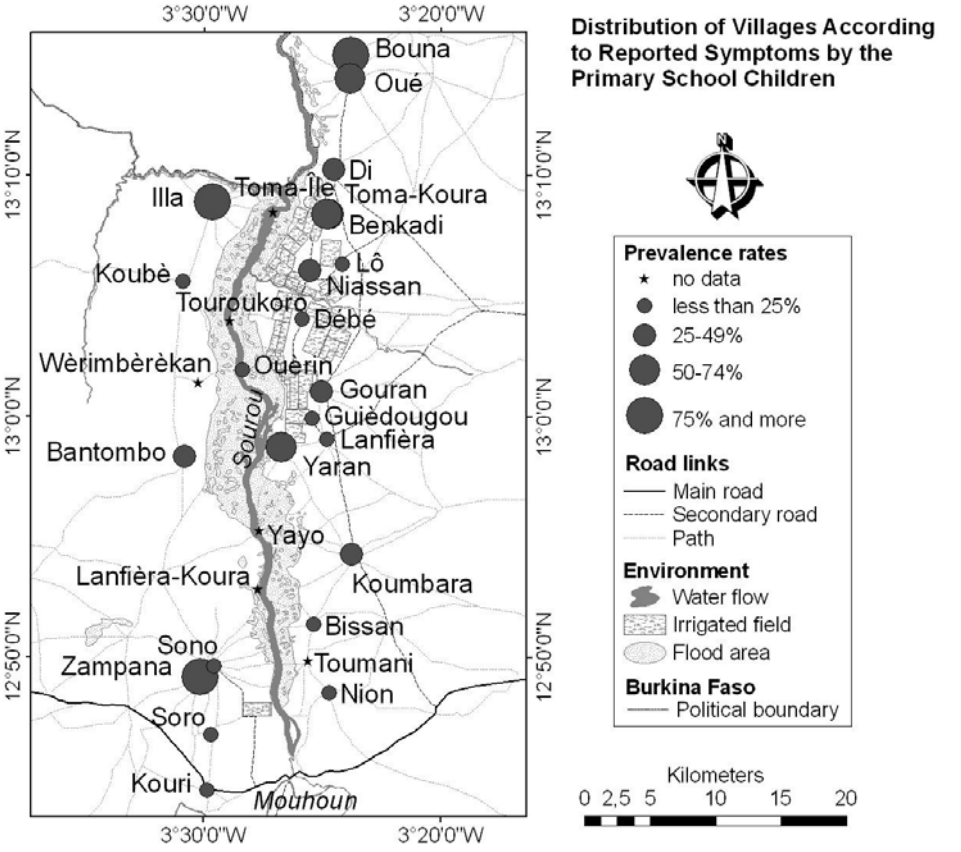

Figure 10: Spatial distribution of villages after the reported BU or GO prevalence rate

4 Discussion

Children of school ages are known to harbor the highest infection rates of urinary schistosomiasis in endemic communities and therefore the prevalence of infected

children will give a very good idea of the overall prevalence (WHO, 1995). We found through this fieldwork that the school-based questionnaire is an appropriate approach on which to base the estimates of urinary schistosomiasis prevalence rates village by village, but with some limitations.

The questionnaire was applicable to 79% of our AOI villages (23/29). Among these villages, 78% (N= 18) have schools. The highest respondents' samples were encountered in those villages. We encountered some small numbers problems (Gatrell, 2002) in the remaining 22% (N= 5) villages that had no schools and children attended classes in the neighboring villages. The lowest numbers of participants were encountered in those villages (see Table 5). However prevalence distribution did not depend on whether schools were sited in some villages or not (see figure 6).

Primary schooling net rates of Kossi and Sourou provinces were 54.1% and 69.7% respectively. But, those net rates were higher among boys than girls. Like all studies that were based on primary schools, we may have certainly missed an important proportion of infected school-aged children (mainly girls) who did not attend classes (Lengeler et al., 2002; Koukounari et al., 2011). School based surveys, underestimate the total number of infected people, as younger and older people were excluded from the study (Lengeler, 1991a). The legal age to be enrolled in primary school in the country is 6-7 years old. From 14-15 years old, pupils leave the class 6, the last class in the primary education system, for the grammar school. This explains the small number problems (Gatrell, 2002) we encountered for investigation of pupils under 6 and over 15 years old. Therefore the representativeness of the questionnaire survey was higher among pupils of 6-15 years old. The rising tendency of *S. haematobium* infection in childhood and declining in adulthood has been observed by other field studies (NAUS et al., 2003; Kapitotembo et al., 2009). Similarly we found that the global prevalence curve showed an increasing trend of reported BU or GO among children from 6 years to eleven years with a decline from 14 years. However, symptoms manifestation persisted in time among boys than girls.

On the other hand, the questionnaire method did not work in 21% of the AOI villages, i.e. the no data group in Figure 10. At the time of the questionnaire survey, no single child from those villages did attend classes. Four of them are lakeside villages that were found as high-prevalence settings (PODA et al., 2004). It means that the questionnaire technique was not extendable to all villages in the study area. Therefore, the number of villages with high-prevalence of urinary schistosomiasis was probably under-estimated.

In the present study, results showed few oscillations of answers between questionnaire sessions, suggesting consistent and more reliable answers. It means that the daily recall-period used was overlapped to the circadian variation of the presence of blood in urine (Doehring et al., 1985; Lengeler et al. 1991, cited Lengeler et al., 1991b). Apparently, the pupils were not lying. For example, during a compound survey in Niassan village where parents were asked if certain members currently

suffer or have experienced urinary schistosomiasis (results are not presented here), a mother responding by the negation was automatically contradicted by her seven year old child (see Figure 3). Asking him why, he simply answered that he frequently sees blood in his urine. Further questions allowed us to know that he was a primary school boy of the class 1. This daily recall-period, coupled with the several times interrogations, allowed us to detect more positive cases (see last column of Table 4).

Two main reasons could explain the moderate sensitivity and specificity of the questionnaire. First, the use of the centrifugation method instead of filtering has probably diminished the change to detect more infected cases during the laboratory examinations. Second, the small number of urine samples, coupled with a single testing day. Even by urine filtration, one misses about one-third of the egg-positive people on a single testing day (Lengeler, 1989, cited Lengeler et *al.*, 1991a). That is because of the circadian variation of eggs excretion (McMahon, 1976; Doehring et al., 1985). However, it is difficult to say that results obtained by the parasitological approach were more objective than those obtained using the self-report questionnaire because eggs were identified in the laboratory by human eye. Nevertheless, the parasitological survey allowed us to ensure that school children who reported BU or GO were infected at about 21.7%.

During the questionnaire gathering at the end of the survey, teachers gave feedback about their experiences in carrying out the study. Some of them confided in us that once the first courageous child raised his hand, all others having the symptoms began to raise theirs as well. Not only positive feedbacks were given, there were certain teachers that complained about older-girls in classes 5 and 6. They thought they probably had urinary schistosomiasis and were ashamed to tell the truth publically, and that they have just written down what the older-girls reported. These feedbacks were proofs of the adhesion of both teachers and children to the study, and that teachers have not modified children answers nor influenced them. No only teachers and children, but also the central authorities at the provincial direction level have manifested their interest in the study. The idea to couple the questionnaire with a poster to clearly show symptoms to children was suggested by those pedagogic authorities. However, we could not evaluate whether the poster was helpful or not because it was systematically used in all classrooms. However, it provided a good basis for practical and water-related diseases-oriented health education. We also hope that growing awareness about the danger of urinary schistosomiasis will go a long way in encouraging pupils to feel free and not ashamed in declaring their disease status.

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23 Schistosomiasis around the Lake Victoria, Northwest Tanzania

Humphrey D. Mazigo and Martin Kappas

1 Abstract

Schistosomiasis is among the most prevalent afflictions of humans who live within the Lake Victoria basin, north-western Tanzania. Over 20 millions people living within the basin are at risk of the disease and significant numbers have the chronic complications of the disease. Two forms of the disease exist, urinogenital and intestinal schistosomiasis, both cause severe morbidities in individuals with moderate to heavy infection intensities. Because of the geographical overlap of schistosomiasis and other tropical diseases within the lake regions, co-infections are common. However, little informations are available on schistosomiasis epidemiology in the form that can be accessed easily. Informations on the epidemiology of schistosomiasis around the Lake Victoria are highly needed for understanding and planning for integrated control approaches. In the present review, the epidemiology, co-infections, morbidities and control of schistosomiasis within the Lake Victoria basin are discussed.

2 Background

Schistosomiasis or bilharziasis is a chronic tropical parasitic disease caused by the blood dwelling dioecious flukes of the genus schistosome. The disease is highly

endemic in sub Saharan Africa and worldwide, it is estimated that over 200 million people are affected by the disease, of whom 97% are resident of sub-Saharan Africa [1]. Over 700 millions people are estimated to be at risk of acquiring the disease worldwide (85% in sub-Saharan Africa) [1]. Four species of schistosomes are responsible for causing schistosomiasis, includes:- *Schistosoma haematobium* which cause urogenital schistosomiasis while *Schistosoma mansoni*, *S. intercalatum*, S. *mekongi* and *S. japonicum* are the causative agents of intestinal schistosomiasis [1, 2, 3].

3 Methods

Data for this review were identified and collected using manual and electronic search strategies of published and unpublished sources. Electronic data search was done using PubMed and MEDLINE databases for both urogenital and intestinal schistosomiasis. Manual search for unpublished surveys, conference abstract and university thesis was done at the National Institute for Medical Research, Mwanza, Tanzania. To identify relevant studies on schistosomiasis in Tanzania, the terms schistosomiasis, bilharzia, schistosomiasis epidemiology and Tanzania/Tanganyika, *Schistosoma mansoni* and Tanzania/Tanganyika were used. Only population based studies, malacological and morbidities studies were included in the review.

4 Biology and life cycle of schistosomes

In general, all members of the genus *Schistosoma* have a complex life cycle which involves a phase of sexual reproduction by adult schistosomes in the definitive host (human or other primates), and an asexual phase in the intermediate host, a freshwater planorbid snail (Figure 1) [4,5,6,7]. After copulation, depending on species, the female schistosome produces hundred to thousands of eggs per day (300 - 3,000 per day) [6]. The eggs of schistosomes are species specific and each contains a ciliated miracidium larva [5, 6]. The ciliated miracidium secretes preoteolytic enzymes, which together with host blood pressure and presence of spines help the eggs to migrate and penetrate into the mesenteric venous plexus for species causing intestinal schistosomiasis into the lumen of the intestines or in the tiny venules of the vesical plexus for species causing urogenital schistosomiasis [8]. It is assumed that approximately 50% of the eggs pass through the colon, the walls of the bladder or the genitourinary apparatus and are excreted by faeces or urine [6]. The remaining 50% of the eggs are trapped within the tissues of these organs [6].In contact with fresh water and guided by light and other chemical stimuli, they hatch to release a miracidium, a free-living larval form of the parasites. It will swim, search and penetrate a compatible intermediate host, freshwater snails. Over the period of 3-8 weeks, within a snail, miracidium multiply by asexual reproduction and develops through primary (mother sporocyst) and secondary (daughter sporocysts) sporocysts into thousands of cercariae characterized by bifurcated tail [6].

After 4-6 weeks, these are shed from the snails into water and can survive in water for about 72 hours searching for definitive hosts [5]. Cercarial shedding process is stimulated by the presence of light and occurs mainly during the daytime. Infected snail can continue to shed cercariae every day for months. When in contact with the skin of the definitive host, the cercariae penetrate and shed their tails and are transformed into schistosomula (Figure 1). The schistosomula migrate passively into the lymphatic system or blood vessels to the heart and then to the lungs [6, 7]. From the lungs are carried to the liver where they grow and mature into adult in a period of 4-6 weeks. In the portal vein, the female schistosome becomes enclosed within the gynaecophoric canal of the male schistosome. The paired adult schistosomes mate and migrate from the liver to settle in the venous plexus or mesenteric where the life cycle starts again. The entire life cycle is completed within 2-3 months [6]. The lifespan of the adult schistosome in the definitive hosts is estimated be on average 3 - 5 years [6] but may live for up to 30 - 40 years [8, 9].

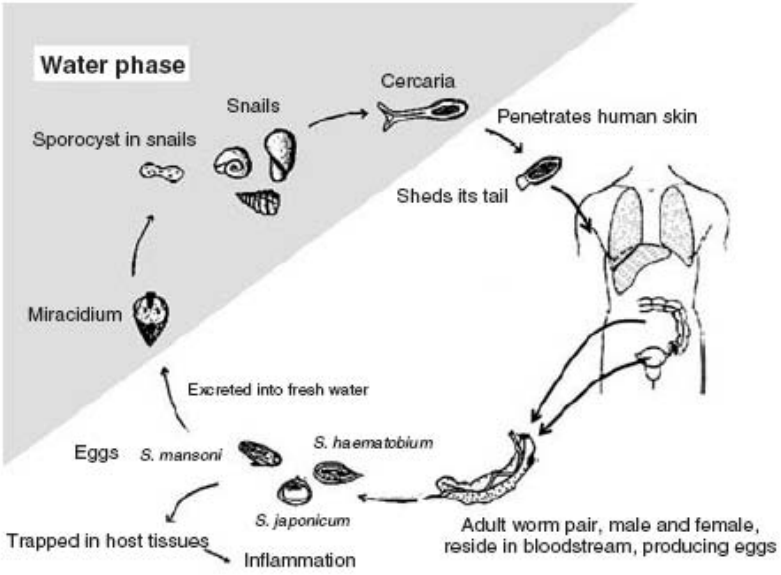

Figure 1: Schematic diagram of life cycle of schistosomiasis [10]

5 Schistosomiasis in Tanzania

In Tanzania, schistosomiasis has long been recognized as a serious public health problem with high transmission rates accompanied by severe morbidities in different regions. The disease is second only to malaria in term of causing morbidities. Only two species of schistosomes, *Schistosoma haematobium* and *Schistosoma mansoni* are responsible for causing urogenital and intestinal schistosomiasis (Figure 2) [3,

11, 12, 13]. Of the two species, *Schistosoma haematobium* is widely distributed while *Schistosoma mansoni* is focally distributed [14]. The wide distribution of intermediate snails host in the country determines the distributions of the disease [14]. The whole Tanzanian population of over 38 millions people is at risk countrywide and in 2000; over 15.2 million people were estimated to be infected with both urogenital and intestinal schistosomiasis [3]. In the country, the young age groups (< 16 years) or school age children carries the largest burden of the disease and the infection prevalence decreases at older ages. Gender variations on the disease prevalence are common observation in endemic communities [15, 16]. Behavioral mediated variations in exposure to risk areas can in part explain the differences of infection between age and sex [15, 16].

6 Epidemiology of schistosomiasis around the Lake Victoria

The Lake Victoria area is on the north-western part of the country, it comprises the regions of Kagera, Mwanza, Mara and Shinyanga [11-13]. The first three regions are located along the southern and western shore of the Lake Victoria. Over 20 million people inhabit the region and the main occupation of the two third of the population are farming within the basin of the lake, fishing, livestock keeping and small scale business [11-13].

Schistosomiasis was first described in the region in 1905 in the irrigation scheme around the southern shore of the Lake Victoria [17]. The disease was identified to be highly endemic within the irrigation scheme with both *S. mansoni* and *S. haematobium* being common [17]. Over 50% of individuals examined had urinary schistosomiasis, with majority being males aged > 5 years old [17]. The distribution of the disease in the region is mainly determined by the distributions of the intermediate snail hosts [18, 19]. *Schistosoma mansoni* is highly endemic immediately along the southern shore of the lake and decreases with distance from the shorelines [15]. Communities living along the shores of the lake in all the three regions are highly affected by intestinal schistosomiasis [11, 12]. Similarly, communities living in small islands within the Lake Victoria such as Ukerewe, Ukara and Kome are highly endemic to intestinal schistosomiasis [20, 21]. At Ukerewe island, of the 1,659 villagers examined for *S. mansoni*, over 86.3% had infections and the prevalence did not differ between gender but males had higher eggs output (median in infected males 208 egg per gram of feaces versus 144 epg in females) [22]. In term of age, the prevalences varied with age, with a maximum in adolescence and a decline in older age groups [22]. The age group 21- 40 years and >40 years had 86.7% and 84.2% rates of infections respectively [22]. In term of median egg output (epg), the age group < 10 years and 11- 20 years had 216 epg and 320 epg while the higher age groups had lower eggs per gram of feaces [22]. At Msozi and Sangabuye villages, located within and immediately along the lake shore, of the 984 and 504 individuals examined for *S. mansoni* at Msozi and Sangabuye, 78% and 38% were

found infected [21]. The geometrical mean intensity of those infected between the two villages were 156 epg and 47 epg respectively [21]. In the two villages, males and the higher age groups (> 30 years) had higher prevalence and infections intensities [21]. However, among those with heavy infections intensities in both villages were in the young age group (14 - 19 years old) [21]. Similarly, in Kome islands, of the 206 individuals examined, 88.3% had *S. mansoni* infections and over 35% of them had heavy infections, excreting > 400 epg [23]. In Sengerema district, of the 400 school children (aged 6-17 years old) attending primary schools located within a radius of 5km from the lake shore, 64% had *S. mansoni* infections and males children had higher infections intensities [23]. Differences between frequency of exposure to water contact between male and female or age groups observed within the communities living within the lake basin may account for such differences in the prevalence of *S. mansoni* [15]. Young age groups contact water more frequently than the other age groups and hence are more likely to have higher infection intensities compared to any other age groups. For older age groups and gender, involvement in risky economic activities such as fishing and rice cultivations may in part explain the sex predominance observed on the prevalence of *S. mansoni*.

Incontrast, the prevalence of *S. mansoni* in the hinterland area is very low, for instance in Misungwi district, intensive epidemiological studies in children age 6 – 16 years, 78% of the children had *S. haematobium* infections and only 12 children had *S. mansoni* infections [24]. Similarly in the hinterland area of Magu district, southern shore of the Lake Victoria, of the 6,897 school children (aged 7 – 20 years) examined only 11% had *S. mansoni* and majority had *S. haematobium* [15]. By contrast, in Kagera region, the prevalence of intestinal schistosomiasis is very low despite the availability of the intermediate hosts in most of the studied villages along the Lake shore [25].

In the region, *S. haematobium* is also highly endemic and the risk of acquiring urogenital schistosomiasis increases with increase of distances from the shorelines of the Lake Victoria [26]. The distributions of the snails intermediate hosts which transmit *S. haematobium* are confined in the hinterland, thus transmission and prevalence of the disease is high in communities living away from the lake shore [15, 26]. Areas along the southern shore of the Lake Victoria or the Sukuma plains in Mwanza and Shinyanga regions are highly endemic to urogenital schistosomiasis

[26]. The results of the earlier studies in the hinterland, on the southern shore of Lake Victoria reported the prevalence of *S. haematobium* to range from 60% to 96% [27]. The incidence of *S. haematobium* was highest in the age group 6-12 years (78%) and the group had the highest infection intensity. The other age groups > 13 years had low prevalence and infection intensity respectively [24]. Recent studies, in the hinterland areas, among primary school children have reported the high prevalence of *S. haematobium* (56.5%) [15]. The *S. haematobium* infection intensity was observed to decrease with increase in age, with the young age groups reported to have low infections intensities as compared to older age groups [15]. There are was a significant relationship between prevalence of *S. haematobium* infections and age and sex, with high prevalence observed in males [15]. The sex predominance could be attributed to male's prolonged exposure to infested water, especially for swimming during the dry seasons when the temperature is high in the region. The observation of dropping of prevalence and infection intensity with increase in age was associated with development of immunity [24].

In Kagera region, transmission of *S. haematobium* does not occur [25]. Multiple factors have been associated with the virtual absence of schistosomiasis, such factors are soil profile, rainfall patterns, vegetation, general topography and human population. However, the absence of snails in the inland waters of Bukoba were directly or indirectly associated with the absence of the diseases in the area [28, 29]. In general, the observed spatial distribution of schistosomiasis within the Lake Victoria basin may be explained by the occurrence of their snail intermediate hosts and their ecological relationship between different types of water bodies [15].

The entire population living within the lake basin is at risk of the disease. However, children between the ages of 6 to 14 years (school age and school children) carriers the largest burden of the infections [15, 16]. The prevalence of the disease decreases with increase in age and the age pattern of infection levels can be influenced by age-related immune responses. Similarly, age pattern is observed in areas where adult individuals have higher water contact due to fishing activities like in the small islands within the lake, the prevalence of infections is higher in the older ages but yet the young age groups will carry the heavy infection intensities [21]. Gender difference in the prevalence of schistosomiasis can be observed in school children or adult population [15, 16, 21]. Several factors such as behaviour or immunology may be important for the observed differences between male and

female may account in term of prevalence and intensities of schistosomiasis [15, 21]. In fact, within the lake basin, fishing activities are mainly carried out by male individuals and thus they have higher frequency of exposure to schistosomes infested water than females. This could in part account for the gender differences in prevalences of disease observed.

Several individuals and community factors are associated with the continuity of schistosomiasis transmission within the lake basin. Human economic activities such as flooding rice cultivation practices, fishing within the Lake Victoria, small seasonal rivers and stream flowing down to the lake and road side ditches whichare created by road contractors, collects water during the rain seasons and acts as good breeding sites of the intermediate snails hosts [14, 30-32]. Furthermore, the increase in population and population movements, swimming in lake especially for the children during the dry season (Figure 3) and introduction of the irrigation schemes in the hinterland contributes to the transmission of the disease [14, 30 - 32]. The wide distribution of the intermediate snails hosts of both urogenital and intestinal schistosomiasis within the lake basin contributes significantly to the transmission dynamics of schistosomiasis [19, 20]. Poor hygiene practices characterized by the lack of safe tape water supply, absences of toilets and use of water direct from the lake are common observations among communities living within the basin. In fact, majority of the community members are knowledgeable of disease and its symptoms, but this does not prevent the inhabitants to come into contact with lake water [33]. This is due to the fact that, the endemic communities have no alternatives for safe water supply, thus they continue to depend on schistosomes infested water for their domestic use. In addition, endemic communities do not have any alternative economic activities for income generation other than fishing and paddy cultivation, which are among the risk factors for schistosomiasis transmissions.

In the region, *S. mansoni* is known to be zoonotic and affecting different species of monkeys and baboons [34, 35]. In Gombe stream National Park located within the Lake Victoria basin, of the 206 olive baboons screened for *S. mansoni*, 69% had positive stool samples [35]. Baboons get infections through water contact during playing and fighting [35]. In the area, juveniles' baboons are commonly observed to play in water and hence are reported to have high prevalence of the disease [35]. However, in the region, the potential roles played by baboons as reservoir host of human schistosome infections require further investigations. The movement of baboons from the national parks to human settlement may establish transmission of intestinal schistosomiasis in areas known to be free of the disease, especially if the intermediate snail hosts are present in the area. Thus, advanced studies are required to understand the roles played by baboons/monkeys in the dynamics transmission of intestinal schistosomaisis.

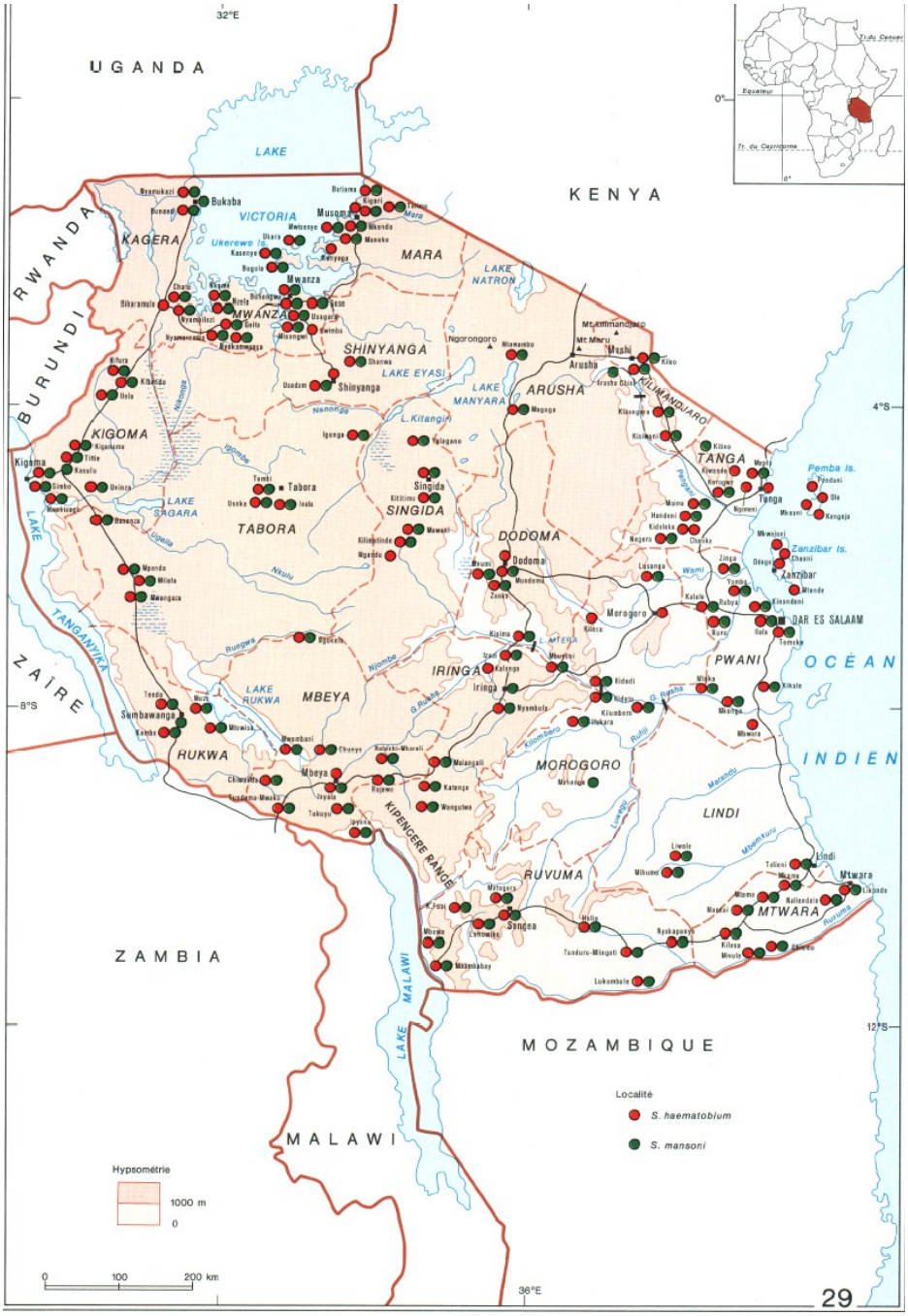

Figure 2. Distribution of schistosomiasis in Tanzania [16] (Source: Doumange 1987)

Figure 3: Active water contact at active sites for intestinal schistosomiasis transmission. Young children (pre-school and school children) and adult washing their clothes and playing along the southern shore of Lake Victoria, Northwest Tanzania.

7 Intermediate hosts of schistosomiasis within the Lake Victoria basin

The earlier studies on intermediate hosts transmitting schistosomiasis within the Lake Victoria basin began in 1950's [19, 20]. The two Planorbidae species were identified to transmit *S. haematobium* and *S. mansoni* within the region [19, 20]. For *S. mansoni, Biomphalaria choanomphala* in Lake Victoria, and *Biomphalaria sudanica*, which is found adjacent to the lake, are the main intermediate snail hosts of *S. mansoni* in the area [15, 30-32, 36]. *Biomphalaria pfeifferi*, which occurs in permanent ponds, has a sporadic distribution and is responsible for only seasonal transmission of *S. mansoni* [15, 30-32, 32,]. In fact, in Ilemela and Nyamagana district, within Mwanza city, *Biomphalaria pfeifferi* is not found in the inland water bodies, instead is commonly seen in permanent water-bodies with moderately abundant aquatic vegetation [24].

This distribution of *Biomphalaria* spp. hosts might, at least in part, explain the high prevalence of *S. mansoni* at the lakeshore and the low prevalence of *S. mansoni* in communities living away from the lakeshore [15, 26].

In contrast, for *S. haematobium*, the main snails intermediate hosts are *Bulinus nasutus*, *Bulinus africanus* and *Bulinus globosus* [36, 37]. The most abundant and widespread is *Bulinus nasutus*, which is found in temporary habitats throughout the inland water bodies because of its ability to survive the long dry season by aestivation [15, 24]. *Bulinus africanus* occurs in temporary streams, while *Bulinus globosus* colonizes permanent ponds [15]. Thus, the snail intermediate hosts of *S. haematobium* occupy a mosaic of habitats throughout the southern shore areas [15]. In fact, on the shores of Lake Victoria in Mwanza region, *S. haematobium* does not occur due to the absence of *Bulinus* spp. but does occur in inland small, static water-bodies which harbour the species [38]. The distribution and density of the snail intermediate host is an important determinant, accounting to a large extent for the seasonal transmission of the disease especially *S. haematobium* within the region [20]. In addition, the transmission seasons varies between the wet rain (January to May) and dry (June – September) seasons, high transmission peak is observed after the rain season between June and September [24]. The distribution pattern of the snail intermediate hosts may in part account for the observed widespread distribution of *S. haematobium* infections on the hinterland areas located on the southern part of the Lake Victoria [15, 24, 26].

8 Co-infections of schistosomiasis with other tropical diseases within the Lake Victoria basin

The Lake Victoria basin is also endemic to a number of tropical parasitic, viral and bacterial diseases [15, 16, 39]. Malaria is highly endemic and the region is classified in stable perennial malaria transmission zones where malaria transmission occurs through out the year [40]. Soil-transmitted helminths, *Ascaris lumbricoides*, *Trichuris trichiura* and hookworms (*Ancylostoma doudenale* and *Necator americanus*) are also highly endemic in the region [15, 16]. Of all the soil-transmitted helminths, hookworms are the most predominant and are highly endemic along the lake shore due to the ability of the larvae stages to survive in sand beaches [15, 16]. For the viral and bacterial infections, Human Immunodeficiency Virus- 1 (HIV-1), tuberculosis and sexual transmitted diseases (such as gonorrhea, syphilis and Chlamydia infections) present a serious public health concern in the region [41, 42]. Because of high prevalence of these diseases, co-infections with schistosomiasis are probably common. In fact, among the primary school children within the region, co-infections of intestinal or urogenital schistosomiasis with either malaria or soil tranmitted helminth has been reported [15, 16, 39, 41]. Of the 6,897 primary school children examined within the lake basin, 22.1% had co-infections of *S. haematobium* and hookworms infections [15]. Similarly, within the region, of the 400 school children studied, 26.5% harbored two parasite species and combination of *S. mansoni* and hookworm co-infections was the most common (69%) [16]. The other co-infections observed were between *S. mansoni* and *P. falciparum* (22.6%), hookworm

and *P. falciparum* (5.7%) and for triple infections of *P. falciparum*, *S. mansoni* and hookworm, the prevalence was 2.8% [16]. Furthermore, in fishing communities along the lake shore, co-infections of schistosomiasis and HIV-1 are common [41]. Of the 457 women of reproductive age examined, 5.7% had urogenital schistosomiasis and 5.9% had HIV-1 infections [41]. Among women with HIV-1 infections, 15% were co-infected with urogenital schistosomiasis. Importantly, urogenital schistosomiasis was associated with HIV-1 infections (OR = 4.0, 95%CI, 1.2–13.5) [41]. Based on the fact that urogenital schistosomiasis can act as a risk factor for HIV-1 transmissions, these findings may have important public health implications for prevention of HIV infection.

9 Schistosomiasis related morbidities in communities living within the Lake Victoria basin

Morbidities due to *S. haematobium* and *S. mansoni* are often associated with inflammatory responses against parasite eggs trapped in host tissues either within the wall of urinary bladder or intestinal organs [21]. For *S. haematobium*, the main clinical signs or symptoms seen in the majority of the primary school children within the Lake basin are gross or microhaematuria (urine containing blood) [37,43-45,47]. Other symptoms observed related to *S. haematobium* are dysuria, pain during micturitions, urine incontinence and urethral dysuria [37, 43-45, 47]. The chronic manifestations of *S. haematobium* reported in children and adult individuals are calcified urinary bladder, calcified and distorted ureters, hydronephrosis, non-functioning kidney and granulomatous pseudopolyps in the bladder [37, 43-45, 47]. The survey of Forsyth and MacDonald at Usagara around the south part of Lake Victoria, where 87% of school children had *S. haematobium* infections (prevalence increased from 79% in standard 1 children to 100% in those in standard 4) identified 22% of the school children with various urological abnormalities [47]. The common urograms abnormalities were calcified urinary bladder, calcified and distorted ureters, hydronephrosis and non-functioning kidneys [47]. In addition, multiple or bilateral lesions were also identified, includes calcified bladder (7%), deformity of the ureter (10.3%), hydronephrosis (9.2%) and non-functioning kidneys (0.3%) [47]. The prevalence of hydronephrosis was lower in girls (3.7%) compared with 13.7% in boys. A direct relationship between intensity of infection and the abnormalities of the urinary tract was observed, in which calcified urinary bladders, deformed ureters and hydronephrosis were significantly more common in school children who excreted > 250 eggs/10ml of urine [47]. It was concluded that occurrence of urological abnormalities related to *S. haematobium* was associated with the intensity of infection [47]. A community based survey in the same locality, using pyelograms noted a number of children with urological abnormalities. The common urological lesions observed were calcification and distortion of the ureters, urinary bladder calcifications, hydronephrosis and non-functioning kidneys [36].

The majority of children (aged 3-12 years) with heavy infections intensities of *S. haematobium* had urinary bladder calcification [36]. The prevalence of urinary bladder calcification was observed to decrease with increased age [36]. In males the prevalence of calcified bladders, damaged ureters and hydronephrosis was less in adult than in young males [36]. In hospitalized cases, co-infections or co-occurrences of urinary bladder carcinomas or adenocarcinomas of the prostate glands with eggs of *S. haematobium* have also been reported within the region (Figure 4) [45,47].

For *S. mansoni* infections, the earlier manifestations of the disease characterized by granuloma formation and obstruction of intestinal tracts were reported in 1958, at Ukerewe Island, which is within the Lake Victoria [48]. In outpatients cases the main complaints associated with *S. mansoni* are vague abdominal pain, general weakness, diarrhea, intermittent dysentery and blood/mucus in stool [49]. Detailed clinical, liver pathology, liver function and haematological findings associated with *S. mansoni* in north-west were described by McMahon in hospitalized cases [50]. Of the 640 participants, 65.2% had *S. mansoni* infections and the majorities were asymptomatic, other complaints were vague abdominal pain, general weakness, diarrhea, intermittent dysentery and blood/mucus in stool [50]. The overall prevalence of hepatomegaly, splenomegaly and hepatosplenomegaly were 20.2%, 7% and 2.4% respectively [50]. The prevalence of hepatomegaly and splenomegaly were observed to decrease with increased age and were higher in the age group 5-10 (28.3% and 9.7%) and 11-15 (19.3% and 6.9%) years [50]. The histological findings demonstrated extensive fibrosis and granulomatous lesions in liver sections of individuals who had heavy infection intensity (≥ 500 epg) [50]. In addition, portal tract fibrosis was severe in liver sections with ≥ 250 eggs of *S. mansoni* per gram of feaces [50]. In hospitalized cases, appendicitis and obstructions of the intestinal tracts presenting as acute cases have been reported among the inhabitants of the region (Figure 6) [51, 52].

Community surveys, along the basin have reported lesions of the liver, portal vein, and spleen, leading to periportal fibrosis, portal hypertension, hepatosplenomegaly, splenomegaly and ascites associated with *S. mansoni* infections (Figure 5) [16,21,22, 49,50,54]. These morbidities are common in individuals with heavy infections intensities (≥ 500 eggs per gram of feaces) [22, 49, 54]. A community based study in Ukerewe Island demonstrated that 86.3% of 1,659 (geometric mean egg output was 514 epg and increased with age) had *S. mansoni* infections and other morbidities reported were diarrhea, bloody stools and blood vomiting [22]. The prevalence of hepatomegaly and splenomegaly by abdominal palpation was 9.6% and 42.8% respectively. Importantly, organomegaly was significantly more common in individuals passing more than 400 epg [22]. On ultrasonographical examination, the prevalence of hepatomegaly and splenomegaly was 35% and 83% respectively [22]. A consistent increase in the proportion of hepatomegaly and splenomegaly with increasing egg output was observed. Individuals excreting > 400

epg had higher prevalence of both hepatomegaly (42.5-50%) and splenomegaly (90.2%) [22].

Similar study in Kome Island within the Lake Victoria, a parasitological survey of 206 (104 females and 102 males) individuals identified 88.3% (182/206) with *S. mansoni* infections and 35% were heavily infected (excreting ≥ 400epg) [23]. Abdominal palpation revealed hepatomegaly and splenomegaly at 34% and 62% respectively. Periportal fibrosis or ultrasonographical signs of hypertension was observed in 10 -15% of the study population [23]. In the same region, a community survey using ultrasonography reported the prevalence of periportal fibrosis to be 41.5% and 16.7% in Msozi and Sangabuye villages [21]. In each of the two villages, males had higher prevalence of periportal fibrosis (50.5% and 33.9%) [21]. Hepatomegaly was observed in 54.5% in Msozi and 46.4% in Sangabuye but was not associated with *S. mansoni* infections [21]. For splenomegaly, the prevalence was 61% and 40.3% at Msozi and Sangabuye respectively [21].

Schistosoma mansoni in pregnancy is a public health concern in the region, not only is the cause of hepatosplenomegaly and other morbidities, but also is the major cause of anaemia during pregnancy [53]. In Ukerewe Island, a cross-sectional survey of 972 pregnant women identified 63.5% excreting ova of *S. mansoni* and the prevalence decreased with increasing of age [53]. The overall prevalence of anaemia was 66.4% and heavy *S. mansoni* infection (≥ 400 epg) was associated with anaemia (OR=1.87, 95%CI, 1.07 – 3.27, P= 0.026) [53].

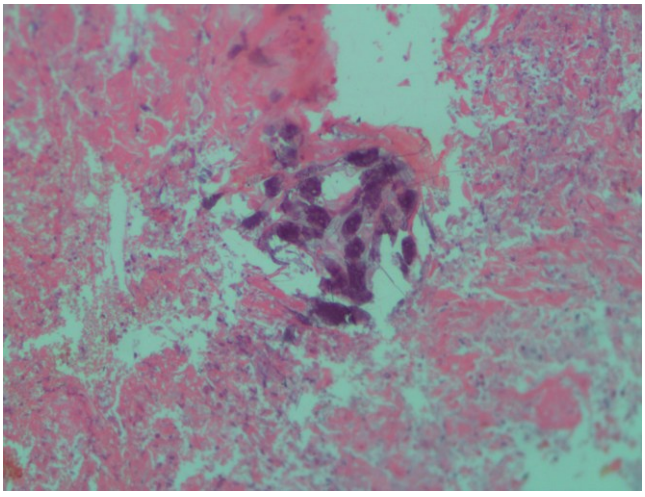

Figure 4: Arrows showing eggs of *S. haematobium* in the urinary bladder wall of 40 years male reported at the Bugando Medical Center, north-western Tanzania with chief complain of genital mass and frequent micturitions. Histological (H & E) examination of urinary bladder biopsy revealed co-infections of urinary bladder carcinoma and S. haematobium eggs in the wall of the bladder and fibrosis (courtesy of Mazigo HD and others 2010).

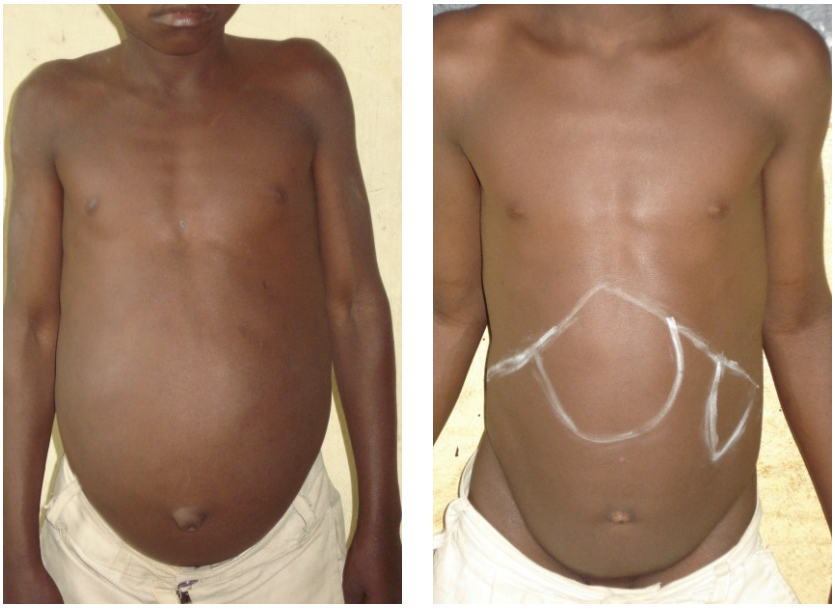

Figure 5. Gross reactive hepatosplenomegaly in two school boys with heavy infections of intestinal schistosomiasis (> 1000 epg), Sengerema district, northwest Tanzania. The photograph was taken during field studies carried out in 2009. (Courtesy of Mazigo HD, 2009).

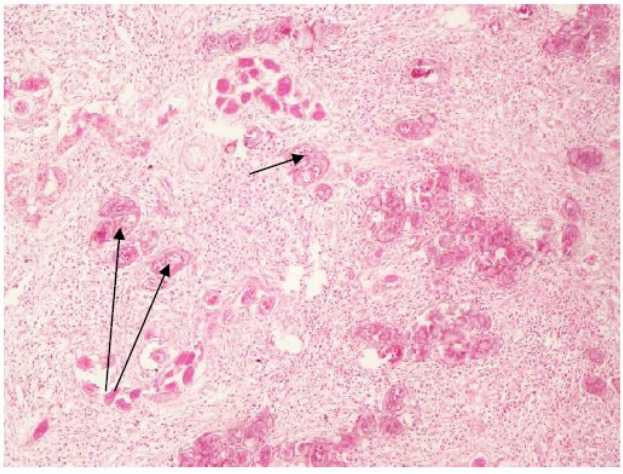

Figure 6: Arrows showing eggs of *S. mansoni* (with lateral spine) in the submucosa and mucosa of the ileum and caecum of 7 years old living within the Lake Victoria basin north-west Tanzania presented with intestinal obstructions (Courtesy of Mazigo HD and others, 2011)

10 Control of schistosomiasis around the Lake Victoria region

The increased transmissions and public health concerns of schistosomiasis in the region have not been resulted into development and implementation of any effective control measures. The early years of 1960's, the main control efforts against schistosomiasis in the region focused only on the intermediate snails hosts by using molluscicides. However, due to wide distributions of the intermediate snails hosts in the regions, coverage of the entire areas and the ecological effects of the molluscicides lead to changes of the control measures [24].

In 2004, the national schistosomiasis and soil-transmitted helminths control programme (NSSCP) under the Ministry of Health and Social Welfare was established with support from the Schistosomiasis Control Initiative (SCI) [55]. The main interventions strategy used is annual treatment of groups at risks such as primary school children using praziquantel (40mg/kgBWT). The main aim of the treatment is to reduce morbidities by decreasing worm burden and intensity of infection, improve children health and prevent irreversible complications in adulthood [55]. The approach of delivering treatment to school children is the school based Mass Drug Administration (MDA) were all primary school children receive praziquantel (40mg/kgBWT) irrespective of infection status [55].

11 Discussion and conclusion

Intestinal and urogenital schistosomiasis continues to be highly endemic around the Lake Victoria and the entire population within the basin is at risk of the infections. School age children and other members of the communities carry the largest burden of the infections. The disease is associated with mild to severe morbidities with majority of the infected population remains asymptomatic and suffers from the chronic manifestation of the disease at older ages. Various social-economic and sociodemographic determinants are associated with disease transmission within the lake basin. However, only few have been identified and more research are required on this area.

The control of schistosomiasis in the region and countrywide depends mainly on the reduction of morbidities through the use of annual single dose of praziquantel (40mg/kgBWT) which mainly target primary school children [55]. However, the major limitation of school-based treatment approach is that, it does not include the non-school going children [56]. In addition, other members of the endemic community are not included and thus, they save as carrier of the disease and continue to transmit it to other community members. The fact which cannot be avoided is that in the basin, infections with schistosomiasis start at very young age below five years and this group should be integrated in the treatment campaign.

Despite the fact that schistosomiasis is highly endemic within the Lake Victoria basin, the status of the disease in many of the areas are still unknown or un-

mapped. For example, majority of the areas in Mara region remain unmapped and the status of the disease in communities considered at risk of acquiring the disease remain unknown. Thus, for planning meaningful and achievable control activities, targeted efforts are highly needed to identify and map the endemic communities within the lake basin. Furthermore, due to variations in behaviours and culture, risk factors associated with the transmission of schistosomiasis may vary between communities within the region, however, little is known on the socioeconomic determinants associated with the disease. On the other hand, the co-infections of schistosomiasis and other tropical diseases such as malaria, soil-transmitted helminthiasis, tuberculosis and HIV are common in the regions, but how these diseases interacts in a single hosts and causes multiple pathology remain a topic of further investigation. Because of high endemicity of schistosomiasis in the region, infections usually starts at very young ages and infants or pre-school children also harbors the infections, however, this group is often excluded from the treatment programmes using praziquantel. Thus, in order to henceforth justify inclusion of the preschool-aged children in mass treatment programmes using praziquantel, there is a need to obtain more information on the disease prevalence, efficacy of praziquantel, side effects and tolerability in the age group.

To achieve maximum control of schistosomiasis, improvement of socioeconomic status and hygiene is highly required. Despite the distance of villages to the Lake Victoria, provision of safe tape water is urgently needed in communities living in the hinterland and shorelines of Lake Victoria. Furthermore, improvement of preventive and curative health services should help to control the disease.

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24 Malaria in Kossi Province, Burkina Faso: An investigation of spatio-temporal incidence pattern

Daniel Karthe, Issouf Traoré, Ali Sié and Martin Kappas

Abstract
By global standards, malaria transmission is intense throughout most of Sub-Saharan Africa; at the same time, incidence pattern vary by magnitudes both in space and time. While disparities at the global and continental level are reasonably well documented (in the African case most notably by the MARA/ARMA project), it is the spatio-temporal variation of transmission pressure at the local and regional level that are most relevant for malaria control. The study presented is based on malaria case data collected by selected rural health centers in Kossi Province, Burkina Faso and assessed the relevance of different environmental (climate, vegetation, hydrology) and socio-economic (population density, practice of irrigated agriculture, preventative measures) factors. In case of Kossi Province, Burkina Faso, incidence rates were found to vary by a factor of more than 10, with the highest rates found in relatively densely populated but non-urban areas close to perennial rivers and irrigation sites. As expected, transmission peaked within two months of the rainy season's onset, but the degree of seasonality varied both spatially and inter-annually. Whereas the differences observed are of relevance for malaria control, the identification of geographic determinants of transmission (including useful proxy variables), are important prerequisites for developing locally adapt malaria transmission models.

Keywords
Malaria; GIS; Burkina Faso; Medical Geography; Epidemiology

1 Introduction

With an estimated 225 million infections in 2009, malaria remains among the most important infectious diseases in the world and is responsible for around a million deaths annually (WHO 2010). However, the malaria burden may actually be twice as high (Breman et al. 2007) as these official estimates suggest, and thus be greater than at any time in history (Hay et al. 2005). When compared to other important infectious diseases, malaria comes second only to HIV/AIDS in terms of disease burden and third in terms of mortality and is the most important vector-borne disease in both respects (Lopez et al 2006). The global malaria burden is distributed very unequally: 60% of all malarial infections, 75% of severe infections caused by *Plasmodium falciparum* and 80% of all malaria deaths occur in sub-Saharan Africa (Hay et al. 2000; WHO 2005). With a total population of about 300 million people, sub-Saharan West Africa represents the region with the largest population exposed to high levels of malaria transmission intensity in the world (Kleinschmidt et al. 2001). This risk is far from evenly distributed across the region, and even within a single country, there may be large disparities in malaria incidence (fig. 1) which depend, among other factors, on the natural environment, landuse and human settlement pattern.

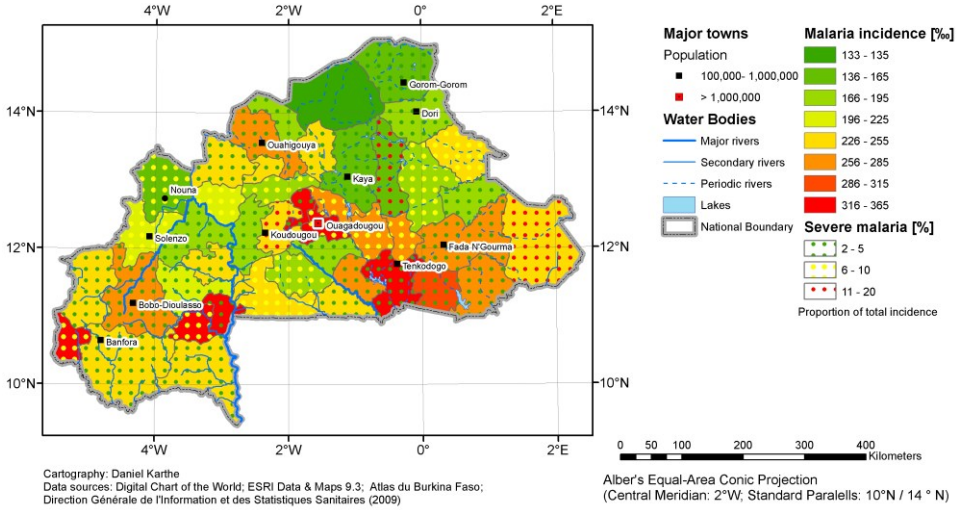

Figure 1: Spatial pattern of malaria incidence in Burkina Faso (2008)

In Burkina Faso, more than 4.5 million (just above 45% of all) medical consultations are related to malaria, and 50.79% of all hospital deaths are caused by malaria (Direction Générale de l'information et des Statistiques Sanitaires 2010).

Even though malaria remains a major public health issue in Burkina Faso, limited resources for public health expenditures mean priorities need to be set for

their allocation. With an annual per capita GDP of $1160 in purchasing power parities, Burkina Faso ranges among the economically least developed countries in the world (Population Reference Bureau 2010). Almost half of the population live below the poverty line, which is currently defined as an annual per capita income of 82,672 FCFA (€ 126 or US$ 173 in January 2011). In such a socio-economic environment where the scopes for health spending are limited at both the government and individual level, disease maps can help to determine suitable intervention strategies (e.g. magnitude, timing, spatial focus of control programs) and to assess control interventions. (Tatem et al. 2004). Hay et al. 1998 proposed the use of malaria risk maps for optimizing the distribution of antimalarials. Worrall et al. (2007) demonstrated that the effectiveness of indoor residual spraying (IRS) depends on its timing. In resource-constrained environments, monitoring and prediction systems therefore have the scope of becoming valuable decision-support tools.

Because of its complexity, the transmission cycle of human malaria depends on a relatively large set of external factors and depends on their impact on both the malaria parasite and its vector. Even though several parasite and vector species do exist, in West Africa the malariologically most relevant species are *Plasmodium falciparum* and the mosquitoes of the *Anopheles gambiae* complex, respectively.

The malaria transmission cycle starts when a parasite is ingested by a susceptible anopheline mosquito during a blood meal. The parasite then has to undergo further development (sporogony) until its infective form is secreted by the mosquitoes salivary glands. A bite of such an infective mosquito may lead to the injection of a parasite into the human bloodstream and thus cause malaria. The speed and integrity of this cycle are the key determinants of malaria transmission dynamics in a region. Since both the physical environment and a number of anthropogenic factors play a role for the dynamics of malaria transmission, an analysis of the spatio-temporal pattern of malaria needs to take into account this complex and interlinked set of parameters. This is an important reason why despite all advances in this field, there is still no model of malaria transmission that works in any transmission setting and can successfully be driven by a limited number of input parameters. An overview of important factors related to malaria epidemiology is presented in table 1.

Table 1: Malariological relevance of selected factors

Factor	Malariological relevance	References
Temperature	- governs the speed and completion of the sporogonic cycle (parasite development) - influences the development of the immature aquatic stages of the mosquito vector - regulates the longevity and biting behaviour of anophelines	Bayoh & Lindsay 2003; Bayoh & Lindsay 2004; Gosoniu et al 2009
Precipitation, surface water and moisture	- surface water is the prerequisite for anopheline breeding and determines their habitats - different types of water bodies differ in their productivity - humidity extends the mosquito longevity (and may reduce the frequency of blood feeding) - extended periods of drought may substantially reduce or eradicate a vector population	Hoshen & Morse 2004; Hay et al. 2000; Kiszewski & Teklehaimanot 2004; Huang et al. 2005; Mutuku et al. 2006
Irrigated agriculture	- may create breeding sites for malaria vectors (particularly in case of rice) - may coincide with malaria control activities (e.g. provision of bednets, use of insectides) - may coincide with infrastructural improvements and greater economic capacity (and thus better access to health care)	Sissoko et al. 2004; Dolo et al. 2004; Ijumba & Lindsay 2001; Diuk-Wasser et al. 2005
Location of vector habitats	- the flight range of mosquitoes is limited (around 2 km for most anophelines) - proximity of vector habitats/breeding sites to settlements or places of human activity increases the risk of malaria transmission	Hoshen & Morse 2004; Service 1993
Quality of housing	- structural integrity determines the entry of vectors - crowding increases the risk of transmission to several hosts (i.e. infection of several household members)	Keiser et al. 2004; Yé et al. 2006
Awareness and Prevention	- education helps to realistically assess risks, take appropriate preventative measures and react properly in case of infection - the use of (impregnated) bednets and application of pesticides helps to reduce transmission risks	Okrah et al. 2002, Hightower et al. 2010, Ngom 2010

The effect of one individual factor can usually not described by a simple linear relationship. In fact, one factor such as temperature affects several processes related to both the vector and the malaria parasite (see figure 2), and at different stages of their development, its effect may not be the same. At the egg stage, temperature has an effect on the duration of embryogenesis and mortality rates. Likewise, the duration of the aquatic larval stages is temperature dependent, with higher temperatures accelerating the development while beyond a critical level also increasing the mortality of the immature mosquitoes. Once they have reached maturity, temperature influences not only the longevity and biting behaviour of anophelines but also has an effect on the parasite development (sporogony) occuring in the mosquito vector. The impact of temperature on a selection of malariologically relevant factors is presented in figure 2. However, it should be kept in mind that under field conditions, various factors are effective at the same time. Adult mosquitoes may, for example, better tolerate a certain temperature if it is sufficiently humid than under dry conditions (Karthe 2010).

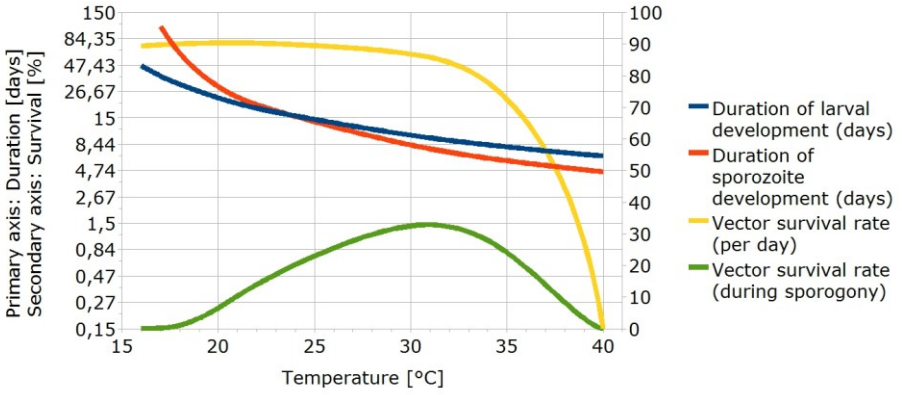

Figure 2: Effect of temperature on selected malariologically relevant parameters
Based on Gilles 1993 and Hay et al. 2000

The study presented first of all aimed at the identification of spatio-temporal pattern of malaria incidence in Kossi Province (Burkina Faso) in order to assess the range of malaria incidence rates and differentiate between periods and areas of high and low transmission risks. The feasibility of obtaining and integrating data of multiple sources was then investigated. This included both the assessment of determinants that are known to have a direct effect on malaria transmission dynamics and potential proxy variables which could be used as simple indicators of malaria transmission risks.

2 Methods

2.1 Study region and population

Kossi Province (see figure 3) covers an area of 7,324 km² close to Burkina Faso's western boarder with Mali. Currently counting about 278,546 (INSD 2008), its population grows at a rate of about 3.0% annually. Subsistence agriculture and pastoralism are the key economic activities of Kossi's multi-ethnic population (Yahmed 2005). In Kossi, only the provincial capital of Nouna may be considered a semi-urban to urban region. Population densities tend to be higher in the south and west of Kossi, while the north is less densely settled. The only hospital in Kossi is located in Nouna; in the rest of the province, state-run health posts (CSPS, *Centre de Santé et pour la Promotion Sociale*) form the backbone of the health services. These CSPS provide basic medical treatment and may refer patients to Nouna hospital (Karthe & Traoré 2009).

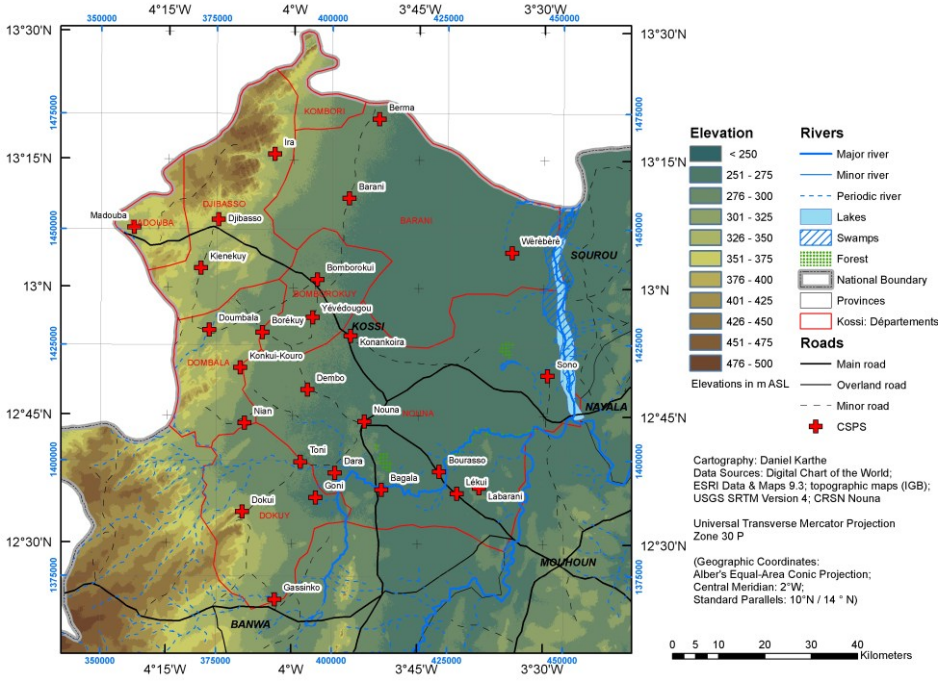

Figure 3: Physical Map of Kossi Province (indicating location of CSPSs)

The region's semiarid climate is characterized by a rainy season lasting approximately from June to September. About 90% of the annual precipitation of around 800 mm fall during July, August and September (Griffiths 1972; Ingram et al. 2002). While temperatures tend to vary relatively little around an average of 28°C,

the hottest months when temperatures may exceed 45°C occur just before the onset of the summer monsoon. The dry savanna, which is strongly influenced by human activities, is interspersed by gallery forests along the region's two major rivers (Mouhoun and Sourou). Rainfed agriculture, in particular the cultivation of sorghum (*Sorghum bicolor*) and pearl millet (*Pennisetum glaucum*), dominates, but irrigation has been introduced along the Mouhoun and Sourou and led to a diversification of crop production in recent years.

Malaria is holoendemic in Kossi Province and the transmission intensity typically ranges between 100 and 900 infective bites per person and year (Becher et al. 2008). As in the rest of Burkina Faso, malaria is the main cause of morbidity and mortality in Nouna Health District (Tipke et al. 2008).

Within the study region, the situation in two villages is exemplarily considered in more detail: Illa (population in 2006: 1536), located in the northeast of Kossi within the zone of Wèrèbèrè CSPS, is adjacent to a zone of swamps (to the north), the Sourou river and the irrigation perimeters of the Sourou Valley Authority (Autorité de Mise en Valeur du Sourou, AMVS; to the east). Toni (population in 2006: 1979), on the other hand, is located in the southwest of Kossi, the seat of a CSPS and located in a region where agriculture is rainfed. In the recent past, plans to dam a nearby episodic stream and use its water for irrigation have been locally discussed but not yet realized.

2.2 Data collection and analysis

Various types of data were collected for the study which was conducted in the working region of the *Centre de Recherche en Santé de Nouna* (CRSN). Malaria case data were obtained from both the CRSN malaria database and local health centers. Personal interviews were carried out in two villages in order to assess both preventative and curative practices. Topographic maps and high-resolution satellite imagery were obtained as the basis for spatial investigations, including the detection of aquatic vector habitats. Both terrestrial measurements and remote-sensing products were used for meteorological monitoring and the assessment of microclimatological information. As far as possible, data were then entered into a GIS (ESRI ArcGIS 9.3) in order to analyse spatio-temporal effects and links between malaria incidence and its potential determinants.

In Kossi Province, malaria cases are routinely recorded and aggregated to monthly statistics at local health centers (CSPSs). Even though some active case detection data exist from previous case studies in the region, a complete coverage of the province is only feasible using passive case detection data. These represent presumed infections in patients reporting to health centers. The diagnosis of malaria at all CSPS (except for Nouna) is symptomatic (usually based on a body temperature of 38°C or higher, and potentially on additional symptoms), thus potentially overestimating the malaria incidence. On the other hand, not all patients report to a CSPS when they feel sick, thus resulting in an underestimation of the

actual burden. Both self-treatment and the consultation of traditional healers are common practice. Even though there is a lack of empirical proof, it is reasonable to assume that the two effects (under- and overestimation) counterbalance each other.

Demographic base data were obtained from the CSPS, some of which are under a demographic surveillance system (DSS) installed at the *Centre de Recherche en Santé de Nouna*. Since the last census in December 2006, data available for subsequent years are projections based on an estimated population growth rate of 2.61% annually. In two villages, Toni and Illa, interviews were carried out at selected households in order to obtain (among other information) data on preventative measures practiced. All households were georeferenced using by GPS. Even though this study (n=251 persons or 5,8% of the population) was not sufficiently comprehensive to provide representative data for the entire province (which was accomplished in surveys conducted by the CRSN and other research team), it was meant to provide an indication whether the differences observed could be large enough to be malariologically relevant.

The latest editions of all topographic maps of the region were obtained at the Institut Géographique du Burkina Faso (IGB). Since these larger scale maps only covered a small part of the province, high-resolution satellite images (QuickBird and Ikonos) of Toni and Illa, two villages located in different ecological (and socio-economic) settings, were acquired. After pan-sharpening, these images were used as the basis for mapping both the location of houses and potential mosquito habitats. During ground surveys carried out during the dry and wet seasons of 2007 and 2008, all depressions that covered about 0.5 m² or more and which were at least 20 cm deep were mapped and considered to be potential vector breeding sites.

Climate data were retrieved from the meteorological station in Dédougou which is situated just outside the study area. Due to frequent malfunctions of the equipment and resulting data gaps, information from 10 meteorological stations set up in Kossi province itself were found to be of little use. To account for spatial varations of meteorological parameters, MODIS land surface temperature (LST) and vegetation index data were assessed regarding their usefulness as proxies for (air) temperatures and precipitation. High spatial resolution images (Quickbird, Ikonos) were used for the preparation of overview maps to be used for derivation of risk zones. Due to prohibitive costs, only two dry season scenes could be obtained. Therefore, besides a general ground truthing, the mapping of potential mosquito breeding sites was carried out during both the dry and rainy seasons.

All georeferenced data collected were entered into ArcGIS 9.3. While annual incidence rates were obtained for all 26 CSPS, the seasonality of transmission was investigated for 14 CSPS distributed throughout the province by calculating a malaria seasonality index (MSI). Incidence maps were created using inverse distance weighted interpolation. A seasonality index was developed and calculated in order to account for differences in temporal distribution pattern. Regression analyses

were carried out to identify correlations between external factors and the incidence pattern observed. However, this was found to be problematic because of differing spatial and/or temporal resolutions and references of the data. These findings are described in the results and discussion sections.

3 Results

3.1 Malaria incidence pattern

Kossi Province is a region of holoendemic malaria and the transmission intensity typically ranges between 100 and 900 to 1000 infective bites per person and year (Kouyaté et al. 2008). In 2008, this resulted in an annual incidence rate of 137,6 cases per 1000 inhabitants (Direction Générale de l'information et des statistiques sanitaires 2009), a figure which varies both spatially and interannually. At the same time, the climatic seasonality means that much of this burden falls into the weeks following the onset of the rainy season.

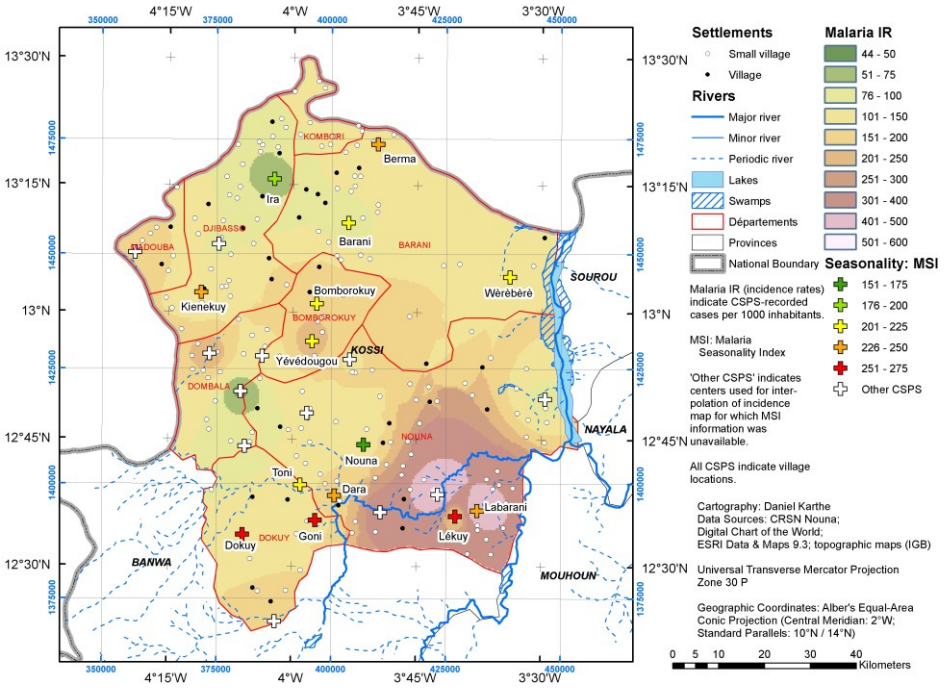

Figure 4: Malaria incidence and seasonality pattern in Kossi Province

In general, the lowest annual incidence rates in Kossi were recorded in the north and west of the province, whereas the highest rates were found in the southeast (see figure 4). At Konkui-Kouro CSPS in Doumbala district (44 cases/1000 inhabitants) and Ira in Djibasso district (67 cases/1000 inhabitants), malaria incidence occurred at relatively low levels. This situation contrasts sharply to settings with very high incidence levels such as Bourasso CSPS in Nouna district (524 cases/1000 inhabitants). The nearly 12fold difference between Konkui-Kouro and Bourasso CSPS compares to a distance of just 48 km between the two health centers and illustrates how little data at province level may reveal about local conditions.

Nearly three fourths of all malaria cases were observed during the second half of the year, with typically 20% to 25% of the annual cases falling into a single month, and incidence rates falling to low levels (but never zero) during the first half of the year (see table 2). A relatively low degree of seasonality was observed in Nouna, the only urban settlement in the province, as opposed to otherwise high seasonality indices in the southern part of Kossi (e.g. Lékuy, Goni).

Table 2: Indicators of malaria seasonality

CSPS	**Malaria cases in 2008**			**Monthly cases**		**Seasonality Index**
	Total (C_t)	**Jul – Dec** (C_2)	**Jan – Jun** (C_1)	**Mini-mum** (C_{min})	**Maxi-xi-mum** (C_{max})	
Barani	2095	1543	552	79	418	215,51
Berma	2114	1627	487	64	397	226,16
Bomborokuy	2020	1518	502	64	315	216,52
Dara	1487	1128	359	32	235	227,74
Dokuy	1485	1243	242	29	368	252,8
Goni	790	677	113	13	161	256,45
Ira	1867	1215	652	73	305	191,53
Kienekuy	1110	867	243	21	217	238,57
Labarani	1259	1009	250	29	272	241,02
Lékuy	814	717	97	6	213	270,69
Nouna	1341	471	870	15	194	155,89
Toni	932	672	260	23	200	223,58
Wèrèbèrè	930	648	282	33	183	208,8
Yévédougou	948	653	295	22	187	216,71
All CSPS	**19192**	**13988 (72.9%)**	**5204 (27.1%)**			**218,5**

C_1: cases during January to June period; C_2: cases during July to December period; C_t: annual cases (total); C_{min}: cases during the month of lowest incidence; C_{max}: cases during the month of highest incidence; MSI = $([2C_2 / C_t] + [C_{max} - C_{min}] / [C_{max} + C_{min}]) * 100$ Higher MSI values indicate a greater degree of seasonal variation of transmission.

3.2 Analysis of determinants and predictors

In order to best target intervention efforts, a monitoring and/or prediction of both of the spatial and temporal pattern of malaria incidence may be valuable resources. Therefore, the observed incidence pattern were analysed in order to identify potential determinants and predictors. Since the present study did not aim at a transmission model, and because of the multitude of factors involved, each factor will be

characterized briefly and its potential role for a transmission model / prediction system be outlined.

Contrastive to previous works in the region (e.g. Yé et al. 2007, Gosoniu et al 2009), temperature was not found to be a reliable and feasible predictor of the spatial pattern of malaria incidence. This was mainly due to two reasons: on the one hand, it was observed that microclimatological effects are substantial, and that meteorological stations (which frequently failed due to technical reasons) did not capture this spatial variability. On the other hand, for much of the year, temperatures recorded were in a suitable range for malaria transmission but not stations not situated in locations representative of mosquito habitats.

The availability of water was found to be a good determinant of both the spatial and temporal pattern of malaria incidence. On the one hand, the seasonality of rainfall was, as expected, well associated with malaria incidence pattern which lagged behind around one month. Spatial pattern of precipitation were, however, difficult to assess because of a relatively coarse station network (often afflicted with data gaps). At the same time, distance to major water bodies, particularly the Sourou, and inundated rice fields were found to be related to higher incidence rates than in surrounding areas. Vegetation indices (particularly MODIS NDVI) were found to be a feasible predictor of malaria incidence for a number of reasons: in the dry savanna setting observed, 16 days' MODIS NDVI composites (a) reflected water availability of any origin (precipitation and irrigation) in both its temporal and spatial pattern, (b) showed the same temporal response to rainfall (and probably the beginning of irrigation) as malaria vector populations and (c) were readily obtainable (at no cost). The NDVIs in a 5 km buffer zone around health centers were found to be the single best predictor of malaria incidence ($r^2 > 0,5$ were observed for monthly malaria incidence and NDVI for 14 CSPS).

High resolution satellite images were found to be a good alternative when other cartographic resources were scarce, particularly because they allowed the detection of major depressions suitable for mosquito breeding. In the Kossi context, excavation pits for clay or loam bricks could well be detected and were the malariologically relevant topographic features not covered on existing topographic maps. Villages falling within a 2 km zone (equivalent to the reported flight range of *Anopheles gambiae*, the main vector of malaria in the region), were found to be particularly prone to high levels of malaria incidence.

The limited data on prophylactic practices collected during interviews in the villages of Illa and Toni were not sufficient for an analysis of their impact but indicated great inter-village differences. Whereas in Illa, 47.7% of the residents covered used a bednet, the respective figure for Toni was just 9%. This was partly related to a campaign providing bednets to pregnant women at Wèrèbèrè CSPS, the health center covering the population of Illa. A similar campaign has been started at Toni CSPS. On the other hand, the use of insecticides was a much more common practice in Toni (protecting 80.0% of the study group) than in Illa (24.5%). In Illa, 41.1% reported not to do anything to prevent malaria, as opposed to 18.0% in

Toni. Even though there is controversy about the degree of protection offered by various strategies, the differences observed suggest that varying degrees of personal protection may contribute towards different levels of malaria incidence.

4 Discussion

In semi-arid regions, the dynamics of malaria transmission and incidence do not only vary seasonally but also exhibit spatial pattern involving differences of magnitude in neighbouring localities. Moreover, not only the incidence ratios but also their seasonality differ markedly even within relatively small regions. The complex set of factors governs the transmission dynamics of malaria mean that individual parameters are often of little value as predictors of the pattern found. Instead, integrated approaches incorporating the physical environment, socioeconomic realities and individual behaviour are required to explain the spatio-temporal pattern of malaria incidence. Among the individual parameters investigated, the present study identified vegetation indices as a feasible approach to routinely detect environmental conditions conducive to malaria transmission in dry savanna regions.

In the future, integrated but reasonably simple approaches will be needed for both the operation of malaria early warning systems and the development of control strategies. For the semi-arid parts of West Africa, land use changes will play a prominent role in this context. A growing population, rising food demand and previously unused potentials mean that irrigated agriculture is on the advance (Seck et al 2010). Malaria early warning systems and models will on the one hand need to be adapted to such developments, but could on the other hand provide valuable insights into epidemiological processes that may help to implement such projects in a way that negative health effects such as increasing levels of malaria transmission can be avoided.

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25 Anemia – What has to be investigated in an African setting?

Silke Kietz, Martina Lange, Ingrid Kühnle and Max Lakomek

1 Introduction

Anemias can be caused by several reasons, such as congential defects in erythrocyte enzymes or erythrocyte membrane, defects in haemoglobin, nutritional anemias like iron defiency or autoimmune haemolytic disorders. Inherited anemias like hemoglobinopathies are found worldwide. Haemoglobinopathies are the most frequent genetic diseases in the world.

Data from the World Health Organization show, that an estimated 250 million people, or 4.5 % of the world population, carry a potentially pathological haemoglobinopathy gene. Every year, 300 000 infants are born with major haemoglobin disorders, the most common being the thalassaemias and sickle-cell disease. Prevalence varies from under 0.1 births per 1,000 in some parts of the world to more than 20 per 1,000 in parts of Africa. The highest prevalence is found in Africa, Asia and the Mediterranean basin.

Worldwide the alpha and beta thalassaemias are the most common inherited single-gene disorders with the highest prevalence in areas where malaria was or still is endemic. The burden of this disorder in many regions is of such a magnitude that it represents a major public health concern. For example in Iran, it is estimated that about 8,000 pregnancies are at risk each year. In some endemic countries in the Mediterranean region, long-established control programs have achieved 80-100% prevention of newly affected births.

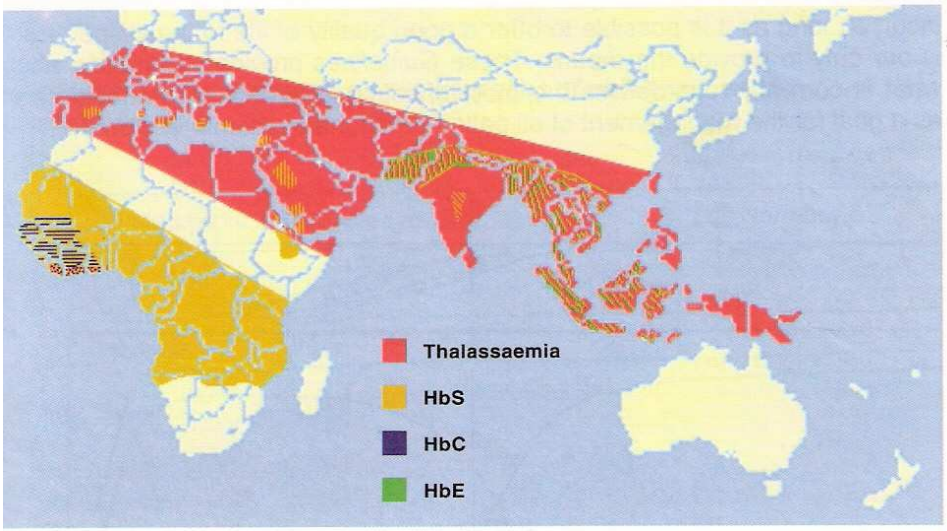

Figure 1: Distribution of thalassemia worldwide

Sickle cell anemia affects millions throughout the world. It is particularly common among people whose ancestors come from Sub-Saharan Africa, South America, Cuba, Central America, Saudi Arabia, India, and Mediterranean countries such as Turkey, Greece, and Italy. In the Unites States about 72,000 people are affected, most of whose ancestors come from Africa. The disease occurs in about 1 in every 500 African-American births and 1 in every 1000 to 1400 Hispanic-American births. About 2 million Americans, or 1 in 12 African Americans, carry the sickle cell allele.

Sickle cell disease can be diagnosed through a simple blood test. In many cases, sickle-cell anemia can be diagnosed when newborns are screened. To prevent major complications, appropriate vaccinations and prophylactic antibiotics, as well as folic acid supplements should be administered. In case of vasoocclusive crisis pain should be managed appropriately. Blood transfusions are indicated for patients with severe anemia or neurologic/pulmonary complications. The only known cure at present is hematologic stem cell transplantation.

Iron overload is the most common and severe complication of thalassemia major, mainly due to the need of life-long blood transfusions required for the treatment of the severe anemia and increased iron absorption from the G.I. tract. Iron chelation treatment is essential in the prevention of long-term organ damage due to iron overload. Iron overload may cause severe damage to almost all organs with subsequent failure of their function. Since the early 1990ies oral iron chelators are being successfully used.

Another problem associated with thalassemia is the early development of osteoporosis. Ineffective erythropoiesis results in the dramatic expansion of the bone marrow which causes mechanical interruption of bone formation leading to corti-

cal thinning. This is considered as a main reason of distorsion and fragility of the bones in thalassemia patients. Other bony abnormalities such as spinal deformities, scoliosis, nerve compression, spontaneous fractures, have also been described in patients with thalassemia. Osteopenia and osteoporosis represent prominent causes of morbidity in young adults of both genders with thalassemia major or thalassemia intermedia.

Other problems in patients with beta-thalassemia are: development of diabetes and hypothyroidism, the parathyroid gland dysfunction, cardiomyopathy, impaired renal function and delay in sexual maturation.

2 WHO report 2010

In the latest WHO report of 2010 it has been shown that, in general, wealthier countries have far lower levels of child mortality than poorer ones – in low-income countries, the median level of child mortality in 2008 was 109 deaths per 1000 live births, compared with 5 per 1000 in high-income countries, representing a more than 20-fold difference. Several low-income countries have achieved comparably low levels of child mortality – with wide variation in levels of child mortality observed in most of the country-income groups. In low-income countries, child mortality in 2008 ranged from 14 to 257 per 1000 live births representing an 18-fold difference. Child mortality rates have fallen since 1990 in all country-income groups – with the rate of decline generally faster in high-income and middle-income countries than in low-income countries. Median child mortality fell by almost 50% between 1990 and 2008 in lower middle-income countries, but by only 31% in low-income countries.

Despite ongoing efforts to enhance disease surveillance and response, many countries face challenges in accurately identifying, diagnosing and reporting diseases due to the remoteness of communities, lack of transport and communication infrastructures, and shortage of skilled health-care workers and laboratory facilities to ensure accurate diagnosis.

Health service coverage indicators reflect the extent to which people in need actually receive important health interventions. Such interventions include the provision of skilled care to women during pregnancy and childbirth; reproductive-health services; immunization to prevent common childhood infections; vitamin A supplementation in children; and the treatment of disease in children, adolescents and adults.

There are several resources available to the health care system – these include physicians; nurses and midwives; other health-care workers; and hospital beds. In general, countries with the lowest density for both physicians and nurses/midwives are in the WHO African Region.

There are differences between rural and urban areas in coverage of key health services such as skilled-attendant at birth and immunization – these differences are

more marked in low-income countries compared with middle-income countries. 80% of urban births take place with the assistance of skilled health personnel compared with only 35% of births in rural areas.

To further reduce child mortality neonatal mortality must be decreased. Globally about 40% of pediatric deaths under 5 years of age are estimated to occur in the first month of life; most within the first week. The under 5 years mortality rate, e.g. the probability of dying by age 5 per 1000 live births is estimated for example in Ghana with 76, and for Namibia with 42. Life expectancy at birth has been shown for low income countries like Ghana for both genders with 62 years and for upper middle income countries like Namibia with 63 years. There are big differences to high income countries like Germany where life expectancy at birth reaches 80 years.

3 Diagnosis and prevention of rare anemias / hemoglobinopathies

Diagnosis of complex haematological pathologies such as e.g. congenital haemolytic anemia caused by rare enzymatic defects and other haematological diseases which are difficult to categorize, requires the advice of dedicated specialists. Red cell morphology, when typical, is the first and foremost diagnostic tool. However, due to the wide heterogeneity of rare anaemias, an expert eye is required to draw exact diagnostic conclusions. For the diagnosis of hemoglobinopathies, Hemoglobin-electrophoresis is needed.
One aim could be to create an on-line image bank of peripheral red blood cell smears from affected individuals, consultable from all hospitals.

Table 1: Tests used for Hematologic Diagnosis:

- Complete Blood Counts
- Peripheral Blood Smear Examination
- Fetal Hemoglobin Estimation
- Hemoglobin Electrophoresis or High Performance Liquid Chromatography
- and Screening of parents for carrier status

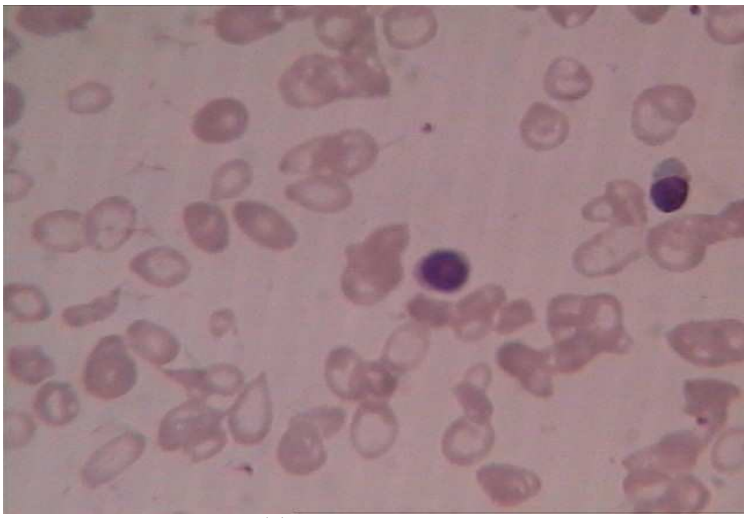

Figure 2: Smear from a Thalassemia major case

In sickle cell anemia, a newborn sickle cell screen, prepared from dried blood spots screening cards is possible. It has been established in the USA and European countries.

Prenatal genetic diagnosis at the embryonic stage for example in ß-thalassaemia has been established in the Mediterranean countries. Chorionic villi samples biopsy during the first trimester of pregnancy can be used for that approach. New approaches are being developed obtaining fetal DNA from maternal plasma from the first trimester onwards. This approach is a useful tool for noninvasive prenatal exclusion of fetal beta-thlassaemia major.

Genetic counselling helps individuals or couples to be fully informed of their genetic risk. It allows them to make appropriate decisions for their descendants. Genetic counselling must provide information on disease characteristics, evolution and treatments, genetic transmission and reproductive options, including prenatal diagnosis. Two main types of severe haemoglobin disorders must be considered: sickle cell anaemia and thalassemias. Sickle cell anaemia stems from a single ß-globin gene mutation, but the resulting phenotypic expression is widely variable, ranging from severe haemolytic anaemia to individuals exhibiting very mild symptoms. The same clinical variability is observed among individuals affected with thalassemia, and this condition may result from heterogeneous genotypes of the alpha and beta globin genes. Moreover, several globin gene abnormalities can be found in a single individual modifying the clinical presentation and complicating the genetic transmission. Most of the haemoglobin disorders are recessively inherited. Thus in the absence of preventive measures, a couple of heterozygotes for an Hb disorder has a ¼ risk to give birth to a baby affected with a severe disorder. To avoid having an affected child, a heterozygote has at least, three main reproductive options. The first one is to avoid marrying another heterozygote. This becomes

possible where premarital screening of heterozygotes is available. The second is to marry another heterozygote but avoid having children. This implies the use of an efficient contraception. The third option is to marry and have babies with another heterozygote, perform some kind of prenatal diagnosis, and, if the fetus is affected, decide to terminate the pregnancy. The challenge is for both, the genetic counsellor and the couple. The woman or couple has to understand genetics and transmission and depending on their educational level this may not be easy. Cultural and religious specificity has to be taken into account.

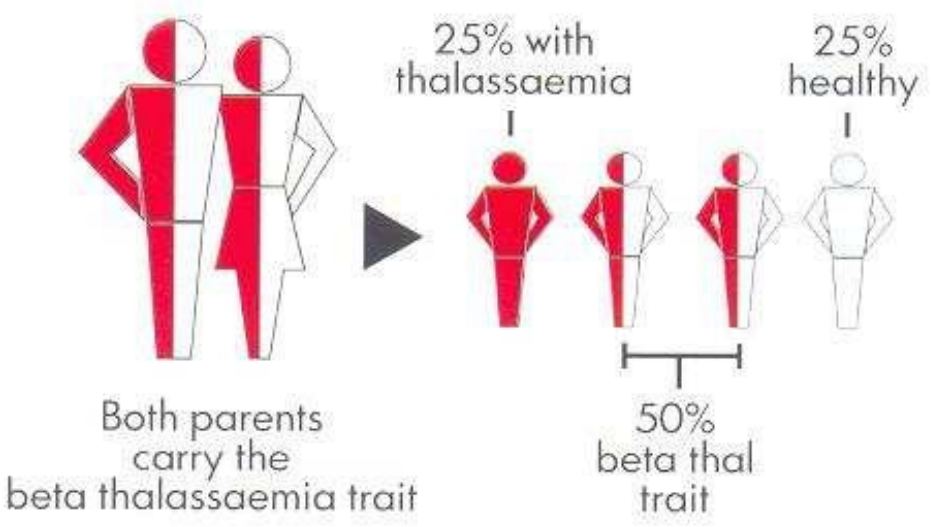

Figure 3: Carriers & patients

4 Therapeutic challenges of rare anemias/hemoglobinopathies

Treatment of patient with rare anemias / hemoglobinopathies requires preventive examinations in health centres supported by a doctor, supplementation with medicines and blood. In the African setting, especially in rural areas there might be problems with blood supply because of limited number, lack of qualified staff, availability of blood donors, problems with quality control assays, and infrastructure.

Ideally the transfusion therapy in thalassemia should fully compensate the anemia and suppress the thalassemic phenotype due to ineffective erythropoiesis. In practical this aim may be achieved in most thalassemia major patients by main-

taining a pre-transfusion haemoglobin level above 9,5-10 g/dl. This promotes normal growth and allows the patient a full integration in social life.

Keeping that haemoglobin level can only be achieved by regular blood transfusion every 3-4 weeks. There might not be enough blood supply in those countries.

Blood transfusion-exchange is necessary in some situations for sickle cell anemia, for example long periods of pain, priapisme, refractive ulcer, orthopaedic surgery, gall bladder surgery.

Blood donor screening and improved infectious disease testing of blood units have contributed to the decreased risk of transfusion-transmitted diseases. However, overall blood safety is threatened by the discovery of new hepatitis agents, the discovery of variant Creutzfeld-Jacob disease and the increasing threat of Chagas disease, malaria, babesia, ehrlichia and bacterial infections. Also Parvovirus B19 infection, usually responsible for benign pathologies, may be transmitted by blood transfusion and may cause a serious clinical outcome in susceptible patients with shortened red cell survival such as thalassemia patients. The transfusion of phenotyped red blood cells (Rh, K) is very important for prevention of alloimmunisation in beta-thalassemia patients and is an essential condition to improve the quality of their lives.

5 Aims to improve national health according to blood disorders

According to a study on thalassaemia, (Qamruz Zaman, Association between the Education & Thalassaemia: A statistical Study, Pak. j. stat. oper. res. Vol.II No.2 2006 pp103-110 107), different suggestions are recommended to control the disease like rare anemias / hemoglobinopathies and its spread in the population.

These are as follows:

1. General awareness of the people regarding the features and complications of rare anemias / hemoglobinopathies, which can be carried out through different media like newspaper, television, radio etc.
2. General health education among the people should also be carried out to arrange treatment for those suffering from blood disorders. This will help to prevent spread of rare anemias / hemoglobinopathies.
3. The Hospitals and welfare societies should cooperate with researchers, in order to reach a good data collection. There is a big need to build up a proper registration system.
4. Every Hospital should maintain proper records of every individual`s case, so that the analysis based on those data is accurate.
5. Properly trained persons should be appointed.
6. Necessary medication, blood and disposable injections should be provided at the Basic Health Units, Centres and free dispensaries should be set up.

7. Se-up basic diagnostic possibilities and rules to detect blood diseases, like laboratory investigations of red cell morphology by blood cell smear, detecting pre-pregnancy Hb level, examinations of Hb electrophoresis.
8. Most patients live in rural areas where easy access to the divisional head quarter hospitals is not possible at all times. It is suggested that there should be a standard Childrens hospital in every subdivision to provide blood products and other medications.
9. Couples should go for a blood test to detect carrier status of the common blood diseases prior to planning to start a family. In that way they will be aware of the possible genetic disease that their children may be born with.
10. Genetic counselling will then be able to advise and present the options for the couple. Prenatal diagnosis will also be able to detect any deformities or genetic disease of the child.

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26 Two weeks cataract surgery in rural Ethiopia

Jörgen Petersen

1 Facts about Ethiopia

Ethiopia is a strongly underdeveloped country being no. 174 of 187 states in the HDI scale (human development index of the United Nations) [1]. The CIA World Factbook [2] presents the following data (in parenthesis: Ethiopia´s rank compared to 238 states of the world): Fertility 6,02 children/wife (7); population growth 3,194%/year (8); median age of population 16,8 years, life expectancy 56,19 y (195), population older than 65 years 2,7%. The mean income (gross domestic product "GDP" per capita) is 971US$ per year (212); 85% of the population work in agriculture. Literacy (age >15y) is 42,7%. Ethiopia´s health expenditures are 3,6% of GDP (170). Arithmetically there is one physician available for about 50.000 inhabitants (187) and one ophthalmologist for about one million inhabitants. But really the majority of doctors practices in the capital Addis Ababa (2,9 million inhabitants), while the 100 million people in rural Ethiopia outside Addis Ababa only have minimal access to medical care. And this applies even stronger for ophthalmology. 1,6% of the population is affected by blindness and 3,7% by low vision according to the "National Survey on Blindness, low vision and Trachoma in Ethiopia 2005-06" [3]. About one half in either group is caused by cataract. These nearly 2,5 million cataract people are a huge challenge for Ethiopia, the international community and its program "Vision 2020 – global initiative for the elimination of avoidable blindness" [4].

2 Eye hospital in Nekemte/Ethiopia

Nekemte is located 250 km west of Addis Ababa at a height of 2100 m. It is an important traffic junction and market place and was the capital of the former Welega Province. The number of inhabitants is currently estimated at about 100.000. There is a provincial hospital but no ophthalmic facility in it.

Figure 1: Nekemte centre **and typical dwelling cottage in rural area**

An independent eye clinic was founded in oct 2007 by the "Mekane-Yesu-Church" of Ethiopia with support by several groups from Great Britain, Germany and Switzerland. The clinic is a bungalow building of about 200m². It has an outpatient area with two examination rooms, and an operation area with two operation rooms, both equipped with operation microscopes. A subsidiary building houses an optical workshop where spectacles are customized and repaired. Impressively the optical workshop is driven by a deaf-mute young woman. An adjacent bungalow bed house with 6 rooms was under construction in june 2010. The staff consisted of one fully-fledged ophthalmologist, one cataract-nurse, 5 operation nurses and a lot of support personnel, altogether about 20 persons. Both, the ophthalmologist and the cataract nurse, were only temporarily engaged. The organizer and driving force of the clinic is the local priest of the protestant church, Kes Alemu. His most severe problem is to bind a fully educated ophthalmologist permanently. Ethiopian doctors do not want to remain at rural regions for a longer period of time but pursuit settlement in Addis Ababa. This is a severe drawback for the continuous patient care and constructive development of the Nekemte eye clinic. The Ethiopian state tries to counteract this general problem by means of the so called cataract nurses. These undergo a supplementary 2years education in ophthalmic surgery after their nursing exam and are allowed to do cataract surgery on their own responsibility.

Figure 2: Nekemte Eye Clinic: Outpatient area and bed house under construction

Currently the clinic performs 10.000 out-patient treatments and 1000 cataract operations per year. The material costs for a cataract operation – intraocular lens, viscoelastics and sutures, about 5 Euro each - amount to 15 Euro. The mean monthly income of the local population is about 13 Euro, for many individuals much less. So they are not able to pay the real costs. They contribute with 3,5 Euro for a cataract operation and 0,5 Euro for an eye examination. The rest is essentially financed by "Licht für die Welt" (Austria) [5], "Schweizer Blindenhilfe-Äthiopien" (Switzerland) [6] and " Leuchtfeuer-Rotary Osterholz" (Germany) [7]. Thus financial pressure is always present. The chance for cost reduction was the reason, why I was asked by "Leuchtfeuer-Osterholz" to visit Nekemte in order to instruct and train the local eye surgeons in sutureless cataract surgery. This took place 24.may - 10.june 2010.

3 Teaching cataract surgery

The peculiarities of cataract surgery in Ethiopia become best obvious by comparison. In western industry countries the indication for cataract surgery is blurred vision. Lowered visual acuity of 0,6 is generally accepted as a sufficient justification for an operation. Blindness because of cataract is a rare exception in Germany. The lenses are sufficient soft to be emulsified by ultrasound (phakoemulsification). The surgical steps are:

1. Cutting a funnel shaped peripheral corneal incision of 2-3mm, sufficient for insertion of the phako-tip and implantation of a foldable lens.
2. The anterior capsule is opened by CCC (continuous curved capsulorhexis). This technique is a precondition for a reliable in-the-bag-implantation of the artificial lens.

3. Lens removal by phakoemulsification under closed-eye-conditions, which minimizes corneal endothelium damage.
4. Cortex removal and capsule polishing under closed-eye-conditions.
5. Implantation of a foldable lens into the capsular bag.
6. Ready, no sutures, the corneal funnel is self sealing, the eye is watertight

Cataract surgery in Ethiopia is different in many aspects. The indication for surgery is complete blindness in the majority of cases. Usually the lens is totally opaque, often dark brown and built up by an extremely hard nucleus only. Emulsification would not work. The lens can only be removed as a whole ("ExtraCapsular Cataract Extraction" ECCE). The surgical steps as observed 4 years ago at Debre Markos/Ethiopia and now at Nekemte again are adapted to these conditions:

1. 10 mm corneo-scleral opening of the anterior chamber using scissors.
2. Opening of the anterior lens capsule by letter-box or can opener technique.
3. Mobilisation and extraction of the nucleus using viscoelastics and lens loop.
4. Cleaning of the capsular bag using a Simcoe cannula (suction by a manually operated syringe).
5. Implantation of PMMA posterior chamber lens (not foldable PolyMethylMetAcrylat).
6. Suture of the corneal wound using 10/0 polyamide thread.

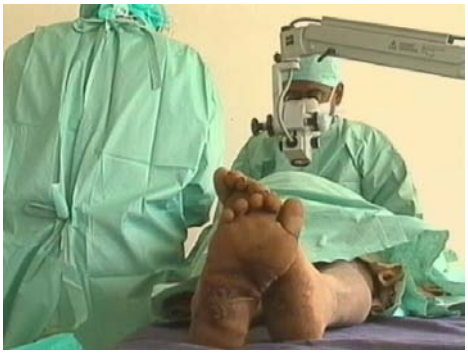
It should be emphasized that the "normal" cataract in Ethiopia would be regarded as a high risk case in the western world and that Ethiopian cataract surgeons are very skilled to manage it, though there is a high rate of complications to be described later. The surgical technique would be nearly the same in Germany – with one exception: Even for a large entrance to the anterior chamber it is possible to construct the corneal wound as a self sealing tunnel without sutures. This is called "SICS" (Small Incision Cataract Surgery, even though the incision can be 8-10 mm broad). It was the aim of my visit to introduce SICS to Nekemte. Both cataract surgeons of the eye clinic learned this modification quickly. Thus the 10/0 polyamide thread, that so far accounted for 25% of the material costs, could be saved.

4 Outpatient statistics

Besides the operations there are between 30 and 50 outpatients daily who get therapy at the Nekemte eye clinic. I used the opportunity to examine 410 eyes of 205 consecutive patients and document the results on a preformed data sheet. The frequencies of the most important diseases in this group were as follows: Cataract 44%, glaucoma 10%, cataract and glaucoma simultaneously 7%, infections 16%, trauma 7%. The predominant importance of cataract becomes obvious here again. Glaucoma is certainly underrepresented. For it causes no or only little symptoms

prior to blindness. Glaucoma usually is a casual diagnosis for patients who visit the clinic for other eye problems. About one half of the cataract patients had pseudoexfoliation, so the real frequency of glaucoma must be very high. This also becomes obvious from the statistics of blindness, where cataract and glaucoma nearly have the same weight: 19% of the new cases were blind in both eyes (mean age 57,5 years). The underlying disease was cataract in 35%, glaucoma in 30%, trauma in 17% and corneal ulcer in 13%. Additionally it became obvious that blindness is associated with poverty: 48% of blind patients had no shoes, while the barefooted fraction in the whole outpatient group was only 25%.

Figure 3: Outpatients with various eye diseases



Cataract extraction in the operation theatre

5 Quality of cataract surgery

The patients came back for control 1day, 1 week and 1 month after cataract surgery. So I could examine 73 recently operated eyes, 7 of which were perforating injuries. In 82% there was a posterior chamber lens implanted, in 10% an anterior chamber lens, and 8% remained aphakic. The following complications could be documented: Damage to the iris and pupil occurred in 47%; vitreous loss happened in 26%; vitreous incarceration into the corneal wound was visible in 16%; remnants of lens material relevant for visual acuity were present in 15%; irreversible damage and decompensation of the cornea occurred in 12%; a dropped nucleus or retinal detachment were seen in 3%, both. The functional results were satisfactory (acuity >0,6) in 33%, intermediate (0,3-0,6) in 41% and insufficient (≤0,2) in 26%.

These results would not be acceptable in Germany, of course. Nevertheless one should be careful not to judge too hastily. The positive message is: About 85% of previously completely blind people regained ambulatory vision, and in 74% acuity was principally even sufficient for reading.

6 Existing deficiencies and possible improvements

There were two reason, why European standards in cataract surgery were not achieved: Insufficient control over refraction and inadequate management of intraoperative complications.

There were a lot of problems with refraction. The existent autorefractor was defect, refraction measurements by the temporary staff was extremely unreliable. Originally ultrasonic biometry equipment had been available but was no longer functioning due to mechanical damage. So lens power calculation could not be performed. All patients got a standard lens of 21 D. As a result even keratometry was not performed neither before nor after operation. So there was no control for astigmatism, the more so as facilities for astigmatic spectacle correction were lacking.

The other point was intraoperative complications. Damage to the iris was a result of pupil constriction during operation. Even corneal damage is a consequence of such worsening of conditions. Insufficient mydriasis relies on the intense iris pigmentation in the African population that binds topical mydriatic agents efficiently. Indeed I could observe that the preoperative drop application was not satisfactory. This could be improved easily.

Vitreous loss is a consequence of the big and hard lens nucleus together with letter-box opening and zonula weakness due to pseudoexfoliation. These conditions could be improved only by an earlier operation. But this is unrealistic with respect to the large number of cataract-blind people. Surgical management of vitreous loss can be optimized using vitrectomy instrumentation, so far not available at Nekemte. This would be an important step forward because 10% of vitreous loss eyes develop retinal detachment, in case of vitreous incarceration even more. The problem with vitrectomy is the high cost, again.

There exist considerable uncertainty on the real position of the implanted lens. A small pupil during implantation and the ragged capsulotomy are high risks for partial or total dislocation of the lens haptics. It was not possible to gather sound data on this topic at Nekemte, but it is known from literature [8] that the risk for a final out-of-the-bag-position of the artificial lens is about 70%. Fortunately in most cases this has no serious consequences except for an elevated rate of aftercataract that can be assumed to be higher than 50% at Nekemte. And this points to another problem: So far there is no YAG-laser available. As a side effect of my stay I instructed both surgeons how to deal with the aftercataract problem by opening the opacified capsule from behind using a pars-plana-needle.

7 Summary

The actual mission - introduction of sutureless cataract surgery in order to save costs - was successful. Additional teaching topics were surgery for aftercataract and combined surgery for cataract and glaucoma. But even severe shortcomings be-

came visible during my two weaks stay. The one is insensitive handling of the technical equipment resulting in mechanical damage of for example slitlamp, operation microscope, ultrasound biometry and autorefractor. As a result of my report the Austrian NGO "Licht für die Welt" thinks about a technical survey and repair service for their projects in the third world. The other shortcoming is fluctuation of the medical staff in rural Ethiopia. Surgical quality can only be enhanced on a sustainable basis if there is personnel continuity in the operation theatre. And last not least: The antagonism between quality and cost on one side and quantity on the other side is an absolutely unfamiliar problem to us and a challenge for optimization.

Figure 4: Farmer and his son after ox-ploughing

On the way to the Nekemte market

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27 Ultrasonography at a rural district hospital in sub-Saharan Africa – a mixed blessing?

Werner Stein

In developing countries health facilities are often poorly maintained, equipped, and staffed. Hence overall efficiency and effectiveness in health service delivery are often inadequate. This is in particular true for rural district hospitals in sub-Saharan Africa and especially applies for sonographic facilities at these hospitals.
In developing countries, sonographic facilities are mainly available at tertiary centers and private hospitals. However typically district hospitals are the primary referral point and quite often district hospitals in rural areas are the only medical facilities. In many developing countries, especially in sub-Saharan Africa sonographic service is frequently either inadequate or even nonexistent[1].

Sonography is a safe diagnostic imaging technique widely used in industrialized countries. For some diagnostic investigations, sonography has replaced other radiographic imaging techniques and has become the method of choice.

In skilled hands, sonography provides accurate and invaluable information that enables the diagnosis and management of a variety of conditions. Sonography has the potential of being crucial in decision making[2].

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[1] Tsige M, Atnafu A. Status of radiological services in Addis Ababa public hospitals. Ethiop Med J. 2011;49:257-63

[2] Mindel S. Role of imager in developing world. Lancet 1997; 350:426–429

Ultrasonography is easy to operate and requires very little patient preparation[3]. In general two transducers, usually a curved array for the range 3 to 5 MHz and a linear array for the range greater than 5 to 10 MHz can be used for examination of all body regions with the B-scan technique and suffice the requirements of a district hospital. Power inconsistency is common and a voltage stabilizer to maintain a constant voltage level seems to be prudent. Sonographic equipment generally needs little maintenance.

Modern ultrasound devices are usually equipped with Doppler function - colour Doppler and PW Doppler - which is in the setting of a sub-Saharan district hospital only of minor importance. The proper use of the Doppler implies deeper knowledge and advanced skills of the sonographer.

Diagnostic and interventional sonography can be distinguished. Diagnostic sonography is characterized by plain imaging without further measures. Interventional sonography is defined as an invasive procedure performed under sonographic guidance for any tissue or organ that is visualized by ultrasound. Interventional sonography can be further subdivided into diagnostic procedures and therapeutic procedures. A diagnostic ultrasound-guided aspiration is performed in order to gain fluid or a tissue sampling for further analysis. A therapeutic ultrasound-guided drainage is defined as the therapeutic removal of a large amount of pus for example in order to accelerate the healing process or prevent imminent rupture of an abscess. A therapeutic ultrasound-guided drainage is sometimes accompanied by injection of medication – e.g. ethanol into a cyst in case of echinococcosis.

Ultrasonography is the ideal tool to extent diagnostic and therapeutic opportunities especially in a resource restrained setting. Therefore the implementation of an sonographic service should generally be recommended. Nevertheless sonography at a district hospital in sub-Saharan Africa is a mixed blessing. Ultrasonography has not only the potential to improve but also to be without any impact or even to deteriorate medical performance.

Poor defined indication for sonography, misconception of sonography as a status symbol, and insufficient training are potential pitfalls.

Ultrasonography does not compensate poor physical examination. For example gross ascites or foetal position are usually identified by clinical means. Only if medical history and physical examination are sketchy and inconclusive sonography would be appropriate. Indications for the use of sonography within diagnostic pathways have to be clearly specified.

As personnel-intensive technology it might distract resources from other areas. Hence staff might be not available to address other and possibly more important needs.

The perception of sonography as a status symbol is more likely in hierarchic societies as in sub-Saharan Africa and it is likely to hamper the full beneficial potential

[3] [No authors listed]. Training in diagnostic ultrasound: essentials, principles and standards—report of a WHO Study Group. World Health Organ Tech Rep Ser 1998; 875:i–46

of sonography. In case an ultrasound machine would be misconceived as a status symbol it might not be used by staff members who have to deal with important treatment decisions. For example the delivery room is usually run by midwives and a medical officer is mostly not available. Implementing sonography in obstetrical care in this setting can only be successful in participating midwives in performing sonography. The perception of an ultrasound machine as a status symbol would make it impossible for the midwives to use sonography.

A sonographer is only able to interpret sonographic images correctly if he knows the differential diagnosis and what to look for. To translate a sonographic image into a diagnosis and consequently into a treatment decision is very challenging. Advanced molar pregnancy for example is a very difficult diagnosis by only clinical means but with sonography it is quite easy. In this case[4] a pregnant woman presented at the hospital complaining missing foetal movement. By sonography neither foetal heart activity was registered nor foetal parts were seen. The image was afterwards described as snowy – the typical sonographic image of a molar pregnancy. Still assuming intrauterine foetal death a caesarean section was finally performed. Only then the diagnosis of a molar pregnancy was realized. Ideally the uterus would have been evacuated. Importance and difficulty to translate an sonographic image into relevant information must not be underestimated.

Considering implementation of ultrasonographic service the following issues should be addressed:

1. Is the hospital functional?
2. Who should perform ultrasonographic examination - specialist vs. clinician?
3. Who should undergo ultrasonographic examination - selective vs. screening?
4. How to organize ultrasonographic training?

1 Is the hospital functional?

This question addresses the overall performance of an institution. A poor set up is not uncommon and accounts for a substantial part of mortality and morbidity.
Already minor organizational changes could result in remarkable improvements. In a malaria ridden area children up to five years of age face the risk of severe anaemia. Many of them die shortly after arrival at the hospital. The reduction of the time interval between arrival and the time to give life saving blood is self-evident. It has been shown that a shortening of this interval below three hours resulted in a reduction of mortality by 30%[5]. A shortage of sodium citrate - which is necessary to produce blood bottles – ad the onset of the annual malaria epidemic is likely to

[4] personal observation

[5] Own data, unpublished

result in many unnecessary death. To concentrate critical ill patients in one room rather than scattering them all over the ward ensures proper monitoring. To secure monitoring of women within the first hours after giving birth decreases the likelihood to miss a life threatening postpartum haemorrhage.

The above mentioned examples are self-evident. A common sense approach is a prerequisite of a functional hospital. But nevertheless the negligence of obvious organizational arrangements increases unnecessary morbidity and mortality. It seems obvious that it would be unwise to introduce a new technology to an institution that is not functional in this respect.

2 Who should perform ultrasonographic examination – specialist vs. clinician?

Ultrasonography could be performed either by a specialist or by a clinician. The specialist sonographer is typically qualified by a formal training, has a deeper knowledge and more advanced sonographic skills. He performs a scan in detail and is frequently not further involved in the clinical evaluation and the final management decision. For example a detailed sonography of a specialist would be required to rule out fetal malformation in a pregnancy complicated by hydramnion.

The clinician on the other hand knows the patient's problem. If medical history or the clinical examination are inconclusive an ultrasound examination would be appropriate. He is performing the sonography having a well defined problem in mind. For example fetal heart beat is not heard with the stethoscope in an obese pregnant woman. Intrauterine death could be easily confirmed or ruled out by sonography. A suspected liver abscess for instance could also easily confirmed with sonography on a basic sonographic level.

3 Who should undergo ultrasonographic examination – selective vs. screening?

In industrialized countries sonography is commonly performed as a screening tool in obstetrical care. It has been favoured to diagnose placental abnormalities, multiple pregnancies, ectopic pregnancies, foetal abnormality, foetal growth retardation and to confirm gestational age.

The introduction of routine ultrasound scanning in a resource-constrained health-care setting could place a large burden on available resources, detracting from other more beneficial services[6]. However it has been demonstrated that screening ultrasonography did not improve clinical outcome as compared with the selective ultrasonography. Selective use of ultrasound in antenatal surveillance can

[6] World Health Organisation, 1994. Mother Baby Package: Implementing Safe Motherhood in Countries, Maternal Health and Safe Motherhood Programme. WHO, Geneva.

be valuable in specific situations in which the diagnosis remains uncertain after taking clinical history and performing physical examination[7].

Nevertheless screening in early pregnancy in order to identify placenta praevia could be a useful indication. In this condition the placenta is covering the cervix and it is a leading cause of life threatening antepartum haemorrhage. Placenta praevia affects approximately 0.5-1% of all pregnancies. Only a minority of women with placenta praevia reaches a health facility in time and it could be assumed that the majority of women with this condition die before. However the value of antenatal sonographic screening for placenta praevia in sub-Saharan Africa has still to be confirmed in future studies.

At present the routine use of ultrasonography as a screening tool cannot be recommended[8]. At a district hospital sonographic service should be strictly selective. Ultrasonography is personnel-intensive therefore ultrasonographic examinations should only be performed in case a change in management seems to be likely. The indication to perform a sonography should clearly be defined.

Other meanings to cut down on dispensable ultrasonographic examinations should be considered. For example urinary schistosomiasis causes urinary tract pathologies which can easily be identified by ultrasonography. However the measurement of albuminuria has been suggested as an alternative tool for monitoring urinary tract pathologies[9]. Therefore in urinary schistosomiasis albuminuria assays could be used as a tool for selecting those with more chronic bladder-wall lesions without resorting to ultrasonography[10].

4 How to organize ultrasonographic training?

Ultrasonographic training is of outmost importance and probably the most serious challenge in establishing a sonographic service. Without providing a proper training the implementation of sonography would probably do more harm than good.

In sub-Saharan Africa sonographic training capacities, facilities and resources are insufficient[11]. Sonographic training abroad – in Europe or America – might be an alternative. However the prevalence and incidence of diseases differ in devel-

[7] Stein W, Katunda I, Butoto C. A two-level ultrasonographic service in a maternity care unit of a rural district hospital in Tanzania. Trop Doct. 2008;38:125-6

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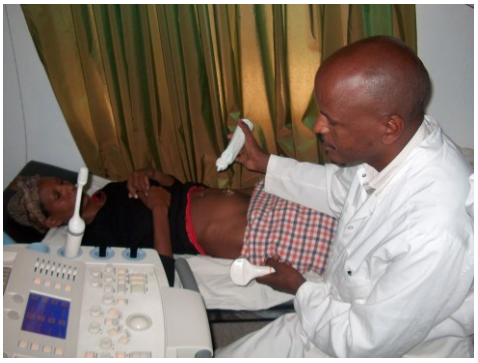
[11] Goldberg BB. International arena of ultrasound education. J Ultrasound Med 2003; 22:549–551

oping countries from those in developed countries. It would be therefore important to provide training appropriate to the environment. And it would be ideally if trainees could perform sonography in patients of their everyday practice.

Hence the training is often individualized and carried out by enthusiastic private persons. The Working Committee Ultrasound in Developing Countries (AKUSEL) has organized several ultrasonograhy courses in sub-Saharan Africa as in Blantyre, Dar es Salaam, and Nairobi. Filling in the need for training these courses were well attended. However single courses do not give the opportunity of a feed back for the trainees.

Sonographic training program at the level of a district hospital has been demonstrated to be feasible[12]. Courses have been scheduled every 4 months for 2 consecutive weeks each time. The sonographic training program lasted 5 years and was divided into three stages in which basic, advanced, and specialized courses were organized. In order to advance to the next stage a trainee had to pass a theoretical and a practical test at the end of every course.

Picture 1: Hands on session at sonographic training in Eritrea. Pregnant women with severe hydramnion.



Picture 2: Hands on session at sonographic training in Eritrea

A two-level sonographic service in obstetrical care was shown to be feasible and effective[13]. The basic obstetric ultrasonograhy as a 24 hour service was performed by midwives. Their findings were controlled by a specialist sonographer. Basic sonography could be trained in a short time and successfully be incorporated in daily patient care. The continuous education on site has assured high quality in sonographic capabilities.

[12] Ferraioli G, Meloni MF. Sonographic Training Program at a District Hospital in a Developing Country: Work in Progress. AJR 2007; 189:W119–W122

[13] Stein W, Katunda I, Butoto C. A two-level ultrasonographic service in a maternity care unit of a rural district hospital in Tanzania. Trop Doct. 2008;38:125-6

In Uganda the Ernest Cook Ultrasound Research and Education Institute (ECUREI) offers different ultrasound courses ranging from three month up to two years[14]. Doctors, assistant physicians, radiographers, nurses, and midwives are eligible for the diploma course. Nurses and Midwives account for more than half of all students. Non-modular and modular courses are offered. The non-modular is single continuous block of training lasting 6 months. The modular training lasts 1 year, and is divided into six modules, each module lasting 2 weeks.

5 Liver abscess

Liver abscesses - amebic and pyogenic liver abcesses – are difficult to diagnose by clinical means resulting in high complication and fatality. Sonography has revolutionized diagnosis and treatment of liver abscesses and will therefore be discussed in detail.

6 Amebic liver abscess

Entameba histolytica, the causative agent of an amebic liver abscess usually colonizes the gastrointestinal tract without producing symptoms. In 1 to 10% an untreated, asymptomatic infection will change into an invasive disease, usually a liver abscess.

Patients usually present with a combination of fever, right-upper abdominal pain, and hepatomegaly. Jaundice is only reported in 5% of the cases. The presence of jaundice may worsen the prognosis. Bacterial superinfection of an amoebic abscess is rare. Needle aspiration of a non-pyogenic liver lesion may accidentally introduce secondary bacterial infection.

The lesion wall of an amebic liver abscess is fragile and because of inner pressure, a rupture may occur at some point of the liver capsule, with extension into the surrounding pericardium, pleural and peritoneal cavities. Amebic liver abscess can lead an incidence up to 20% to several complications as peritonitis, pleural effusion, subphrenic abscess, pulmonary abscess, or empyema.

Ultrasonography is the diagnostic tool of choice. The sonographic feature of an amebic liver abscess tends to be round or oval, hypoechoid, with well-defined margins. The hepatic lesion is usually solitary, and most frequently is located in the right lobe.

[14] Kawooya MG, Goldberg BB, De Groot W, et al. Evaluation of US Training for the Past 6 Years at ECUREI, the World Federation for Ultrasound in Medicine and Biology (WFUMB) Centre of Excellence, Kampala, Uganda. Acad Radiol 2010; 17:392–398

The definitive evidence of hepatic amebiasis is based on a demonstration of Entamoeba histolytica trophozoites. However, trophozoites will be found in only a small percentage.

Metronidazole is the drug of choice for the treatment of hepatic amebiasis. In general patients respond to metronidazole therapy alone within a week. A diagnostic aspiration of a presumed amoebic abscess is generally not required[15]. However a sonographic guided drainage is indicated in the following circumstances[16]:

- Large liver abscesses of the right lobe in imminence of rupture;
- Abscesses of the left lobe;
- Amebic liver abscesses with pleuropulmonary complications;
- Lack of clinical improvement.

In absence of complications, rapid clinical improvement is seen. In large abscesses aspiration generally enhances clinical recovery and accelerates resolution.

Hepatic cavity healing may occur within from 3 to 12 months and must be monitored by ultrasonography. The majority of amebic liver abscesses resolves to a sonographically normal parenchymal pattern. However, a small percentage develops focal hypo- or isoechoic areas surrounded by a hyperechoic wall[17]. These residues do not require further treatment.

7 Pyogenic liver abscess

Pyogenic liver abscess is the result of bacterial infection of the liver parenchyma, with subsequent infiltration by inflammatory cells and formation of pus. Pyogenic liver abscess is a serious, life threatening condition. Pyoogenic liver abscesses are likely to be fatal if left untreated. Poor nutritional status, an immunocomprised state and malignancies are factors contributing to the poor outcome. The clinical incidence varies from region to region, but has been reported up to 2.2% of the hospital admissions[18].

In the last decades a major paradigm shift has taken place in the diagnosis and management of pyogenic liver abscesses resulting in a significant improvement in its mortality. Before the 1970s open surgical drainage was often adopted for the treatment of pyogenic liver abscesses. With the development of imaging tech-

[15] Blessmann J, Binh HD, Hung DM (2003) Treatment of amoebic liver abscess with metronidazole alone or in combination with ultrasound-guided needle aspiration: a comparative, prospective and randomised study. Trop Med Int Health. 2003:8,1030–4

[16] De La Rey NJ. Indications for aspiration of amebic liver abscess. South Afr Med J 1989;75:376

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[18] Huang CJ, Pitt HA, Lipsett PA, et al. Pyogenic hepatic abscess. Changing trends over 42 years. Ann Surg 1996;223:600-7

niques minimally invasive approach combined with systemic antibiotics has become the preferred treatment. Nevertheless pyogenic liver abscess remains a major diagnostic and therapeutic challenge. Early diagnosis and prompt therapy of pyogenic liver abscess are essential in order to reduce its complications as well as the associated morbidity and mortality.

The symptoms are non-specific and include fever, nausea, vomiting, right upper quadrant pain or epigastric discomfort. Less frequently reported symptoms are cough or hiccups due to diaphragmatic irritation.

Systemic antibiotic therapy is one mainstay of treatment. It must be targeted according to locally prevalent organisms and to specimen culture sensitivity. Therapy below four weeks seems to be a significant predictor of failure, requiring subsequent intervention.

In the setting of a rural district hospital sonographic guided drainage of the liver abscess is the first line intervention and it is compared to an open surgical procedure simpler and cheaper. Sonographic guided drainage is suitable to uni-locular abscess, to multiple unilocular abscesses and also to multiloculated abscesses. However surgical management may be appropriate as initial treatment in ruptured abscesses and complicated concomitant biliary disease. Otherwise surgery is increasingly limited to cases of failed radiological management or to the management of complications. The failure of sonographic guided drainage can lead to uncontrolled sepsis. Nevertheless, sonographic guided drainage may be the initial line of drainage to stabilize high risk patients, definitive surgery may still be necessary.

Sonographic guided percutaneous drainage and needle aspiration have emerged as appropriate alternatives to open drainage. Both procedures provide similar high success rates. The decision to perform repeated needle aspirations or to leave a drainage catheter in the abscess cavity following aspiration is disputed.

Needle aspiration is the simpler and quicker method to perform with a decreased risk of procedural complications and post-procedural sepsis. However this approach requires careful follow-up, and often multiple repeat imaging procedures to monitor response to therapy.

In large abscesses larger than 5 cm the insertion of a drainage catheter has been shown to be more effective than needle aspiration. The time to achieve a 50% reduction in size of an abscess cavity was significantly longer and failure rates were higher with needle aspiration[19] [20].

Nevertheless percutaneous catheter drainage has some disadvantages. Multiple percutaneous drainages may be required due to drainage tube block or inadequate drainage.

[19] Rajak CL, Gupta S, Jain S, Chawla Y, Gulati M, Suri S: Percutaneous treatment of liver abscesses: needle aspiration versus catheter drainage. AJR Am J Roentgenol 1998, 170:1035-9

[20] Zerem E, Hadzic A: Sonographically guided percutaneous catheter drainage versus needle aspiration in the management of pyogenic liver abscess. AJR Am J Roentgenol 2007, 189:W138-42

Both procedures show equal comparable results with an equal failure rate of 3%[21]. The duration of antibiotic therapy may be shortened with effective drainage. The following management of pyogenic hepatic abscess has been proposed[22]:

1. Immediate administration of empiric broad spectrum parenteral antibiotics;
2. Ultrasound to confirm diagnosis, with simultaneous radiologically guided aspiration of all abscesses > 5 cm[23], +/- drain placement;
3. Microbiological analysis of abscess aspirates and blood cultures: antibiotic regimen should be adjusted according to culture results and sensitivities;
4. Early recognition of septicemia or organ failure;
5. Surgical intervention should be considered for patients with large, complex, septated or multiple abscesses, underlying disease or in whom percutaneous drainage has failed.

Management and prognosis of amebic and pyogenic abscesses are markedly different, therefore the differentiation of both entities is very important. In case of any doubt it would be prudent to perform a diagnostic[24]. sonographic guided aspiration. Epidemiologic and clinical information, in conjunction with positive amebic titers, may suggest the diagnosis. In non-endemic areas, a positive amoebic serology is very likely to be diagnostic of an amoebic liver abscess. However, in endemic areas seropositivity may reflect prior invasive intestinal infection. Serological titers (indirect Hemagglutination) usually become negative within one year of acute infection, but may remain elevated for five to six years after cure in some patients[25].

8 Conclusion

Ultrasonography is an ideal diagnostic and therapeutic tool to improve patient care in many aspects. Nevertheless the decision to implement a sonographic service at a rural district hospital in sub-Saharan Africa should be individualized considering carefully potential pitfalls. Certainly sonography will not improve the outcome in a malfunctioning facility. Formal ultrasound training is still in the fledgling stages. Nevertheless ultrasound training is a precondition of an efficient sonographic service and weaknesses or even lack of ultrasound training are still the main obstacle.

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Of outmost importance are strictly defined indications and the integration of sonographic findings into clinical management.

Sonography has revolutionized diagnosis and treatment of liver abscesses that have been discussed in detail as an example of successful sonographic intervention.

28 Medical geography and travel-related health risks in overseas tourism

Daniel Karthe and Tobias Reeh

Abstract
Subtropical and tropical countries play a major role for the European long-distance travel market. Both statistical data and numerous case reports demonstrate that the multitude of destinations is reflected by a multitude of health problems experienced abroad or imported into travellers' home countries. Despite such evidence, relatively little is known about the links between travellers' risk awareness, risk behaviour and health problems actually encountered. Interdisciplinary approaches integrating the perspectives of tourism research, health science and medical geography are required for the assessment of travel-related health risks. A case study on Egypt, one of the most important overseas destinations for the European market, illustrates the contributions of and challenges for geographic research in this context.

Keywords
Overseas Tourism, Health Risks, Medical Geography

1 Linking Tourism Research and Medical Geography

The travel industry is a business selling positive holiday experiences (Bentley & Page 2001), and staying healthy is „an integral part of the 'tourist experience' which affects overall satisfaction levels of tourists and can ultimately affect their quality of

life. […] Adverse effects on the health of tourists may significantly tarnish the resulting experience of a holiday or destination" (Lawton & Page 1997: 89). Regions for which tourists report a high incidence of health problems during their visit may ultimately face negative consequences (Bentley & Page 2001). Because of this, health issues associated with international and domestic tourism are now beginning to attract the interest of researchers from a wide range of social science and medical disciplines (Lawton & Page 1997; Vingerhoets et al. 1997; Karthe & Reeh 2011). Increasing numbers of overseas travellers and the emergence of new tourist destinations mean that tourism now has a significant public health impact (Scharlach et al. 2010). One important reason is that trends like last-minute offers and online bookings result in insufficient time for preparation, including vaccinations and information about potential health risks at destinations (Karthe & Reeh 2011). Adequate analyses are needed to improve travel health advice (Cossar 1996).

Since the turn of the century, several crises have put travel-associated risks into the focus of tourism science (Mansfeld & Pizam 2006). Consequently, the investigation of these risks has become established as one branch of the discipline (Clift 2000; Freyer & Groß 2004; Pechlaner & Glaeßer 2005; Becken & Hay 2007), with the key aspects being natural calamities, terrorism and crime, as well as healthy travel. There is a considerable need for research on travel-related health risks (Gach 2010). At the same time, the importance is manifested both in public health statistics and perceived as a relevant problem by travellers (see table 1).

Table 1: Risk perception of travellers

Risks perceived to be most frequent	**Risks perceived to be most severe**
Disease (66.6%)	Disease (66.2%)
Crime / Fraud (36.6%)	Accident (54.3%)
Theft (35.4%)	Natural calamity (incl. weather) (44.4%)
Problems with hotels (33.7%)	Crime / Fraud (36.4%)
Lost or damaged luggage (22.2%)	Unrest / Terror (35.1%)
Technical problem (15.2%)	Theft (21%)
Natural calamity (incl. weather) (14.3%)	Problems with hotels (14.2%)
Problems with tour operator (11.8%)	Lost or damaged luggage (7.7%)
Unrest / Terrorism (8.6%)	

Problems actually encountered	**Improvements desired**
Disease (45.5%)	Safety of public transport (55%)
Problems with hotels (25.4%)	Safe food and water (44%)
Lost or damaged luggage (19.5%)	Flight safety (37.1%)
Unrest / Terrorism (2%)	Information (33.2%)
	Border controls (32.4%)
	Road safety (31%)
	Health (22.3%)
	Luggage Handling (19.3%)

Source: Demski (2009)

In the context of the SARS pandemic, Wilder-Smith (2007: 318) pointed out how close the connexion between tourism and health is: „SARS, travel and travel medicine were intricately interlinked. Travelers belong to those primarily affected in the early stages of the outbreak, travelers became vectors of the disease, and finally, travel and tourism themselves became the victims." According to the World Travel & Tourism Council, the impact of SARS in 2003 for the tourist industry was four to five times greater than that of the terrorist attacks on September 11, 2001 (Wilks et al. 2006). The H1N1 influenza virus ("swine flue") in 2009 illustrated two significant relations: On the one hand, tourists are an important risk group (e.g., in Mexico and Mallorca). On the other hand, international travel facilitated a rapid, global spread. Originating from Mexico, the virus quickly reached the industrialized nations as the source markets of long-haul tourism. HIV/AIDS is another example of an infectious disease whose spread was partly driven by tourism (Kleiber & Wilke 1995; Clift & Carter 2000; Kumar & Pathania 2010). In the recent past, research has concentrated on three major topics: (a) the assessment of travel-associated health risks; (b) the investigation of risk awareness and behaviour among travellers; (c) the import of health problems by travellers.

1.1 Assessment of travel-associated health risks

Dawood (1989) pointed out that roughly half of all tourists who spend their holidays in overseas countries experience some sort of health disorder. Besides accidents, common causes of morbidity among tourists include cardio-vascular problems related to heat-stress, skin damages due to overexposure to UV radiation, gastro-intestinal disorders resulting from the consumption of microbiologically contaminated food or water and vector-borne infectious diseases such as malaria or dengue (Shandera 1993; see table 2)

Table 2: Selected studies on travel and health

Authors	Study group and design	Findings
Cossar et al. (1990) (cited by Lawton & Page 1997)	Interviews with Scottish travellers after their return	• 36% reported illness • 28% reported alimentary problems (diarrhoea and/or vomiting)
Cartwright (1996) (cited by Lawton & Page 1997)		• alimentary problems are the most common ailments (attack rates of ≥ 50%)
Bryant et al. (1991) (cited by Lawton & Page 1997)	Health clinic reports on Canadian travellers after their return	• ≥ 50% of the travellers visiting a health clinic after their return had experienced diarrhoea
Werner et al. (1976), Dannenberg et al. (1982)	Cruise ship passengers	• Gastroenteritis identified as the most common problem
Shlim & Houston (1989)	Trekking tourists in Nepal	• Mean morbidity and mortality rates of 24.89 ‰ and 4.98 ‰ respectively (per person year) • Acute mountain sickness as the main cause of morbidity
Steffen et al. (1987)	Europeans travelling to developing countries	• 15% encountered health problems • 8% consulted a doctor • 3% were unable to work for an average of 15 days
Steffen et al. (1987)	Europeans travelling to developing countries	Mean monthly incidence rates • giardiasis 7 ‰ • amebiasis 4 ‰ • hepatitis 4 ‰ • gonorrhea 3 ‰ • malaria 3 ‰
Hall & Mc Arthur (1991) (cited by Bentley & Page 2001)		• 70% of all adventure injuries and 50% of all fatalities in Australia associated with white water rafting
Paixao et al. (1991)	952 Scottish tourists who died abroad between 1973 and 1988	Causes of mortality: • 69% cardiovascular diseases • 21% accidents

Hargarten et al. (1991)	2463 deaths of American tourists who died overseas between 1975 and 1984	Causes of mortality: • mainly cardiovascular diseases • 25% accidents
Nichol et al. (1996)	Medical record data of 7 regional hospitals in Queensland, Australia admitting overseas visitors	• 37.6% of all admissions related to injuries and poisonings
Bentley & Page (2001)	Public hospital morbidity data from New Zealand on non-residents	Causes of tourist injury morbidity: • motor vehicle accidents: 28.4% • sports accidents: 53%
Cossar et al. (1990)	13816 travellers returning to Scotland (1977-1989)	• 36% experienced at least one health problem • 28% reported gastro-intestinal disorders • higher attack rates among tourists on package holidays
Steffen et al. (1983) (cited by Cossar et al. 1990)	16568 randomly selected Swiss travellers	• 28% reported gastro-intestinal disorders

During recreational travel, the risk for accidents is often higher than in visitors' home countries. This is due several factors including the use of accident-prone forms of transport (e.g., off-road vehicles, motorcycles), inexperience or risky behaviour of travellers (e.g., motorcycling in shorts and without helmet, boating without nautical skills), poor road conditions or vehicle maintenance, adventurous activities (river rafting, bungee jumping, caving, mountain biking) and excessive use of alcohol (Dawood 1989; Shandera 1993). Particular risks exist in marine environments, including strong waves or currents, bites as well as envenomations, and various types of diving injuries (Shandera 1993).

1.2 Investigation of risk awareness and behaviour among travellers

Many of the tourism-related health risks can be minimized because they are typically associated with specific risk behaviours (e.g., exposure to UV radiation or insect bites). Despite this, research on the links between risk awareness and behaviour is still in its infancy. In an explorative study, Schmude & Heumann (2009) identified (1) the individual inclination to take risks, (2) personal experience and (3) the per-

ceived risk levels at the travel destination as important determinants of travellers' risk behaviour. Three adaptation strategies to risks are distinguished in tourism geography (Adelphi Consult 2005; Petermann et al. 2005):

1) Informed adaptation: Travel plans and preferences remain essentially unaffected, but information on risks is actively sought in order to minimize risks. This pattern is frequently associated with individual travellers.
2) Passive adaptation: Package tourists often feel overwhelmed by too much information and expect simple-to-follow recommendations from travel agents and tour operators.
3) Risk-averse adaptation: In this case, people who used to travel much reduce or completely stop their travel activities. People who did not travel in the past see themselves reaffirmed in their position.

About 50% of all European travellers seek information on health risks at their destination prior to departure, but only 14% consult a local health department or a centre specialized in tropical medicine (Europ Assistance 2008; Priese 2008). Interviews of long-haul travellers at Frankfurt International Airport (Gach 2010; Michels 2010) demonstrated that there is a great sensibility for travel-related health risks. At the same time, knowledge on the specific risks connected with the travellers' destination was often deficient, as was the practice of preventive measures.

Health risks remain a taboo topic in the tourism industry and tour operators face a dilemma: On the one hand, they have a duty to inform their customers about the risks associated with specific destinations. On the other hand, they want to sell worry-free leisure time (Becker 2009). Interviews conducted at 24 randomly selected travel agencies in Lower Saxony and North Rhine-Westphalia revealed that 62% of their clients ask about health risks at their destination, while 71% of the staff interviewed replied that they informed customers about health risks (Michels 2010). An exemplary check of seven online travel portals popular in Germany showed that only four of them offered the possibility to get informed about health risks (Michels 2010). Therefore, long-distance travellers need to consult additional sources such as medical doctors or websites specialized in travel health.

Risk awareness does not always translate into risk prevention. For example, 79% of the travellers who were registered with malaria at the German Robert Koch Institute in 2007 did not use any chemoprophylaxis, and those who did often failed to comply with the recommended dosages (RKI 2008). The fact that it remains unclear to which degree this is a result of an information deficit illustrates the need for more research on the links between risk awareness and tourist behaviour.

1.3 Import of health problems by travellers

„Speed is the new factor introduced by air travel. It is a matter of careful consideration that aerial journeys from distant infected countries can now be accomplished in times less than the incubation periods of certain major infectious diseases." This warning was spoken out in the mid-1920s, and led its author, a British Medical Service officer, to the conclusion that "the only safeguard which readily suggests itself for general application, is to impose observation at destination over an appropriate period upon all those landed here by air from tropical countries" (Massey 1929: 317f.) – a measure that is hardly feasible and desirable given today's volume of international travel. Nevertheless, in a globalized world where a passenger can reach almost any place in the world within a day or two, it must be kept in mind that the same is true for many pathogens (Scharlach et al. 2010).

Several infectious diseases are largely imported into countries of the Western world. In Germany, for example, about 40-50% of the Hepatitis A cases recorded in 2003 were acquired by tourists travelling to risk areas ("travel hepatitis") (Wagner & Hohmann 2004). 13.5% of the imported cases originated in Turkey, followed by Egypt, Pakistan, Spain, Morocco, Italy, India, Tunisia and Russia (RKI 2004). Steffen & Gyurech (1994) (cited by Iwarson 1998) estimated a risk of infection ranging between 3‰ and 20‰ among non-immune travellers. Even though absolute case numbers are low for Typhus abdominalis (59) and Paratyphus (72; data for 2007), the percentage of imported cases is very high at 89% and 84%, respectively (RKI 2008). In the case of schistosomiasis, all infections are imported, usually by travellers returning from West Africa (RKI 2002). Despite a generally low risk for tourists, a few studies (e.g., Jelinek et al. 1996; Potasman et al. 1996) demonstrated that adventure tourism may be associated with higher risks when it involves contact with contaminated water.

2 Geographic determinants of travel-associated health risks

Travelling carries with it the inherent risk for minor and major health problems. The health risks experienced by a traveller depend on several factors which can be categorized as environmental determinants and tourist behaviour as well as disposition (see figure 1). Whereas some environmental factors are more or less stable (e.g., landscape, hydrology), others are more variable (e.g., tourist infrastructure) or show seasonality (e.g., climate). Environmental factors are external and unchangeable by the tourist, but each tourist makes individual decisions regarding his or her exposition to these environmental factors. Many factors also have a temporal dimension: Climatic seasonality for example influences the populations of disease vectors and determines UV radiation levels. Tourists are affected by the factor time as decisions influencing health risks are taken before (e.g., vaccination), during (e.g., sun protection) and after (e.g., hospital care) a vacation. Moreover, the time and duration of a visit plays an important role.

In order to determine travel-associated health risks, it is necessary to (1) observe preferred holiday activities and the linked spatial behaviour of tourists (exposition), (2) investigate health-related environmental variables in their spatial and temporal dimension and (3) assess the spatio-temporal pattern of the factual incidence of health problems encountered by tourists. Geographic information systems (GIS) can help to visualize and analyse such data (Kistemann & Schweikart 2010), and could in the future allow for more individualized health advice.

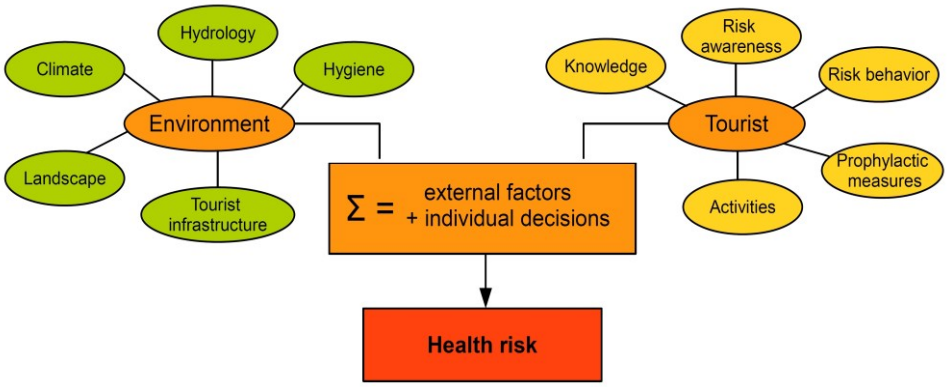

Figure 1: Model of tourism-associated health risks
Source: Karthe et al. 2009

3 Case study: tourism and health in Egypt

In the 19th century organized tourism in Egypt started with „the development of package tours from [...] Europe and steamship services on the Nile established by Thomas Cook" in 1869 (Helmy & Cooper 2002: 518). During the 20th century, Egypt's tourism industry experienced a massive growth, paralleled by a diversification of the destinations and services offered to holidaymakers. By 2010, the number of foreign visitors had crossed the 14 millions mark (Egyptian Tourist Authority 2011), and Egypt has until recently remained one of the favourite overseas destinations of European tourists. Nevertheless, there have been several setbacks caused by terrorist attacks and the consequences of the changing political situation remain to be observed. With regard to European visitors, at least three forms of tourism can be currently found in Egypt (Karthe et al. 2009; Karthe & Reeh 2011):

1. Sun and Sea resort tourism (e. g., sunbathing and diving in Hurghada and Sharm El Sheikh)
2. Cultural tourism and city trips (e. g., cruises in the Nile valley; visits to Cairo and Alexandria)

3. Individual and adventure tourism (e. g., safaris in the Libyan desert, trekking in the Sinai's interior)

Combined packages, including for example a Nile cruise, a beach holiday in one of the Red Sea resorts and short visits to Cairo/Alexandria or one of the desert regions have become an important trend (Ibrahim & Ibrahim 2006). Moreover, tourism in Egypt is in the process of a spatial expansion; new destinations within Egypt are added to the portfolio and existing capacities increased (Richter & Steiner 2007).

Egypt has a hot desert climate with a latitudinal gradient in temperature, rainfall and daily duration of sunshine. Figure 2 shows selected climate data for Aswan. During the summer months, the Egyptian climate may represent a severe thermophysical strain for visitors travelling throughout the country; during the winter months, visitors to southern Egypt may not be accustomed to prevailing temperatures which may already exceed 40°C in February. Potential consequences of prolonged heat exposure are dehydration, sunstrokes and heat strokes which may be fatal (von Wichert 2008).

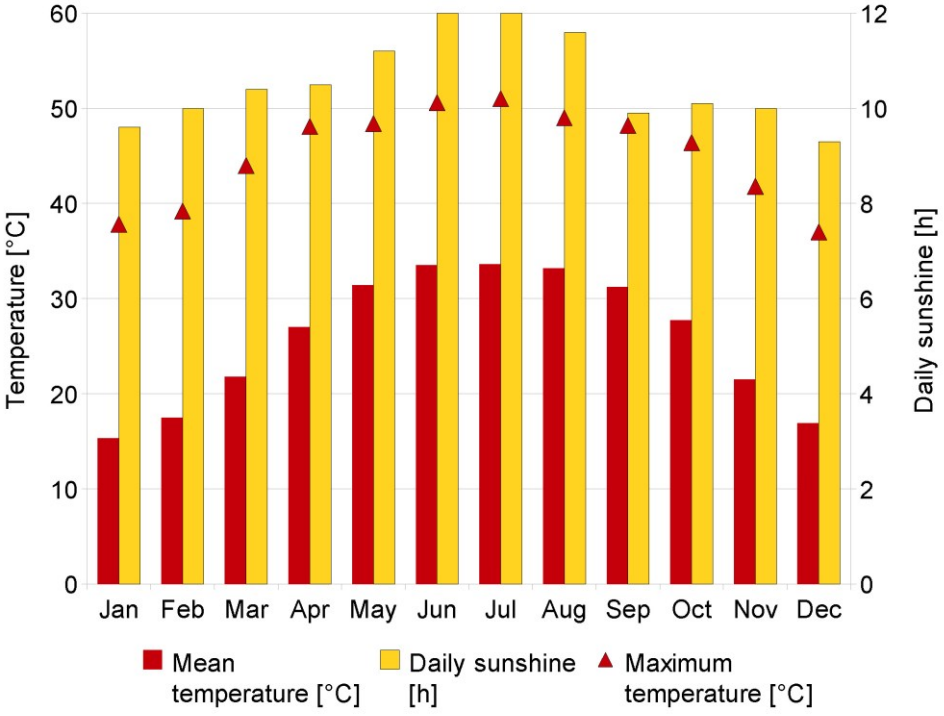

Figure 2: Selected climate data for Aswan
Source: Karthe et al. 2009

Due to Egypt's geographic position, visiting tourists are exposed to comparatively high levels of UV radiation. Activities such as sunbathing and snorkeling lead to a particularly high exposure. The intensity of the UV radiation within Egypt depends mainly on the geographic latitude and increases from the North to the South. The highest average doses are measured in the South in July, the lowest in the North in December. The average daily UV radiation dose at the Mediterranean coast (Alexandria, El Arish) is 1800 J/m² in February and more than 7000 J/m² in Aswan in July (Basset 2007). For European tourists spending a lot of time outdoors, the critical dose (e.g., 250 J/m² for skin type II, i.e. people with a pale skin, light brown or blond hair and green or blue eyes) can thus be exceeded easily (Steinmetz 2000). For office workers, a three-week summer holiday on the Mediterranean coast may account for almost 50% of their annual UV radiation dose (Knuschke et al. 2007). One particular problem in this context is that sun blockers with high protection factors are quite costly in Egypt and hard to obtain outside major tourist centres.

Food and water-borne infections, ranging from mild and self-limited diarrhoea to more severe infections requiring medical treatment are the most common health problem encountered by foreign visitors to Egypt. Foods served by street vendors and small restaurants are often particularly problematic (e.g., due to improper handling, use of contaminated utensils and water) during preparation, storage and display (El-Sherbeeny et al. 1985). Bacterial contamination of food and drinks is quite frequent in Egypt. In recent years, there have been numerous reports of European tourists returning with bacterial dysentery caused by *Shigella sonnei*, a severe form of diarrhoea that usually requires antibiotic treatment (McKeown et al. 2005). Other forms of *Shigella* are also common, including *Shigella flexneri* and *Shigella dysenteriae* (Abu-Elyazeed et al. 2004).

High prevalences of hepatitis in Egypt are a major risk factor for non-immune visitors. Hepatitis A and E are of particular importance to tourists since they are typically transmitted by food and drink. A high prevalence of hepatitis A in the local population (exceeding 25% of the population in many North Egyptian communities) combined with poor standards of hygiene mean that there is a considerable risk of transmission to visitors. Consequently, there are numerous reports of foodborne hepatitis. A major outbreak occurred between July and September 2004, when at least 271 German tourists returning from the same hotel in Hurghada were diagnosed with hepatitis A. All of them had spent between 6 and 21 days at the hotel, and interviews carried out in Germany revealed the consumption of orange juice as the most likely cause of infection (Frank et al. 2007). With prevalence rates of up to 60% in some communities, hepatitis E is another reason for concern (Fix et al. 2000).

Several vector-borne diseases, including schistosomiasis, filariasis and malaria, have been present in Egypt since pharaonic times (Nunn & Tapp 2000). While malaria has, after a massive decline of case numbers in the 20th century, almost disappeared today, other mosquito-borne diseases have become more frequent. Filariasis was considered to be almost eliminated in the 1960s (Weil et al. 1999), but Egypt experienced a resurgence of lymphatic filariasis after the completion of the Aswan High Dam in 1971, which changed both water levels in the Nile and irrigation practices (Molyneux 2006). Currently, about 44% of Egypt's population are at risk of filariasis infection (Lindsay & Thomas 2000), particularly in the Nile Delta (Weil et al. 1999). As the disease is transmitted by *Anopheles*, *Aedes* and *Culex* mosquitoes and no vaccination is available, tourists travelling in these regions are also at risk. A rapid population growth, the absence of drainage provisions and higher water tables since the construction of the Aswan High Dam led to an increase of infections with *Schistosoma mansoni* in Egypt's Nile Valley (El Katsha & Watts 1997). Skin contact with water infested by the vector of the parasite, e.g. when swimming, is the major risk factor (Panjarathinam 1990). More than 80% of all schistosomiasis infections imported to Germany are acquired in Africa, with Egypt being among the top five countries of acquisition (RKI 2002). Several other vector-borne diseases have been recorded in Egypt, frequently in coastal areas, the Nile valley (particularly the Nile Delta) and the oases. Visceral leishmaniasis, a chronic disease leading to irreversible damage to inner organs which is caused by protozoal parasites transmitted by sandflies of the genus *Phlebotomus* is found predominantly along the Mediterranean coast (El Sawaf et al. 1984; Killick-Kendrick 1999). While *Leishmania major* has been present in the country for a long time, infections caused by *Leishmania tropica* were diagnosed for the first time in 2009 (Shehata et al. 2009). Moreover, mosquitoes of the genera *Culex, Anopheles* and *Aedes* may transmit several arboviral infections, including (potentially hemorrhagic) fevers such as dengue fever, chikungunya fever, sindbis fever (named after its first occurrence in a village 30 km north of Cairo), Rift Valley fever and West Nile fever. While prevalence data from Egypt suggest that the risk for travellers of contracting any of these arboviral diseases is minimal, the combined risk of an arboviral infection is at least noteworthy (Darwish et al. 1987; Corwin et al. 1992). A differentiation between tourists' travel motivations, which often determine the destinations visited and activities pursued, can help to assess the main risks to be expected (see table 3 and figure 3).

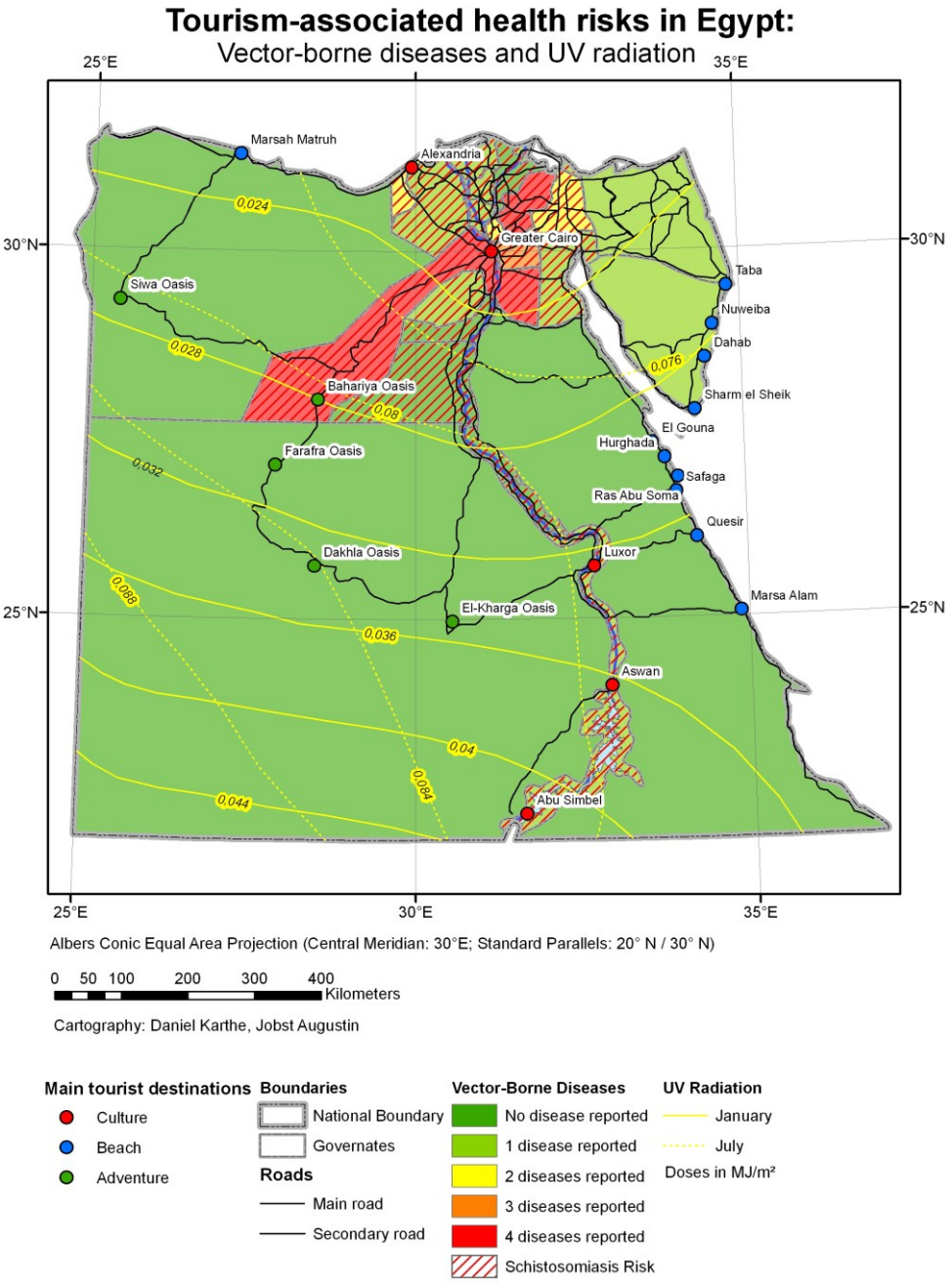

Figure 3: Tourism and tourism-associated health risks in Egypt
Source: Karthe et al. 2009

Table 3: Main travel motives, destinations, activities and associated health risks

Main travel motivation	Typical Destination(s)	Typical Activities	Main Risks
Culture	Nile Valley	Nile cruise, visits to temples and pharaonic tombs	Vector-borne diseases, gastrointestinal infections
Adventure	Western desert and oases	Jeep or camel safaris, trekking	Heat stress, gastrointestinal infections
Sun and Sea	Hurghada, Sharm El Sheikh	Swimming, sunbathing, snorkeling, diving, partying	Sunburn, gastrointestinal infections, sunstroke

Source: Karthe et al. 2009

At popular destinations such as Hurghada or Luxor, local travel agencies offer short excursions which may bring tourists into regions they were not originally planning to visit. This aspect should be kept in mind when health advice is given to prospective tourists.

4 Conclusions

Medical geography offers a broad, holistic perspective on the relationship between health problems, environmental conditions and human leisure activities by integrating and complementing the perspectives of clinical medicine, public health and tourism research. Health disorders during travel are often not registered in tourists' home countries. Moreover, there is still a paucity of information on the risk awareness and behavior of travellers. In this interdisciplinary field, several topics of geographic relevance have recently emerged.

Currently, there is a considerable knowledge deficit related to travellers' decision-making processes and health status. Little is known about risk awareness, information seeking and preparation of prospective overseas travellers and the links between these aspects. Moreover, there is a lack of empirical data on risk behaviour, preventative measures and the consultation of health services while travelling. In recent years, databases on travel and health have been established but are still not comprehensive.

The role and importance of actors in the tourist industry (e.g., travel agencies, tour operators) are still poorly understood. Their range of influence, the quality of information provided and the reception of recommendations by tourists need to be investigated systematically. Moreover, the full supply chain, including restaurants and hotels/lodges, needs to be taken into account.

From the geographic viewpoint, systematic studies of health risks at specific tourist destinations are another necessity. These should incorporate the spatio-temporal stratification of risks and their dependence on different activities and forms of tourism. Even for popular travel destinations, it remains difficult to assess health risks for tourists. Local health statistics and other information sources on public health risks do not only vary greatly for different destinations but may in the end not be representative for the risks encountered by overseas travellers. Geographic information systems could be used to integrate data from various sources, perform analyses of spatial disparities in disease risks and their determinants. Ultimately, such information could be used for an individualized, differentiated health advice for prospective travellers.

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BIOS

Abu Tholib Aman, after graduated from Faculty of Medicine, Universitas Gadjah Mada (UGM), Yogyakarta in 1986, Abu Tholib Aman worked for the General Hospital as General Practitioner, before joining the Faculty of Medicine UGM in 1989, as a junior staff. He then studied molecular biology at Faculty of Science University of Ottawa, Canada, where he got his MSc in 1994. His research interest is on the agents causing gastroenteritis, therefore when he was doing his PhD at the Faculty of Medicine, University of Bristol, England, his research project was on cholera toxin (2000). After brief appointment as Head of Department of Microbiology, Faculty of Medicine, UGM (2001-2) he then pursued his interest in research, by studying the major cause of diarrhea in children, rotavirus, where he was doing his Post Doc at the Centre for Disease Control and Prevention (CDC), Atlanta, Georgia (2002-3). He has been involved in the research group on rotaviruses until now. On coming back to UGM, he was reinstated as Head of Department of Microbiology, FM UGM until 2008. In 2008 he was appointed as the Vice Dean at the Faculty of Medicine, UGM until the end of 2011. In addition, he has been involved in several professional organizations, both at national and international level. At national level, he is a member of Indonesian Society for Clinical Microbiology PAMKI (He has been elected as the chairman of the Yogyakarta Chapter, since 2005), and also a member of Indonesian Society for Microbiology, PERMI (he is a member of executive committee since 2007 up to now). At the international level, he is a member of the steering committee, South East Asia Clinical research Network (SEACRN), and also a representative for UGM at South East Asia One Health University Network (SEAHOUN).

Medical Faculty, Gadjah Mada University, Yogyakarta, Indonesia
E-Mail: atholib04@yahoo.com

PD Dr. rer. nat. Abdul Rahman Asif is associate professor (Priv.-Doz.) of molecular medicine and head of the proteomics and mass spectrometry research group at the University Medical Center Göttingen. Beside this, he is responsible for various diagnostic units at the central laboratory of University Medical Center Göttingen. PD Dr Asif has extensive experience in the field of proteomics, in particular differential protein profiling, target elucidation and characterization of post-translational modifications of proteins. His research focuses on identifying novel molecular targets of drugs, protein - protein and protein – drug interactions, immuno-proteomics for identification of new diagnostic and vaccine targets. His research group is collaborating with several national and international partners in wide range of clinical research topics. Since 2009, he is the president of African-Asian Academics Working Group Association (AAAAA) and founding president of German-Pakistan Working Group Association (D-PAK e. V.). PD Dr. Asif is editorial board member and reviewer for several proteomics, molecular and clinical journals. He has authored and co-authored more than 40 peer reviewed articles on clinical proteomics and molecular medicine.
Clinical Proteomics & Mass Spectrometry,
Department of Clinical Chemistry, University Medical Center Göttingen,
Robert-Koch-Str. 40, 37075 Göttingen, Germany
Phone number: +49 551 39 22945, Fax: +49 551 39 12505,
E-mail: asif@med.uni-goettingen.de

Ranajit Bandyopadhyay is a plant pathologist at the International Institute of Tropical Agriculture (IITA) based in Ibadan, Nigeria. He obtained his BSc and MSc degrees from G. B. Pant University of Agriculture and Technology, Pantnagar, and PhD degree in plant pathology in 1980 from Haryana Agriculture University in India. He has been working in international agriculture research centers since 1980 – first as a sorghum pathologist at the International Crops Research Institute for the Semi-Arid Tropics (ICRISAT, India) from 1980 to 2001, and then as a plant pathologist at the International Institute of Tropical Agriculture (IITA, Nigeria) from 2002 to present. He spent two sabbatical leaves at Cornell University during 1990-91 and at Texas A&M University during 1998-1999. Ranajit has more than 32 years of extensive experience in agricultural research in Asia, Africa, North America and Latin America. At present, he is responsible for IITA's Africa-wide research and development activities related to diseases of maize, soybean, cowpea, cassava, banana and yam. His donor-funded research on mycotoxins focuses on developing an understanding of their occurrence, bio-ecology of toxigenic fungi, policy and institutional issues, and methods to manage mycotoxins with focus on biological control, diagnostics and integrated management. He has 175 publications as refereed journal articles, edited books (four), book chapters, newsletter

articles, conference proceeding articles. In 2005, he organized an international conference on impact of mycotoxins in health and trade, with special reference to Africa. He serves on editorial board of two journals and international advisory committees of a series of international conferences on mycotoxins organized by the European Union. He has been invited to give lectures in scientific meetings in Asia, Africa, Europe and the Americas.
International Institute of Tropical Agriculture (IITA).
PMB 5320 Ibadan, Nigeria
E-Mail: R.Bandyopadhyay@CGIAR.ORG

Dr. Azucena Bardají is graduated in medicine at the University of Zaragoza (Spain), and specialist in family and community medicine. She followed post graduate training in Epidemiology at the London School of Hygiene and Tropical Medicine, and completed a PhD in medical sciences at the University of Barcelona on prevention of malaria in pregnancy in African women.
She is assistant research professor at the Barcelona Centre for International Health Research (CRESIB), at the Hospital Clinic in Barcelona, Spain. She has been working in CRESIB since 2002, when she joined the Manhiça Health Research Centre (CISM) in Mozambique as clinical epidemiologist, and worked and lived there for several years. There, she was involved in several studies and clinical trials on maternal and reproductive health mainly focused on malaria, and maternal and child health, and also had clinical responsabilities attending pregnant women and children at the Manhiça District Hospital, a public rural hospital in southern Mozambique.
Her main areas of research interest have been the burden and clinical characterization of P.falciparum and P.vivax malaria during pregnancy and its impact on maternal and child health, the evaluation of preventive strategies for the control of malaria in pregnancy, the burden of maternal morbidity and mortality due to infectious and non-infectious diseases in developing countries, and more recently the evaluation of operational issues in the introduction of new vaccines such as the HPV vaccination to prevent cervical cancer in low and middle income countries.
Currently, she is the technical coordinator of a multicentre study on P.vivax infection in pregnancy with almost 10.000 pregnant women, a project funded by the EU FP7 and lead by the CRESIB, which is part of the research agenda of the Malaria in Pregnancy Consortium (MiPc). This project includes several sub-projects, and involves the interaction with partners from 9 countries including Europe, Latin America, India and Papua New Guinea.
She participates as lecturer in two master degree programmes on Tropical Medicine and International Health at the University of Barcelona, and at the Instituto Carlos III in Madrid, and coordinates a postgraduate course on maternal and reproductive health at the University of Barcelona.
Barcelona Centre for International Health Research (CRESIB),
Hospital Clínic-Universitat de Barcelona, Roselló, 132, 4-2,

08036, Barcelona, Spain,
E-mail: ABARDAJI@clinic.ub.es

Dr. Dharam Pal Bhadoria earned his five year medical graduate (MBBS) degree in 1980 from Meerut University, Utter Pradesh, three year doctorate in medicine (MD) degree in Internal medicine in 1985 from All India Institute Of Medical Sciences, New Delhi, and two year DM) degree in Pulmonary and Critical Care Medicine in 1997 from Postgraduate Institute of Medical Education and Research, Chandigarh, India. He started his academic and teaching career in 1988 and has been Professor of Medicine since 1996 at Maulana Azad Medical College, heads a Medical Unit and conducts Chest Clinic in Lok Nayak Hospital in central Delhi under the Government of Delhi, India. He was awarded fellowship in respiratory medicine in 1993 at Birmingham Heartlands Hospital Birmingham, UK, under Colombo plan. He has been teaching medicine to medical students (MBBS and MD) and guiding thesis based research of MD students and PhD students, caters to patient care services in Medicine, Pulmonary and Critical Care Medicine. He has been a clinical research investigator and been collaborating research in genetics of bronchial asthma and COPD and immunogenetics of allergic bronchopulmonary aspergillosis (ABPA).
Maulana Azad Medical College and Lok Nayak Jaiprakash Narayan Hospital New Delhi-110002, India
E-mail: dharampbhadoria@yahoo.co.in

Dr. Boubacar Coulibaly, Biologist by training, he is senior scientist at the Centre de Recherche en Santé de Nouna. After a scientific baccalaureat diploma obtained in College de Tounouma, Bobo-Dioulasso (Burkina Faso), he did laboratory engineering studies at University of Lomé (Republic of Togo). In 2001, he completed a Master degree in Molecular Biology & Physico-chemistry of Macromolecules and Applied Microbiology at the University of Ouagadougou (Burkina Faso). He has been the Head of the Department of Microbiology and Parasitology at the occupational health laboratory of Ouagadougou. In 2004, he is graduated (PhD) from the University of Heidelberg, (Germany). Since, he is the Head of the laboratory of the Centre de Recherche en Santé de Nouna and the laboratory of the Nouna Health District Hospital. His main domains of research are malaria, schistosomiasis, clinical microbiology and clinical parasitology. Dr. Coulibaly has long standing experience in clinical laboratory management, clinical research such as old and new antimalarial efficacy, basic science research and research on health systems.
Centre de Recherche en Santé de Nouna,
BP : 02 Nouna / Kossi – Burkina Faso, E-mail: boubacoulibaly@hotmail.com

Prof. Dr. Dr. Claus-Peter Czerny studied Veterinary Medicine from 1979 - 1984 at the Ludwig-Maximilians-University (LMU) Munich. He finished his doctoral thesis with Dr. med. vet. in 1986, received a licence as Veterinary Specialist in Mi-

crobiology in 1990, habilitated in 1991 (Dr. vet med. habil.) and obtained the venia legendi for Veterinary Virology and Bacteriology. After a research visit in 1997 at the National Institute of Health (NIH) in Bethesda, he became appointed as director of the Central Institute of the Bavarian Animal Health Service. From 2000 – 2001 he has been an extraordinary Professor for Veterinary Virology and Bacteriology at the LMU Munich. Since 2001 Claus-Peter Czerny is Professor for Animal Hygiene at the Georg-August-University of Göttingen and head of the Division Microbiology and Animal Hygiene of the Department of Animal Sciences. From 2009 – March 2012 he was also the managing director of the department. Beside cattle microbiology and hygiene, research interests of Claus-Peter Czerny are pathogenesis, molecular epidemiology, and diagnostic development of zoonotic poxviruses and Mycobacterium avium ssp. paratuberculosis. A prominent research field is the structure/function analysis of poxvirus envelope proteins in virus/host interactions and mapping of B-cell epitopes. In the recent years a prominent research field was established in immunoglobulin genetics and antibody engineering as well as in veterinary antibody immunology. Claus-Peter Czerny serves actively inside various scientific societies. He is a reviewer for the German Science Community and since 2010 head of the Division Tropical and International Veterinary Medicine of the German Society of Veterinary Medicine (Deutsche Veterinärmedizinische Gesellschaft; DVG). From 2003 to 2011 Claus-Peter Czerny was a Guest Professor at the Huazhong Agricultural University in Wuhan, China.
Animal Hygiene and Microbiology,
Department of Animal Sciences, Georg-August-University Göttingen,
Burckhardtweg 2, 37077 Göttingen, Germany,
Phone number: +49 551 39-3375 or -3376, Fax: +49 551 39 13513,
E-mail: cczerny@gwdg.de

Nicholas T.K.D. Dayie graduated with a BSc. (Hons) in Agriculture from the University of Cape Coast in 2002. In 2006, I graduated with a Master's degree in Microbiology from the University of Ghana and was employed as a Research Assistant on a Paediatric Pneumococcal Project funded by Global Alliance for Immunization and theVaccine Fund Agency. I was appointed as an Assistant Lecturer in October 2006 and in June 2007, I was appointed a Lecturer in the University of Ghana Medical School. As a lecturer, I always viewed my students as people with great potential which when guided can add value to the institutions they might work for in the future. This mentality has underscored the earnest desire to always go to the lecture room fully prepared with a clear cut objective to inspire and inform appropriately bacteriological techniques needed for their career. In December 2010, I gained admission and received a Danish government scholarship to pursue a PhD degree in the University of Copenhagen, Denmark. My research interest lies in the field of antimicrobial resistance and molecular epidemiology of Gram positive organisms.

Department of Microbiology, University of Ghana Medical School P O Box 4236, Accra Ghana,
E-mail: nickdayie@yahoo.com

Prof. Dr. Hartwig de Haen is retired Professor of Agricultural Economics at the Department of Agricultural Economics and Rural Development at the Georg-August University of Göttingen. He has studied agricultural sciences and economics at the Universities of Kiel and Göttingen and at Michigan State University/USA. He holds a Ph.D. in Agricultural Economics (1970). Until 1990 he was professor at the Institute for Agricultural Economics in Göttingen, where his research and teaching covered spatial economics, environment and development economics. He has undertaken research in a number of Asian and African countries, including extended periods in South Korea and Egypt. During his academic career he was a member of various research and policy advisory bodies, including the Chair of the Council of Scientific Advisors to the Federal Ministry of Economic Cooperation and Development. From 1990 until his retirement in 2005, de Haen was Assistant Director-General of the Food and Agriculture Organization of the United Nations (FAO) in Rome, where he was first head of FAO's Agriculture Department and from 1995 in charge of the Economic and Social Development Department. The latter included responsibility for FAO's work on development and food security policy, statistics, markets and trade policy, early warning, long term perspective studies as well as nutrition, consumer protection and food safety. Since his retirement he has been working mainly on issues related to food security analysis and policy. Since 2008 de Haen has been member of the Supervisory Board (Präsidium) of the German relief organization Welthungerhilfe.
Department of Agricultural Economics and Rural Development,
Platz der Göttinger Sieben 5, 37073 Göttingen, Germany
Phone number: +49 551 39 4820,
E-mail: h.dehaen@web.de

Dr. med. vet. Ulrike Sigrid Diesterbeck studied Veterinary medicine at the University of Veterinary Medicine Hannover, Foundation until 2004. She graduated as a Dr. med vet in Hannover in 2006. Following Ulrike became a member of the working group of Claus-Peter Czerny. Her research focuses on livestock and horse infectious diseases and immunoglobulin genetics.
Centre for Tropical and Subtropical Agriculture and Forestry (CeTSAF) -
Animal Hygiene and Microbiology, Burckhardtweg 2, 37077 Göttingen, Germany
Phone number:: +49 551 39 13958, Fax: + 49 551 39 13512
E-Mail: udieste@gwdg.de

Natalie Diffloth holds a B.A. degree in Sociology from Wesleyan University (Middletown, Conn., USA, 1987) and a degree in Graphic Design from the Massachusetts College of Art (Boston, Mass., USA, 1995). Integrating these two disci-

plines in her work as a consultant, she focuses in the areas of communication strategy, visual design and online multimedia. Her clients include a broad selection of non-profit community organizations as well as NGOs working in South and Southeast Asia. She has a strong interest in transcultural projects and collaborations — bringing together partners in both Western and developing countries to creatively address pressing needs. Recent cooperations include public health projects in Indonesia and Cambodia, a documentary film training venture in Afghanistan, and several programs supporting immigrant women in Germany.
Freiburg, Germany
E-Mail: natalie@diffloth.com

Dr. Busie Maziya-Dixon After graduating with BSc (Home Economics), MSc (Food Science) and PhD (Food Science) degrees from Kansas State University, Manhattan, Kansas, USA, Dr. Maziya-Dixon worked as Associate Lecturer, Department of Food Technology, University of Ibadan, Nigeria before joining IITA as Food Scientist in 1999.
Dr. Maziya-Dixon, a citizen of Swaziland, conducts research on nutritional quality, processing, utilization, and product development and evaluation of IITA mandate crops (maize, cassava, yam, soybean, and cowpea). This is aimed at (i) providing a diversity of secondary food products to avail the market with either low cost staple food for the rural and urban poor or high value products for the richer urbanites; (ii) processing crops into higher value, more nutritious products that can open new opportunities for market sales and also offer the possibility of improving dietary intake. She also coordinates demonstrations to increase awareness of postharvest technologies developed at the institute and disseminates information to create awareness on nutritional quality of IITA mandate crops and their products.
Dr. Maziya-Dixon has experience in managing projects that involve a variety of partners from national and international institutions, as well as colleagues with specialization in a range of disciplines. Among other things, these projects focus on enhancing levels of micronutrients in staple food crops through (i) identification of the best maize and cowpea varieties; cassava and yam genotypes with high iron, zinc, and provitamin A content for multiplication and distribution to farmers (ii) improved processing and storage of maize flour and products, yam and cassava products and (iii) food to food fortification of cassava products and maize meal and flour with target micronutrients. Together with national partners, she is also involved in devising a mechanism for promoting strong linkages between agriculture and nutrition with a gender perspective in order to reduce food insecurity and malnutrition on a sustainable basis.
International Institute of Tropical Agriculture (IITA).
PMB 5320 Ibadan, Nigeria
E-mail: b.dixon@cgiar.org

Dr. Rousseau Djouaka borne in 1969 is resident and researcher in Benin. He had an Msc. Degree in Cellular Biology and Genetics from the University of Ibadan in 2005. He completed his PhD program in the same University with most of his PhD research works conducted at the Liverpool School of Tropical Medicine, UK. Between 2006-2008. His PhD. Research works were focussed on the analysis of molecular basis of metabolic resistance in malaria vectors. Dr.Djouaka, has experience and expertise in various aspects of malaria transmission and control. He has a good knowledge on the analysis of links between poor agricultural practice and the emergence of water borne diseases. With a team from the Liverpool School of Tropical medicine, he pioneered in 2008 the discovery of candidate genes implicated in the detoxification of insecticides in resistant populations of Anopheles. With the active collaboration of WHO, he launched in 2011 an "Agro-Eco-Health System thinking" initiative for controlling diseases such as Buruli Ulcer and Malaria in wet Agro-ecosystems. He got several grants for research projects from World Health Organization (WHO) from 2003 to 2009. Member of many organizations involved in the study and the control of malaria, he has published 15+ papers in peer-reviewed literature. He has studied the effect of environmental changes on malaria transmission, and intensively collaborates with European institutions such as the Liverpool School of Tropical Medicine. He is involved in studies that elucidate the potential impact of agricultural/ecological transformations on malaria and Buruli Ulcer transmission. Dr. Djouaka joint the IITA team of Cotonou in Benin in 2009 where he leads activities on the development of environmentally sound package of innovations for mitigating health risks associated with poor agricultural practices.
E-mail: R.Djouaka@cgiar.org

Dr. Padma Dolma has served as chief obstetrician at the Sonam Norbu Memorial Hospital in Leh District, India since 2006. She received her MBBS (Bachelor of Medicine, Bachelor of Surgery) from Lady Hardinge Medical College in New Delhi and completed a residency in Obstetrics at Safdarjung Hospital. In 2011, Dr. Padma completed a DNB (Diplomate of National Board) at Safdarjung in Obstetrics & Gynecology with a PhD thesis on reproductive endocrinology.
International Institute of Tropical Agriculture (IITA), BP 08-0932 Cotonou, Benin
E-Mail: padmadolma@hotmail.com

Christabel Enweronu-Laryea completed her postgraduate training in paediatrics in the United Kingdom in 1994 (MRCP, MRCPCH). There after she worked as a research fellow in child health and staff grade paediatrician until 1997 when she moved to United Arab Emirates as a specialist medical officer in neonatology at Tawam Teaching hospital. She returned to Ghana in the year 2000 and has been a member of the Faculty Child Health, University of Ghana Medical School and a practicing paediatrician and neonatologist at Korle Bu Teaching hospital in Accra, Ghana. She is presently a Senior Lecturer in Child Health and Consultant Paedia-

trician in charge of the neonatal unit at Korle Bu. Her research interests are broad but mainly focuses on neonatal health, infection control and rotavirus disease. She has been offering consultancy services on neonatal health in the sub-region to international non-governmental agencies since 2009. She is a member of the editorial board of Ghana Medical Journal and an ad hoc reviewer for other medical journals. Christabel is a founding member of the Royal College of Paediatrician and Child Health of the United Kingdom and a founding fellow of the Ghana Dept of Child Health.
University of Ghana Medical School P O Box 4236, Accra Ghana
College of Physicians and Surgeons
E-mail: chikalaryea@yahoo.com

Elena Gross obtained a German Diploma degree in economics (5 year program) from the University of Göttingen in 2008. Since 2009 she is working as a research assistant and doctorate candidate at the Chair of Development Economics of Prof. Stephan Klasen, PhD. at the University of Göttingen. Her research interests are health economics and here especially the impact of water and sanitation infrastructure on health and well-being outcomes. She gained first field and survey experience during a survey in 2008 in Vietnam on vulnerability to poverty in South East Asia (DFG-Project FOR 756). During her doctoral thesis she works on an impact evaluation project analyzing the impact of German Development Assistance in the water and sanitation sector in rural Benin (West Africa).
Development Economics Research Group, University of Göttingen, Platz der Göttinger Sieben 3, 37073 Göttingen, Germany
Phone number: +49 551 39 8175, Fax: +49 551 39 7302,
E-mail: egross@uni-goettingen.de

Prof. Dr. med. Uwe Groß has studied Medicine at the University of Hamburg, Germany, from 1980-1986 and earned his title M.D. through a scientific project on virulence factors of Yersinia enterocolitica. He extended his research as a postdoctoral fellow at the University of California at Los Angeles (UCLA), USA, from 1987-1989 and as a visiting scientist in 1989 at the Palo Alto Medical Foundation, USA. Returning back to Germany, he began his medical specialization in microbiology, virology, and infection epidemiology at the University of Wuerzburg, where he also initiated a research group on toxoplasmosis. Working on diagnosis and pathogenicity of this parasitic disease, Dr. Groß obtained the "venia legendi" for Microbiology and Hygiene in 1995 and became Professor for Parasitology at the University of Wuerzburg in 1998. Since 1999, he is appointed as Professor of Bacteriology and Head of the Institute of Medical Microbiology of the University Medical Center Göttingen (UMG), Germany. In addition to toxoplasmosis, he and his team have extended their scientific interest to include epidemiology, diagnosis and pathogenesis of mycoses and campylobacteriosis. As a consequence, Uwe Groß is heading the German National Reference Center for Systemic Mycoses

since 2001 and the National Consulting Laboratory for Toxoplasmosis since 2002. In 2000, he began to establish microbiological laboratories in three Ghanaian missionary hospitals, which since then provide diagnostic service for their communities. Following the devastating tsunami in South-East-Asia in late 2004, Dr. Groß initiated a partnership between the Medical Faculty of the University in Banda Aceh/Indonesia and the UMG, which since then has been extended into the DAAD-funded Indonesian-German Health Education Partnership (IGHEP) which consists of seven German and more than 30 Indonesian biomedical institutions. In 2011 and together with members of other faculties of the University of Göttingen, Uwe Groß established the Göttingen International Health Network (GIHN) which aims to improve the health conditions of mothers and their children especially in sub-Saharan Africa.
Institute of Medical Microbiology of the University Medical Center Göttingen (UMG), Kreuzbergring 57, 37075 Göttingen, Germany
Phone number: +49 551 39 5801/5806, Fax: +49 551 39 5861,
E-mail: ugross@gwdg.de

Prof. Dr. Kim Gutschow is the Chair of the Anthropology of Public Health at the Center for Modern Indian Studies at and a Professor at the Institute of Ethnology at Göttingen University. Gutschow earned a PhD (1998) and MA (1995) in Social Anthropology from Harvard University, where she subsequently was awarded a three year post-doc at the Harvard Society of Fellows. She is the author of Being A Buddhist Nun: The Struggle for Enlightenment in the Himalayas (Harvard University Press, 2004) which won the Sharon Stephen's book prize in 2005 from America's oldest and largest association of socio-cultural anthropologist, the American Ethnological Society. Her research interests span a number of disciplines including medical anthropology, gender and sexuality studies, public health, Asian studies, and South Asian religions. She has authored over 20 other essays on diverse topics including maternal health, gender and the social economy of Buddhism, the body and Tibetan medicine, Buddhist nuns and religious identity, Himalayan irrigation, and the relationship between social power, ritual, and gender in the Himalayas. She is currently running a five year study of how maternal death reviews conducted in two Indian districts can tell us about the quality of obstetric and midwifery care at the community and facility levels and how such reviews can be tools for policy reviews and quality improvements in obstetric care across India. She received a Humboldt Fellowship for Experienced Researchers before joining Göttingen University for an ongoing study of the shift of birth from home to hospital in India and the US. She is the Honorary Editor of Ladakh Studies, a journal published by the International Association of Ladakh Studies where she has been an executive board member since 1992, and she is a member of the American Association of Anthropology and the Society for Medical Anthropology. Since 1991, she has served as Project Coordinator for an NGO, Gaden Relief, in the Indian

Himalayas dedicated to sustainable and appropriate technology in the such as passive solar houses, greenhouses, and plantation or water delivery projects.
Universtity of Göttingen, Centre for Modern Indian Studies (CeMIS), Waldweg 26, 37073 Göttingen, Germany
Phone number: +49 551 39 20246/20236, Fax: +49 551 39 14215,
E-mail: kgutsch@uni-goettingen.de

Christiane Hennecke, University Medical Centre Göttingen, UMG, is Director of the Department of International Relations and the EU-Liaison Office at UMG. She studied Pedagogic, Child and Youth Psychiatry and Intercultural Didactics at the University of Göttingen and the University of British Columbia, Vancouver, Canada. She earned her MA Master Degree in 1990 at the University of Göttingen. During her career she gained extensive experience in project management and training.
She established one of the first skills labs for medical training in surgery in Germany at UMG followed by a skills lab in cardiology with the patient simulator "Havey" and reformed the curriculum in surgery for the clinical part of the curriculum. She acts as project manager for the interactive CD-ROM "Surgery Interactive" together with Christoph Daetwyler, Philadelphia, USA and established a log book for the "Practical Year together with 6 European partners within the LEONARDO DA VINCI programme complemented by a teacher training.
She is the administrative Coordinator of several small and large scale European research projects coordinated at UMG and represents UMG in national and European advisory groups for the European Framework Programme. She is the administrative coordinator of the EUROLIFE network for UMG and Member of the External Advisory Board for PhD Studies at Trinity College Dublin.
For more than 10 years she was acting ERASMUS Coordinator of the Faculty of Medicine at University of Göttingen.
Together with Andrea Holzäpfel and Uwe Groß she initiated the Göttingen International Health Network (GIHN) at UMG side which aims to improve the health conditions of mothers and their children especially in sub-Saharan Africa.
University Medical Centre Göttingen, Dept. of International Relations, Robert-Koch-Str. 40, 37075 Göttingen, Germany
Phone number: +49 551 39 8770, Fax: +49 551 39 22593,
E-mail: christiane.hennecke@med.uni-goettingen.

Andrea Holzäpfel successfully completed a Triple Qualification course in Languages and Business at the University of Applied Sciences Cologne, Germany in 2005 and was awarded a B.A. First Class Honours, a Maîtrise and a German Diploma (FH-Dipl.). In addition, Ms. Holzaepfel earned a MSc in Public Health from the London School of Hygiene and Tropical Medicine (LSHTM) after studying for three years as a distance learning student while working in a fulltime position. The special focus of her studies was on environment and health. Ms. Holzaepfel gained

her first work experience in internships at the United Nations Information Service (UNIS) in Geneva, the German United Nations Association (DGVN) and the NGO Transparency International in Berlin. In 2006, she joined the Department of International Relations and EU-Liaison Office at the University Medical Centre Göttingen where she worked for 5 years as a project manager and Deputy Director. During her time at the University Medical Centre she supported the foundation of the Göttingen International Health Network (GIHN). Since 2011, she has been working for the KfW Development Bank in the Sector and Policy Division for Health, Education and Social Security in Frankfurt, Germany**.**

Former Project Manager for GIHN
University Medical Center Göttingen, Robert-Koch-Str. 40, 37075 Göttingen, Germany
E-mail: int.office2@med.uni-goettingen.de

Prof. Dr. Frank T. Hufert is acting head and professor at the Department of Virology of the University Medical Center Göttingen Germany. He obtained his medical degree at the University of Hamburg and received his MD working on Flavivirus epitope mapping at the Bernhard Nocht Institute (BNI) of Tropical Medicine. He also obtained a Diploma in Tropical Medicine from the BNI and is a Consultant of Medical Microbiology & Hygiene. His research interests range from the pathogenesis of HIV, HCMV and Arboviruses to the development of rapid diagnostic tools for use in clinical virology. He authored and co-authored 89 international scientific publications.

Department of Virology, University Medical Center Göttingen, Kreuzbergring 57, 37075 Göttingen, Germany,
Phone number: +49 551 39 10550, Fax: +49 551 39 10552,
E-mail: fhufert@gwdg.de

Ichsan, after graduating from Medical Faculty of Syiah Kuala University, Banda Aceh - Indonesia (2005), Ichsan worked as a physician in Red Crescent Hospital in Banda Aceh District, Aceh Province. At the same year, he began his carrier as a lecturer in the Faculty of Medicine, Syiah Kuala University (UNSYIAH) appointed in the Department of Anatomy. In October 2006, he began his Master study in Molecular Medicine at Georg August University Göttingen, Germany to study Molecular Diagnosis of Mycobacterium tuberculosis in ancient bones. He received his Master degree in 2008. In 2009, he was enrolled as a PhD student in Molecular Biology at Georg August University Göttingen, Germany to study the adherence capacities in the cell wall of Candida glabrata. Currently, Ichsan is joining the mycology research group in the Institute of Medical Microbiology of the University Medical Center Göttingen (UMG).

Medical Faculty, Syiah Kuala University, Banda Aceh, Indonesia
E-Mail: ichsanmd_aceh@yahoo.com

Dr. Julia Inthorn is a Medical Ethicist with a Background in Philosophy. She earned a Diploma in mathematics and statistics from the University of Munich, Germany in 1997. She also holds postgraduate degrees in adult's education (1998) and philosophy (2000). She gained her PhD in philosophy of social sciences with a study on research methods in social sciences in 2010. The research was funded by a scholarship from the Bavarian state. After having been research assistant in ethics for Prof. F.W. Graf at the Faculty of protestant Theology, University of Munich, she worked with a DFG funded project on clinical ethical committees, which analysed organizational forms of Ethics and shared decision making processes on moral questions combining empirical research and philosophical questions in the field of ethics. 2007-2010 she was Research assistant at the Department for Ethics and Law in Medicine, University of Vienna. There she continued her focus on empirical ethics within several research projects, like the evaluation of the Austrian Law on Living Wills and End-of-Life-Decisions, a project on Decision-Making Processes in Child Protection Groups as well as media analysis of public debates on bioethical questions. Since 2010 she has been Research assistant at the Department for medical ethics and history of medicine at the University Medical Center Göttingen. Her main research interests are Intercultural Bioethics, Empirical Ethics, End-of-Life Decisions, Ethics of Genetic Testing as well as Perspectives on Health and Justice. Dr. Inthorn has been and is lecturer at various Universities in Germany and Austria mainly in the field of ethics for health care providers (medical students, nurses, dieticians, social workers etc.). Furthermore, Dr. Inthorn was Visiting Lecturer at the Ateneo de Manila University, Philippines in 2008.
Department for medical ethics and history of medicine at the University Medical Center Göttingen, Humboldtallee 36, 37073 Göttingen, Germany,
Phone number: +49 551 39 9008, Fax: +49 551 39 9554,
E-Mail: julia.inthorn@medizin.uni-goettingen.de

Prof. Dr. Martin Kappas earned a German Dipl.- Geography (six year running program) degree from University of Bonn, Germany in 1989 and a PhD in Environmental Sciences/Climatology from the University of Mannheim in 1993. After his PhD ("summa cum laude") Dr. Kappas started a six year running "habilitation" program at the University of Mannheim to obtain the international "venia legendi" for Geography in 1998. Since 2000 Martin has been a University Professor of Geography and the head of the Cartography, GIS and Remote Sensing Section of the Georg-August University of Göttingen. His Remote Sensing laboratory is a full member of EARSeL (European Association of Remote Sensing Laboratories) and takes part as active member of DesertNET (Competence Network for Research to Combat Desertification). Moreover he is the Director of the Institute of Geography at the Georg-August University of Göttingen and a member of the Interdisciplinary Center for Sustainable Development and the Center of Applied Informatics. His research interests are broad and include topics such as landscape evaluation using techniques of geoinformatics and ground truth data collection (e.g. field

spectrometry). His main research theme is the use of Remote Sensing and GIS to study land cover / land use change. He is currently working on diverse projects in Kazakhstan (grassland carbon sequestration and ecological site classification), West- and East-Africa (ecosystem services for food security, health topics), Europe (South France, landscape degradation in the Mediterranean area) and Germany (mapping biomass potentials for future bioenergy use, advising the German Government of Lower-Saxony). In 2005 and 2009 Martin was a visiting Professor at the University of Colorado at Boulder and the National Center for Atmospheric Research (NCAR). He is a reviewer for the German Science Community (DFG) and the German Humboldt foundation. Martin serves also actively inside various societies such as the German Society of Photogrammetry and Remote Sensing or the Remote Sensing and Photogrammetry Society (UK).
Institute of Geography, Dept. Cartography, GIS and Remote Sensing,
University of Göttingen, Goldschmidtstr. 5, 37077 Göttingen, Germany,
Phone number: +49 551 39 8071, Fax: +49 551 39 8020,
E-mail: mkappas@uni-goettingen.de.

Dr. Daniel Karthe earned his State Examination in Geography and English at Mannheim University, Germany in 2001. In 1999/2000, he spent two semesters at Presidency College in Kolkata, India and worked on the issue of water management in megacities. A doctoral degree for the natural sciences was awarded in 2010 by the Faculty of Geosciences and Geography at Göttingen University for research on the geographic determinants of malaria transmission in West Africa. Currently, Daniel works at the Helmholtz Centre for Environmental Research in Magdeburg where he coordinates a German-Mongolian research project on Integrated Water Resources Management. Key research interests include Medical Geography (particularly water- and vector-borne diseases), Water Management and Environmental Research and Education. Daniel currently lectures at both the University of Göttingen and the German-Kazakh University in Almaty, Kazakhstan. Moreover, he is a speaker of the working groups on Hydrology and South Asia in the German Geographical Society.
Helmholtz Centre for Environmental Research - UFZ,
Department Aquatic Ecosystem Analysis, Brückstraße 3a, 39114 Magdeburg, Germany
Phone number +49 391 810 9104,
E-mail: daniel.karthe@ufz.de

Prof. Dermot P. Kelleher took up position as Principal of the Faculty of Medicine on 1 October 2012. A graduate of medicine from Trinity College, Professor Kelleher completed specialist training in gastroenterology in Dublin and subsequently received a Fogarty Scholarship for a research fellowship at University of California San Diego. He returned to Trinity in 1989 as the Wellcome Senior Fellow in Clinical Science and was subsequently appointed as Professor of Clinical

Medicine in 2001. In 2006 he was appointed Head of School of Medicine and Vice-Provost for Medical Affairs. Professor Kelleher's research has focused on the cell biology of immune responses both in terms of basic lymphocyte function and in relationship to mucosal immunology. His research has been focused on the immune response to many of the leading causes of infectious disease worldwide. He is the author of approximately 200 publications and 14 patents.
Faculty of Medicine Office
Level 2, Faculty Building
South Kensington Campus
Imperial College London
Exhibition Road
London SW7 2AZ
E-mail: dermot.kelleher@tcd.ie

Dr. Silke Kietz has studied medicine at the Martin Luther University Halle/Wittenberg, Germany, (six year running program, finishing 1995 "cum laude"). After a preregistration period for physicians of 18 months she worked as MD student at the Institute of Anatomy and Cell Biology of the Martin Luther University Halle/Wittenberg (1997 – 2000). The project "Alterations of gene expression in rabbit embryos after exposure to polychlorinated biphenyls." was supported by the German Research Group DFG, (GK 416). The MD-Thesis was finished in May 2000 ("summa cum laude"). From 2000 until 2003 she has been post-doctoral researcher in the group of Prof. Dr. J.-Å. Gustafsson at the Department of Biosciences at Novum, Karolinska Institute, Stockholm. The project: "Crosstalk between aryl hydrocarbon receptor and estrogen receptors." was supported by Marie Curie Fellowship, QLK4-CT-2000-52111. After one year of residency in Martin Luther University Halle/Wittenberg, Department of paediatrics, she moved to Göttingen and is working here in the hospital at the Department of paediatric hematology and oncology. Her research interests include haematological and malignant disorders in infancy.
Deptartment of Pediatric Hematology and Oncology, University Medical Center Göttingen, Robert-Koch-Str. 40, 37075 Göttingen, Germany,
Phone number: +49 551 39 202, Fax: +49 551 39 6231,
E-mail: silke.kietz@med.uni-goettingen.de

Prof. Dr. Stephan Klasen is a professor of development economics at the University of Göttingen. He holds a Ph.D. in economics from Harvard University and has since held positions at the World Bank, the University of Cambridge, and the University of Munich. His research focuses on issues of poverty, inequality, and growth in developing countries. Of particular interest are policies to promote health and reduce gender bias in mortality in developing countries.
Development Economics Research Group, University of Göttingen,
Platz der Göttinger Sieben 3, 37073 Göttingen, Germany

Phone number: +49 551 39 7303, Fax: +49 551 39 7302,
E-mail: sklasen@uni-goettingen.de

Ingrid Kühnle, Dept. of Pediatric Hematology and Oncology, University Medical Center Göttingen, Robert-Koch-Str. 40, 37075 Göttingen, Germany,
Robert-Koch-Str.40, 37075 Göttingen, Germany
Phone number: +49 551 39 6202, Fax: +49 551 39 6231,
E-mail: ikuehnle@med.uni-goettingen.de

Prof. Dr. med. Max Lakomek, Dept. of Pediatric Hematology and Oncology, University Medical Center Göttingen, Robert-Koch-Str. 40, 37075 Göttingen, Germany
Phone number: +49 551 39 6200, Fax: +49 551 39 6231,
E-mail: lakomek@med.uni-goettingen.de

Dr. med. Martina Lange is a paediatrician. She is working at the Department of Paediatric Cardiology and Intensive Care Medicine at the University Medical Center Göttingen (UMG), Germany. She is specialized in neonatology, paediatric cardiology and palliative medicine. Her research interests include life-threatening disorders and coping strategies, which was also the theme of her MD-Thesis. She has visited several parts of Africa, on one hand for medical projects (e.g. participation in a project to improve neonatal care in a district hospital in Ghana), but also for research projects.
Department of Pediatrics, Pediatric Cardiology and Intensive Care Medicine, Robert-Koch-Str. 40, 37075 Göttingen, Germany
Phone number: +49 0551 39 6262,
E-mail: mlange1@gwdg.de

Victor M. Manyong holds a degree in agriculture from IFA Yangambi in the Democratic Republic of Congo (DRC) in 1978. He completed his national services for two years respectively with the extension services with the Ministry of agriculture and the Ministry of education up to 1980. Thereafter, he was awarded an EU fellowship to complete both the MSc and PhD degrees in Agricultural Economics at Université Catholique de Louvain la Neuve (UCL) – Belgium in 1981 and 1986 respectively. For six years he worked in various capacities with the private sector, foreign-based non-governmental organizations and as an independent consultant in DRC. He travelled extensively within the country. Early 1992, he was employed as researcher at the International Institute of Tropical Agriculture (IITA) covering 14 countries of west and central Africa in a GIS-based characterization of farming systems. He progressively moved up on the ladder as a Senior researcher in agricultural and health economics. His research experience has been on the economics of food crops in sub-Saharan Africa, market and impact studies, and analysis of production economics. He has published extensively more than 150 articles in referred

journals, books, chapter books, etc. He has also contributed to capacity building with supervision of more than 20 post graduate students (MSc and PhDs) and he organized several sessions on group training. He attended international conferences, meetings and symposia in Africa, Europe, Japan, South Asia, North and South America. He is a member of many scientific professional societies such as the International Association of Agricultural Economics, African Association of Agricultural and Resources Economics. He is the leader of the Social Science Research Group and the Coordinator of research on Agriculture and Health in the same institute. As a research manager, he is the Director for East and Central Africa and member of the Research for Development Directorate at IITA, based in Dar es Salaam, Tanzania.

Director, R4D Directorate, IITA Regional Hub, Plot 25, Mikocheni Light Industrial Area, Mwenge CocoCola Road, Mikocheni B, P.O. Box 34441,
Dar es Salaam (Tanzania)
Phone number: +255 22 2700092, Fax: +255 22 2775021,
E-mail: v.manyong@cgiar.org

Muh. Nasrum Massi. After graduating from the Medical Faculty of Hasanuddin University, Indonesia (1994) Muh. Nasrum Massi worked as a physician in Nene Mallomo Hospital in Sidrap District, South Sulawesi. In 1996, he began his carrier as university lecturer of the Faculty of Medicine, Hasanuddin University (UNHAS) appointed in the Department of Microbiology. Until 2000, he jointed several infectious disease studies in the field of microbiology (Leprosy and Salmonella). In April 2000, he began his doctoral studies at the International Centre for Medical Research (ICMR), Kobe University, Japan to study Molecular Diagnostic of Salmonella typhi and received his Ph.D in 2005. In 2008, he was elected as a chairman of Microbiology Department, Faculty of Medicine, UNHAS and still hold this position today. Currently, Muh. Nasrum Massi is working as a TB Clinical Investigator in Novartis Institute of Tropical Disease (NITD)-Hasanuddin University Clinical Research (NHCR), a unit affiliating to Wahidin Hospital and Hasanuddin University Hospital in Makassar concentrating on tropical diseases research. Since 2009, he was a member of National Committee of Emerging and Re-emerging Disease of Health Department of Indonesia. He was inaugurated as a Professor in Clinical Microbiology at the Medical Faculty, Hasanuddin University, Makassar, Indonesia in 2010.

Hasanuddin University, Makassar, Indonesia
E-Mail: nasrumm@hotmail.com

Humphrey D. Mazigo trained at Sokoine University of Agriculture in Tanzania where he received a Doctor of Veterinary Medicine degree (2001-2006). Between May 2008 and November 2011, he received Master of Sciences in Medical Parasitology and Entomology and Masters of Public Health from the Graduate School of Health Sciences, Institute of Tropical Medicine and Infectious Diseases, Nairobi

Kenya and School of Public Health, Weill-Bugando University College of Health Sciences (by then a constituent College of St, Augustine University of Tanzania). He works as a lecturer in the Department of Medical Parasitology, Catholic University of Health and Allied Sciences, Tanzania and serves as a visiting lecturer to other medical schools in the country. He is currently a PhD fellow of THRiVE and WELLCOME TRUST for School of Public Health, Makerere University (Uganda) and the University of Cambridge, UK. His research interest focuses on neglected tropical diseases with focus on their interactions with disease which received much priority example malaria and HIV. Since 2010, He has gained international research experiences and has published over 25 publications in local and international peer reviewed journals on epidemiology of neglected tropical diseases, entomology and public health issues. He also serves as a reviewer in several journals of tropical medicines, parasitology and Public Health.
Humphrey D. Mazigo* and Martin Kappas**
Department of Medical Parasitology and Entomology, School of Medicine,
Catholic University of Health and Allied Sciences, P.O. Box 1464,
Mwanza, Tanzania.
E-mail: humphreymazigo@bugando.ac.tz

Stephen Mshana, MD, M.Med, PhD. Dr. Mshana obtained his MD from University of Dar es Salaam, Tanzania, Master of Medicine in Microbiology (M.Med) from Makerere University, Kampala Uganda and his PhD from Saint Augustine University of Tanzania a sandwich programme with Institute of Medical Microbiology Giessen, Germany. Dr. Mshana is Senior Lecturer in the Department of Microbiology at Weill School of Medicine of Catholic University of Health and Allied Sciences. Dr. Mshana scientific interests are the mechanisms of antibiotic resistance among gram positive and negative bacteria and diagnosis of Infectious Diseases. Dr. Mshana is recipient of a number of personal (peer-reviewed) research grants from DAAD and National Medical Research (NIMR) Tanzania. He is the author and co-author of over 30 publications in peer-reviewed journals.
Catholic University of Health and Allied Sciences-Bugando,
Senior Lecturer Microbiology/Immunology, BOX 1464, Mwanza Tanzania,
E-mail: mshana72@bugando.ac.tz

Mercy Jemima Newman earned a Ghanaian medical degree from the University of Ghana Medical School (UGMS), Accra in 1974 and an MSc in Microbiology from the London School of Hygiene and Tropical Medicine, University of London in 1980. From 1980-1985, Dr Newman worked as a microbiologist in Hammersmith Hospital, London (Royal Postgraduate Medical School). As a consultant microbiologist, she returned to Ghana Medical School as a lecturer in 1986. She was appointed Associate Professor of Microbiology in 2001 and had also been head of department of Microbiology. In addition to teaching microbiology to medical students and other health professionals, she had supervised several postgradu-

ates at the masters and doctoral levels. She had been an examiner for the School of Medical Sciences, Kwame Nkrumah University of Science and Technology, Ghana College of Physicians and Surgeons and West African College of Physicians. In 1996-1997 Prof Newman was a visiting professor at the University of Virginia School of Medicine, Charlottesville (Dept of Geographic and International Medicine). The UGMS and University of Virginia continues to collaborate in research and training of scientists. Prof Newman is an editor of the Ghana Medical Journal. She is currently the project Manager in charge of the Ghana component of the Antimicrobial Resistance (ADMER) Project, collaboration between Ghana and Denmark. Her research interest covers fungal and bacterial infections in neonates and the adult population in Ghana and other places. In addition to the ADMER project, her current research includes hospital and community infection, antimicrobial susceptibility, diarrhoea diseases and plasmids in enterobacteria.
Department of Microbiology, University of Ghana Medical School
P O Box 4236, Accra Ghana
E-mail: newmerci@yahoo.co.uk

Prof. Dr. med. Dr. h.c. Michael Oellerich is a chemical pathologist (Facharzt für Laboratoriumsmedizin) and chairman of the Department of Clinical Chemistry/Central Laboratory at the Medical Faculty (UMG) of the Georg-August-University Göttingen, Germany. He received the honorary Fellowship of the Faculty of Pathology of the Royal College of Physicians of Ireland (FFPath RCPI) and the Fellowship of the Royal College of Pathologists (FRCPath) in 2006 as well as the honorary membership of the Romanian Society of Laboratory Medicine in 2007. From 1996 to 1998, he served as dean of the Faculty of Medicine and as the deputy of the chief executive for research and teaching on the executive board for the Medical Center and Faculty of Medicine from 1999 to 2004. He was president of the International Association of Therapeutic Drug Monitoring and Clinical Toxicology (IATDMCT) from 1997 to 1999, president of the German Association for Laboratory Medicine from 2001 to 2002, president of the German United Association for Clinical Chemistry and Laboratory Medicine (2003-2005), secretary-treasurer of the World Association of Societies of Pathology and Laboratory Medicine (WASPaLM) from 2005 to 2007, and president of WASPaLM from 2009 to 2011. Currently he is the immediate past-president of WASPaLM. From 1999 to 2010, he was a member of the Steering Committee of EUROLIFE, a network of European centers of excellence in life sciences. He is Editor-in-Chief of the journal Therapeutic Drug Monitoring and Associate Editor of Clinical Chemistry. He was Associate Editor of Clinical Biochemistry (1996–2007). His current research interests are in the fields of therapeutic drug monitoring, with particular focus on endogenous biomarkers to achieve personalised immunosuppression in transplantation, as well as pharmacogenetics. Further topics include proteomics, analytical techniques (e.g. LC-MS/MS), and molecular diagnostics. He and his collaborators have authored more than 400 publications (articles contributed to scientific jour-

nals, book chapters, books edited). He served as External Examiner for the Second Professional Examination 2009/2010 of the Faculty of Medicine at the Chinese University of Hong Kong. He received the Ludolf-Krehl prize of the S.W. German Soc. for Internal Medicine in 1971, the IATDMCT Award, Cairns 1999, the IATDMCT Charles Pippenger Award for Outstanding Contributions to Therapeutic Drug Monitoring, Washington 2001, the 2002 Canadian Society of Clinical Chemists Travelling Lectureship Award, the Professor-Landbeck-Award of the Society for Thrombosis and Hemostasis Research, Hamburg 2004, the Perth PathCentre Visiting Lectureship, Western Australia 2004, and the WASPaLM Medal of Honor, Las Vegas 2011.
Department of Clinical Chemistry/Central Laboratory at the Medical Faculty (UMG) of the Georg-August-University Göttingen, Robert-Koch-Str. 40, 37075 Göttingen, Germany
Phone number: +49 551 39 8561, Fax: +49 551 39 8551,
E-mail: Michael.Oellerich@med.uni-goettingen.de,

Dr. Anna Okello graduated as a veterinarian at the University of Melbourne (Australia) in 2002. After three years in mixed rural practice in New Zealand, Anna spent 12 months in north and west Africa working for a British Non Governmental Organisation (NGO). After some time in private practice in the United Kingdom, Anna moved back to the NGO sector as a veterinary advisor for a large British organisation, working with veterinarians in Asia and East Africa to develop veterinary capacity within existing government and private systems. At this time Anna also undertook a part time Masters degree in International Animal Health at Scotland's University of Edinburgh. Upon completion of her Masters degree, Anna started a PhD at Edinburgh's School of Social and Political Science, looking at public health policy, particularly the effects of global public health on developing countries and the potential role of integrated health systems. She is currently the project manager for the large collaborative European Commission seventh framework programme "Integrated Control of Neglected Zoonoses" (ICONZ) – www.iconzafrica.org.
Okello, AL, Gibbs, EPJ, Vandersmissen A, Welburn SC (2011) "One Health and the Neglected Zoonoses: Turning Rhetoric into Reality", Veterinary Record, Vol 169, pp 281-285, doi 10.1136/vrd.5378
Global Health Academy, College of Medicine and Veterinary Medicine, The University of Edinburgh, Chancellors Building, 49 Little France Crescent; Edinburgh EH16 4SB
E-mail: Anna.Okello@ed.ac.uk

Jessica Olbrich is a state-certified Translator and Interpreter for German, English and Spanish. In June 2010, she graduated with a Master of Arts of the first class in International Management and Languages from Heriot-Watt University Edinburgh (Scotland) and received the Watt Club Medal for an excellent performance in her

final examinations as well as for outstanding academic achievements in her Master thesis. Her main fields of expertise are economics, commerce and marketing. Since she joined the Department of Agricultural Economics and Rural Development of the Georg-August University Göttingen in September 2010, she expanded her expertise in the fields of agribusiness and risk management.
Department of Agricultural Economics and Rural Development, Platz der Göttinger Sieben 5, 37073 Göttingen, Germany
Phone number: +49 551 39 4439,
E-mail: jolbric@uni-goettingen.de

Prof. Dr. Elke Pawelzik earned a German Dipl.-Engineer degree from the Humboldt University of Berlin, Germany a PhD (Dr.-Ing.) in Food Technology from the same University. After her PhD Elke Pawelzik worked as postdoc at the Moscow Technical University of Food Technology (former Soviet Union) as well as a senior engineer in the milling company of East Berlin. Afterwards, she started a "habilitation" program at the Humboldt University to obtain the "venia legendi" for Food Technology. Since 1995 Elke Pawelzik has been a University Professor of Quality of Plant Products at the Faculty of Agriculture of the Georg-August University of Göttingen. Her research interests focus on quality changes in the value added food chain with special emphasis of the pre- and postharvest periods. The main research theme includes topics such as nutrient effects, abiotic and biotic factors influencing the quality of plant products. She is currently the speaker of the Joint project Quality-related plant production under modified basic-conditions: mycotoxins in the context of production, quality and processing (FAEN-3, supported by the Government of Lower Saxony, Germany) and working there about the impact of pathogens on cereal grain and grain products quality. Furthermore, she is working on diverse projects as nutrient effects on potato quality and traceability of plant products. She has scientific cooperation's with colleagues in several countries, e.g. in Indonesia, Brazil, Thailand and African countries. Elke Pawelzik is the speaker of the German Alumni Food Network (supported by the DAAD) and permanent visiting professor at the Chiang Mai University (Chaing Mai, Thailand).
University of Göttingen, Department of Crop Sciences, Quality of Plant Products,
Carl-Sprengel-Weg 1, 37075 Göttingen, Germany
Phone number: +49 551 39 5545, Fax: +49 551 39 5570,
E-mail: epawelz@gwdg.de

Prof. Dr. med. Jörgen Petersen born 1943 at Lübeck; studies of physics and medicine at Kiel and Göttingen; PhD and MD; education in ophthalmology at Göttingen and Frankfurt, specialisation for vitreo-retinal surgery; advanced training in Boston, NewYork and Memphis/Tennessee. 1994 leader of the vitreo-retinal department of the Göttingen University Eye Clinic; 2004-2006 temporary head of the Göttingen University Eye Clinic; retired since 2008.

Third world activities: 2 times surgical teaching and operation campaigns in rural Ethiopia; 2 times teaching in Indonesia, advanced surgical training of an Indonesian colleague at the Göttingen University Eye Clinic.
Department of Ophthalmology, University Medical Center Göttingen,
Robert-Koch-Strasse 40, 37075 Göttingen, Germany
E-mail: jpet@med.uni-goettingen.de

Dr. Anjali Radkar has completed her Masters in Statistics from University of Pune, India. After that, working in Population research for a few years she earned her masters in Population Studies followed by doctorate in Population Studies from International Institute for Population Sciences, Mumbai, India. Anjali worked as 'Independent Researcher' after her doctorate for few years when she undertook studies in the areas of sex preference and women's health. During this period she received the grant from MacArthur Foundation for the study on abortions. Then she undertook a faculty position in Interdisciplinary School of Health Sciences, University of Pune. She has been teaching Biostatistics, Demography and Research Methods for postgraduate and doctoral students for many years now. She also is a visiting faculty in different departments of many universities in the state of Maharashtra. Her long time area of research has been maternal and child health, child survival and maternal and child nutrition. She also has worked on the health of urban poor and their cost of healthcare. Recently she completed two projects; one on consequences of adverse sex ratio on the marriages in Haryana and the other, evaluation of Safe Adolescent Transition and Health Initiative (SATHI) in Maharashtra. Most of her research work pertains to India where there is a diversity by area of residence, culture and social norms. She is a reviewer for both international and national level journals on reproductive health and social sciences including, Maternal and Child Health Journal.
Gokhale Institute of Politics and Economics, Deccan Gymkhana, B.M.C.C. Road, Pune 411004
Phone number: +91 20 25650287 or +91 20 25654288
Fax: +90 20 25652579,
E-mail: anjaliradkar@yahoo.co.in

Dr. Tobias Reeh (Dipl.-Geogr., Dr. rer. nat.) is a lecturer at the Department of Human Geography, Georg-August-University of Göttingen since 2007. His main research themes are tourism geography, managing landscape change, environmental education and heritage interpretation. Currently he is working on diverse projects in Tyrol and South Tyrol (tourism and transportation), Lower Saxony (business tourism, urban planning, heritage interpretation), Saxony-Anhalt (cultural tourism, sustainable regional development) and Thuringia (environmental history). Tobias Reeh is a member of the German Society of Tourism Research (DGT), the Working Group Leisure and Tourism Geography of the German Geographic Society, the Association for Pacific Studies (APSA), the Centre for Empirical Re-

search into School and Education of the Georg-August University of Göttingen (ZeUS) as well as the chief executive officer of the Centre for Environmental Interpretation and Tourism Göttingen (ZELT e.V.).
Department of Human Geography, Georg-August-University of Göttingen,
Goldschmidtstr. 5, 37077 Göttingen, Germany
Phone number: +49 551 39 8074; Fax: +49 55139 12140,
E-mail: treeh@gwdg.de

Prof. Dr. med. Utz Reichard has studied medicine at Göttingen University, Germany, from 1980 to 1987. Thereafter he specialized for Medical Microbiology and Infectious Diseases first working at the Department of Internal Medicine for two years and subsequently at the Department of Medical Microbiology at the University Hospital of Göttingen. There he still cares for diagnostics of infectious diseases particularly at the German National Reference Center for Systemic Mycoses which is also located at the facility. In addition, he is running a research lab which is focused on improving understandings for the molecular basis of mechanisms used by pathogenic fungi causing diseases in the human host. His research on Aspergillus fumigatus, which is the most threatening fungus for leukemia patients causing invasive diseases of the lung, is supported by the German José Carreras Foundation. In this field Dr. Reichard has broad experience and cooperation since years in particular with the Department of Clinical Chemistry at the University Hospital of Göttingen and with the Institute of Genomics and Integrative Biology, New Delhi, India.
University of Göttingen, Department of Medical Microbiology,
Kreuzbergring 57, 37075 Göttingen, Germany
Phone number: +49 551 39 5856, Fax: +49 551 39 5860,
E-mail: utzreicha@gwdg.de

Eva Schröer-Merker obtained a Master of Science degree at the Agricultural Faculty of Georg-August University Göttingen, Germany in 2009 investigating arboviral diseases of cattle. Since 2009, she has been working at the IFCN (International Farm Comparison Network) Dairy Research Center in Kiel, focusing her research on dairy economics. She is currently leading the Dairy Sector Analysis team at IFCN. Her main research interest is the development of the dairy sector worldwide based on the detailed analysis of approximately 90 countries.
Dairy Sector Analysis, IFCN Dairy Research Center,
Schauenburgerstrasse 116, 24118 Kiel, Germany
Phone number: +49 431 5606260, Fax: +49 431 5606 262
E-mail: Eva.Schroeer-Merker@ifcndairy.org

Dr. Marco H. Schulze, MD, DTMH (Liv), specialist in internal medicine, infectious diseases and tropical medicine. Working experience in Cameroon (2006-2009) as medical officer in charge of St. John of God Health Centre in Mamfe,

health coordinator of Bamenda Ecclesiastical Province, and medical advisor of Bamenda Ecclesiastical Province Health Assistance, a mutual health organisation. Interests: development of appropriate microbiology in resource-constrained countries.
University Medical Center Göttingen, Institute of Medical Microbiology, Kreuzbergring 57, 37075 Göttingen, Germany
Phone number: +49 551 39 5810, Fax: +49 551 39 5861,
E-mail: schulze.marco@med.uni-goettingen.de

Prof. Gainda L. Sharma completed his Master of Sciences in 1976 from Kanpur University, India and Ph.D. in Immunology from the Postgraduate Institute of Medical Education and Research, Chandigarh, India. After obtaining his Ph.D. in 1983, Prof. Sharma was appointed as Scientist-B in Regional Research Laboratory, Jammu, India. In 1988, he joined as Scientist-C at Centre for Biochemical Technology, Delhi, India, now known as Institute of Genomics and Integrative Biology where he was promoted to higher positions. At present he is working as Scientist-G and Senior Deputy Director at the same Institute. He was on deputation as Director of Institute of Biomedical Sciences, Jhansi, India from 2004-2005. He visited Thomas Jefferson University, USA in 1995 and worked on the development of transgenic systems. He was invited for a Meeting on advances against aspergillosis at Athens, Greece in February 2006. From 2007, Prof. Sharma has been Principal Investigator of an Indo-German collaborative research project on immunoproteomics and has been visiting Georg-August University, Göttingen Germany very frequently. Prof. Sharma has been significantly contributing in the major research areas such as Proteomics, Drug Development, Experimental Immunobiology, Immunodiagnostics and Functional Genomics. He is the life member of several academic bodies such as Association of Microbiologists of India, Association of Progressive Zoologists of India, Society of Biological Chemists of India, Association of Clinical Biochemists and Indian College of Allergy and Applied Immunology. He was awarded fellowship of Indian College of Allergy and Applied Immunology for his scientific contributions. Prof. Sharma has published 57 research papers, 1 book and 13 national/international patents. He has also participated in more than 60 scientific conferences/symposia/seminars as invited speaker or chairperson.
Institute of Genomics and Integrative Biology, University Campus,
Mall Road Delhi-110007, India
E-mail: drglsharma@hotmail.com

Ali Sié, Centre de Recherche en Santé de Nouna,
BP : 02 Nouna / Kossi – Burkina Faso
E-mail: sieali@yahoo.fr

Bharat Singh received Masters Degree in Biomedical Sciences from University of Delhi, India in 2003. In 2004 he joined as a research fellow in a Govt. of India Laboratory (Institute of Genomics and Integrative Biology, CSIR, Delhi, India) and worked on in vitro evaluation of genetically engineered drugs till 2007. In the same institute he joined an Indo-German collaborative research project (DBT-BMBF funded) and also enrolled for PhD in University of Kurukshetra, India. He is recently working on the identification and validation of Aspergillus fumigatus immunogens for global application in diagnostics and therapeutics. He has also visited Department of Clinical Chemistry, UMG, Göttingen, Germany several times as a part of collaborative research work. He is specialized in the field of proteomics and recombinant production of proteins from different sources.
Institute of Genomics and Integrative Biology, University Campus,
Mall Road Delhi-110007, India
E-mail: bharatsingh1601@gmail.com

Seema Singh earned post-graduation degree in Biomedical Sciences from University of Delhi, India in 2006. Being among the meritorious students of the batch she availed the CSIR-Catch them young fellowship throughout the Masters program. On completion of the course in 2006 she joined VP Chest Institute, University of Delhi, India as a project fellow. Later in 2007, she joined a Govt. of India Laboratory (Institute of Genomics and Integrative Biology, CSIR, Delhi, India) for her doctoral work and has been currently enrolled in the University of Pune, India. She is working on the screening, selection and characterization of antifungal molecules for the treatment of infections due to a major fungal pathogenic mould Aspergillus fumigatus.
Institute of Genomics and Integrative Biology, University Campus,
Mall Road Delhi-110007, India
E-mail: seema.acbrdu@gmail.com

Dr. med. Werner Stein has specialized in pediatrics as well in obstetrics and gynecology with the subspecialities of perinatology and gynecologic oncology. Currently he is establishing a department for endoscopic surgery.
He has worked in several countries of sub-Saharan Africa concerning maternal and child health issues with a focus on the meaning of ultrasonography at rural health institutions.
University of Göttingen (UMG), Department of Gynecology,
Robert-Koch-Str. 40, 37075 Göttingen, Germany
E-Mail: werner.stein@med.uni-goettingen.de

Prof. Dr. med. August Stich was born in 1960 in Nürnberg, Germany. After his medical studies he specialised in internal and tropical medicine. In the last 20 years he had various assignments to tropical countries as medical doctor, health coordinator, advisor or research fellow, among others Zimbabwe, Somalia, Cambodia,

Angola and Tansania. He has a Master of Science degree of the London School of Hygiene and Tropical Medicine where is still enrolled as lecturer. Today he lives and works in Würzburg, Germany, where he is the Head of the Department of Tropical Medicine of the Medical Mission Hospital (since 2004), the chairman of the Medical Mission Institute (since 2008) and Medical Advisor of the German Leprosy Relief Association (since 2009). He is currently vice-president of the German Society of Tropical Medicine and International Health. Since 2012 he is also member of the Board of the multidisciplinary Africa Center of the University of Würzburg. He was awarded Full Professor in January 2012.
Göttingen International Health Network, Medical Mission Institute,
Salvatorstr. 7, 97074 Würzburg, Germany
Phone number: +49 931 7912821, Fax: +49 931 7912826,
E-mail: stich@missioklinik.de

Syrhul, Medical Faculty, Syiah Kuala University, Banda Aceh, Indonesia

Prof. Dr. theol. Martin Tamcke studied Protestant Theology, Philosophy and Oriental Studies. After PhD (1985) and Habilitation (1993), both at Philipps-Universität Marburg, he was appointed Professor at Georg-August-Universität Göttingen (1999). Professor Tamcke is the Director of the Department of Ecumenical Theology and Oriental Church- and Mission-History. Maintaining a large network with universities all over the world, Professor Tamcke taught as Visiting Professor at numerous institutions in Europe, Asia, Near East and North America; he also teaches at Orthodox and Islamic Faculties abroad on a regular basis. Professor Tamcke is Director of Studies both in the international "Intercultural Theology" M.A. programme and in the Erasmus-Mundus "Euroculture" M.A. programme; both programmes of study were co-founded by him. He is Assistant Director of KEMA (Centre for the Study of the Cultures of Europe and the Mediterranean in Antiquity). Additionally, he is member of several academic societies and is appointed to different functions for the Evangelical Church of Germany (Evangelische Kirche in Deutschland). The focus of Professor Tamcke's research lies on the Christian cultures of the Near and Middle East, Eastern Europe, and India with special emphasis on interreligious coexistence, intercultural hermeneutics, and oriental-occidental relations, on which topics he has published widely. In recognition of his academic work, he was awarded a Doctorate honoris causa from the University of Joensuu (Finland) in 2009. www.theologie.uni-goettingen.de/tamcke
University of Göttingen, Faculty of Theology,
Department of Ecumenical Theology and Oriental Church and Mission History,
Platz der Göttinger Sieben 2,
37073 Göttingen, Germany
Phone number: +49 551 39 7196, Fax: +49 551 39 7488
E-mail: martin.tamcke@theologie.uni-goettingen.de

Marut Tangwattanachuleeporn was born on March 18, 1981 in Bangkok, Thailand. He graduated with the Bachelor degree of Science in Microbiology from Burapha University, Thailand in 2003 and Master degree of Science in Medical Microbiology from Chulalongkorn University, Thailand in 2005. In 2006, he got a position to be a lecturer in the Department of Medical Science, Faculty of Science, Burapha University, Thailand. Since 2009 he has been a Ph.D. student in the Institute of Medical Microbiology, University Medical Center Göttingen. During his Ph.D. study, he is the representative for Southeast Asia of Young ISHAM (International Society for Human and Animal Mycology) since 2011. His current research interest is focusing on cell wall proteins of Candida. Moreover, he is investigating the prevalence of pathogenic yeast infection and the prevalence of Cryptococcus in the environment in Southeast Asia, especially Thailand and Indonesia.
E-Mail: poonkung1@hotmail.com

Issouf Traoré is graduated from University of Ouagadougou, Burkina Faso. Mr. Traoré obtained his Master Degree in rural Geography (Maîtrise) with subject Geography of Health with the financial support of the Laboratory "Schistosomoses en Orbite" of the Health Sciences Research Institute (IRSS/CNRST-Burkina Faso) in 2004; and a Master of Advanced Studies (D.E.S.S.) in Sustainable Wetlands Management with subject Health Impact of Wetlands in 2009, co-funded by the Nouna Health Research Centre (CRSN-Burkina Faso) and the International Network for the Demographic Evaluation of Populations and Their Health in Developing Countries (INDEPTH-Ghana). Since 2008, Mr. Traoré occupies the position of Geographer at the CRSN with Environment and Health as strong point. Through the partnership between the CRSN and Universities in Germany, Mr. Traoré is, since April 2010, a PhD Candidate at the Department of Geography-University of Göttingen and supported by the German Academic Exchange Service (DAAD).
Institute of Geography, Department Cartography, GIS and Remote Sensing, Goldschmidtstr. 5, 37077 Göttingen, Germany
Phone number: +49 551 39 8029, Fax: +49 551 39 8020
E-mail: issouf.traore@geo.uni-goettingen.de

PD Dr. rer. nat. Manfred Weidmann is a senior scientist at the Department of Virology of the University Medical Center Göttingen Germany. He graduated in Biology at the Johannes-Gutenberg University of Mainz where he also received his PhD working on the pathogenesis of Clostridium difficille. Ever since he has worked on rapid diagnostic tools for the detection of arboviruses and haemorrhagic fever viruses in cooperation with partners from developing countries. He obtained the 2003 Abbot Diagnostic Award. He authored and co-authored 36 international scientific publications.
Department of Virology, University Medical Center Göttingen,
Kreuzbergring 57, 37075 Göttingen, Germany

Phone number: +49 551 39 10554, Fax: +49 551 39 10552
E-mail: mweidma@gwdg.de

Prof. Sue Welburn is Professor of Medical and Veterinary Molecular Epidemiology, Centre for Infectious Disease, The University of Edinburgh and group leader of the sleeping sickness research group. Sue has more than 20 years experience working on human sleeping sickness and zoonotic trypanosomiasis and other neglected zoonoses in domestic wild and animal populations. Research concentrates on the design and use of molecular diagnostic tools for the study and management of the neglected zoonoses. Research has encompassed research ranging from 'grass-roots' fieldwork in Africa to laboratory-based dissection of the problem at the gene level. Experience ranging from the management of high-tech laboratory research to the running of applied field projects in developing countries. Sue started her career at what was the Tsetse Research Laboratories in Bristol, a facility supported by ODA.
Sue has supervised over 35 PhD and research Masters students and has projects ongoing in Uganda, Kenya, Nigeria, Zambia, Mozambique, Mali, Morocco and Tanzania collaborating focussing on medical and veterinary sector interventions for disease control (in partnership with National Institutes of Medical Research, Ministries of Health, Ministries of Agriculture) supported by funding from World Health Organization /DFID /Wellcome Trust/Leverhulme Trust, European Union FP7, Cunningham Trust and NTI, Global Health and Security Initiative). Sue has published of over 120 peer reviewed scientific articles, reviews and book chapters.
Sue has a strong commitment to Capacity Building in HEI and Research Institutions in the Global South and is Director of the Edinburgh Global Health Academy and Assistant Principal for Global Health at the University of Edinburgh.
Global Health Academy, College of Medicine and Veterinary Medicine,
The University of Edinburgh, Chancellors Building, 49
Little France Crescent; Edinburgh EH16 4SB
E-mail: sue.welburn@ed.ac.uk

Kerstin Wydra earned a Dipl. Ing. of Agricultural Sciences in 1985, with an additional M.Sc. in Phytomedicine from University of Göttingen. After her PhD in Phytopathology from the same university, she worked as short term consultant for the World Food and Agriculture Organization (FAO) before joining the Consultative Group of International Agricultural Research (CGIAR) of the UN system from 1993 to 1999, as collaborative research project leader at the International Institute of Tropical Agriculture (IITA) in Benin, West-Africa, with research activities spread over several West-African countries, associated to universities in Europe. The follow-up of these commitments was the leadership of an EU financed project with France, UK, Benin and Togo, located at the University of Göttingen, later at the University of Hannover, where she also submitted her habilitation on

'Development of integrated control of bacterial diseases of cassava, cowpea and tomato' and obtained her Venia legendi and title of Professor in Phytopathology. Further international projects with Asian and African countries associated to University of Hannover followed, allowing the graduation of high numbers of students from developing countries. In 2004, she received an award of the 'Foundation for the German Science' through the German Research Foundation (DFG) for her research. Her research on sustainable management of crop diseases and use of biodiversity spans from ecosystem to field and molecular. As Managing Director of the Centre for Tropical and Subtropical Agriculture and Forestry, University of Göttingen, from 2009 to 2012, she was co-founder of the GIHN. She initiates and organizes collaborative international, highly interdisciplinary research projects and workshops on food security and biodiversity worldwide. She is evaluator for project proposals for national and international agencies, board member of an international journal, referee for 25 international journals, member of a committee of the Humboldt Foundation, and advisor for the definition of research for development strategies for the German government and international institutions. Since 2010 she is member of the Committee on World Food Security (CFS-HLPE). Since 2012, she is Professor of 'Plant Production under Climate Change' and elected President of the Erfurt University of Applied Sciences.

Prof. Dr. Kerstin Wydra
Erfurt University of Applied Sciences
Altonaer Str. 25
99085 Erfurt
E-mail: kerstin.wydra@fh-erfurt.de

Muhammad Yani has studied Medicine at the University of Andalas in Padang, Indonesia and earned his title M.D. in 1987. He received his Magister of Public Health in 2000 and the Magister of Family Physicians in 2001, both at the University of Indonesia. Following the devastating tsunami of late 2004, he was a member of the steering committee for Health Assistance for Recovery of Aceh Province, HARAP and for GITEC. From 2004 to 2008, he was appointed Vice Dean for Academic Affairs of the Faculty of Medicine Syiah Kuala University (USK), Banda Aceh, Indonesia. In addition, he was serving as Head of the Psychology Program Study of USK from 2007 until 2010 and as Head of the Community Health Service Management in 2008 and 2009. In 2008, he became Secretary of Governor Health Assistance. Since 2010, Dr. Yani is Head of Aceh Provincial Health Office and has implemented universal coverage of health insurance for all Aceh population. In this regard, Aceh province is the first province in Indonesia which is conducting the total coverage on health insurance.

Medical Faculty, Syiah Kuala University, Banda Aceh, Indonesia,
E-Mail: m_yani61@yahoo.com

Maurice Yé, MD (University of Ouagadougou, Burkina Faso, MPH (University of Heidelberg, Germany), PhD student (Institute of Public Health, Heidelberg, Germany).
He is currently the Head of research, training and communication department at the Centre de Recherche en Santé de Nouna, Burkina Faso since 2007.
He has 7 years working experience at government health services level as a health district manager, and 3 years experience at health research area as a research, training and communication coordinator.
With an extensive knowledge in health system management, he has worked in a multidisciplinary team research with various countries in the areas of health system research such us malaria programs interventions, monitoring and evaluations of health programs and nutrition including HIV/AIDS, implementation of bednets programs.
He has been also involved in many proposals writing with collaborative research institute and University such us the University of Heidelberg in Germany, University of Montreal in Canada. Currently he is the Burkina leader of an EU Funded project on improving quality of Maternal and neonatal care currently ongoing in Nouna research centre.
He is also a facilitator on the regional workshop in monitoring and evaluation of malaria program in Burkina Faso, co-dispensed with MEASURE Evaluation/USAID training program for African Region since 2011.
Centre de Recherche en Santé de Nouna,
BP : 02 Nouna / Kossi – Burkina Faso, E-mail: yemaure@yahoo.fr

Dipl. - Biol. Ortrud Zimmermann,
Institute of Medical Microbiology, University Medical Center Göttingen,
Kreuzbergring 57, 37075 Göttingen, Germany
Phone number: +49 551 39 5863, Fax: +49 551 39 5865,
E-mail: ozimmer@gwdg.de

Human, animal and plant health is a field of work which offers opportunities for inter- and trans-disciplinary research. The whole topic bridges the natural and social sciences. Today, in a world of global environmental change it is widely recognized that human societies and their wellbeing depend on a sustainable equilibrium of ecosystem services and the possibility of cultural adaptation to global environmental change. The need to identify and quantify health risks related to global environmental change is now one of the most important challenges of humankind.

Describing spatial (geographic, intra/inter-population) and temporal differences in health risks is an urgent task to understand societies' vulnerabilities and priorities for interventions better. The Göttingen International Health Network (GIHN) is a research and teaching network in relation to this cross-cutting topic. The book provides a collection of articles which contribute to this issue of overriding importance and presents an overview of the GIHN launch event.

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