Developing countries in Asia are at high risk for new and emerging infectious diseases and have become hotspot for many zoonoses, drug-resistant pathogens and vectorborne diseases. Better understanding of the epidemiology of and the broader social, economic, cultural, environmental, ecological and political dimensions are some of the challenges for today’s research in communicable diseases. Research is essential for the development of new tools and interventions, and should be geared towards the development of evidence-based policies and interventions to increase efficiency and effectiveness of programme development and management of health promotion and diseases prevention and control.

The need for research as a part of strategic information and evidence base for developing effective and efficient disease interventions, that contribute to the scaling up and sustaining of interventions that work, cannot be underestimated. Besides old challenges, research should address new challenges such as climate change and its impact on health.

This document is a compilation of views of several leading experts on research priorities in field of communicable diseases.
Priority Areas for Research in Communicable Diseases
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Preface

The WHO South-East Asia Regional (SEAR) consists of 11 Member Countries*. It includes three of the ten most populous countries in the world (India, Indonesia and Bangladesh). The SEAR bears a disproportionately high burden of communicable diseases, i.e. 65% of the prevalent global leprosy burden; 50% of clinical cases of lymphatic filariasis; 34% of the tuberculosis morbidity; 20% of visceral leishmaniasis, and 30% of the global malaria morbidity. Avian influenza continues to threaten populations of this Region; of 359 human cases of avian influenza reported globally since 2003, 152 were in three SEAR countries. Moreover, some of the old diseases are re-emerging about which we know little; for example, during 2006-2007, approximately 1.4 million cases of chikungunya occurred in the Region. Due to competing priorities, research has received little attention and funding. However, more recently, donors such as the Global Fund for AIDS, TB and malaria have expressed explicit interest in funding operational research projects to guide national programmes. To ensure that resources are invested in generating relevant evidence that is critical to control of communicable diseases, it is important to analyze gaps in knowledge and accordingly provide guidance on priority research agenda that should be addressed by national programmes as well as by independent researchers and the academia.

To promote relevant health research for control of communicable diseases by guiding the research agenda of national programmes and independent researches, as well as, by influencing donors to fund appropriate research, the aim of the publication is to include the following topics:

(1) Avian influenza and pandemic influenza
(2) HIV
(3) Tuberculosis
(4) Malaria
(5) Dengue
(6) Chikungunya
(7) Leprosy
(8) Visceral leishmaniasis

*Bangladesh, Bhutan, DPR Korea, India, Indonesia, Maldives, Myanmar, Nepal, Sri Lanka, Thailand and Timor-Leste
(9) Neglected tropical diseases (including yaws, lymphatic filariasis and helminthiases

(10) Zoonoses

(11) Laboratory methods for control of communicable diseases

Each topic includes a short introduction on the disease burden in SEAR, a synthesis of the knowledge gaps, and a list/description of key priority research questions.

The process followed was to ensure that these articles reflect the country realities as well as that they are scientifically rigorous. In most cases, we have consulted global and regional experts and also been in contact with country office focal persons and HQ colleagues from the respective technical units. We have tried to ensure compliance with the required editorial and stylistic standards.

The expectation from this publication is identification of broad priority areas for research, to general evidence that can be used for policy formulation and implementation, and for developing strategies relevant to the Region. Publication of these research priorities will promote research and boost science capacity locally and regionally.

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1. The overview of communicable diseases in the South-East Asia Region and research priority setting

Jai P. Narain

Magnitude of the problem

The distribution of communicable diseases globally and in the South-East Asia (SEA) Region conforms roughly to the distribution of poverty in the world and in the Region. It is therefore not a surprise that the SEA Region suffers heavily from the burden of communicable diseases. For instance, the Region has 80 per cent of global leprosy burden, 38 per cent of tuberculosis, and the highest rate of drug resistant malaria. An estimated 2.9 million deaths in the Region are caused by infectious and parasitic diseases and an estimated 89 million disability-adjusted life years (DALYs) are lost as a result. Each year, 250 000 children die of measles and 750 000 adults die of TB. More than 6.5 million people in the countries of the Region have been living with HIV/AIDS and 250 million are at risk of contracting malaria. Furthermore, epidemics of infectious diseases occur frequently and in new areas; many of them are predictable but some of them take health system by surprise. SARS, avian influenza and Nipah virus are recent examples of such surprises and are capable of causing enormous socioeconomic hardship beyond national borders. Also, dengue/dengue hemorrhagic fever (DHF) and new strains of cholera are spreading to areas where they were not common in the past. Age-old diseases like leprosy and kala-azar still cause considerable suffering and psychosocial disruption in the Region.

Resistance of some communicable diseases to drugs is an emerging threat faced across all disease control programmes. The countries of the Region are becoming epicentres of antimalarial drug resistance, putting more than 30% of the populations of the countries at risk. Hot spots for TB drug resistance are emerging and the countries have to tackle the problem of drug resistance in Shigella dysentery, enteric fever, and sexually transmitted infections (STIs). Resistance to artimisinine-based combination therapy (ACT) in malaria in Thai-Cambodia border is a matter of grave concern. Drugs for the treatment of multi-drug resistant (MDR) TB cost more than 100 times the

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cost of medicines used to treat simple form of pulmonary TB. Fortunately, however, MDR levels remain low in the Region, due in part to the well-performing TB programmes.

In addition to the large number of deaths, communicable diseases often take a heavy toll on human productivity by causing disability and personal disfigurement. Severe and sometimes permanent disabilities affect an estimated population of one billion in the world, according to Global Defence Against the Infectious Diseases Threat (2003). These disabilities include impaired cognitive development, retarded mental growth, deformed limbs (by elephantiasis) and eroded faces (by leprosy), as well as many other related physical problems.

The interplay between communicable diseases, poverty and undernutrition adversely affect socioeconomic development in the countries. Evidence also links the occurrence of cancer and some degenerative diseases to infectious causes. For example, hepatitis B and C viruses have been traced to subsequent development of liver cancer.

The scenario of communicable diseases is shaped by three factors. Firstly, there is a real and immediate threat of resurgence of infectious diseases, which can be attributable to the natural history of microbes. Pathogens and microbes constantly evolve through processes of multiplication, mutation, migration and adaptation eventually attaining resistance to commonly-used medicines and insecticides. Secondly, cultural aspects such as close animal-human interface where the two share the common habitat also play an important role in the spread of communicable diseases of zoonotic nature such as avian influenza, SARS, and Nipah virus. Thirdly, the potential impact of climate change specifically on vector-borne diseases such as malaria, dengue and chikungunya, and on diarrhoeal diseases in particular cholera, which is likely to felt greatly in poor people in Asia. In addition, during the last few decades, while the arsenal of antimicrobial drugs has not expanded, the appearance and spread of antimicrobial resistance has been on the increase, thereby narrowing the limited number of means available for the control of infectious diseases. The spectre of the continual emergence of drug resistant microbes is threatening to undermine the gains achieved in reducing morbidity and mortality due to infectious diseases.
Success stories and opportunities ahead

There are, however, many success stories. They demonstrate that if effective approaches are scaled up, both in coverage and quality, reinforced by high-level commitment and political will, these problems could be overcome. For example, smallpox and guinea worm disease have been eradicated from the countries of the Region. Poliomyelitis is on the verge of eradication and leprosy elimination is within our grasp. Significant progress has been made towards increasing population access to directly-observed treatment – short course, or DOTS, at the community level. Many countries have achieved global TB targets and others are on the way to do so. Highest level of commitment has been expressed by all affected countries for elimination of visceral leishmaniasis (Kala-azar). The progress in LF elimination also is encouraging. Political commitment made in recent years, and the participation of academic institutions, networking, intercountry cooperation, and planning are all contributing to the emerging success.

Partnerships among diverse organizations to tackle communicable diseases are expanding and this cooperative trend must be sustained. The partnership with the pharmaceutical industry, in particular, has been very encouraging, as increasing access of common man to lifesaving generic drugs is gradually changing diseases such as AIDS from a virtual death sentence to a chronic manageable condition. Considerable success has also been achieved by Member States in mobilizing substantial funds from the Global Fund to fight AIDS, TB and malaria (GFATM) for scaling up their response against the three diseases. These incidents clearly offer optimism in the Region’s continual fight against communicable diseases.

Role of WHO in communicable disease control and research

The vision of the WHO Regional Office for South-East Asia Region (SEARO) is to assist Member States in reversing the trend of communicable diseases, reducing morbidity and mortality, and improving the quality of life, thereby contributing towards achieving the Millennium Development Goals (MDG) and poverty reduction in the coming decade.
To translate this vision into reality, the Communicable Diseases (CDS) Department of WHO’s Regional Office for South-East Asia (SEARO) has been reorganized to deal with three main objectives:

(1) To enhance preparedness to tackle the threat of emerging diseases through strengthened epidemiological surveillance, outbreak alert and response,

(2) To intensify control of priority communicable diseases such as HIV/AIDS, TB and malaria in an integrated manner, and

(3) To eliminate/eradicate diseases such as leprosy, yaws, kala-azar and lymphatic filariasis.

In addition, there are crosscutting areas such as laboratory support, data management and capacity-building activities including training, which also fall within the purview of the vision. The Department works in collaboration with other WHO programmes in the Regional office and with country office, which are now primarily responsible for providing technical support to the Member States. Partnerships are being built with various stakeholders such as governments, academic institutions, civil society, and multi- and bilateral agencies who share common goals of alleviating suffering from humanity, reducing morbidity and mortality, and improving the quality of life, particularly of poor and disadvantaged sections of the society. Equitable access to health services and protection of the vulnerable populations by scaling up effective interventions are other principles that guide the action of the CDS Department.

The vision and the guiding principles of the Department have been clearly spelled out in the following statement: to, “by the end of the decade, reverse the trend of communicable diseases, reduce morbidity and mortality, and improve the quality of life, thereby contributing towards achieving the Millennium Development Goals and poverty reduction.”

The task ahead is by no means easy, for it demands high levels of commitment and resolve from all partners. The context of involvement becomes even more challenging when we bear in mind that the Region has approximately 30% of the population living below an income of US$ 1 (one) per day, and the interactions between infectious diseases, poverty and undernutrition pose a complicated challenge to the effective control of the diseases. Due to the epidemiological transition, countries in the Region are faced with the burden of non-communicable diseases in addition to that of the infectious diseases. This cumulative burden places a heavy strain on their fragile and overstretched health systems.
**The research priorities and actions**

Based on our experience, and given the ground realities, we have identified the following principles that guide our action:

**Prioritization**

Selection of priority communicable diseases to focus the limited resources and capacity available, with a view to ensuring maximum impact on health and socioeconomic development. Continuing and strengthening WHO’s role of enlisting political commitment to solve health problems. Mobilizing additional resources by using advocacy plans and implementing them in the countries.

**Consensus building**

Regional technical advisory groups have been established to provide technical guidance to countries in the control, elimination and eradication programmes and in monitoring activities.

**Emphasis on an integrated and collaborative approach**

Promoting and supporting inter-country collaboration and horizontal cooperation among countries. Encouraging interdepartmental collaboration, which is critical to effective control of communicable diseases. Harmonizing such collaboration, especially among departments involved, in the elimination and eradication of diseases preventable by vaccination, and control of childhood communicable diseases. Increasingly adopting, where relevant, an integrated approach with an increased focus on addressing crosscutting issues, strengthening public health laboratories and containing antimicrobial drug resistance. Supporting the preparation of harmonized work plans and tracking progress through regular monitoring and evaluation.

**According research a high priority**

The department accords a high priority to research. It is clear that scientific and technological progress through research and development has led to a dramatic improvement worldwide and in the Region in the control of communicable diseases. Yet, these diseases continue to take their toll.
Therefore, attention to research in communicable diseases could first be focused on the application and scaling up of available know-how and technology. However, at the same time, research for the development of new tools is also remains a high priority given the potential in the Region and through public-private partnership. Furthermore, research to increase the efficiency and effectiveness of programme development and management in the areas of disease prevention and control is crucially important. To increase the efficiency and effectiveness of disease control, operational, social and economic as well as health systems research are needed.

While research on priority communicable diseases remains the primary responsibility of scientists and academicians; national health programme managers cannot afford to isolate themselves from research institutions. The research agenda of academic institutions can be integrated into national health policies and programmes; in particular, health systems research, operational research and evaluative research. For this to occur, energetic advocacy is needed at the policy and decision-making level.

According to Dr Samlee Plianbangchang, the Regional Director, WHO Regional Office for South-East asia “in disease control, one could no longer afford to look at a disease only from the point of view of its agent without a thorough consideration of its host and environment”. In this context, WHO has been supporting Member countries in research activities by mainstreaming research into the ongoing programmes, identified research priorities in various communicable diseases, and managing a modest TDR small grant programme.

Some of the priority actions that we have identified for the department include the following:

- Capacity building at country level in preparing good quality research proposals based on sound methodology, in implementation of these research projects, in scientific writing and dissemination and ensuring a forum for publication locally and regionally
- Forging and sustaining partnerships in research such as with academia and with private sector especially in technology development such as of vaccines, drugs and diagnostics by pharmaceutical agencies in the Region where potential is truly vast; and in engagement of private medical sector in programme implementation based on national policies and strategies.
Learning from past experiences including small grant programmes in the area of tropical diseases of poverty as a mechanism for obtaining quickly information that is relevant for application in programme situations. It is for consideration that such an approach could be applied in other disease areas as well.

Using communicable disease outbreak investigations to generate epidemiological and clinical data which could contribute to medical and health literature and to our greater understanding of diseases epidemiology, mode of transmission, risk factors and populations at risk, and sharpening the methods of control.

Finally and perhaps most importantly, promoting a research process at the country or programme level in a step-by-step manner --- starting off with situation assessment, identification of needs and gaps, developing research protocols keeping these needs in mind, followed by use of data so generated for programme planning and strategy development as well as for evaluation.

Ultimately, finding better ways for evidence based policy making and knowledge translation and application within health sector and beyond is need of the hour, with the understanding that research or evidence generated is crucially important for:

Clear strategic framework and evidence-based planning. Developing and refining regional strategic plans that would guide the work of WHO and could be a framework for action at country level, leading to country-specific plan of action. Identifying interventions that are practical and cost-effective, and scaling them up for the control of communicable diseases. Enhancing research capacity to address the problems with the help of WHO collaborating centres (WHO CCs) and national centres of expertise.

Focusing on results. Identifying some key outcome and impact indicators as well as targets for each programme areas, indicating how (or by using what methods) the targets will be measured, and systematically measuring the progress towards the targets. If the progress is not on track, finding ways to assess bottlenecks to successful implementation, and devising correctional measures to overcome them.
Communicating research for action. Placing increased focus on research communication, media interaction and information technology as important tools for influencing policy through advocacy at community level.

Conclusions

Research and development is critical for an effective communicable disease control, elimination or eradication as it provides evidence base for policy development, formulation of strategies and interventions and evaluating the impact of these strategies and interventions. Accordingly, WHO has accorded research a high priority and assists Member countries in the formulation and implementation of research projects as well as documentation of best practices, that can be used for advocacy as well as for planning purposes. We feel that identification of research priorities in communicable diseases can be an important step and contribute to the overall research and development initiatives in the Region. The enormous opportunities presently available at the country level such as partnerships with the Global Fund to fight AIDS, TB and Malaria and GAVI alliance can be used to strengthen research activities in the Member countries.
2. Human, avian and pandemic influenza in the South-East Asia Region: research priorities

Rick Brown*

Introduction

The timeline for the identification of avian influenza A/H5N1 as a potential threat to public health runs back to 1996, when this subtype was first identified in a farmed goose in Guangdong Province, China. In 1997, influenza A/H5N1 was identified as the cause of a poultry outbreak in Hong Kong associated with 18 human infections, including six deaths. Sporadic human cases were also identified in China in 2003, but the detection of the current global epizootic dates back to late December 2003 when poultry outbreaks in the Republic of Korea led to the identification of outbreaks in other countries and the reporting of confirmed human cases in Viet Nam in January 2004. By 10 September 2008, the epizootic of avian influenza A/H5N1 had spread to Asia, Europe and Africa, with 387 confirmed human cases and 245 deaths in 14 countries.1

Over the past 10 years, much has been learned about avian influenza A/H5N1. However, significant gaps in knowledge exist and have been highlighted previously.2 In contrast to the current epizootic, the outbreak in Hong Kong in 1997 lasted a short period of time and occurred in a small, well-defined geographical area. The combination of an established research culture, significant technical capacity and strong government commitment to investigate the outbreak led to a timely and sustained research effort resulting in a number of scientific publications covering virological, epidemiological and clinical features of human infection.3-9 However, in contrast, the current epizootic has been characterized by relatively few human cases occurring sporadically or in small clusters, but often widely dispersed in terms of geographical location and time. In some affected countries a relative lack of technical capacity was compounded by the need to prioritize urgent response activities over any research considerations. In some countries, research studies were commenced and human cases promptly stopped occurring. In addition, some affected countries also initially lacked capacity for laboratory diagnosis of influenza viruses, especially where this required working in a biosecure environment.

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Four years into this current epizootic, research capacity in many affected countries has improved significantly. However, many experts consider that research efforts have been unbalanced between disciplines; for example although laboratory-based virological research has been strong, progress in characterising the epidemiology of the disease and gathering other information required to inform effective public health interventions has been less rapid. Therefore, a review of current research priorities is both timely and appropriate.

**Knowledge gaps at the animal-human interface**

Clearly, the risk of human infection with the avian influenza virus is related to both the presence and “amount” of circulating virus in animals and the environment. Therefore, any research aimed at controlling disease in animals and reducing environmental contamination has the potential to benefit human health. However, this paper only considers research needs for avian influenza in animals in respect to what has been termed the “animal–human interface”.

**Which animal species have the potential to infect humans?**

Most human cases have been associated with poultry contact, but other species of birds have been implicated (de-feathering of swans was a risk factor in Azerbaijan) and infection of non-avian animal species has been described. However, knowledge of the range of species that can become infected with avian influenza and their potential to infect humans is incomplete.

**Focus of research**

Experimental studies on the susceptibility of different animal species to infection, combined with virus-shedding studies, would help to define species with the potential to infect humans, but can only be undertaken in biosecure animal laboratories. In addition, observational studies detailing the behavioural interactions between humans and the various animal species that can transmit infection would facilitate the design of culturally appropriate interventions.
Are there other potential sources of infection for humans?

Although most human infections appear to be related to direct contact with poultry, in a significant minority of cases, the source of infection is unclear. However, studies currently being undertaken in live bird markets in Indonesia have indicated that contamination with avian influenza viruses may be widespread and that the potential risk of indirect contact may be significant. However, there is a need to have a better understanding on the extent and role of such exposures to infection in humans.

Focus of research

Studies designed to assess the extent of environmental contamination in other settings combined with the use of quantitative assays to determine viral load in contaminated sites will provide additional information on risk. In addition, systematic sampling of surfaces, soil and water around human cases when they occur (especially those with no clear history of poultry contact) would provide critical information to inform risk assessment.

Knowledge gaps in epidemiology

Risk factors for human infection: why are children and young adults mostly affected?

An unexplained feature of the current epizootic is the greater risk of infection in younger age groups. Possible explanations include an intrinsic property of the virus itself, innate host susceptibility to infection, differences in risk behaviours and acquisition of cross-immunity with age. However, whether these factors are sufficient to explain the above observations remain unclear and thus needs further research.

Focus of research

Observational and case control studies would be of great utility in describing and quantifying the interactions between children and poultry and assist in the design of targeted interventions. Studies to establish the possible role of protective cross-immunity to H5N1 infection in adults (and in poultry workers) may also be of value.
Does contact with an infected human pose a significant risk?

Another feature of the current epizootic which deserves careful interpretation is the frequency with which clusters of human infections have been reported. When studied on a case-by-case basis, it is difficult to establish with any certainty if infection in members of a cluster occurred due to human-to-human transmission or to exposure to an “external” point source (usually poultry in the backyard). However, when considered collectively, the appearance of so many clusters despite an ‘overall’ pattern of rare, sporadic and spatially/temporally displaced human infections is perhaps one of the most striking features of the current epizootic. A partial explanation might be that clusters are overrepresented because of detection bias (anecdotally, a diagnosis of avian influenza may only be considered when a second case occurs in the family).

Focus of research

The most useful tool to clearly describe transmission of infection in a cluster is a thorough outbreak investigation to characterise the descriptive epidemiology; combined with the virological testing of patients, animals and the environment. The key to achieving this aim is more standardized and standardized field investigations. A study to determine the possible role of genetic susceptibility is also currently being planned in Viet Nam and may be extended elsewhere.

What are the most important risk behaviours, risk groups and risk settings and how can we better identify the most important risk factors for infection?

At the beginning of the current epizootic, the groups expected to be at greatest risk of infection were farmers and cullers. However, in the past four years, human cases in these groups appear to be the exception rather than the rule. Instead, the vast majority of human cases have occurred in ordinary members of the public living with poultry in their backyards in semi-urban communities. The explanation for this pattern of disease is not clear. Although a better understanding of the specific risk factors for human infection would undoubtedly be greatly facilitated by more systematic and structured data collection on all human cases, the fact that families with
backyard poultry are the main risk group complicates the use of a simple
descriptive approach, because infected individuals often give a story of
contact with live poultry which they then slaughter, prepare for consumption
and eat. As a consequence, many individual human cases describe multiple
sequential types of exposure, any of which may have been responsible for
causing infection, but which could each represent different levels of risk. In
addition, although human cases often give an account of exposure to sick
poultry, it is also commonly reported that other individuals living in the same
community were exposed but did not fall ill. For this reason, in addition to
documenting the exposures that confirmed human cases report (descriptive
epidemiology), it is arguably more important to clearly define what they did
that was different from other people living in the same community who did
not become ill (analytical epidemiology).

Focus of research

The undertaking of appropriate and standardized analytical studies in
currently affected counties should be strongly advocated to complement the
limited information already obtained from the small case-control studies
conducted in Thailand and Viet Nam.21,22

What are the most important occupational risk groups and
risk settings?

Focus of research

Further carefully designed seroprevalence studies of different occupational
groups and different settings (poultry farms, live bird markets,
slaughterhouses) would be of value, especially if combined with
environmental sampling studies.19,23 Several published studies suggest health-
care workers are not at risk in the current epizootic, so the need for
additional studies is perhaps doubtful.24-26 However, it should be noted that
infection of health-care workers likely occurred in Hong Kong in 1997.9 It is
also of note that the only well-documented instance of human-to-human
transmission in the current epizootic occurred in a hospital, although it
involved transmission of infection from a child to the mother.27
What are the virus transmission characteristics in relation to human infection?

Knowledge of the incubation period and period of infectiousness in humans is important in determining the length of time required for isolation and quarantine, but is currently incomplete because the precise time of infection and onset of symptoms are not consistently recorded.

Focus of research

Time-line studies (which could form a part of a standardized investigation protocol for cases and clusters) and virus-shedding studies in cases and contacts should be encouraged. The potential significance of alternative modes of transmission could also be clarified by systematic studies to quantify virus levels in the faeces, urine and blood of confirmed cases over time.

Knowledge gaps in clinical management

Why does the case-fatality rate for human infection appear to be so high?

The apparent high case-fatality rate (CFR) for human avian influenza infection requires careful consideration. One possible explanation is that the observed CFR may not reflect the “true” rate because less severe cases in the community are not recognized. However, the few published studies addressing this issue do not provide any evidence to support the occurrence of extensive mild disease.

Focus of research

The most useful approach to clarifying this important issue would be to undertake large seroprevalence studies in “at-risk” populations and the introduction of systematic screening in selected health-care facilities of all patients with a respiratory disease and fever at times of high relative risk (for example, when poultry outbreaks are occurring locally).
Is treatment with oseltamivir effective?

It has also been suggested that the high CFR may be due to delays in the delivery of care to patients and there are suggestions from the experience in Indonesia and Egypt that clinical outcome can be improved with early diagnosis and care. One critical issue to consider in relation to this is how effective antiviral drugs are (if they are effective, then early case recognition becomes of paramount importance). The limited data available suggest that patients treated early with oseltamivir may have a better prognosis, but such descriptive data should be interpreted with caution. However, the good news is that a multicentre, prospective, double-blind randomized control study is currently being undertaken to compare standard and double dose oseltamivir.

Focus of research

Trials on the use of combination antiviral therapy should also be encouraged and advocacy for pharmaceutical companies to conduct research and develop effective new low-cost antiviral drugs is strongly recommended. Monitoring of emergence of any anti-viral drug resistance is also useful for appropriate case management.

Is late presentation to health-care facilities or late case detection a factor in the high case-fatality rate?

If late presentation to a health-care facility contributes to the high apparent CFR, then health-seeking behaviour, access to care and early case recognition all become important issues which deserve careful consideration. Prompt case recognition is problematic because the early symptoms of human avian influenza infection are non-specific and because respiratory infectious diseases are common. However, from the limited clinical data available,\textsuperscript{15,27-33} it appears that some potentially distinctive features are seen relatively early in the course of disease, for example, neutropenia (which is relatively common in atypical pneumonia) and thrombocytopenia (which, in contrast, is unusual in respiratory infections). Similarly, the few publications that describe the radiological appearances of human avian influenza suggest that some distinctive appearances appear relatively early.\textsuperscript{34,35}
Focus of research

Health-seeking behaviour and issues related to access to care are best studied through a socio-anthropological approach in the local context and such research should be encouraged. There is clear value in collating good-quality data on the clinical, biochemical, haematological and radiological features of disease at different stages of the illness, but focusing on the features likely to be seen early at the time of presentation. This would allow the drafting of a comprehensive clinical “clinical case description” of the early clinical features of human avian influenza infection for dissemination to front-line clinicians to supplement the surveillance case definitions currently employed. In addition, a meta-evaluation of arrangements for surveillance activities in affected countries would also help to determine which approaches to case detection are the most useful and effective.

Do we know the spectrum of clinical presentation of human infection?

Although human avian influenza A/H5N1 infection is currently perceived as a respiratory disease, atypical presentations have also been described and it is plausible that additional clinical syndromes may occur.28,31

Focus of research

At times of high relative risk (during poultry outbreaks and when human cases have occurred locally), consideration should be given to influenza testing in patients presenting with other clinical syndromes occurring in association with fever, especially when no clear diagnosis is apparent.

How can we improve understanding of the pathogenesis of human avian influenza infection?

Focus of research

Systematic and standardized data collection on the clinical features over the course of the illness, when combined with quantitative viral assays and measurement of cytokines, would facilitate better understanding of pathogenesis. Autopsy data would provide additional information, but should only be undertaken if acceptable from a sociocultural perspective and if it can be done safely. Studies on antibody kinetics would facilitate a better
understanding of antibody responses, cross-reactivity and protective immunity. This information would help in planning studies (for example, to determine the optimal time to conduct a seroprevalence study after a poultry outbreak) and may have implications for vaccine development.

**Knowledge gaps in virology, laboratory diagnosis and vaccine development**

**What are there gaps in knowledge of virological characteristics?**

Research on the virological features of avian influenza A/H5N1, including the evolution of antigenic and genetic characteristics and patterns of antiviral resistance, has generally progressed much more rapidly than other areas because of the supply of representative viruses to WHO Collaborating Centres [CCs] for Influenza and WHO H5 reference laboratories.

**Focus of research**

Work is currently underway is to link data on diversification of viruses into clades and subclades with related human case epidemiological and clinical data to look at possible explanations for observed intercountry variations in patterns of disease. More detailed information on survival of the virus in the deceased would inform risk assessment of culturally determined burial practices.

**How can laboratory diagnosis for human avian influenza be improved?**

Laboratory diagnosis of avian influenza was reviewed in February 2007 at a WHO “Consultation on diagnosis of H5N1 avian influenza in humans”, 36 which noted the importance of rapid and accurate diagnosis in reducing morbidity and mortality. The report of the meeting concluded that both industry and global public health would mutually benefit from collaborative implementation of a number of recommendations, including some with research implications, for example the “continuation of development and commercialization of rapid, sensitive and specific ‘point of care’ (POC) screening tests for H5N1 infection in humans”.

Knowledge gaps in sociobehavioural research and risk communication

What is known about the sociobehavioural aspects of human avian influenza infection?

Evidence on risk factors, risk groups and risk settings only becomes useful in any practical sense when it is communicated to the communities who need to be protected. The ‘process’ of transferring this information can only be truly effective if the current knowledge, behaviour and sociocultural norms of the target communities are clearly understood. Studies on knowledge, attitudes and practices (KAP) have been undertaken in several affected countries using a variety of methodologies, but only a minority have published in summary form and (therefore subjected to critical peer-review).

Although these studies often need an individual approach determined by context and setting, greater effort could be made to standardize approaches, improve quality and encourage the dissemination of findings. An initiative to undertake social and behavioural research on avian influenza in Indonesia is a welcome development.

Focus of research

Observational studies to improve understanding of how people live with animals in affected and “at-risk” communities would help in crafting risk communication messages. Moreover, understanding the most appropriate messages and delivery channels in different cultural setups provide useful information for designing effective public health messages. The delivery of information, education and communication (IEC) and behaviour change campaigns would benefit from more systematic attempts at evaluation of effectiveness so that modalities of implementation can become more evidence-based.

Conclusion

Since the end of 2003, much has been learned about human avian influenza infection, but significant gaps in knowledge remain. Progress on acquiring knowledge on virological aspects of disease has been much more rapid than epidemiological and socio-behavioural research. Better data on risk
behaviours would be of especially great value in assisting the development of focused interventions aimed at preventing infection and thus allow better use of limited resources for IEC and behaviour change programmes. Evidence on effectiveness of early treatment oseltamivir will make improved knowledge of modifiable factors affecting access to care and early case recognition critical in improving clinical outcomes. Increasing awareness of knowledge gaps for human avian influenza infection amongst researchers and national policy makers will assist in advocating for a more coordinated and collaborative approach to operational research.

References


3. Research priorities in HIV/AIDS prevention and control


Introduction

The South-East Asia Region has the second-highest burden of HIV/AIDS globally, with an estimated 3.6 million persons living with HIV infection. While the regional prevalence of the disease is estimated to be 0.3%, there is significant diversity in the scale and burden of the epidemic, both within and across Member countries of the Region. In some Member countries, the epidemic had remained at a low level, with very few infections reported, while other countries are experiencing a concentrated epidemic, with HIV prevalence and transmission in high-risk groups. Despite these differences, each country requires a well-coordinated response to HIV/AIDS, with the goal of preventing new infections, and providing appropriate care and treatment services to those who are already infected.

<table>
<thead>
<tr>
<th>Country</th>
<th>Estimated number of people living with HIV (PLHIV)</th>
<th>% of adult population infected with HIV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bangladesh</td>
<td>12,000</td>
<td>&lt;0.1</td>
</tr>
<tr>
<td>Bhutan</td>
<td>&lt;500</td>
<td>&lt;0.1</td>
</tr>
<tr>
<td>DPR Korea</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>India</td>
<td>2,400,000</td>
<td>0.3</td>
</tr>
<tr>
<td>Indonesia</td>
<td>270,000</td>
<td>0.2</td>
</tr>
<tr>
<td>Maldives</td>
<td>&lt;100</td>
<td>&lt;0.1</td>
</tr>
<tr>
<td>Myanmar</td>
<td>240,000</td>
<td>0.7</td>
</tr>
<tr>
<td>Nepal</td>
<td>70,000</td>
<td>0.5</td>
</tr>
<tr>
<td>Sri Lanka</td>
<td>3,800</td>
<td>&lt;0.1</td>
</tr>
<tr>
<td>Thailand</td>
<td>610,000</td>
<td>1.4</td>
</tr>
<tr>
<td>Timor-Leste</td>
<td>&lt;100</td>
<td>&lt;0.1</td>
</tr>
</tbody>
</table>

Nearly 80,000 people living with HIV also have active tuberculosis


Note: Countries with HIV prevalence <0.1% and <100 PLHIV.

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** Independent Research Consultant
Over the past several years, there has been an impressive scale-up of both preventive as well as care and treatment services for HIV in the Region. Countries have adopted a public health approach to addressing the epidemic. The key steps of such an approach include defining the problem and risk factors, developing effective prevention and care strategies, scaling up these interventions, and monitoring and evaluating programme impact. This approach has led to the development of certain successful strategies for both prevention and care. It has also highlighted data gaps and questions that remain unanswered in the development of an effective, coordinated response. These questions can be answered through the conduct of simple, well-designed and programme impact-oriented research. With data-driven evidence to guide policy and programme initiatives, the public health approach and the overall scale-up and response to the HIV/AIDS epidemic in the Region can be greatly strengthened.

A successful response to the HIV/AIDS epidemic requires a coordinated response across multiple issues. Similarly, public health research priorities span a spectrum of topics. These range from the need for reliable epidemiological estimates of the number of persons requiring HIV treatment,
the design of evidence-based targeted interventions and harm-reduction strategies to prevent infection, to the need for data-driven methods to enhance treatment outcomes in care and treatment services, with the goal of effectively decentralizing HIV health sector services through a strengthened health system. This paper describes HIV/AIDS public health research priorities for South-East Asia across four broad areas: epidemiology, prevention, treatment and care, and health systems and communities.

**Epidemiological research priorities**

Relevant and reliable data are needed to plan for and scale up HIV prevention, care and treatment services. In most countries, second-generation HIV surveillance systems and mathematical models are used to obtain the required data. While progress has been made in collecting the relevant information for planning and monitoring HIV programmes, several data gaps remain. In particular, there is a critical need to understand the number of people and characteristics of the population groups most at risk for HIV, the proportion of individuals who have become newly infected with HIV, the number of prevalent HIV infections, the number of HIV-infected individuals who require antiretroviral therapy (ART) and the estimated mortality due to AIDS.

**Improving mapping and size estimation of most-at-risk populations**

In most countries of the South-East Asia Region, estimates of populations most at risk for HIV infection remain unreliable and imprecise. In part, this is due to the fact that individuals who are most at risk for HIV are often members of hidden and/or stigmatized groups, such as men who have sex with men (MSM), injection drug users (IDUs), and sex workers (SW) and their clients. This lack of reliable estimates makes it difficult to plan prevention, care and treatment services for these populations. Moreover, without reliable denominators, it is hard to measure and monitor trends in service coverage. Several methods have been employed with varying degrees of success for estimating the size of these hard-to-measure populations, including the capture–recapture method, the multiplier method, the population survey method, census and respondent-driven sampling. Research is needed to develop better methods and tools to map and measure the size of most-at-risk populations more precisely.
Measuring HIV incidence

HIV incidence is the most valuable information to identify programme needs and effectiveness. Unfortunately, direct measures of HIV incidence using population-based cohort studies are logistically difficult and expensive. At present, countries use alternative methods as a proxy for measuring HIV incidence, such as trends in HIV prevalence among 15–24-year-olds, mathematical modelling, or measuring HIV in repeat testers such as blood donors. The recent development of a simple serological assay that can distinguish recent from established HIV infections, known as STARHS (serological testing algorithms for recent HIV seroconversion), provides an opportunity for countries in this Region to more directly estimate HIV incidence. Because of assay variability due to various factors including HIV subtype, countries will first need to ascertain the window period between HIV seroconversion and the time at which the STARHS testing algorithm reaches a pre-set cut-off. In addition, operations research should also be conducted at the country level to ascertain the correction factor to account for false-positive test results among patients on ART.

Measuring HIV prevalence among the low-risk (general) population

It is important to measure HIV prevalence in low-risk populations to know the extent of HIV spread to the general population, and to plan for care and treatment services at a national level. The unlinked anonymous testing (UAT) approach has been used for sentinel surveillance among antenatal clinic (ANC) attendees as a proxy for the low-risk population. With the expansion of prevention of mother-to-child transmission (PMTCT) programmes and the call of universal coverage, it is difficult to ethically justify a UAT approach to HIV testing for pregnant women. Thus, switching to surveillance among PMTCT centres offers many benefits over the UAT approach, including improved representativeness and coverage due to a large number of sites, a higher precision of prevalence estimates due to a larger sample size and cost savings. However, a major drawback of PMTCT data is that HIV prevalence estimates from prevention of parent-to-child transmission (PMTCT) programme data could be biased if some women refuse to take the HIV test. Therefore, research is needed to characterize the quantity and direction of bias in PMTCT data compared with UAT data as a gold standard. Also, because pregnant women are not truly representative of the standard for the general population, periodic population-based surveys will still be required in
selected geographical areas to ascertain the calibration factor for adjusting HIV data obtained from ANC attendees.

**Measuring HIV-associated mortality**

Information on HIV-related deaths is important for monitoring HIV care and treatment programmes as well as for demonstrating the relative impact of HIV-related mortality as compared with other causes of death in a given country or region. Most deaths in South-East Asia occur at home. Given the weak vital registration systems in Member countries, verbal autopsy may be a useful approach to measure HIV-associated mortality as part of larger mortality studies. Standard tools and questionnaires for conducting verbal autopsies exist. However, operational research efforts are required to first validate and adapt the generic procedures, questionnaires and other verbal autopsy tools to the social and cultural milieu of South-East Asian countries. Measuring the impact of HIV-related care and treatment on mortality is equally important. Conducting operations research at sentinel ART centres within each Member country will permit the analysis of routine ART programme cohort data to calculate HIV/AIDS-related mortality among patients receiving treatment.

**Estimation of antiretroviral treatment needs**

Presently, countries rely on mathematical models for estimating ART needs among adults and children. The models use generic assumptions based on data from mainly African and a few Thai studies. There is a need to generate regional data to modify and refine these generic assumptions. The specific data needed to refine key assumptions are: (1) the cumulative proportion of adult men and women and children progressing from HIV infection to advanced infection (needing ART), and to AIDS death; (2) the proportion of adult men and women, and children surviving and remaining on first-line drugs at 12 months and 24 months after the start of treatment. The second of these goals can be readily accomplished by analysing routine ART programme cohort data.

**Research priorities in HIV prevention**

**Preventing sexual transmission of HIV/STI**

The sexual transmission of HIV and other sexually transmitted infections (STIs) in the South-East Asia Region is disproportionally driven by high-
incidence sex work areas and other settings where rates of partner change are high. In these settings, low rates of condom use and high rates of other STIs are key determinants of HIV transmission. Regional experience has shown that successful prevention of sexual transmission of HIV involves increased condom use, enhanced identification and treatment of STIs, and the presence of an enabling environment supportive of prevention efforts. Targeted interventions directed at the highest-risk populations which address these key factors are further strengthened by improved linkages to HIV health and support services. For bridging populations and the general population, prevention objectives are more general and less intensive, and include raising awareness of HIV risk, and improving access to quality clinical services for STIs and HIV testing and counselling. The research priorities for improving the outcomes of and impact related to prevention of sexual transmission of HIV follow this programme logic (Figure 1).

**Figure 1:** Regional operations research opportunities in HIV prevention

<table>
<thead>
<tr>
<th>Engagement</th>
<th>Providing Basic Interventions</th>
<th>Linking to HIV Services</th>
</tr>
</thead>
<tbody>
<tr>
<td>Outreach</td>
<td>Targeted condoms</td>
<td>Targeted STI control</td>
</tr>
<tr>
<td></td>
<td>Enabling environment</td>
<td>HIV Diagnosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pre-ART Care</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ART Initiation</td>
</tr>
</tbody>
</table>

- Mapping & outreach to populations at highest risk
- Structural approaches to increase condom use
- PPT & STI screening: uptake, continuation, outcomes
- Improving linkages to HIV services
- Strengthening community engagement
- Referrals & co-management

Note: PPT = Presumptive prophylactic treatment

Targeted condom programmes: Experience from Thailand and other countries in the Region demonstrates that structural approaches to increasing condom use in sex work settings, such as 100% condom use policies (CUP), can lead to rapid increases in condom use and reduction in the incidence of STI and HIV. Peer- and community-based interventions have also been used
to achieve high rates of condom use in a variety of settings, including less organized non-brothel settings. On the other hand, some countries have faced cultural resistance when attempting to establish condom policies. Research priorities include formative research in the adaptation of successful intervention models, and operations research to improve condom use rates among clients of SWs. Factors that are important in successful peer programmes should be systematically identified and subsequently used to guide targeted interventions. Additionally, research to explore the feasibility and uptake of other barrier protection for SWs, including female-controlled methods, such as the female condom and the diaphragm, should also be supported. As data accumulate on the effectiveness of microbicides, it will be important to evaluate whether these new barrier methods truly reduce the number of unprotected sex acts, rather than simply substituting for male condom use.

Targeted STI services: STI services for female, male and transgender SWs form an integral part of targeted interventions. Unlike services provided for the general population, STI screening and presumptive treatment may be justified in high-risk populations due to the high prevalence of asymptomatic STIs. Similarly, different approaches to counselling and partner treatment may be employed among high-risk populations. Key questions that require systematic investigation focus on quantifying the coverage, uptake, quality and continued utilization of STI services among high-risk groups. Operations research should further evaluate methods for increasing the uptake of services, as well as quantify the optimal frequency of screening visits for presumptive STI treatment. In addition, innovative approaches to partner treatment, such as take-home doses for partners, should be studied and validated under field conditions to provide evidence for wider implementation of such programmes.

Access to HIV services for high-risk populations: SWs, MSM and IDUs have a disproportionately high prevalence of HIV, yet their access to health services may be limited by social marginalization, stigma and discrimination. In fact, providing care and treatment can serve to augment prevention efforts for these populations. Access to health-care can be facilitated through referrals and linkages between targeted intervention sites and HIV treatment facilities. The co-management of patients between specialized ART or PMTCT sites and providers at targeted intervention sites is a largely unexplored area of operations research that merits further attention.
Prevention among drug users

Injecting drug use is a major mode of transmission of HIV in South-East Asia and the prevalence of HIV among IDUs continues to be high. Harm reduction programmes have demonstrated effectiveness in preventing and reducing the transmission of blood-borne viruses. Interventions are focused on preventing unsafe injecting and sexual risk, and reducing the frequency of injecting itself by providing sterile injecting equipment, condoms and opioid substitution therapy (OST). However, the coverage and reach of these interventions in the Region remains largely suboptimal. Operations research at the local level to understand the determinants of ongoing access and uptake of services is crucial to increasing the coverage of harm reduction programmes for IDUs. Systematic evaluation of these factors can also provide data to guide which model of service delivery is appropriate to a specific context or locality.

A major challenge to effective HIV prevention for substance users in South-East Asia is posed by the widespread and increasing use of both injected and non-injected amphetamine-type stimulants (ATS). During the past decade, there has been a major transition from opioid drugs to ATS use in both Thailand and Myanmar. Use of ATS has been also reported among MSM and SWs. The increased frequency of unprotected sexual encounters among those using ART poses significant challenges for preventing HIV spread. Furthermore, the lack of therapeutic options such as OST for ATS users complicates treatment and reduces options for the prevention of unsafe injections. Research to identify effective treatment options for ATS users is an urgent necessity. In addition, operations research on interventions and strategies to reduce sexual risk-taking and unsafe sex among ATS users is also essential.

Key factors impacting on treatment outcomes for IDUs in relation to OST and ART are retention and adherence. In terms of drug treatment, good outcomes are associated with retention in treatment for a duration of two years or more. Some common proximate factors that may affect treatment retention include adequacy of withdrawal management, satisfaction with the programme, efficacy of trigger management and relapse prevention strategies, optimal and individualized treatment planning, and adequate treatment of depression and co-morbidities. Socioeconomic factors such as access to stable housing and support for transport costs are also likely to have a bearing. However, actual research on the determinants of retention and adherence to OST in this Region is lacking. In order to design effective OST
and ART, understanding the key factors that determine adherence and retention is a priority.

**Research priorities for HIV care, support and treatment services**

Over the past two decades, HIV clinical research efforts have focused on the development of potent ART regimens, effective treatment of opportunistic infections (OIs), and appropriate ART monitoring, among many other important issues. The results of these research efforts have greatly benefited thousands of HIV-infected people by extending survival and reducing morbidity. The scale-up of HIV treatment programmes in the South-East Asia Region over the past several years has also raised several important challenges and questions for which evidence-based answers are needed (Figure 2). Key issues that require further investigation include effectively expanding HIV diagnostic services, enhancing ART treatment outcomes, determining the best approaches to manage persons coinfected with HIV and tuberculosis (TB), preventing and evaluating the emergence of HIV drug resistance (HIV DR), and determining effective methods to decentralize HIV treatment services.

**Figure 2:** Regional operational research opportunities in HIV care and treatment

Note: LFTU = lost to follow-up
Effectively expanding HIV diagnostic services

In concentrated epidemic settings, which characterize most of the countries in the South-East Asia Region, HIV testing is often done through provider-initiated testing and counselling (PITC). Determining methods to ensure that the appropriate at-risk persons are referred and tested for HIV is the first step toward linking at-risk and infected persons to necessary care and treatment. The next programmatic challenge is to evaluate methods to improve the linkage between HIV testing services and clinical care. Advanced disease at the time of treatment initiation has been repeatedly shown to be associated with poorer treatment outcomes and early mortality. Therefore, understanding the factors that contribute to successful and prompt linkage to care, as well as the barriers that prevent such linkage, will be important to inform programme policy as both HIV testing and care services continue to expand in the Region.

These challenges and questions apply equally to testing and counselling of pregnant women for HIV infection. In the South-East Asia Region, Thailand has made impressive progress toward providing universal access to HIV testing, counselling and appropriate prophylaxis for pregnant women with HIV infection. However, many challenges remain in the other countries to effectively expanding the implementation and uptake of PMTCT services. In order to increase the effectiveness of PMTCT programmes across the Region, it is critical to systematically determine the barriers and facilitators to the uptake of PMTCT services in Member countries. These barriers may also include structural issues such as overall low uptake of ANC services and/or low rates of birth/delivery inside the medical system. As such, collaboration with appropriate partners in reproductive and child health would be both useful and recommended. Such systematic investigation can provide data and guidance for the further development and refining of PMTCT services in Member countries. Such services should appropriately support testing and counselling pregnant women for HIV, and subsequently successfully link women diagnosed with HIV infection to necessary and timely prevention and treatment interventions.

Enhancing ART outcomes

In the past several years, there has been an impressive scale-up of HIV treatment services in the South-East Asia Region. This massive scale-up of ART services has extended the lives of thousands of persons living with
HIV/AIDS. As HIV-infected persons receiving ART in the Region enter their second, third, and fourth years of therapy, the attention of national programmes has appropriately begun to focus on the issue of successfully retaining patients on lifelong treatment. Analysis of routine ART programme data in India and other countries in the Region indicate that loss to follow up among patients receiving ART is a significant issue requiring attention. The systematic evaluation of factors related to treatment failure and loss to follow up, as well as the outcomes of patients who are classified as lost to follow up is thus a priority for Member countries. Understanding the causes and consequences of these issues is a critical step to further strengthening ART and HIV treatment services for people living with HIV in the Region.

Treatment adherence remains one of the key elements in ensuring sustained ART benefits. Multiple studies have demonstrated the association between adherence and treatment outcomes as well as survival. However, inconsistent or suboptimal treatment adherence remains a significant issue for many patients receiving ART in the Region, and systematic examination of this issue is urgently required. Assessment of clinical and field-based strategies to maximize ART adherence in the Region include validation of feasible and accurate objective measures of adherence, and evaluation of factors that prevent and facilitate high-level treatment adherence. These factors may be related to individual patient behaviour or linked to structural factors such as transportation or cost barriers. The systematic identification of these factors can serve to guide programmes to develop effective interventions that can enhance adherence and subsequently improve overall treatment outcomes.

Improving the management of HIV and TB coinfection

TB remains the most common OI and a leading cause of death among HIV-infected persons in the Region. Thus, efforts to improve the diagnosis, treatment and prevention of TB among HIV-infected persons are a high priority. From an operational perspective, three areas can be highlighted as priorities for programmatic research. First, the development and evaluation of simple screening tools that are both sensitive and specific for the identification or exclusion of active TB among HIV-infected persons is an urgent priority. Validation of such a screening tool in field conditions will be necessary to ensure that patients seen even outside major medical centres can be referred early for the appropriate management of HIV/TB coinfection. Second, because TB is so prevalent among HIV-infected persons in the South-East Asia Region, and because such persons remain at risk for TB even
after initiating ART, appropriate field methods to implement isonicotinic acid hydrazide (INH) prophylaxis therapy warrant prompt evaluation. While INH prophylaxis has been demonstrated to clearly reduce the risk of active TB, programmatic questions related to effectiveness in the field, and appropriate duration of prophylaxis remain, and should be systematically evaluated at the country level. Finally, due to the expansion of ART services, HIV-infected persons with varying levels of immunosuppression are often congregated in the same facility. Because of the high prevalence of TB among HIV-infected patients, these facilities can inadvertently serve as a platform for nosocomial transmission of TB. Therefore, the evaluation and identification of low-cost measures to reduce the spread of nosocomial TB transmission urgently needs investigation.

**Evaluation and prevention of HIV drug resistance (HIV DR)**

The development of some degree of HIV DR is inevitable in populations taking ART because of the occurrence of mutations during HIV replication, the chronic nature of HIV infection and the need for lifelong treatment. The development of HIV DR can result in reduced effectiveness of ART, and has also been associated with poorer survival. In order to systematically address the issue of HIV DR, it is essential for each Member country to establish a countrywide strategy for the prevention and monitoring of HIV DR as part of the national AIDS control programme. The main components of such a system include the collection of early warning indicators, ART site factors that are associated with treatment success/failure and the preventable emergence of HIV DR, and conducting periodic surveys at sentinel ART sites to evaluate the emergence and patterns of transmitted drug resistance among recently infected HIV-positive individuals, and acquired HIV DR among patients receiving ART through the national programme. The collection and analyses of these data will ultimately serve to strengthen the provision and success of first-line ART services in Member countries.

**Research priorities for health systems and community awareness**

The successful scale-up of HIV prevention, care and treatment services depends heavily on the existence of sound health systems in a country. Several health systems issues that will play a key role in the success of scaling
up require evaluation and attention, including methods for decentralization of care, mobilization of a well-trained and adequate health workforce, and the development of effective health information systems.

**Strategies to decentralize HIV treatment services**

HIV care services in several Member countries have initially been introduced at tertiary-level institutions, often in large metropolitan centres. However, for successful provision of lifelong HIV treatment, these services will need to be expanded to more peripheral levels in the coming years. Such expansion and decentralization are key factors in ensuring improved access to HIV healthcare services. Identifying successful methods of providing primary-level care and treatment for HIV-infected persons at the peripheral level is thus a priority. Certain strategies, including the Integrated Management of Adult Infections (IMAI), which involve engaging and training primary-level healthcare workers to effectively triage and refer HIV-infected patients for additional medical care, and to community care centres, that provide routine follow-up care for HIV patients close to their residence, have been successfully piloted at the district and regional levels in some South-East Asian countries. Such strategies need to be further adapted to the local health-care and sociocultural structure and subsequently evaluated in order to strengthen decentralization efforts.

**Health workforce mobilization**

The sustained success of HIV prevention, care and treatment services relies equally heavily on the presence of a stable and trained health workforce. In part, this will require innovative approaches to ensure that medical and paramedical workers are offered appropriate and ongoing training to ensure that quality care and treatment services can be delivered. At the same time, the expansion of HIV services to more peripheral locations highlights the need to explore and evaluate the increasing role of community health workers and community volunteers to deliver and support prevention and care services.

**Revitalizing health information systems**

The scale-up of HIV treatment services in many South-East Asian countries has underscored the need for reliable, flexible and simple health information systems that can be used in a variety of health-care settings. Because
programme monitoring and evaluation relies at its core on reliable patient data, the health information system should ideally provide a useful platform for clinical management as well as readily analysable data for programme management at a national level. Operationally, these systems will need to be piloted, evaluated and validated in a variety of field conditions in order to ensure that such an information system will truly be effective for a diverse population.

Enhancing community involvement

Community building is a key component for the success of prevention, care and support initiatives throughout the Region. The involvement of peers and community leaders has been demonstrated to help improve the uptake and outcomes of targeted interventions as well as treatment services in several countries. Furthermore, peer and community involvement plays a key role in reducing HIV-related stigma, which in itself continues to act as a barrier to successful treatment outcomes in many settings. Strategies to develop and sustain community and peer involvement in prevention services have been employed in several key settings in the Region, and warrant systematic evaluation and potential further implementation. Similarly, the appropriate roles of community leaders and peer supporters in enhancing treatment outcomes and providing psychosocial support need to be explored further. Evaluating and quantifying the benefits of such community involvement will provide necessary evidence for the future financial and governmental support of such community-based initiatives.

Taking the research agenda forward

The research priorities for HIV/AIDS in the South-East Asia Region range from those focused on prevention to those related to enhancing treatment outcomes and further strengthening the health systems on which all these programme activities rely. While some of these research priorities can be applied equally to different Member countries, others will have more relevance in countries with a higher burden of HIV/AIDS. The national HIV/AIDS programmes in each country will have to prioritize specific research needs in light of the local context of the epidemic. Furthermore, the implementation of quality research requires national-level commitment to ensure trained practitioners and experts of varied backgrounds, who can effectively design, conduct, supervise and analyse research studies.
Ultimately, the goals of such research activities are to advance, improve and enhance a given country’s national response to HIV/AIDS. For research results to truly impact programme activities and policy, mechanisms will be required to ensure that research findings can be broadly communicated to local stakeholders as well as national decision-makers. The success of research ultimately relies on effective partnerships between local, nongovernmental, state, national and international partners, who can together effectively translate research findings into policy and practice to better control the HIV epidemic in this Region.

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4. Control of tuberculosis in the South-East Asia Region: priority areas of research

Nani Nair* and Santha T.*

Introduction

Countries in the South-East Asia Region (SEAR) continue to make steady progress in tuberculosis (TB) control following the adoption of the new Stop TB strategy in 2006. Overall treatment success rates among new smear-positive cases has remained above the set global target of 85% since 2002, while a case detection rate of 68% was achieved in 2006. Member countries in the Region are actively engaged in expanding interventions for the diagnosis and treatment of TB patients affected with multidrug-resistant forms of TB (MDR-TB) or co-infected with HIV (HIV/TB). The number of laboratories accredited for quality assurance for culture and drug susceptibility testing for the diagnosis of all forms of TB including smear-negative, extrapulmonary, paediatric and MDR-TB has nearly doubled. Substantial progress has also been made in involving an increasing number of other sectors, particularly public and private health providers through partnerships. National TB programmes are also increasingly engaging with medical colleges to introduce the principles and practices of TB control as defined in the International Standards for TB care into the medical and paramedical training curriculum. Strong community-based TB care initiatives have been established in nine of the eleven Member countries of SEAR. India, with the largest number of TB cases, is recognized as having made the largest contributions to operational research in TB control.

While progress is being made in TB control in the South-East Asia Region, national TB control programmes continue to face a number of challenges in effectively implementing the Stop TB strategy. These challenges relate to health systems constraints, such as insufficient numbers of skilled staff at the various levels of national health systems; weak laboratory networks and surveillance mechanisms; and inadequate infrastructure and logistics support. Major impediments to improving case detection and treatment success include low community awareness, poor health-seeking behaviour.

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and widespread utilization of private sector services\textsuperscript{7} that are not linked to the national programmes with ready access to non-quality controlled anti-TB drugs. Establishing and sustaining the complex interventions required for the management of MDR-TB and HIV/TB are also proving difficult.

In the context of the six major interventions proposed under the new Stop TB strategy, the challenges faced in implementing them call for the generation of new information through effective research to answer questions on how to maximally benefit from existing tools and interventions, and the feasibility, efficiency and cost-effectiveness of the proposed newer interventions. Besides research into programme areas to improve the implementation of programme interventions, fundamental or basic research to develop new tools - new vaccines, diagnostics and drugs - to improve TB control interventions is equally essential at this point in the global TB epidemic.

Research areas that could be fruitfully pursued to improve programme implementation are: (i) operational research into programmatic approaches to increase case-finding and ensure access to quality treatment for all forms of TB, including smear negative, extrapulmonary, paediatric, MDR and HIV-associated TB; (ii) social, economic, and behavioural research that examines the larger domain of social and other determinants such as poverty, malnutrition, diabetes, smoking, alcohol abuse, ethnic and gender differentials that affect the seeking and receiving of care for TB; and (iii) policy and health systems research that will provide insights into how TB control services are positioned and delivered through public health-care systems. Such research would also include finding the means to strengthen the delivery of TB care and, at the same time, address some of the inherent constraints of these systems.

Another major area is epidemiological research, which examines the outcomes and impact of programme implementation, and also helps to assess the cost-effectiveness of various interventions for TB control and their impact on overall health, social and economic development. Epidemiological or evaluative research differs from operational research in that the outcomes could be specific to an individual country, region or project. However, an evaluation of the outcomes and impact does provide useful information to guide policy, strategies and plans in that setting. These evaluations also provide insights into processes that can be used to make these assessments in other settings.
Concurrent with research relating to programme implementation and evaluation as outlined above, basic research aimed at developing new tools is equally essential for achieving the long-term goal of TB control – TB elimination. It is basic research that will help develop newer, more effective vaccines that would prevent progression from infection to disease; quicker, cheaper, robust, and yet more sensitive and specific tests to diagnose all forms of TB including latent TB; and new, less toxic drugs that would significantly shorten the duration of treatment with better outcomes and lessen the chances of relapse.

While this paper draws on the deliberations and recommendations of the scientific working group of the UNICEF/UNDP/World Bank/WHO Special Programme on Research and Training in Tropical Diseases (TDR) for priority research in TB control, the research agenda proposed in this paper identifies the key research areas for TB control in the context of national TB programmes and health settings in the SEA Region.

Besides identifying research questions relevant to the three major areas described, this paper attempts to define areas that could be considered as the most important to accelerate the programmatic management of TB in the SEA Region over the next 5–10 years.

**Research priorities in TB, 2008–2015: aims**

The aims of undertaking research would be to ensure that cost-effective approaches and appropriate new tools are applied in countries of this Region towards improving TB control. Ideally, research performed should contribute to:

- Improving case detection and reducing diagnostic delays through improved access to existing and newer diagnostics
- Reducing individual morbidity and mortality and continuing TB transmission through effectively treating and curing all TB patients, including those with drug-resistance and HIV coinfection through a wide range of providers
- More accurately estimating the burden of and impact of interventions on TB including MDR-TB and TB/HIV in countries of the Region, and applying this information to both guide strategies and interventions, and better inform health policy, planning and financing for TB control
- Contributing to the development of new effective vaccines, simple, accurate, diagnostics and inexpensive, less toxic drugs that can shorten treatment regimens
Research into programme implementation

Case-finding

The key questions to be addressed are where are the missing cases and how can case detection be improved? Case detection rates in the Region have slowly but steadily risen to the current 68% level among new smear-positive cases. However, this represents less than half of all TB patients if TB patients with all forms of TB are taken into account, including previously treated smear-positive TB, smear-negative, extrapulmonary and particularly paediatric TB cases which remain underdiagnosed and, if diagnosed, remain underreported. For national programmes to increase case detection rates of all forms of TB, it would be essential to first identify barriers to accessing diagnostic facilities, including transportation costs, work-related factors and gender discrimination. Second, the true availability of quality diagnostic facilities at various levels both within public health systems and in the private sector, must be analyzed. Third, case-finding among hard-to-reach and neglected populations must be improved; these include people living in remote rural areas, urban slums, conflict or disaster areas, the homeless, orphans, migrants, workers in exploitive employment situations, drug users and prisoners. Last but not least, the quality and mechanisms for reporting on cases detected need to be assessed. Appropriate alternative strategies to the ones being currently utilized are therefore definitely required to reach services to all TB patients and diagnose and notify all cases. An understanding of the knowledge, attitudes, social and behavioural practices of different population groups that lead them to seek or not seek care, and where, would form the basis of targeted messages for interventions to reach these population groups. For example, seminal research in the 1990s in India revealed that over 60% of TB patients sought care in the private sector, leading to the development of approaches to involve private providers of various denominations. These approaches are now well established under the ambit of private–public mix DOTS (PPM-DOTS) by national programmes in the Region.\textsuperscript{9,10} Reports from India, Indonesia and Myanmar now indicate that, where initiated, private–public collaborative interventions have resulted in increments of up to 25% in cases notified\textsuperscript{11,12,13}. 
Case finding: some research questions

- What factors lead to delays in establishing a diagnosis of TB?
- How do user fees affect the seeking and accessing of care and, in turn, case detection, diagnosis and treatment?
- What community-based social research can enhance the identification of the most vulnerable subgroups?
- What strategies would help to enable TB patients to obtain quality TB care?

Diagnosis

Sputum-smear microscopy remains the cornerstone of the laboratory diagnosis of TB. However, it is well recognized that sputum-smear microscopy alone is inadequate for diagnosing those with smear-negative and extrapulmonary forms of TB, children with TB, and many of those coinfected with HIV. Diagnosing smear-negative and extrapulmonary disease requires more complex, and much more expensive modalities such as chest X-ray, mycobacterial culture, histopathology, and other radiological and immunological tests. While mycobacterial culture of sputum or other specimens remain the gold standard for the definitive diagnosis of TB, it entails delays in diagnosis. Most national TB control programmes lack efficient quality-assured laboratories that can reliably undertake culture and drug susceptibility testing for the diagnosis of MDR-TB. Few national programmes in the Region are unable to offer cultures or other modalities for the diagnosis of TB throughout the country at present.

Other tests are often inconclusive due to their lack of sensitivity and specificity for diagnosing active disease and, in addition to cost concerns, can also be misleading in the presence of concurrent HIV infection. There is a particular need to improve the diagnosis of paediatric TB. There are a number of questions that need to be answered in the context of current algorithms to diagnose TB in children. The current diagnostic approaches to detect and confirm smear-negative and extrapulmonary TB in adults, and among people living with HIV/AIDS (PLHA) against the backdrop of the varied prevalence of HIV in the different settings in the Region also merit review. Thus, particularly in the context of this Region with the highest burden of TB, the absence of a simple, cheap and reliable point-of-care diagnostic test for all forms of active TB disease perpetuates underdiagnosis or misdiagnosis of a large number of TB cases.
Diagnosis: some research questions

**Laboratory diagnosis**

- What is the value and role of sputum processing and concentration (e.g. through the use of bleach, centrifugation, sedimentation and combinations) in improving the accuracy and yield of smear microscopy?
- What is the role and feasibility of using newer diagnostics in routine field conditions?
- What is the impact of introducing the use of two smears as opposed to three smears and applying the revised case definitions for diagnosis of smear-positive TB in high-burden settings?
- What mycobacterial culture systems, including automated systems and molecular methods, are appropriate for the diagnosis of TB including MDR-TB in resource-limited high TB prevalence settings, and at what level of laboratories should they be used?
- Is there value in including presumptive treatment using first-line anti-TB drugs i.e. “therapeutic trials” in the diagnostic algorithms for smear-negative TB, particularly in situations such as among PLWA with strong clinical suspicion of TB?

**Ensuring access and adherence to treatment**

The feasibility and cost-effectiveness of treating patients through the DOTS strategy in countries of the Region has been well documented. However, ensuring access and adherence to treatment has been a difficult area, particularly when large numbers of patients continue to seek treatment through private providers, large private sector hospitals, traditional healers, NGO clinics or under the health schemes of large public sector employers such as the Ministries of Railways, Defence, Mining, Agriculture, etc. many of whom follow treatment regimens that are not in line with those of national programmes. Little has been documented on the magnitude, quality, performance and determinants that affect private providers' practices in the context of treating children, patients with suspected or confirmed drug resistance, or those co-infected with HIV. Research into approaches that could optimally involve this diverse group of providers to apply uniform treatment practices in line with DOTS and the international standards of TB care would go a long way in ensuring successful treatment outcomes, given their acceptance by the community, flexible timings and respect for confidentiality. This is particularly critical in the context of preventing the emergence of MDR-TB, and in extending treatment to those with MDR and possibly even extensively drug-resistant (XDR)-TB.
In addition, an analysis of user fees even where services are ostensibly free, need to be made to uncover any cost recovery schemes inbuilt within public health systems or applied by the providers themselves. If treatment involves frequent travel, long distances and transport costs, loss of earnings and neglect of household responsibilities, approaches to reduce these indirect barriers that affect treatment adherence will need to be designed. Other provider- and patient-related factors such as the time spent to counsel and motivate patients or the use of patient enablers or provider incentives and the effect of these on adherence also need to be analysed.

**Access and treatment adherence: some research questions**

- What strategies would help to enable TB patients to obtain quality TB care?
- What are the outcomes of case-finding and treatment by other providers outside of national TB programmes (NTPs)?
- What is the impact of DOT as opposed to other adherence support strategies (including community-based support)?
- What is the optimum frequency and duration of support interventions on treatment outcomes?

**Clinical management**

Implementing the Stop TB strategy includes the management of MDR-TB, TB/HIV, and management of TB in specific clinical situations. While the management of these cases is built on the core principles of programmatic approaches, an understanding of specific clinical aspects is also required. Field-level research to simplify treatment through adaptation of drug regimens, establish the optimal duration of treatment for those with HIV/TB and MDR-TB patients, and develop new strategies for treatment adherence among these patients being treated with more toxic combinations of anti-TB drugs, possibly even in combination with antiretroviral therapy (ART), are critical as countries begin to manage such cases. In the context of TB/HIV and MDR-TB, studies are essential on the use of standardized versus individualized regimens for treatment and the most effective methods of supporting adherence and validating outcomes from these. Specific clinical areas for clinical research include the treatment of patients with other concomitant medical conditions such as pregnancy, diabetes, hepatitis, renal impairment, drug or alcohol abuse, which necessitate defining optimal treatment regimens to avoid drug interactions, address issues of safety and toxicity, and manage the immune reconstitution inflammatory syndrome (IRIS).
Clinical management: research questions

Diagnosis of TB in PLHA
- What of the currently available is the best diagnostic test for detecting latent infection and active TB disease, including smear-negative and extrapulmonary TB, in persons with known HIV infection?

Diagnosis of MDR-TB
- What is the best diagnostic approach for persons with suspected MDR-TB in a given country?
- Which of the currently available rapid tests for drug resistance would be the most useful for national programmes to field-test and consider for use?
- At what level of the national laboratory network should the various tests be introduced?
- What proportion of new smear-positive cases that fail or relapse develop drug resistance on category I regimen?

Treatment of TB/HIV co-infection
- What is the optimal duration of treatment and what are the adherence support strategies to ensure completion of treatment for TB among HIV-infected people?
- What is the impact of early vs late introduction of ARTs?
- What is the utility and cost effectiveness of isoniazid preventive therapy (IPT) and co-trimoxazole preventive therapy (CPT) for people with HIV infection?
- What is the optimum duration of treatment of latent infection?
- What are the best counseling support approaches that help improve adherence among intravenous drug users or those with alcohol abuse disorders?

Treatment of MDR-TB
- What are the optimal regimens for the treatment of the MDR-TB in country-specific situations?
- Which of these are the most cost-effective? Could sputum smear examinations replace culture examinations?

Treatment of TB in special situations
- What is the safety and efficacy of the current drug formulations for the treatment of patients with non committant clinical disorders?
Social, economic and behavioural research

DOTS is a proven intervention for TB control. However, it is now recognized that DOTS has not been able to achieve the set targets as expected, largely due to lower levels of realization and implementation of each of the five components than were necessary for the strategy to be fully effective. Besides health systems and programme-related factors, social, economic and behavioural factors have played a significant role. Research to identify the determinants of health-seeking behaviour, including gender differentials, which affect the uptake of available services and exert an independent effect on the outcomes of programme implementation are relevant to the settings in the Region. The central focus of this kind of research would be to identify barriers that limit timely case detection and effective treatment in the context of poverty, other social inequities and cost constraints, and then formulate appropriate interventions that would mitigate these constraints.

There are a number of studies from countries of the Region on the economic losses at individual, family and national levels due to costs incurred by patients for TB treatment and diagnosis. Other studies have shown the disproportionate social impact on women and young children due to the coping strategies adopted by families. While the sex distribution of cases notified in the Region follows the recognized gender differential in the epidemiology of TB, there is evidence that women often have less knowledge of TB and tend to accord a lesser priority to health-seeking besides having poorer decision-making powers. At the same time, there are encouraging examples of community-based approaches that deploy women to address these same constraints. A wealth of initiatives largely generated by NGOs and communities themselves, particularly for case finding and treatment support, have increasingly been incorporated into routine service delivery by national programmes. These community studies have also revealed people’s perceptions, which have helped to design social and behavioural interventions to address these perceptions, resulting in a decrease in the stigma towards TB in some communities.
Social, economic and behavioural factors: research questions

- How can case-finding and case-holding be improved in the context of TB- and AIDS-related stigma?
- What are the attitudes of health-care workers towards working with TB patients?
- What best practice examples exist? How can barriers as identified be overcome?
- What is the impact of current advocacy and communications strategies on changing behaviour - among patients, communities, providers and policy-makers?

Health systems, policy and financing

Both the strengths and weaknesses of general health systems affect the way that national TB control programmes are able to deliver TB control services. Experience from countries is increasingly indicative of the difficulties in “scaling up” interventions in the face of poorly functioning health systems. How to address health system constraints in the context of TB control is therefore a major area for research. This includes a wide range of topics on access to health care, inequities in health service delivery to different population groups, technical capacity within health systems, health planning, financing, management and priority setting. Studies on the economics of health service functioning and service delivery, including cost-effectiveness studies and modalities for sustainable cost-sharing, also fall in this area of research.

Studies that supported the cost-effectiveness of DOTS undertaken in individual countries and by the World Bank\textsuperscript{23} helped to both increase the uptake of the strategy in countries as well as to attract major funding for the expansion of DOTS programmes in countries. Important insights have also been gained from studying health policy and health reform processes in countries of the Region that have undertaken major health sector reforms. As a result of analyses of the impact of health sector reforms in Bangladesh, Indonesia and Thailand, steps are being taken by the Ministries of health in these countries to redress elements that were perceived as adversely impacting TB control programme activities\textsuperscript{24,25,26}. Health systems research can therefore contribute significantly to supporting evidence-based formulation of national policies to benefit service delivery, both specifically for TB control and more wider for general health care provision. However, investments in
health systems research in countries of this Region are as yet far from adequate to sufficiently influence policy formulation, and truly translate research into affordable interventions.

Health systems, policy and financing: research questions

- Where are the gaps and what are the opportunities for effective delivery of TB control services within the current health systems frameworks?
- How can the available epidemiological data be more effectively used to guide health policy, priority-setting, financing and human resource development and management to provide greater benefit to TB control programmes? Do more data need to be generated in this context?
- What lessons could be learnt from the current mechanisms and processes used for procurement, recruitment, financial disbursement, etc. within national health systems which could help guide health sector reform?
- How can health providers outside the public health sector, including private practitioners, NGOs and traditional healers, contribute to TB control?
- What is the optimum configuration of a national laboratory network? What is the role of and what are the models for improving private laboratories?
- What operations research studies (including mathematical and simulation models) could be used to determine resource needs, delivery sites, care models, costs and impacts of the delivery of TB services and TB/HIV collaborative activities?

Epidemiological research: trends, outcomes and impact of interventions

One third of the world’s TB cases or 4.8 million cases are estimated to be in the SEA Region\(^2\). More TB cases are diagnosed among males than among females, the male: female ratio being 3:1\(^2\). Though deaths due to TB have reduced after the introduction of the DOTS strategy, the disease still claims more than 500,000 lives each year in the Region. The prevalence of MDR-TB among new cases in the Region is estimated to be around 2.8% and 18.8% among new and previously treated cases respectively.\(^2\) Data on the magnitude of drug resistance to second-line TB drugs is as yet limited.

While information on smear-positive cases has become fairly reliable due to the recording and reporting systems in place under DOTS, other
forms of TB remains largely underreported. The calculation of TB incidence based on case notifications, annual risk of infection surveys, and mathematical modelling using the Styblo principle\textsuperscript{30} are beset with imprecisions for various reasons. This, therefore, results in a number of questions around the denominator used to determine case detection rates in countries of the Region.

More accurate estimates of the TB burden can be obtained from population-based surveys (REF 29) as well as special studies. Unfortunately, data from such surveys are limited in this Region, since these are time-consuming and require considerable investment. It is also recognized that the incidence and prevalence of TB can vary widely within a country, due to a number of local factors that need to be analyzed to determine the epidemiological differences at the sub-national level. Information on the actual numbers of people dying from TB is also lacking. India, Indonesia and Myanmar are among the countries that have undertaken TB mortality surveys. However the methodologies for determining mortality from TB in the community need to be further refined.

**Epidemiology: research questions**

- What are the most effective survey methodologies to accurately determine the impact of interventions so far on TB incidence, prevalence and mortality?
- What new diagnostic tools can be used to identify latent TB infection and conduct TB prevalence surveys?
- What is the impact of other cofactors (tobacco, alcohol, diabetes) on the TB epidemic?
- What are the best measures to evaluate the quality of data being reported through the routine recording and reporting systems in place?
- What can be done to improve the analysis and use of routine programme data at the various levels of health systems (a) to monitor trends in the disease, and (b) as a means to improve programme implementation?
- What factors are attributable and need to be addressed to prevent the further emergence MDR-TB?
Fundamental or basic research

Development of new vaccines

The Bacillus Calmette-Guerin (BCG) vaccine is currently the only vaccine in use against TB. The efficacy of this vaccine is limited to prevention of severe forms of TB among children. It has little or no effect on adult disease.\textsuperscript{31} Recent progress in vaccine research has resulted in several candidate vaccines which are in Phase I and Phase II clinical trials.\textsuperscript{32}

Development of new diagnostics

Building on advances in mycobacterial genome sequencing and profiling, highly accurate but simple to use, point-of-service diagnostic tests are expected to become available within the next five years.

Several new diagnostic tests at various stages of development are in the pipeline. The Foundation for Innovative New Diagnostics (FIND), established in 2003, is a lead agency within the new TB diagnostics working group of the Stop TB Partnership. FIND is currently supporting the field-testing of rapid culture techniques in a number of developing countries, including in India. Given the burden of the disease in countries of this Region, field-testing of new diagnostics such as the use of light-emitting diode (LED) microscopy, liquid cultures, molecular line probe assays, simple nucleic acid amplification techniques, etc. would contribute significantly to the body of knowledge that is required to routinely begin using these new diagnostics for national programmes.

Development of new drugs, including immune modulators

Not only is TB a significant problem in SEA but the Region has the capacity and potential to contribute locally and globally to the development, manufacture and deployment of current and new drugs. Only a few pharmaceutical companies in the Region are involved in TB drug discovery and development. Major issues concerning the development of new tools include lack of facilitation of private sector involvement with various groups working in a parallel, unlinked manner, and a lack of dialogue between industry and national programmes. Moreover, the industry is often not involved at the ideation stage of product development or modifications
proposed by national programmes. There is also limited access to technology transfer, particularly by small pharmaceutical companies in countries of the Region.

Besides the development of new drugs, the primary challenge of identifying the best combination of individual drugs for clinical use remains unresolved. High TB burden countries of the Region could contribute significantly to determining the best regimens for use through clinical field trials, and reducing the timelines for testing and deploying new regimens, in consultation with drug regulatory authorities.

**Development of new tools: operational research questions**

- Evaluation new diagnostics in field trials, including nucleic acid amplification, antigen and antibody detection methods for diagnosis?
- Which TB vaccine trials could countries in the Region contribute to (vaccine trial design, efficacy, etc.)?
- What support is required to evaluate new drugs and/or new combination regimens of novel TB drugs in countries of the Region?

[Impact of the introduction of FDCs into NTP regimens?]

Quality of anti-TB drugs available in private sectors in member countries and implications for treatment outcomes and development of DR-TB?

**Conclusions**

This is an opportune time for research in TB. Global investment in TB research has increased several fold. The potential today for significant returns on these investments is also greater than ever before, given that much more research can now be undertaken in countries of the world where the disease has the highest prevalence. However, firm and proactive links need to be established between researchers and national TB control programmes in order to better address programmatic issues, and not biomedical advances alone. Capacity to undertake research will also need to be strengthened by empowering institutions, training research staff, ensuring appropriate technology transfer and adequate financing for research. Research institutions, both in the public and private sectors, and national programmes in the Region must engage much more proactively in contributing to the development of new approaches and new tools for the diagnosis, treatment
and prevention of TB. In addition, while a great deal of research information is already available in countries, these need to be better documented in order to maximize their public health impact.

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5. Malaria in the South-East Asia Region: research priorities

Krongthong Thimasarn*

Introduction

Malaria is a major public health problem in South-East Asia (SEA). Ten of the 11 countries in the Region are endemic for malaria. There is intraregional heterogeneity and variability in the risk of malaria transmission between and within Member countries. In recent years, malaria has been practically eliminated in the Maldives and the incidence has sharply declined in Sri Lanka, Bhutan, DPR Korea and Thailand. In other countries, however, it continues to pose an indomitable challenge. Generally, infection with *P. vivax* is predominant in several countries such as India, Indonesia, Sri Lanka and DPR Korea, whereas the proportion of cases due to *P. falciparum* is relatively high in Bangladesh, Myanmar and Timor-Leste (up to 73.6%). In 2006, about 2.5 million cases were reported and there were 4515 deaths due to malaria in the SEA Region. Earlier studies had suggested that annually this Region accounts for about 25% of the estimated 300–500 million cases of malaria in the world and 12% of the one million deaths due to malaria.¹ This means that the estimated number of malaria cases in the SEA Region is between 90 and 167 million and estimated deaths attributable to malaria about 125 000 per annum.

Currently, India, Indonesia and Thailand account for the bulk of malaria cases in the Region. According to the World Health Report, 2002, malaria and other tropical-cluster diseases are responsible for the loss of 3.8 million disability-adjusted life years (DALYs) in India alone.² Kumar et al.³ reported that 1.86 million DALYs were lost due to malaria alone in India. In the SEA Region, there is a need to adopt a strategic approach which would help in meeting the Millennium Development Goal (MDG) of halving the morbidity and mortality from malaria by the year 2015. Such an approach must address political, economic, technical and administrative ground realities within Member countries. In countries where malaria continues to pose a major challenge, there is a need to estimate the true burden of malaria. This would help in advocacy and priority setting for health planning and allocation of much-needed resources for control.

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Challenges and knowledge gaps

Although efforts have been made to control malaria by various agencies in the Region, in addition to research on various parameters of the disease, there are still a number of gaps in knowledge, which pose challenges for management. These include the lack of reliable estimates of the disease burden, increasing drug resistance especially of *P. falciparum* and vector resistance to insecticides, re-emergence of vivax malaria, difficulties in early diagnosis in inaccessible regions, management and prevention of malaria in pregnancy, and poor control of epidemics. The general lack of progress in malaria control is aggravated by problems in deployment and implementation of existing approaches and, most importantly, effective partnerships. Varied economic, epidemiological and social environments also complicate the development of effective strategies.

Priority areas for research

Research is needed on both the basic and operational aspects. While operational research is important for framing policies, basic research is essential for devising them. Given below are some of the potential areas for malaria research in the SEA Region.

Basic research

Basic research is the key to developing new tools to diagnose, treat, prevent and ultimately eliminate malaria. Identification of new molecular targets for the diagnosis of malaria, characterization of malaria parasites to identify mechanisms of drug resistance and identification of new targets for drug development are important issues to be addressed. This will help in discovering next-generation drugs to be used when resistance to artemisinin-based combination therapy (ACT) inevitably appears. Genomic research on vaccine candidates will help in the identification of effective vaccines.

Operational research

Epidemiology

The nature of the problem of malaria is different in each region, country and even within a country. Local initiatives are needed to frame appropriate
Understanding the epidemiology is therefore a prerequisite for prioritizing research in malaria. Various aspects of operational research include:

- **Dynamics of malaria**: The pattern and distribution of malaria has changed over the years. New paradigms are being identified. Global warming and climate change also have an influence on transmission dynamics. Studies are therefore needed on new tools such as a geographical information system (GIS) and remote sensing (RS) to understand and predict these changes, including outbreaks.

- **Actual burden of malaria**: Estimating the burden of a disease is of utmost importance for allocation of resources to plan preventive strategies and manage cases including the treatment of severe and complicated ones. The actual burden of malaria in the Region is not known. Malaria is underreported in both the public and private health sectors. This warrants studies on the actual burden of the disease in the Region.

- **Economic burden of malaria due to P. falciparum and P. vivax**: Malaria-endemic countries are among the poorest in the world. The economic consequences of malaria are enormous in these countries, with an estimated loss of GDP of about US$ 12 billion per year and a loss of 45 million years of productive life due to deaths and disability. An episode of malaria can send a family living on the borderline to below the poverty line. Studies are needed to find the actual economic burden of the disease on the community.

- **Impact of climate change on malaria and vector-borne diseases (VBDs)**: Taking into account the present malaria situation in different paradigms, there is a need to identify areas vulnerable to climate change and study its impact on the future scenario of malaria. The Intergovernmental Panel on Climate Change has stated that in between 2050 and 2100, global warming will lead to a rise in temperature of between 1.4 to 5.8 °C, and precipitation to the tune of 7%.

- **Characterization of the population at risk for malaria**: Certain populations are at risk for the development of malaria while others are resistant (e.g. patients with sickle cell disease, glucose-6-phosphate dehydrogenase [G6PD] deficiency, etc.). Identification of vulnerable groups and focusing interventions on them is an important area of research.
- **Malaria in pregnancy:** Pregnant women form a high-risk group for malaria infection, which may cause abortion, stillbirth and premature labour. Pregnant women with falciparum or vivax malaria are known to be more anaemic than pregnant women who are not infected or infected women who are not pregnant. Cerebral malaria is a common complication of severe Plasmodium falciparum infection and has a high mortality rate during pregnancy. Pregnant women are known to deliver low birth-weight babies. There are chances that the babies delivered may also acquire malaria.

  Thus, the issues related to malaria in pregnancy which need to be addressed are assessment of magnitude of the problem, pathogenicity of malaria in pregnancy, and effective and safe malaria prevention including chemoprophylaxis.

- **Entomological studies on incriminated vectors:** Entomological studies are important for understanding the basic biology of the vectors of malaria. Research should be conducted on their tolerance to various extreme environmental conditions, species diversity, taxonomic status with molecular markers, life-cycle studies, etc. Vector control has to be formulated based on local entomological information.

- **Vector bionomics:** Studies may include host preference, biting behaviour, feeding behaviour and seasonal variation of the vector species. Such studies can be of utmost importance in planning vector control strategies.

- **Health impact assessment of developmental projects:** Developmental projects, if not managed properly, can lead to conditions hazardous to the health of the people and their environment. This may lead to waterborne, airborne and VBDs. Malaria is known to flare up at such project sites if appropriate vector control measures are not taken. All such projects warrant a systematic study of the change in health risk that can be reasonably attributed to them.

  All developmental activities must look at the associated health issues and ensure that appropriate and durable safeguards are in place. The adverse effects of developmental projects should not be passed as hidden costs to a health sector that is already constrained by inadequate financial resources.
Such studies can also recommend interventional or precautionary measures to the appropriate authorities to combat project-induced diseases.

- **Social marketing and health education:** Research on social marketing can help to improve interventions at the individual and community levels, especially for the distribution of public health products such as mosquito nets. Health education can facilitate the acceptance of new strategies.

**Malaria control**

- **Surveillance, monitoring and evaluation:** Surveillance, monitoring and evaluation are essential components of a malaria control programme. Surveillance measures the extent of the problem and helps in implementing policies; monitoring measures the implementation while evaluation measures the extent to which the objectives are being reached. Projects need to focus on these aspects.

- **Microstratification for malaria control:** Stratification of areas is useful for suitable and effective malaria control in resource-limited settings. Different epidemiological, entomological, parasitological and environmental parameters can be and have been used for malariogenic stratification. Various tools that can be used for malariogenic stratification include sibling species prevalence, RS, GIS and seroepidemiology.

  Stratification of the country can be done based on sibling species of *Anopheles*. Such stratification can help devise appropriate intervention measures which are specific to different locations. Similarly, stratification can also be done based on the *Plasmodium* species and drug resistance which, in turn, could help devise species-specific strategies, and diagnostic and treatment policies in different areas.

- **Application of GIS and RS for epidemic forecasting:** A GIS-based system can be effectively used for forecasting epidemics. It can also be used for efficient planning, implementation and evaluation of malaria control. With this, one can also study malaria dynamics both in space and time.
Prevention

Studies are needed to address the following issues:

- Cost-effectiveness and impact of insecticide-treated bed nets (ITN)/long-lasting insecticidal nets (LLIN), and biological control in different epidemiological settings
- Development of a well-defined integrated vector management (IVM) strategy according to local needs using tools such as environmental control, indoor residual spraying (IRS), larvicidal agents, larvivorous fish and ITN/LLIN guided by microstratification using GIS or RS
- Identification of cost-effective strategies to deliver and implement intervention strategies
- Prevention of malaria during pregnancy in different epidemiological settings
- Identification of safe drugs/regimens for intermittent preventive treatment (IPT).

Diagnosis

Early diagnosis is the key to preventing mortality. Microscopy is not feasible in all situations. Therefore, treatment is given on the basis of clinical diagnosis, which has a low specificity (20–60%). Rapid diagnostic tests (RDT) with a sensitivity and specificity of 90% are now available. The majority of RDTs are targeted against falciparum malaria. Lactate dehydrogenase (LDH)-based tests are available for detecting vivax malaria but these are unstable at high temperatures and lack sensitivity. There is a need to develop more stable and sensitive RDTs. Therefore, studies are needed to:

- Improve the sensitivity/specificity of RDTs
- Establish practical quality control systems for RDTs
- Develop RDTs with better temperature stability and longer shelf-lives.
- Explore the possibility of diagnosis using other body fluids such as urine or saliva.
- Study the cost-effectiveness and impact of different methods of case detection in areas with low and moderate levels of transmission.
Application of G6PD deficiency screening test and prevalence survey of G6PD deficiency: Use of primaquine in patients with G6PD deficiency may lead to haemolysis. Research to identify a test that will detect G6PD deficiency in a short time may help the clinician to decide whether or not to use primaquine. Similarly, attempts can be made to find out areas where G6PD deficiency is common, and this information used to make appropriate changes in the drug policy on primaquine use.

Treatment

Prompt and effective treatment is the most important element of malaria control and failure to do so leads to severe malaria and death. There is thus a need to use effective and safe drugs. Monitoring should be done on a regular basis to ascertain the efficacy of drugs.

- Efficacy of antimalarials in P. falciparum malaria: The results of tests for therapeutic efficacy are crucial for determining whether an antimalarial drug is still effective. A systematic sentinel surveillance system needs to be put in place and strengthened for continuous monitoring.

- Therapeutic efficacy study for P. vivax: There is a felt need for a paradigm shift from a focus on P. falciparum to the neglected burden of P. vivax malaria, which is predominant in the Region (57.3%). Chloroquine-resistant vivax malaria has been reported in Indonesia, India and Myanmar. This calls for carrying out therapeutic efficacy studies on vivax malaria as well.

- Clinical and field trials of new treatment regimens with special attention to ACT: Currently, a number of antimalarials are available. However, two of the most widely used drugs, chloroquine and sulfadoxine-pyrimethamine (SP), are not effective in many parts of the world due to drug resistance. ACT is effective and considered by the World Health Organization to be the best antimalarial in terms of efficacy and a lower propensity for developing resistance. In order to prevent the occurrence of drug resistance to artemisinins and to address the issue of its relatively short half-life, artemisinins are recommended to be given in combination with another partner drug. ACT is being widely used in many countries of the Region. However, there are reports of resistance to several partner drugs (e.g. SP, mefloquine,
amodiaquine, etc) from various parts of the Region. Therefore, new partner drugs need to be developed by carrying out clinical and field trials on new drug combinations, especially fixed-dose combinations for better compliance.

- **Pharmacovigilance for antimalarials:** Due to the growing problem of drug resistance, Member countries are moving towards new drugs/new combinations that have the potential to produce adverse reactions. Once marketed, a medicine leaves the secure and protected scientific environment of clinical trials and is legally set free for consumption by the general population. It is essential that new, evolving treatments are monitored for their effectiveness and safety. More information is needed about their use in specific population groups, notably children, pregnant women and the elderly, and about the efficacy and safety of long-term use, especially in combination with other medicines. Experience has shown that many adverse effects, interactions (i.e. with food or other medicines) and risk factors come to light only during the years after the release of a medicine. Presently, most of the data are generated by pharmaceutical companies as part of phase IV post-marketing surveillance. Since new antimalarial combinations are hitting the market at a rapid pace, there is a need to develop focused pharmacovigilance programmes for antimalarials in the Region.

- **Drug quality study (prevalence of fake and substandard antimalarial drugs):** Model on establishment of a drug quality control system: The presence of substandard drugs due to non-compliance with Good Manufacturing Practices (GMP) possibly leads to the development of drug-resistant strains of *P. falciparum*. Another aspect related to poor quality drugs is the increasing problem of fake drugs, though this problem is related to crime. Counterfeit antimalarials are becoming a major threat to malaria control in SEA, threatening hundreds and thousands of people. Recently, Paul Newton and colleagues from Oxford University have reported that at least 12 different types of counterfeit antimalarials are in circulation in SEA and their manufacture has reached industrial levels. Manufacturing fake drugs such as mefloquine and ACT is a lucrative trade. It has been suggested that 30–50% or even more of the antimalarial drugs bought along the Thai-Myanmar-Cambodia border are fakes and the problem of counterfeit antimalarials is particularly serious. Incidentally, this is
the area from where multidrug-resistant (MDR) strains of malaria parasites came into circulation and, if the latest and most effective antimalarials become ineffective due to misuse, it will spell disaster for malaria control not only in the SEA Region but also throughout the world. There is thus a need for advocacy at the country level to establish drug quality monitoring systems and institute strict regulatory measures to combat the counterfeit drug trade.

- Patient compliance to radical treatment for P. vivax: The issue of compliance by patients to treatment is particularly important in the case of vivax malaria since radical treatment is needed for a long duration (14 days) in order to prevent relapse. This can be done by conducting studies on drug use practices and by retrospective studies.

- Role of the private sector in diagnosis and treatment: Private health-care practitioners have an important role in the management of malaria as the private sector caters to a large population. The diagnostic and treatment practices of doctors in the private sector must be studied, as well as their conformity with the guidelines of the country. Very few practitioners, especially those practising in low-income areas, rely on a peripheral blood-smear test to make a diagnosis. There is a trend to use rapid diagnostic tests (RDTs) and injectable antimalarials. Studies are needed to assess the magnitude of these practices and rectify them.

**Information, education and communication (IEC), and social studies**

- Socioeconomic and ecological changes, and malaria epidemiology: The impact of malaria on society could be social, economic, cultural or ecological. Malaria in the poor is associated with suffering, retarded physical and cognitive development of children and thus educational performance, related malnutrition, anaemia and potential vulnerability to other diseases. It also affects tourism, business and thus economy. Studies on the dynamicity and diversity of malaria epidemiology in relation to changing lifestyles and economics would help devise targeted interventional strategies.

- Surveillance on malaria risk behaviours among different ethnic groups: Individual and community-level characteristics—dynamics, location, density, organizations of ethnic minority
groups and migrants, and the environment—as well as their malaria-risk behavioural patterns need to be studied.

- Treatment-seeking behaviours among different population groups: In developing countries, many people prefer to take treatment from unqualified doctors and that too without a slide examination. Treatment-seeking behaviour varies in different areas. Some prefer injectables and others tablets. Studies on this aspect in relation to the health system through conducting a situation analysis would help formulate an appropriate diagnostic and treatment delivery system that is suited to local conditions.

- Development and usage of appropriate IEC materials/packages in different ethnic groups: Effective IEC campaigns are necessary to promote an understanding of malaria transmission and motivate community- and family-based activities for malaria control and prevention. Existing IEC materials must be studied and situational analyses conducted on the existing IEC strategies. Most of the available IEC material is outdated in content as well as in form.

**Summary and conclusions**

Spatial and temporal maps for populations at risk and malaria distribution should be developed at the regional, country, district and local levels, highlighting the intensity of transmission, and prevalence of insecticide and drug resistance with the aim of sharpening the focus of malaria control by selecting appropriate control tools. Selective vector control approaches involving the use of ITNs, focal IRS and environmental measures could help in maximizing the gains from control efforts. A mix of the available intervention tools need to be adopted based on local transmission dynamics and the amenability of vectors to control with such available tools. There is a growing argument in favour of reintroduction of DDT for vector control. Hence, large-scale studies are warranted on the current susceptibility status of target vector populations in countries where DDT could be re-introduced profitably. Introduction of DDT would make vector control affordable for resource-poor countries and previous experience with the use of this insecticide would be an added advantage as in South Africa. The introduction of ITNs in inaccessible and \( P. falciparum \)-predominant regions needs to be stepped up to reduce the burden of morbidity and mortality. In such areas, there is a need for enhanced use of RDTs for on-the-spot treatment to contain transmission.
There is a felt need for a paradigm shift in focus from P. falciparum to the neglected burden of P. vivax malaria, which is predominant in the Region (57.3%). This has become necessary because of the ominous signs of development of resistance to chloroquine, and recent reports of involvement of P. vivax in complicated malaria and mortality due to this.

Recommendations

The WHO Regional Office for South-East Asia (SEARO) may act at various levels to implement research activities related to malaria on the following:

- New and improved tools and delivery methods for malaria treatment and prevention
- Higher standards of safety and quality of products for malaria diagnosis, treatment and prevention
- Better estimates of disease burden
- Improved monitoring and surveillance tools, and validation of methodologies for monitoring and evaluation including a standard set of core indicators
- Periodic study on the cost-effectiveness of interventions specific to each epidemiological setting
- Improved tools for monitoring drug resistance
- Better strategies to contain drug resistance

These research activities can be facilitated by the following means:

- A task force on malaria may be formed. It can have various subgroups such as basic research, operational research, etc.
- Annual review meetings can be held on the status of the research projects.

References


6. Research priorities in dengue

Rajesh Bhatia* and Jai P. Narain*

Introduction

Dengue fever (DF) has emerged as the most important arthropod-borne viral disease of public health significance in the world. First recognized in the late 1700s, the severe form of dengue haemorrhagic fever has become a leading cause of child mortality, overall morbidity and economic loss in more than 70 Asian and South American (Fig 1) countries.\(^1\)\(^-\)\(^3\) The main factors responsible for the recent re-emergence of DF are related to the increased vector population attributed to urbanization, travel, migration, climatic change, and unsatisfactory water management at the household and community level.

Globally, an estimated 2.5 billion people are at risk for dengue, of which about 1.8 billion (more than 70%) reside in countries of the Asia-Pacific region. Based upon reports received from countries in South-East Asia, it is estimated that during 2002–2007, on an average more than 200,000 cases of DF were detected every year. New outbreaks have been reported at an interval of every three to four years, indicating an increasing trend. This Region is recording an overall decline in mortality as a result of improved case management.

Historically, DF/DHF has been reported to occur predominantly among urban populations. Rural epidemics occurred as early as 1976 in Indonesia.\(^4\) Today, Thailand has an incidence rate that is higher in rural (102.2 per 100,000) than urban areas (95.4 per 100,000).\(^5\) Similarly, in India, entomological investigation showed a widespread distribution of the vector Aedes aegypti, both in rural and urban areas, during the outbreaks in Gujarat in 1988 and 1989.\(^6\)

Seasonality of dengue fever in several countries of South-East Asia Region is well established (Fig 2). However, global warming and climate change have provided new dimensions to the epidemiology of DF.\(^7\) Climatic factors, particularly temperature and rainfall, affect viral propagation and allow potential mosquito vectors to coexist long enough to maintain the rate

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of transmission. The suppression of Aedes aegypti using practical methods; strengthening of linkages between research and academic institutions; addressing issues related to unplanned poor housing, unsatisfactory living conditions, undernutrition, migration and resettlement; organization of integrated vector management (IVM); behavioural change communication strategies; and implementation of targeted interventions along with implementation and improvement of community-based vector-borne disease control programmes are important challenges.

**Fig 1:** Number of countries affected by dengue fever during 1955-2005

![Number of Dengue Affected Countries](image)

As most of the vector-borne diseases are ecological diseases, efforts need to be made to adopt a community development approach and move beyond the realm of health areas. Prevention and control of DF requires active community participation. Many communities have good knowledge of the disease, but they perform less well in attitude and practice, indicating that behaviour change is one area to be targeted in social mobilization programmes.

The global case-fatality rate (CFR) for DHF/DSS has been declining in most of the endemic countries according to government statistics. The overall CFR in the South-East Asia Region is now less than 1%.
A hospital-based study during the dengue outbreak in Delhi revealed that the mortality was very low in patients who came early to the hospital. The short interval between the onset of haemorrhage and death, especially in young children, makes rapid medical intervention for DHF/DSS a critical factor.
for survival. For most communities at highest risk for the disease, intensive care
care facilities are available only at distant capitals requiring motorized transport,
usually beyond the reach of many. However, research into the predictive
factors for severe illness is neither abundant nor conclusive.

Dengue fever and dengue haemorrhagic fever/dengue shock syndrome (DHF/DSS) are caused by four viral serotypes transmitted from viraemic to
susceptible humans mainly by the bite of the Aedes aegypti and Aedes
albopictus species of mosquito.

Dengue infection can cause a spectrum of illness ranging from mild,
undifferentiated fever to illness up to seven days' duration with high fever,
severe headache, retro-orbital pain, arthralgia and rash, but rarely causing
death. DHF, includes haemorrhagic tendencies, thrombocytopenia and
plasma leakage. DSS is a medical emergency that requires hospitalization in
an intensive care unit.²

In Asia, DHF is typically acknowledged to be a childhood disease and is
an important cause of hospitalization among children in developing
countries. There is, however, evidence that the incidence of DHF is
increasing among older age groups. Since the early 1980s, several studies in
Asia have reported a higher association of DHF with older age.³⁻⁶ ³⁻⁹⁻¹¹ Adults
accounted for as much as 82% of all cases in a hospital-based surveillance
study during the 2000 epidemic of dengue in Bangladesh; the highest
proportion of cases occurred in the 18–33 years' age group. All deaths in the
Bangladesh outbreak in 2000 were in persons older than 5 years.⁷ ¹²

DF is responsible for significant economic loss. A detailed study on costs
of care in three hospitals in Bangkok estimated the direct adult patient costs
at US$ 67. When opportunity costs were included, this figure rose to US$ 161.49. The net hospital cost for each DHF patient was US$ 54.60 and the
public sector cost of prevention and control of the outbreak was US$ 4.87
million.¹² ¹³

Research priorities

Operational/implementation research on disease transmission, epidemiology,
vector management, treatment as well as on the socioeconomic and
behavioural aspects of the disease is urgently needed. The results of such
studies can be used to revise policies and strategies.
The broad areas identified as priorities for research in DF are epidemiology and surveillance including estimation of disease burden, vector biology and control, laboratory diagnosis and molecular studies, case management, environmental research, socio-anthropological research, vaccine development and programmatic reviews for quality assurance.

Specific areas of research include the following:

**Epidemiology**

- To further improve and standardize the case definitions of dengue fever to improve the reporting system by using standard case definitions.
- To carry out feasibility studies on the application of geographical information systems (GIS) in risk mapping for dengue prevention and control.
- To estimate the disease burden and consequent economic loss, and impact on poverty at the community, family and individual level.
- To understand the role of migrant workers in epidemic transmission.
- To ascertain the role of vertical transmission in disease epidemiology.
- To elucidate the epidemiological features of disease in rural and urban settings.

**Vector biology and control**

- To identify the ecological determinants of disease transmission including man-made vector breeding places.
- To understand bottlenecks in the effective implementation of vector control measures.
- To undertake analysis/review of existing research studies on vector bionomics to improve/formulate policies.
- To develop model bye-laws for the construction of buildings, and legal provisions for the prevention and control of breeding places. This includes the study of bye-laws that exist, what more is needed, what legislations need modification and how to improve
their compliance/applicability within the overall umbrella of healthy public policies in the Region.

- To define standard sampling methods and indicators for dengue vectors, including validation of the application of pupal index along with the existing larval indices used for vector surveillance.
- To assess efficacy of new vector-control tools e.g. residual insecticides, traps etc and strategies in different settings.
- To identify essential elements of integrated vector management and ecosystems interventions in different contexts.
- To conduct feasibility study on the eco-bio-social aspects of vector control for dengue.

Laboratory diagnosis and molecular studies

- To develop and evaluate new, field-applicable and rapid diagnostic tools with high sensitivity and specificity in different settings.
- To undertake molecular characterization of DEN viruses and vectors to understand their genetic diversity for use in molecular epidemiology/diagnostics.
- To develop and implement protocols for assuring quality in the Public/private diagnostic laboratories.
- To identify mechanism of antibody-mediated enhancement and protection.
- To acquire a better understanding of the clinical and laboratory features of early stage of infection.

Case management and immunological prophylaxis

- To review prevailing treatment practices for dengue in the public and private sectors and develop effective and safe methods of managing severe haemorrhages, dengue in pregnancy and with co-morbidity.
- To develop standard protocol for assessing clinical signs of shock in children.
- To identify and assess the causes of severe outcomes of the disease including DHF/DSS.
To analyse the causes of dengue deaths including treatment failures
To develop and evaluate correlates of protective immunity for use as an endpoint in vaccines trials
To undertake research on transmission-blocking vaccines.
To develop new products or assess existing licensed products for their efficacy as drugs against dengue virus

Conclusion

Vector-borne diseases are re-emerging in the WHO South-East Asia Region due to a number of natural and man-made factors. DF is spreading rapidly to newer areas and outbreaks are more frequent. To prevent and control DF, it is essential to have high political commitment, multisectoral collaboration and community participation. Locally relevant operational research will facilitate better understanding of the disease and factors that may influence the epidemiology of DF.

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7. Research priorities in chikungunya

Sarala Subbarao* and Rajesh Bhatia**

Background

Chikungunya (CHIK) fever is an emerging vector-borne viral disease that occurs in several parts of the world, especially Asia and Africa. In Africa, the virus is maintained through a sylvatic transmission cycle between wild primates and mosquitoes, while in Asia, the CHIK virus is transmitted by human-to-human spread mainly through mosquitoes belonging to Aedes aegypti or Aedes albopictus species. The disease affects people in new geographical areas, while herd immunity develops in infected communities.

Since the first documented Asian outbreak in 1958 in Bangkok, Thailand, outbreaks have been documented in several countries. In India, the first CHIK outbreak was recorded in 1963 in Kolkata, followed by epidemics in other states. CHIK re-emerged in an explosive epidemic form in India during 2005–2006 after a gap of 32 years, causing 1.3 million cases in 13 states. CHIK outbreaks have also been reported in the Maldives, Sri Lanka and Indonesia. A CHIK outbreak in Italy in 2007 proved that the disease may be found in temperate zones due to geographical spread of potential vectors and movement of infected people. In the past 50 years, the anthropophilic Ae. albopictus has spread to all continents and adapted to most climates.

Ae. aegypti is the major vector of the disease wherever it is present. In the recent past, however, there have been reports from various locations of Ae. albopictus as a vector of this virus. The role of Ae. aegypti and Ae. albopictus in the transmission of CHIK depends on the vector competence and vectorial capacity of these species. Although Ae. aegypti is capable of transovarial transmission of dengue vertical transmission appears to have a limited role in disease outbreaks. So far there appears to be no evidence of transovarial transmission of CHIK virus in these vectors.

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Chikungunya virus (CHIK) is a member of the Alphavirus genus of the family Togaviridae. Three main laboratory tests are used for diagnosing CHIK fevers: virus isolation, molecular technique of RT-PCR (Reverse Transcriptase-Polymerase Chain Reaction) for which blood should be collected within 2-3 days after the onset of fever and serological tests—IgG ELISA of the paired sera from acute and convalescent (after 10-14 days of infection) phases and MAC ELISA for IgM antibodies (within 2-3 days after the onset of fever). MAC ELISA gives cross-reaction to flaviviruses, but these are rare in South-East Asia region, hence, positive MAC ELISA is accepted as a confirmation for CHK fever. Though virus isolation is the most definitive test, positive RT-PCR with C (capsid) and or in combination with Envelop 1 or 2 primer sets is accepted as confirmed.

Chikungunya fever has a debilitating effect on patients. One of the common complications of CHIK includes arthralgia of prolonged duration. There is currently no effective antiviral treatment for CHIK. Treatment is therefore purely symptomatic and is based on non-salicylate analgesics and non-steroidal anti-inflammatory drugs. Synergistic efficacy was reported between interferon-alpha and ribavirin on the CHIK virus in vitro. A clinical trial in southern Africa failed to confirm the beneficial effect of chloroquine on arthralgia.

CHIK virus infection seems to elicit long-lasting protective immunity. Experiments in animal models have shown cross-protection between the CHIK virus and other alphaviruses. There is currently no commercial vaccine for the CHIK virus, although some candidate vaccines have been tested in human beings. In the trials conducted by the US Army Medical Research Institute, highly satisfactory seroconversion rates (98% on day 28) and neutralizing antibody titres were obtained, which persisted in 85% of cases for one year.

As there is neither any specific clinical treatment nor any vaccine available against CHIK infection, general public health measures have to be instituted for the prevention and control of CHIK fevers. Prevention constitutes taking steps to avoid mosquito bites and eliminating mosquito breeding sites. Surveillance is also important for early identification of outbreaks. A good surveillance programme designed to avoid infestation is much less expensive than an eradication or control programme that must be established after infestation has occurred.
In the absence of a vaccine against this disease, vector control is the major preventive strategy that is available to combat Chikungunya and dengue fevers. However, effective control of Ae. aegypti has rarely been achieved and never sustained. The emergence of Ae. albopictus as an efficient vector for the CHIK virus is an additional challenge. Recent data show the different degrees of insecticide resistance in Ae. aegypti and Ae. albopictus. Furthermore, vector control is an endless, expensive and labour-intensive measure, and is not always well accepted by local populations, whose cooperation is crucial for success. Social mobilization and public awareness should be an integral part of the disease control programme. Recently there has been renewed interest in developing environmentally safe genetics-based vector control strategies. Two notable advancements in this direction are: (i) development of a dominant lethal RIDL strain and (ii) introduction of a life shortening Wolbachia strain (wMeoPop) in to Ae. aegypti. Though these and many other strains that are being developed are far from being ready for field use, there is need to study ecological and population-genetic aspects of these species for these strategies to implement in the field.

Keeping in view the recent large-scale appearance of epidemics and the morbidity and financial loss that is caused to the community, economic loss to the nation; and challenges in the diagnosis, treatment and vector control, WHO/SEARO organized a technical meeting in 2007 and a workshop in March 2009 to identify priority areas of research. Following are priority areas of research in different aspects of CHIK infection/fever that were identified with a hope to combat this vector-borne disease effectively.

Priority areas for research

Diagnosis and molecular characterization of virus

- To develop new and field-applicable rapid diagnostic methods with required sensitivity and specificity.
- To evaluate available diagnostic tools for their sensitivity and specificity in different settings.
- To undertake molecular characterization of the virus and vectors to understand genetic diversity for use in molecular epidemiology.
Epidemiology and surveillance

- To review and fine tune the existing case definition of chikungunya and validate it during outbreak investigation and management.
- To identify critical parameters in the transmission of CHIK and develop protocols for the recognition of sites of transmission in order to interrupt the disease transmission.
- To assess risk factors related to exposure, infection, disease development and severe outcomes.
- To study the natural history of the disease and underlying causes/dynamics of its rapid spread.
- To delineate threshold levels of entomological and virological parameters and validate these to develop early warning systems.
- To undertake studies on immunological correlates to understand the level and longevity of herd immunity.
- To assess the burden of CHIK disease in countries in terms of morbidity/mortality, disability-adjusted life years (DALYs)/quality-adjusted life years (QUALYs) and impact on poverty.
- To develop strategies for improving surveillance for CHIK, including the use of laboratory-based surveillance and certification of laboratories for this purpose.

Vector biology and control

- To undertake field studies on vector competence of Ae. albopictus, and role of other possible vectors namely Ae. vittatus and Culex quinquefasciatus.
- To establish relative roles of Ae. aegypti and Ae. albopictus in the transmission of the disease where the two species are sympatric.
- To identify biological, ecological and socio-cultural determinants influencing vector bionomics and disease transmission with reference to both vectors.
- To develop community-based vector control technologies including source reduction and use of insecticides.
- To undertake analysis/review of existing research studies on vector bionomics including species specific adult resting and breeding sites to improve/formulate vector control strategies.
To define standard sampling methods and indicators for dengue vectors, including validation of the application of pupal index along with the existing larval indices being used for vector surveillance.

To assess efficacy of existing and new vector-control tools and strategies in different settings.

To identify and implement essential elements of integrated vector management and ecosystems interventions in different epidemiological and entomological contexts.

To undertake genetic characterization using molecular markers of Ae. aegypti and Ae. albopictus from different geographical regions to understand population structure, genetic variability and gene flow.

Environmental research

To quantify the potential impact of climate change on the transmission of CHIK and dengue diseases.

To develop protocols for use of remote sensing (RS) and geographical information systems (GIS) in mapping risk factors and monitoring them, for making decisions on controlling outbreaks, and also for exploring the possibility of using such technologies to develop an early warning system.

Social and behavioural research

To understand the treatment and health-seeking behaviour of the population;

To develop models and document the role of the private sector and nongovernmental organizations (NGOs) (public-private partnerships and intersectoral collaboration) in disease prevention, control, surveillance and development of diagnostic/intervention tools.

To evaluate the social, cultural and community behavioural practices leading to disease transmission including studies on knowledge, attitude and practices (KAP) in relation to different stakeholders such as the general population, decision-makers, health-care providers, etc.;

To undertake feasibility studies for applying the communication and behavioural impact (COMBI) strategy for effective community involvement in disease prevention/control.
Clinical management

- To evaluate the potential effectiveness of chloroquine and other drugs in mitigating long-duration arthralgia in patients with CHIK.
- To identify the factors predisposing to clinical illness and severe outcomes as well as the pathogenesis of severe outcomes of CHIK.
- To document and correlate the spectrum of clinical features in co-infection of CHIK with other diseases, notably dengue fever, HIV, tuberculosis (TB), immune deficiency disorders and acute respiratory infections.
- To understand the presence of asymptomatic infection with CHIK virus and its impact on disease transmission/epidemiology/re-emergence.
- To identify and assess the causes of severe outcomes of the disease and ascertain the contribution of the disease in causing mortality.

Vaccine development

- To develop and evaluate transmission-blocking vaccines.
- To develop and evaluate correlates of protective immunity for use as an endpoint in vaccine trials.
- To develop new products or assess existing licensed products for their efficacy as drugs against dengue virus.

Conclusions

The re-emergence of CHIK fever in epidemic form during the recent outbreaks in India, Sri Lanka, the Maldives and the Indian Ocean islands is a matter of public health concern. The man-made environment in urban and periurban areas has created excellent conditions for the proliferation of vectors that are common for dengue and CHIK viruses. Outbreaks of CHIK fever highlight the importance of the need for monitoring vector-borne and zoonotic diseases. The clinical manifestations are highly variable and may be more severe than previously reported.

Several lessons can be drawn from these outbreaks for which research can lead to a better understanding of the disease and at the same time develop evidence base from which effective interventions can be
appropriately targeted in the face of limited resources. Basic and applied research is needed for understanding the natural history, epidemiology and transmission dynamics of the disease, and for developing reliable prevention, diagnosis and treatment interventions. Ecological, behavioural and environmental research helps in making evidence-based decisions at the community level. Operational research is needed for programmatic monitoring and assessment, bridging knowledge gaps, and assuring quality implementation and scaling up of interventions. Partnerships are needed among national institutions, private sector/NGO, community and international agencies to find solutions for the control of CHIK fever by promoting needs-based research.

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8. Leprosy: priority areas for research

Sumana Barua*

Introduction

The global fight against leprosy has come a long way from the time when leprosy was considered an incurable disease leaving affected people and their families to suffer the devastating consequences without hope. Today, the scenario has changed significantly from what it was even a few decades ago. Simplified diagnosis and treatment were made available free of charge at the nearest health centre. Globally, the number of countries that are yet to achieve the goal of elimination of leprosy as a public health problem has reduced from 122 in 1985 to only four by early 2007. Between 1985 and the beginning of 2007, about 16 million leprosy cases were diagnosed and treated with multidrug therapy (MDT). The number of relapses remains low, at less than one case per 1000 patients per year. Of the 16 million cases, about 12.8 million were from the SEA Region and more than 11.8 million of them from India. Thus, the Region has contributed significantly to the reduction in the global leprosy burden. Nine of the 11 countries in the SEA Region have achieved elimination at the national level. Remaining two countries (Nepal and Timor-Leste) are making concerted efforts to achieve this goal1,2,3. The decreasing trend in the detection of new cases of leprosy in South-East Asia Region from 2001 to 2007 is shown in the figure below.

The main control strategy focusing on early diagnosis and timely treatment with MDT led to the remarkable and progressive decline in prevalence and new case detection and helped in averting disability in about 4 million cases globally. However, the burden of disability persists because of high transmission of the disease in the past and delays in obtaining effective treatment, resulting in a low, but persistent, incidence of disability. In recent years, major steps have been taken to simplify prevention of disability (POD) for integrated programmes4.

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Research gap

Research activities in past decades contributed to simplify diagnosis, in developing the MDT regimens, shortening the treatment duration, improving population and geographical coverage. However, leprosy research was given less priority while focusing on intensified implementation of the main control strategy in collaboration with concerned partners. It is generally considered that the remarkable decline in prevalence and new case detection of leprosy are the outcome of the concerted efforts on case finding and treatment with MDT.

No formal review of global research expenditure has been conducted. However, the International Federation of Anti-Leprosy Associations (ILEP) estimates US $ 3 million was spent in 1998 down from US $ 6.5 million in 1990 by ILEP alone\(^5\). Substantial contributions have also been made by other agencies like the National Institute of Health (NIH) and the European Community (EC) etc. However, there is an extensive need for research on various aspects of leprosy as the problems are compounded by lack of fundamental knowledge about the epidemiology of leprosy, the sources of infection, the precise mode of transmission and the importance of the contact patterns\(^6\). In addition to these basic understanding of the disease, research activities will be of prime importance in improving the operational
factors of the control programmes. The geographic coverage of effective MDT services is still not complete and thus access for patients is imperfect, especially, amongst marginalized populations. The seventh expert committee on leprosy recommended epidemiological research to facilitate the development of "post-elimination" control strategies. During its various meetings, the WHO Technical Advisory Group (TAG) on Leprosy Control has recommended conducting research on relevant issues and areas such as treatment duration, legislation on people affected by leprosy and integration of leprosy services into general health services.

Research priorities on leprosy in the Region

A wide-range of research areas may be identified from transmission, diagnosis to development of new diagnostic tools and new drug regimen that may need extensive resource allocation. However, focusing to complement the control strategy based on MDT, the following are the broad categories of research priorities on leprosy in the Region:

Clinical research topics

- Effectiveness of shorter treatment duration with existing MDT regimens
- Effectiveness of other combination of drugs with shorter treatment regimens
- Incidence of disabilities during treatment with MDT and after release from treatment (RFT)
- Validating more specific diagnostic tools for field application
- Prevention of nerve damage and impairments in nerve functions

Epidemiological research topics

- Analysis of age-specific incidence trend among new cases focusing on factors affecting child proportion among new cases
- Identification of high risk groups from an interventional perspective
- Validation of under-diagnosis through examination of identified suspects where diagnosis was rejected
Operational research topics

- Alternative cost-effective service delivery options/models for areas with reduced leprosy endemicity
- Health seeking behavior of leprosy disabled persons
- Effectiveness of integrated two-way referral system for leprosy cases in low endemic situation
- Assessment of leprosy service delivery in the integrated settings
- Identification of high risk groups from an operational perspective
- Contribution of local socio-cultural factors and operational factors affecting delayed diagnosis and initiation of treatment with MDT

Research topics related to stigma and social discrimination

- Analysis of existing legislation towards the people affected by leprosy
- Extent of involvement of the people affected by leprosy in various community activities.
- Gender factors influencing detection of leprosy and utilization of services
- Commonalities and differences between leprosy-related stigma and stigma related to other conditions focusing on common stigma reduction strategies

Conclusion

Major challenges that remain include maintaining the quality of services, strengthening referral systems, establishing a drug monitoring system in the integrated leprosy control services, and building effective partnerships based on mutual trust especially in low-endemic situations. Further reducing the stigma and discrimination against affected persons and their families and rectifying outdated legislation is also important.

In most of the leprosy endemic countries leprosy control services are integrated into the general health services and in other countries the integration process is underway. Findings from the above research priority will contribute immediate implication in improving the present control strategies.
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9. Visceral leishmaniasis in the South-East Asia Region: research priorities

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Introduction

Visceral leishmaniasis (VL), or kala-azar, is endemic in a total of 109 districts in Bangladesh, India and Nepal.¹,² An estimated 200 million people are at risk for infection. Approximately 25,000-40,000 cases and 200-300 deaths are reported every year from these disease-endemic countries, but these are gross underestimates.² Recently, multicentric studies identified a VL burden of 21 cases/10,000 in the Indian subcontinent (136,500 cases in Bangladesh, 270,900 in India and 12,600 in Nepal).² The total estimate of 420,000 cases per 200 million at-risk population clearly indicates that the disease is highly underreported. More than 50% of cases are reported from the border districts and extension to new geographical areas has been observed. The disease occurs predominantly among the poorest of the poor. The actual incidence of the disease is estimated to be about 8-10 times higher than that reported in all three countries. It is noteworthy that the private sector, which covers 70% of health care in India, does not report cases of VL to the national reporting system. However, in Bangladesh and Nepal, treatment facilities are not available in private sector and ultimately cases report to public health facilities for treatment.

Steps towards elimination

A Regional Technical Advisory Group (RTAG) for the elimination of VL was set up with policy-makers and researchers, and the first meeting was held in December 2004. A regional strategy for elimination of VL was developed and endorsed by RTAG and partners.³,⁴ In May 2005, a memorandum of understanding (MoU) was signed between the three countries at the World Health Assembly meeting and a regional strategic framework developed and endorsed.

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The goal of the strategic framework is to eliminate VL in the three countries so that it is no longer a public health problem by reducing the incidence to below 1/10,000 at the district and subdistrict levels in India, Bangladesh and Nepal by the year 2015. The main strategies are (1) effective disease surveillance, (2) early diagnosis by the dipstick method and complete treatment, (3) effective vector control through integrated vector management (IVM) with a focus on indoor residual spraying (IRS) and environmental management, (4) social mobilization of the population at risk, and (5) clinical and operational research to support the elimination programme. A number of supportive strategies such as nutrition supplementation, poverty alleviation, improved housing and environmental sanitation are needed for VL elimination.

**Factors facilitating the elimination of visceral leishmaniasis**

Visceral leishmaniasis is considered to be suitable for elimination because technological developments have been promising and there are simple diagnostic tools for field use (rK39 strip test); there is effective treatment (miltefosine, paromomycin, and rescue drugs such as amphotericin B and AmBisome); there is no animal reservoir; IRS continues to be effective; and DDT spraying in the past led to near elimination. In the field of vector control, useful strategies include adoption of the IVM approach, use of geographical information system (GIS) and remote sensing (RS) technology, and environmental management and manipulation. In addition, there is strong political commitment in the three countries, and India has allocated a budget to realize elimination.

Although the tools for elimination have improved considerably during the past few years, they are far from perfect and continued research is required to make them robust and effective. For their application, implementation strategies will be required to evolve best practices.

**Implementation research on visceral leishmaniasis supported by TDR**

The Special Programme for Research and Training in Tropical Diseases (TDR) has supported implementation research on VL in Bangladesh (one site), India
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(three sites including one site devoted to policy research) and Nepal (two sites). This research focuses on estimation of the burden of the disease, health-care seeking behaviour, behaviour and knowledge of care providers in the formal and informal sectors, and policy applications both in the public and private sectors.

The findings of phase 1 were reviewed at a meeting held in Varanasi, India in April 2007. The main findings are summarized below.\(^5,6\)

The major findings revealed that the current burden of disease in Bangladesh, India and Nepal (21 cases/10,000 population) is 10–20 times higher than the elimination target for 2010/2015; there is considerable delay in seeking treatment (symptoms to diagnosis >3 weeks in 20%; diagnosis to treatment >3 weeks in 31%); community knowledge about VL and the precautions to be taken is adequate in India and Nepal, but not in Bangladesh. The rK39 test is used by 45–58% of care providers in India and Nepal, but not yet in Bangladesh; knowledge among care providers on drugs other than antimony, miltefosine in particular, is good in India and Nepal, but unsatisfactory in Bangladesh. Policies on VL treatment examined in Bihar and West Bengal were found to be deficient and not available for the private sector. A blueprint for a focused intervention in VL “hot spots” identified by GIS mapping was presented.

Based on phase 1 findings, future key research on the management of VL to improve case detection, diagnosis, treatment and follow up in the three countries will be based on the assumption that active case finding in highly affected areas may be cost-effective. Active case detection will therefore be the key element of the phase 2 research approach. At the same time, the rK39 strip test will be applied as a diagnostic tool within the programme and the feasibility of miltefosine treatment at community level will be assessed. Following the discussions at the meeting, VL was defined as cases with fever for >14 days, splenomegaly, rK39 positivity and malaria negativity. An algorithm comprising active case finding by community health workers, confirmation of the diagnosis at the hospital level, treatment at the community level (directly observed treatment [DOT]) and referral of complicated cases to the district hospital or equivalent was proposed as a common algorithm for a three-country approach.\(^6\)
The need to monitor miltefosine if administered at the community level and means/mode of monitoring were important issues. About 2–3% of patients on miltefosine develop life-threatening side-effects (1% severe diarrhoea/vomiting, 1.6% renal toxicity, 0.3–0.4% clinical hepatitis)\(^6\). Antimony, given unsupervised at the community level, has a 5% treatment fatality rate\(^6\). India and Bangladesh lack laboratory facilities to monitor renal and/or liver functions at the community level. Nepal proposes to hospitalize patients on miltefosine for three days. Only a few district-level health facilities are equipped to monitor renal and liver functions.

Routine microscopy misses about 20% of cases of VL and the polymerase chain reaction (PCR) test is available in a few specialized laboratories (only in India). Several tests are available for the field diagnosis of VL infection. All of them have their advantages and disadvantages. Among the rapid tests available, rk39 is highly sensitive and easy to perform. It is the most convenient test for use in the field. The limitations of the test relate to specificity. Detection of asymptomatic infections remains a challenge since such people can be a source and reservoir of infection.\(^5\) Asymptomatic persons outnumber symptomatic patients by a factor of about four. The high cost and toxicity of the medicines precludes the treatment of asymptomatic persons. It is important to understand the public health importance of asymptomatic individuals.

While antimony remains the cornerstone of VL treatment all over the world, it is toxic and can be used in susceptible areas only. Its toxicity is a constraint to its widespread use. Amphotericin B administration requires hospitalization for several weeks. The need for prolonged hospitalization is a limitation in endemic countries of the Region. Liposomal amphotericin B is a safe and effective rescue drug. The high cost of the drug has been a limitation but the recent arrangements with WHO for cost reduction if used for public health purposes and the simpler schedules of administration appear promising. Initial experience of one-day treatment with liposomal amphotericin B has been positive. This schedule should be evaluated through a multicentre trial. Miltefosine is the only oral drug available. To avoid the emergence of resistance, complete treatment in the right dose and regimen is recommended. The drug should be avoided in pregnant women and patients with known renal or hepatic disease. Pharmacovigilance is important to delay or contain drug resistance. Paromomycin is a potentially useful first-line drug that is awaiting completion of phase IV trials.
Ongoing TDR-supported research on leishmaniasis in the Indian subcontinent

Ongoing research on VL includes the following:

- Implementation research in the area of vector management and treatment in Bangladesh, India and Nepal
- Evaluation of a fast agglutination screening test (FAST) for field serological diagnosis of VL (India)
- Development of new drugs in partnership with private industry: miltefosine, the potential first-line oral drug against VL (phase III and phase IV trials have been concluded in India. These are in progress in Bangladesh and Nepal). Phase III trials on paromomycin have been concluded in India while phase IV trials are in progress. These studies are supported by the Institute of OneWorld Health.7,8

Research priorities for visceral leishmaniasis in the Indian subcontinent

Strategies and policies

- Develop economic, social and health systems to enhance implementation of the elimination programme.
- Conduct cost-effectiveness studies for advocacy with partners.
- Develop support systems for early warning to predict outbreaks and responses.
- Conduct analytical studies to develop drug policies and policies to support the availability of effective drugs for the programme.
- Monitor the spread of drug resistance.

Intervention methods

A screening and confirmatory test for VL is available. However, the reliability of the test is questionable. Based on evidence, rk39 has been recommended but quality assessment is important. Currently, interpretation in done based
on the clinical presentation and test results. Invasive tests such as bone marrow and splenic puncture are confirmatory and suggested in cases that have been referred or have treatment failure. Research is needed in the following areas:

- Evaluation of rapid diagnostic tests for VL and PKDL
- Development of algorithms for new treatment regimens
- New/combination treatment to reduce the duration of treatment
- Evaluation of insecticide-treated bednets (ITNs) for vector control as a part of the IVM approach

**New and improved tools**

- Development and evaluation of immunotherapeutics
- Novel and non-toxic short-course chemotherapy; combination drugs
- Identification of target molecules and development of novel assays
- Diagnostics to discriminate active asymptomatic and resistant phenotypes
- Tools to identify sandflies at the species level and to identify infected flies

**Vector control technologies**

To improve the performance of existing control technologies and provide necessary new knowledge, it is important to compare the cost-effectiveness of different vector control options, develop methods for case finding and conduct studies on risk factors. Research is suggested in the following areas.

- Vector ecology and efficacy of non-chemical technologies
- Efficacy of insecticide-treated curtains and other materials in reducing vector density
- Cost, feasibility, acceptability and sustainability of strategies using insecticide-based vector control tools (IRS/ITNs) or non-chemical ecological interventions
- Study the occurrence of the disease and its relation to different aspects of the vector
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Post kala-azar dermal leishmaniasis (PKDL)

Research priorities in this area include a therapeutic vaccine-related study for PKDL, and clinical trials of newly developed drugs including miltefosine, AmBisome, paromomycin in suitable doses. Validation of the diagnosis of PKDL will also be essential.

Pharmacovigilance

The aim of pharmacovigilance as a component of the VL elimination programme is important for improving patient care and safety, detecting problems related to the use of medicines and communicating these findings in timely manner, thereby contributing to an assessment of the benefits, harms, efficacy and risk of medicines. Research in pharmacovigilance should be designed such that it is based on the country's need.

Social-behavioural research

Social and behavioural research requires investment. Social and behavioural scientists should be involved fully right from the planning stage. This research will be very useful in sustaining advocacy for VL and contributing to elimination through behaviour change to enable early diagnosis, treatment adherence and prevention among affected communities. The following may be considered as priorities:

- Behavioural studies on the living and sleeping habits of affected communities
- Social determinants of utilization of health-care services and health care-seeking behaviour
- Readiness to participate in interventions on environmental management and manipulation
- Economic and social consequences of VL
- Identification of behavioural bottlenecks in completing treatment and exploring ways to overcome these problems

Economic research

This involves research to provide systematic information at various levels of the decision-making process and mobilize all resources such as finances and
economic resources, states, civil society and the general community to produce regional public good. Priorities include the following.

- Review and assessment of the national health policy for VL
- Impact of health and fiscal policy with regard to VL
- Defining elimination of VL as a public good
- Impact of incentives to control VL
- Relationship of VL with the Millennium Development Goals (MDGs)
- Poverty reduction and its impact on VL

**Developing and implementing a VL-specific policy and sustaining elimination programmes**

- A proper assessment of resource needs and designing large scale interventions to achieve elimination
- Decentralization of the health system and its impact on VL management
- Assessment of resources required for VL elimination

**Evaluating the impact of programmes and achieving desired outcomes**

- Service utilization and its relation with income and poverty level of households
- User fees and demand for health care regarding VL
- Costs and access to health services
- Willingness to pay for VL treatment and prevention
- Impact analysis of the existing VL policy, poverty, catastrophic payment and its relation with service utilization.
- Utilization of health services and studies related to health care-seeking behaviour
- Cost-benefit and cost-effectiveness analysis of different components of the VL elimination programme (vector control, case-finding strategies, treatment used, and diagnosis and other educational interventions)
Constraints and challenges

The epidemiology of VL is not well understood. The disease occurs in clusters and often as a slowly emerging epidemic probably related to the migration of people, resettlement, malnutrition and unplanned housing. There is limited access to effective diagnosis where it is most needed and diagnostic tools have to be validated under field conditions.

The availability of effective drugs for the rural population is limited because of high costs and logistic problems. Medicines have to be given parenterally for up to four weeks or longer. This leads to poor adherence to treatment. Introduction of effective therapy for VL, and monitoring and evaluation is essential to achieve the objective of elimination. Drug resistance seems to be spreading but monitoring for drug resistance is inadequate. Therefore, there is a need to assist Member countries of the South-East Asia Region (SEAR) in capacity development for treatment and diagnosis. The important areas in which assistance will be required are IVM and behavioural change communication.

The overlapping of VL and HIV/AIDS has led to the emergence of a new entity - leishmaniasis/HIV coinfection. This is likely to occur in “at-risk” populations comprising migrants, seasonal workers, refugees, sex workers and truck drivers. Undernutrition and immunosuppression are the likely individual risk factors for coinfection.

Even though political commitment is high, resource allocation until recently has been low, implementation inadequate, and the capacity of the health systems insufficient. The disease is not notifiable. It was made notifiable in one state (Bihar) in India but this did not work because of poor implementation. Even though new diagnostics and drugs are available, their availability in the programme mode is too slow to have an impact. Vector control through the application of IRS has not been sustainable because of logistic constraints and high costs.

The gravity of the problem in Member countries calls for efforts to undertake advocacy for global commitment, mobilize additional resources and build partnerships for the elimination of VL.

At the regional and country levels, partnerships are needed and have to be sustained. Since VL is a local and focal disease in countries of the Region, action is required at the subnational and district levels to support the scaling up of VL elimination efforts. The adoption of a decentralized approach is
acceptable to countries and is national policy in many of them. The following measures must be put in place:

- Capacity building for research
- Strengthening the inputs of health economics in the elimination of VL
- Developing links between clinical trial and surveillance networks
- Strengthening global and regional networks, e.g. leishmaniasis clinical trial group (LCTG)

There is a need to implement the “regional strategies” within the suggested time-frame to achieve a uniform rate of decline in the affected countries.

**Sustainability of research on kala-azar**

The successful implementation of research would require the following:

- Financial support from all partners (global, regional and national)
- Networking of research institutions and partner organizations
- Development of common protocols
- Coordination between research bodies and national elimination programmes (regular exchange of information, organization of review meetings)
- Strengthening of research capacity including training
- Working out mechanisms for monitoring the quality of research (use of research monitors)
- Organization of multicentre studies using common protocols
- Constitution of scientific working groups
- Coordination with RTAG of SEARO

**Conclusion**

For the elimination of VL, immediate action must be taken to expand the delivery of effective tools, strengthen the capacity of the health system and utilize innovative delivery systems. Research can provide evidence and support for overcoming several important issues, either directly or indirectly through improving commitment and mobilization of resources, both internal and external. These issues include estimating and improving the required
coverage of the population and utilization rates of health services, duration required to minimize the number of cases to achieve VL elimination and its relation to endemicity levels and vector–parasite complexes. It is critical to define criteria for monitoring and evaluation, and demonstrate the public health and socioeconomic impact of the elimination programme. This would help in expanding the programme and strengthen the commitment of donors and partners.

Resources should be allocated so that a balance is struck between implementation of the programme and conducting research. Research and development should be needs-driven to overcome the challenges and improve the prospects of elimination. Well-defined research policies and strategies for the short-, medium- and long term can effectively support the VL elimination programme. National programmes should be encouraged to address and respond to their challenges by incorporating a research component in their programme.

References


10. Research priorities on neglected tropical diseases in the SEA Region: focusing on soil transmitted helminthes, trachoma and yaws

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Introduction

Approximately 2 billion people – one sixth of the world’s population suffer from one or more Neglected Tropical Diseases (NTDs). Some of these parasitic diseases such as soil-transmitted helminthiasis (STH), Trachoma and Yaws have long been recognized as diseases of poverty as the affected people are generally the poorest and most vulnerable segment of the population. Some diseases affect individuals throughout their lives, causing significant morbidity and physical disability and in some cases, gross disfigurement. Other possible manifestations of these diseases are acute infections, with transient, severe and even fatal outcomes. Patients may face social stigmatization and abuse, which add to the sufferings already caused by the disease itself.

Although these diseases are no longer a public health problem in most of the western world, infection rates differ according to the ecology. STH is considered endemic in 130 countries and trachoma in 55 countries. About 500 million people are chronically infected with STH in the South-East Asia Region, where in some region infection rate is as high as 95%. Trachoma is particularly prevalent in large regions of Africa, the Middle East, Southwestern Asia, the Indian Subcontinent, aboriginal communities in Australia, and there are small focuses of blinding disease in Central and South America, it is estimated to be responsible for 2.9% of blindness worldwide. The endemic burden of yaws In 1995, WHO estimated the infectious cases to be 460,000 worldwide of which, 400,000 were in west and central Africa, 50,000 in

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South-East Asia and the rest in other tropical regions.\footnote{5} yaws leads to crippling and disfiguring consequences if untreated.

**Eradication: Early attempts, failure, and lessons learned**

Globally, only six countries have achieved more than 75% treatment coverage and 51 out of 122 countries have reported STH.\footnote{2} Currently 130 endemic countries, including 40 small island states of which 17 have reached all disease specific targets for “preventive chemotherapy” (against schistosomiasis, STH, lymphatic filariasis and onchocerciasis).

Although the SEA Region has set a goal of reducing the morbidity and mortality caused by STH by 50% and regularly treating (deworming) at least 75% of all school-age children at risk by 2010, scaling up of deworming for STH is lagging far behind; the treatment coverage of filariasis was 38% in 2005 but only 8% for STH.\footnote{2}

Trachoma control has a long history and is among the major disease control programs initiated by the World Health Organization (WHO), almost since its inception.\footnote{3,4} In 1987, a simplified grading system was adopted, enabling basic health workers to identify and manage trachoma cases.\footnote{6,7} In 1993, the community approach to trachoma control was developed by the WHO and published in collaboration with the Edna McConnell Clark Foundation.\footnote{6,7} The 1990s heralded the introduction of the surgery, antibiotics, facial cleanliness, and environmental strategy (SAFE), which was based on proven and cost-effective interventions. In 1996, the Prevention of Blindness program of the WHO established a large partnership of member states, non-governmental development organizations, research institutions, philanthropic foundations, and industry: the Alliance for the Global Elimination of Trachoma by 2020 (GET2020).\footnote{7}

Yaws was a major disease control effort undertaken by WHO just after its establishment in 1948.\footnote{8,9,10} Control programmes were established in 46 countries and, by the end of 1964, the number of cases had been reduced from 50 million to 2.5 million (a 95% reduction).\footnote{11} In the late 1960s, there was a shift in strategy from the vertical programme to integration of yaws surveillance and control into primary health care to tackle the remaining 5% of cases. This approach, however, did not succeed. By the end of the 1970s, reemergence of yaws in many countries prompted a World Health Assembly
Resolution requesting the implementation of integrated treponematoses control programmes.\textsuperscript{11} Renewed control efforts were not succeed.\textsuperscript{11,12} Since then, yaws has remained as a public health problem in a few pockets, including two countries in the SEA Region - Indonesia and Timor-Leste. India achieved elimination in 2006 and now heading for eradication of the disease.

**Issues and challenges**

“Some of the issues and challenges that have hampered eradication include the lack of an effective mechanism for surveillance and case detection, limited political commitment and resources, limited capacity of general health staff to recognize and treat, ensuring drug supply and logistics management, creating community awareness through appropriate advocacy/IEC [Information, Education, and Communication] campaigns and extending the services to remote and hard-to-reach areas” Among the most neglected diseases and there is little global attention or focus on these diseases, although primarily affects the most poor and vulnerable sections of the society- the tribal or indigenous people living far away from mainstream.

A large amount of good-quality drugs are required to expand and sustain interventions. For scaling up the programmes through an integrated approach, a number of research and monitoring questions will also need to be addressed.\textsuperscript{13,14,15,16}

Comprehensive evidence is required for advocacy, mobilizing resources and expanding partnerships. A large quantity of good-quality drugs are required to expand and sustain interventions.

**Research priorities**

There are still gaps in knowledge on disease dynamics and treatment. We still do not fully understand the epidemiology of STH, Trachoma and Yaws, the relationship between transmission intensity, disease pattern, and severity of the disease and subsequent complications. We still need to know more about the optimum treatment schedules using the newer drugs and have more insights on the effect of mass treatment compared with targeted treatment, given the cost of the medication.
Cultural issues like people’s knowledge and perceptions about trachoma, how and when to deal with it, and where to seek treatment, are important but not fully understood. We need to conduct studies in the community to understand what happens at the community level, how health-seeking behaviour develops, and how effective health education may be offered to children and adults for prevention.

**Improving the coverage of interventions among school-age children**

In STH infections, the occurrence of disease is directly related to the intensity of infection and is highest in school-age children. In young children, subclinical intestinal nematode infection causes wasting, malnutrition and anaemia. Some countries in the SEA Region have shown a good reduction in infection rates following mass deworming. In yaws, the occurrence of disease is directly related to the intensity of infection and is highest in school-age children. In young children, intimate contact is highest at school activity especially in children with a poor hygiene. Some countries in the Region have shown a good reduction in infection rates following mass eradication programme through penicillin shots. These ongoing programmes needs to be sustainable, ensured and their impact should be evaluated.

**Integrated multi-intervention package**

A comprehensive pro-poor strategy should be formulated to integrate programmes for the control or elimination of some tropical diseases (ascariasis, trichuriasis, ankylostomiasis, lymphatic filariasis and trachoma) using existing guidelines. Such integration efforts are particularly relevant in the Region as these diseases exhibit a high degree of geographical overlap. The four-drug regimen – albendazole, ivermectin, azithromycin and praziquantel – would also target ectoparasite infections such as scabies, pediculosis, tungiasis and their resulting secondary bacterial infections, and possibly also important respiratory bacterial pathogens including Pneumococcus. Such a package could reduce tens of millions of DALYs annually and simultaneously address seven of the eight Millennium Development Goals (MDGs).
Detection, monitoring and prevention of drug resistance

There are a few reports that suggest resistance to drugs in human nematodes.\(^{17}\) Frequent treatment with the same drug will increase drug pressure on the parasite and microbiological population resulting in a selection that carry resistant genes. The most worrying scenario would be to see the benefits of periodic chemotherapy hampered by generalized treatment failure. The rate of post-treatment re-infection and relapse need to be addressed and the efficacy of drugs should be monitored regularly as efficacy diminishes with frequent and periodic use. As a result, there are justifiable concerns about the possibility of emerging resistance, which is now common for Penicillin in other bacterial infections. Effective monitoring of large scale eradication programme needs to be established. Since there are only a few anti-helminthic drugs on the market and almost none under development, no alternative treatment will be available once resistance develops against the currently used drugs. Targeted treatment of high-risk groups, treatment at intervals greater than the nematodes’ generation time and use of combinations of anti-helminthic drugs are all strategies that can reduce and delay the selection of resistant strains.\(^{8}\) Development of methods for detection, monitoring and prevention of drug resistance was one of the priority recommendations from the WHO Expert Committee.\(^{3}\) Treatment strategies should be carefully designed in order to achieve a maximum reduction in morbidity, and balancing the risk to increase selection pressure for resistance.\(^{18}\)

Integration of multi-intervention package into primary health care

A comprehensive pro-poor strategy should be formulated to integrate programmes for the control or elimination of some tropical diseases using existing guidelines.\(^{19}\) Such integration efforts are particularly relevant in the Region as these diseases exhibit a high degree of geographical overlap. This problem is strictly related to the lack of awareness of many decision-makers and their lack of support to the elimination activities. Resources available to date, human and financial, are grossly inadequate to achieve the elimination.
**Improving the personal hygiene and environmental changes:**

In general, poor hygienic conditions favor the transmission of STH, Trachoma and Yaws. Several studies have been carried out to identify the specific components of hygienic conditions associated with a lower risk. The ocular and nasal secretions of pre-schoolchildren in trachoma areas are clearly a potential source of infection. Improving facial cleanliness may decrease the likelihood of transmission from these secretions. Studies need to be carried out to identify the specific components of hygienic conditions associated with a higher risk of these diseases.

**Diagnostic dilemma and surveillance and drug safety**

The lack of reliable serological or morphological tests to distinguish T. pallidum subspecies obviously limits diagnostic accuracy, which can have serious detrimental effects. For example, treatment for a pregnant woman with burnt out yaws and one with active syphilis should be different, and assigning the wrong treatment may result in a negative outcome. The absolute safety of anti-helminthics during pregnancy needs to be confirmed by further studies.

**Focus of research**

- Impact assessment of eradication programmes along with improving personal hygiene and environmental sanitation on the prevention of re-infection among schoolchildren and the community.
- Review and assessment of the current coverage of different interventions and suggestions for improving the strategy to reach non-enrolled schoolchildren.
- Operational research should be conducted to determine the most effective approach to integrate multiple interventions as appropriate for the targeted populations. Developing and testing integrated data management systems is also a priority.
- Mapping the co-endemicity of other diseases with STH can provide further information for integrating programmes.
- Identify sensitive and resistance genes in disease populations at an early stage. Sensitive molecular tools to monitor drug efficacy need to be developed.
➢ Design clinical trials for the development of vaccines against STH, Trachoma and Yaws and encourage collaboration between research and control efforts.

➢ Develop standardized protocols for reliable and valid in vivo and in vitro tests to confirm suspected drug resistance in humans under the conditions prevailing in developing countries.

➢ Improving facial cleanliness, personal hygiene and environmental sanitation among schoolchildren and the community and environmental control of flies and primate

➢ Promoting the idea of ‘self-help’ for prevention of disease through community mobilization and partnerships.

Future directions

Basic and applied research should provide knowledge that contributes to the prevention, treatment, and control of these neglected and marginalized diseases. Development of Pre School Age Children (PSAC) needs to be confirmed and properly tested in different epidemiological settings. Adverse Event Reporting Forms (AERS) need to be included in any campaign delivering drugs so as to routinely capture data on the number of children having problems with drugs. In the meantime, WHO and UNICEF should continue advocating for the development of novel paediatric formulations (rapid dissolving tablets or alternative drug like new generation macrolides and anti-helminthics). Evaluating drugs with Vaccine interactions: Possible synergies and interactions related to delivering drugs with different vaccines (measles, BCG, polio) in large-scale vaccination campaigns needs to be further evaluated and properly followed up in the mid and long term.

Malaria/TB/HIV: Interactions of STH, Trachoma and Yaws with the management of the three big killers-malaria, TB, and HIV- needs further study and science-based evidence to advocate and suggest novel means of combating malaria, TB, and HIV infections in yaws endemic areas.

Conclusion

We need to build the network and develop necessary partnership for tackling Soil Transmitted Helmenthiasis, Trachoma and Yaws in a sustainable manner. Indeed, collaboration with existing programs could allow resources to be shared and facilitate elimination and surveillance activities. There is also a
clear need for increased advocacy and generation of interest, both in the disease itself and in engaging countries. What seems most interesting about the renewed effort in South-East Asia is that it is aggressively targeting both cases and their contacts which may overcome the earlier challenges. The disease is amenable to eradication epidemiologically, technologically, historically and from political point of view. We believe also that efforts on Soil Transmitted Helmenthiasis, Trachoma and Yaws eradication could be an entry point for primary health care for the most marginalized populations. The total amount of money required to achieve eradication would be only a small fraction of what is being spent for polio eradication annually. Eradication of yaws could become another great success story for mankind like the historical event of small pox eradication in 1978, one of the greatest achievements for public health! The other side of the coin is that a second failure against this not-so-invincible enemy could generate mistrust and frustration about the other ongoing eradication efforts. Thus, urgent and effective measures must be taken by the governments of the affected nations to free our humanity from the curse of this neglected disease once for all.

References


11. Lymphatic filariasis: priority areas for research

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Introduction

Lymphatic filariasis (LF) is one of the most prevalent tropical diseases, endemic in 83 countries and territories. It is estimated that 1.3 billion people are at risk for developing the disease and some 120 million people are infected. Over 40 million patients are seriously incapacitated and disfigured by the disease. Of these, 95% are infected with Wuchereria bancrofti, and the remainder with Brugia malayi or Brugia timori.

Epidemiological trends during the past decades have varied widely between different regions of the world. Filariasis was eliminated as a public health problem from several islands in the Pacific, People's Republic of China and the Republic of Korea has seen a dramatic reduction in infection levels. Unfortunately, in a number of areas in African, Americas and South East Asia where disease is endemic, there has been no significant decline in the prevalence of filarial infection even an increase in some areas. This increase is often associated with urbanization, environmental change, etc. A major reason for the persistence of the disease is the lack of effective implementation of the control tools and strategies in a cost-effective manner appropriate for the endemic countries.

Burden of disease

More than one billion people are at risk of contracting lymphatic filariasis (LF) which is known as elephantiasis. LF is a devastating parasitic infection spread by mosquitoes. Currently 120 million people are already infected, with more than 40 million incapacities or disfigured.

Lymphatic filariasis is a major public health problem in the South-East Asia Region. Nine out of eleven countries (except Bhutan and DPR Korea) in the Region are endemic for filariasis. It is estimated that there are about 860 million people who are living at risk in South East Asia Region constituting

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about 66% of the global burden with about 60 million persons either harbouring microfilaraemia or suffering from clinical manifestations which constitute about half of the global figure, 14 million of whom have chronic lymphoedema and 2.5 million people are affected with hydrocele.

Fig: Mass Drug Administration (DEC+Alb.) for LF in South-East Asia Region

India has now adopted the 2-drug regimen

The disease is usually acquired in early childhood and causes considerable morbidity and social stigma because of the deformities it produces, though it is not fatal. It predominantly afflicts poor people in both urban and rural areas as well as neglected populations. LF is a major impediment to socioeconomic development and is responsible for immense psychosocial suffering among those affected. The disease is reported to be responsible in worldwide for 5 million disability adjusted life-years (DALYs) lost annually, ranking third among the UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases (TDR) diseases in terms of DALYs, after malaria and TB. The South-East Asia Region accounts about 57% of the total global burden. India's losses due to LF have been estimated at US$ 1 billion per year.
In 1997, as a result of advances in the diagnosis and treatment of LF, the disease was categorized as one of six infectious diseases considered to be “eradicated” or “potentially eradicable”. Consequently, the World Health Assembly adopted Resolution 50.29, calling for elimination of the disease as a global public health problem. The strategy proposed by WHO to achieve the goal of elimination comprises two components: interruption of transmission of filarial infection in all endemic countries through reduction of the prevalence level of microfilariae below the threshold which is unable to sustain transmission, and prevention and alleviation of disability and suffering in individuals already affected by LF by the year of 2020.

Issues and challenges

Progressively reducing and ultimately interrupting the transmission

Effective drug delivery with the currently available drugs is one of the major challenges. Out of 1.3 billion globally there are 860 million people are at risk in SEA Region. However, due to limited resources and lack of a clear policy in some places such as non-epidemiological criteria used, only 48 million persons have been treated with diethylcarbamazine (DEC) and albendazole. Another 373 million have been treated with DEC alone. About 270 million have no access to mass drug administration (MDA) and scaling up of MDA for the elimination of LF by the year 2020 is urgently needed. Low priority is given to the elimination of LF in many places and at different levels, as it is not a fatal disease. This leads to low coverage and inadequate compliance with treatment through MDA. Mobilization of resources, strengthening the commitment of stakeholders and expansion of partnerships, especially at the regional and country levels, are crucial steps for scaling up. Strategies and tools for advocacy and information, education and communication (IEC) based on research findings relevant to the regional and country situation could accelerate the scaling up and effectiveness of MDA. Rapid mapping of bancroftian filariasis, using the card immunochromatographic (ICT) test and spatial sampling strategy is currently in progress in Africa which can be possible to use in the South East Asia Region where diseases prevalence is very high.
Prevention and reduction of disability

Although the strategy has two main components, reduction in morbidity cannot progress satisfactorily. Lack of data on morbidity make it difficult to plan and implement the programme. The pathogenesis of morbidity, especially the underlying causes of lymphoedema, is not fully understood. Sustained delivery of new, simple management procedures for lymphoedema and cost-effective management especially for hydrocele are available but are not in implementation. This situation needs to improve, especially at the community level. Community health providers, both from the health sector and the community, need to be trained to screen for scrotal swelling and refer them for further evaluation to primary health care physicians, and to advise on lymphoedema care. Training of the communities, in the simple techniques of disability limitation, requires effective health education and mass communication. The focus of health education is on the thorough washing and careful drying of the affected part of the body, wound care, exercise (but not during acute attacks), elevation of any affected limb, and the wearing of comfortable footwear.

Research priorities

Improving the coverage and consumption rates of MDA

The reported drug coverage in the Region in 2006 was only 64.03 %⁸ and 73% reported in 2008⁹. To interrupt transmission, at least 65% treatment coverage of the total population is required. Although reported drug coverage is between 80% and 90%, the treatment coverage/consumption rate is very low; over one third of those who received the medicine did not actually consume it, especially in urban areas⁹. High coverage with MDA is crucial for achieving the elimination of LF within the set time-frame and round tow to six. It will result in the optimal and efficient use of all kind of personal and technical resources in the endemic countries.

Research priorities

Studies to identify the barriers to increasing MDA coverage, such as knowledge, attitudes and practices of the community; drug delivery system; strategies for better management of lymphoedema and hydrocele etc.
Studies on the perception of LF in the community and its impact on individuals, families and communities; the effectiveness and appropriateness of messages and approaches used for social mobilization and advocacy.

Studies on behavioural change communication focused on addressing the confidence of community in the treatment being offered.

Study on the effectiveness of management of the elimination programme and drug delivery system so that the results can be used for better programming;

Health System Research studies to explore the reasons for the low coverage and consumption rates. Innovative strategies for an effective drug delivery system with a focus on an integrated approach, especially in urban areas, can be developed based on research findings. Research findings will support the formulation of approaches to improve treatment coverage and can also provide evidence that can be incorporated in advocacy strategies to sustain high treatment coverage.

Impact of MDA on disease transmission

The available data indicate that between two and six rounds of MDA co-administered with other drugs could bring down the microfilaraemia (mf) rate below 1%. In some areas, more than six rounds may be necessary depending on the initial infection level, the treatment rate achieved and the types of mosquito vectors\textsuperscript{10}.

Research priorities

Studies to predict the required duration of MDA for resource mobilization and achieving the target within the set time-frame

The impact of treatment with the current drug combinations on transmission and the parasite reservoir. Longitudinal studies would be helpful for this.

Exploring modelling to predict the required duration of treatment for elimination in areas with varying endemicity and treatment coverage.
Stoppage of MDA

It is expected to achieve elimination level in each IU after 5-6 round of MDA. All IUs will need to undergo assessment of verification of elimination status before the stoppage of MDA as per WHO guidelines. However, MDA could not be implemented every year in some implementing units (IUs) and was covered partially in some IUs because of resource limitations. Baseline mf rates are not assessed in some areas before commencing MDA. Lack of data from sentinel and spot check sites in some places, inconsistent reporting from many sentinel sites and lack of coverage survey leading to lack of understanding of actual coverage in the member countries of SEA Region where MDA programme have been carried out.

Research priorities

- To study the mf rates before commencing MDA
- To estimate the number of cases through community assessment

Mapping

Mapping had been completed in all countries except Indonesia which expected to complete the exercise by 2007. Mapping was delayed due to limited accessibility and technical issues, and was also time-consuming and needed more resources. For rapid mapping and efficient monitoring and evaluation, the current tools, guidelines and methodologies should be simplified. Affordable and field-applicable tools are also required. Multi-country study (has been carried out in Ghana, India, Myanmar and Tanzania) have shown that rapid assessment of the geographical distribution of lymphatic filariasis (RAGFIL) is an effective method for mapping the geographical distribution of filariasis, which is crucial for determining which communities to target with mass treatment. However, as the study sites were limited in size (Ghana, India, Myanmar and Tanzania), some further evaluation and fine-tuning of the method should be included in large-scale applications of RAGFIL. As there is no field-applicable diagnostic test for B. malayi which can help replace the night blood survey, this is a major bottleneck for control in areas endemic for Brugian filariasis.
Lymphatic filariasis: priority areas for research

Research priorities

- To study and generate improved mapping methods; ensure efficient mapping of cross-border foci and explore the use of climatic and other environmental factors to predict endemicity
- To improve current diagnostic methods/alternative mapping methods to facilitate measurement of endemicity and cost-effective mapping; development and field-testing of new affordable and field-applicable diagnostic tools, including a diagnostic test for Brugian filariasis.

Effectiveness and efficacy of drugs

Drug resistance may become a critical issue after prolonged mass treatment with the currently available drugs. Monitoring the efficacy of the drugs and development of second-line drugs or drug combinations is required to sustain the suppression of mf. The current treatment has limitations and, as it does not kill the microfilariae, requires to be repeated annually\(^1\).

Research priorities

- Development of new drugs or drug combinations for curative treatment or sustained suppression of the (larval) microfilarial (mf) forms of the parasite.
- Drug development to achieve the elimination objectives in the limited time frame with a focus on drugs that have better community compliance.

Combination of strategies

Integration and collaboration with other programmes can facilitate the expansion and effectiveness of the ELF programme and would also result in the best utilization of available tools and resources.

Research priorities

- Identifying the most efficient and most cost-effective ways of delivering MDA in different epidemiological and social circumstances in a sustainable manner
 Validation through field-testing and integrated operational research targeting more than one disease, e.g. training, IEC materials, quality of information and the surveillance system, monitoring and evaluation, integrated planning and implementation, and vector control. These studies should be conducted taking local cultures into account.

 Designing, developing and implementing innovative methods for promoting public-private partnerships and integrating it into different activities of the ELF programme.

**Vector control**

The type of mosquito vector has an impact on disease transmission. It can prolong the duration of MDA and also increase the cost. Some studies show that infection rates and morbidity were reduced by all combinations of MDA, but not to levels sufficient for interrupting transmission, even after five rounds of treatment.

Vector control could be supplementary to MDA. Critical epidemiological situations and the role of vector control could be defined by research studies. The impact of on ELF of vector control for other programmes such as malaria should be examined. The role of zero monitoring may become critical for post-elimination surveillance.

**Research priority**

- To study the impact of insecticides, ITNs and IVM on different vectors for LF and in different epidemiological settings
- The most important operational research question that remains is—whether the addition of LF specific vector control to MDA is a cost-effective strategy?

**Impact of MDA on public health and socioeconomic status**

The socioeconomic impact of the consequences of LF on patients and families can be devastating. The impact of LF on the productivity of patients is considerable. In India, for example, a estimated US$ 842 million are lost by patients and households every year in treatment costs and reduced working time through acute and chronic disease. It is also becoming increasingly important to be able to predict and demonstrate the public health and
socioeconomic impact of elimination efforts, especially in areas where interruption may not be easily or completely achieved.

Research priorities

- Country-based assessment studies on the impact of MDA on socioeconomic development to stimulate long-term investment and sustainability of the efforts
- Reassessing the estimation of DALYs for LF as it is probably underestimated currently because it does not fully consider long-term chronic disabilities

Preventing and reducing disability

Implementation research is needed on cost-effective and sustainable strategies for the management of lymphoedema. The ELF programme should be integrated with other programmes that require simple interventions at the community level. The final goal will be to establish a public health implementation mechanism for self-care of these diseases through a home-based, long-term care approach.

Conclusion

The priority today is immediate action to expand the delivery of effective tools, strengthen the capacity of health systems and develop innovative delivery systems. Research can provide evidence and support to overcome several important challenges, either directly or indirectly through improving commitment and mobilizing both internal and external resources. Research is also needed for the estimation and improvement of required coverage and consumption rates, the duration of annual treatment to achieve elimination and its relation to endemicity levels and vector-parasite complexes. It is also critical to define criteria for monitoring and evaluation and demonstrate the public health and socioeconomic impact of the ELF programme for its expansion, and to strengthen the commitment of donors and partners.

Allocation of resources should be balanced between implementation of the programme and conducting research. Research and development should be needs-driven to overcome the issues and challenges, and improve activities for elimination. Well-defined research policies and strategies for the short-, medium- and long-term can effectively support the ELF programme.
Although, the main issues and challenges are common especially sustained delivery of new, simple management procedures for lymphoedema. For hydrocele, the most prevalent chronic complication, there is currently no cost-effective management, the interventions may be different depending on the local current situation. National programmes should be encouraged to address and respond to their issues by incorporating a research component in their programmes.

References


12. Zoonoses in the South-East Asia Region: research priorities

Gyanendra Gongal*, Rajesh Bhatia*, Maureen Birmingham** and F.-X. Meslin***

Introduction

Zoonoses are diseases that are transmissible from vertebrate animals to man or vice versa.¹ Zoonoses are as old as human civilization and infectious diseases, including zoonoses, have shaped human history. Animal diseases are believed to be the origin of many human diseases.

Today, there are over 300 zoonotic diseases. Of the 30 new human pathogens that have been detected in the past three decades, 75% are of animal origin.²

In recent years, some zoonotic agents such as anthrax spores have become potential tools for biological warfare, capable of infecting large numbers of people at a time and leading to their death.

Socioeconomic burden

The socioeconomic impact of the zoonoses is serious, causing not only death but also an economic burden by way of the huge amounts of money spent in treating them. For example, rabies, the leading cause of death in the zoonotic diseases group, accounts for between 40 000 and 60 000 deaths per year.³ The plague outbreak in 1994 cost India approximately US$ 1.7 billion in lost trade and tourism.⁴ The Nipah virus outbreak in 1998 devastated the Malaysian pig industry, as over 1 million pigs were culled and hundreds of farms were closed in order to contain the spread.⁵ The 2003 outbreak of severe acute respiratory syndrome (SARS) provides an example of a virus that emerged from an animal reservoir, spread globally, and might have resulted in an even greater pandemic. SARS cost the Chinese and Canadian...
economies over US$ 50 billion in costs due to medical treatment, disease control and lost revenue associated with the abrupt halt of their tourism industries.  

**Zoonoses in South-East Asia**

The status of zoonotic diseases differs from country to country but most countries face similar challenges. In the South-East Asia (SEA) Region, there are endemic, emerging and re-emerging zoonotic diseases. The major endemic zoonotic diseases are rabies, leptospirosis, Japanese encephalitis, anthrax and brucellosis. Emerging diseases with epidemic potential include SARS, avian influenza and Nipah virus infection. Outbreaks of avian influenza H5N1 have been reported from Bangladesh, India, Indonesia, Myanmar and Thailand. Other diseases of public health concern include cysticercosis, hydatidosis, plague, and toxoplasmosis.

Considering the importance of zoonotic diseases and their impact on the economy and public health security, the WHO Regional Office for South-East Asia has developed a regional strategic framework for the prevention and control of zoonoses, which is a step towards implementing the Asia-Pacific Strategy for Emerging Diseases (APSED). APSED highlights emerging zoonoses as one of six priority programme areas. The role of research has been highlighted in these strategies.

Research studies are needed to identify problems and develop appropriate intervention techniques in order to protect public health interest in a cost-effective manner. Research is particularly critical for the control of zoonoses because of the multidisciplinary nature of these diseases. Operational research helps to identify important gaps among various components of the public health plan through analysis and recommend concrete actions to fill the deficiencies. This paper focuses on the research priorities for important zoonotic diseases of public health significance such as rabies, Nipah virus infection, Japanese encephalitis, plague, leptospirosis, anthrax and toxoplasmosis.
Rabies

Canine rabies is widespread in this Region. Prevention of rabies requires dog population management and their effective immunization. Several priority areas in which research is required to develop appropriate public health interventions for rabies control are given below.

**Basic and applied research**

- Developing improved tests for confirmation of exposure to rabies virus to obviate unnecessary postexposure immunization
- Developing cost-effective molecular techniques to characterize the biological properties of lyssaviruses for better understanding of its pathogenesis and possibility of inducing self limitation of infection.
- Identifying the role of bats and wild animals in rabies epidemiology in the SEA Region
- Estimating the effectiveness of a combination of parenteral and Oral Rabies Vaccine for dogs and other carnivores
- Developing antiviral drugs
- Immunization of elephants, monkey and food animals.

**Operational research**

Operational research should be conducted to remove or alleviate the main constraints and obstacles to rabies control programmes, which are outlined below.

- Developing tools to assess the magnitude of the problem and feasible interventions
- Studying and promoting implementation, where feasible, of alternative approaches such as the implementation of “soft” population control projects (e.g. Animal Birth Control) and education on responsible dog ownership and proper garbage disposal
Conducting studies on the basic parameters of dog populations (size, turnover, accessibility and ownership status) in different settings in country-specific situations

Promoting behavioural change in the communities for first aid/management of animal bites, pre- and post-exposure prophylaxis, responsible pet dog ownership and dog population management

Nipah virus infection

Nipah virus is an emerging zoonotic disease of public health importance in the SEA Region which has been shown to have human to human and nosocomial transmissions.

The research priorities for Nipah virus infection are as follows:

**Basic research**

- Studying epidemiological dynamism of Nipah virus infection.
- Estimating the transmissibility of Nipah virus and the role of inanimate objects in disease transmission.
- Finding out the factors influencing the seasonality of Nipah virus outbreaks including climate change.
- Characterization of the virus and studying its pathogenesis and tropism.

**Operational research**

- Developing methods for early case detection and rapid diagnostic test kits.
- Developing methods for surveillance and an early warning system for Nipah virus outbreaks.

Japanese encephalitis

Japanese encephalitis (JE) is the leading cause of viral neurological disease and disability in Asia. Out of the approximately 50,000 cases of JE estimated...
to occur each year, about 10 000 end fatally, and about 15 000 of the survivors are left with neurological and/or psychiatric sequelae.\textsuperscript{9}

The research priorities for JE are as follows:

**Basic and applied research**
- Identification of potential animal reservoir hosts and their role in disease transmission?
- Use of biological methods for vector control.
- Immunological parameters that induce susceptibility to JE in only a fraction of infected individuals.

**Operational research**
- Developing a sentinel surveillance system for early warning purposes
- What are the outcomes of different vaccination strategies (human, human + animal, animals) and their impact on disease epidemiology?

**Plague**

There are natural foci of bubonic plague in India, Myanmar and Indonesia and the disease has a cyclic nature. Various areas of research are:

**Basic and applied research**
- Molecular characterization of various \textit{Y. pestis} strains isolated from humans, rodents and fleas and their epidemiological implications
- Development of a safe and effective vaccine against \textit{Yersinia pestis}

**Operational research**
- Developing early warning triggers for the detection of potential plague outbreaks (ratfall, disaster, climate change, human activities such as deforestation, farming)
Conducting a risk assessment for plague in previously known natural foci in endemic countries

Seromonitoring of dogs as sentinel animals in the urban situation for plague surveillance

Creating community-based awareness programmes to educate the local population in endemic areas on plague risks including environmental management of the rodent population

Studying development of resistance to insecticides in rat-fleas

**Leptospirosis**

Leptospirosis is an emerging zoonotic disease in SEA. Outbreaks have been periodically reported from India, Indonesia, Thailand and Sri Lanka. Major outbreaks have been reported during the rainy season in Orissa (1999) and Mumbai (2005) in India, and Jakarta (2003) in Indonesia. Periodic outbreaks are reported in northern Thailand and Gujarat, India following heavy rainfall and flooding.

There is no effective vaccine and chemoprophylaxis is practised to prevent human infection. Preventive measures are directed at eliminating or minimizing human contact with infected animals, contaminated water, soil or vegetation. Rodent control is essential in limiting the spread of infection. The priority research areas for leptospirosis are as follows:

**Basic and applied research**

- What is the disease burden of leptospirosis? And identification of different serovars and their role in disease transmission in different settings
- Which are the animal species involved in disease transmission?
- What are the risk factors responsible for leptospirosis outbreaks in an animal farming system?
- Can a vaccine be developed for human immunization?
Operational research

- Screening for leptospirosis as a part of the differential diagnosis of patients with pyrexia of unknown origin (PUO)
- Developing early warning triggers for outbreaks of leptospirosis
- Developing an integrated surveillance system for humans and animals

Anthrax

Anthrax is enzootic in most countries of the SEA Region in the so-called “anthrax belt”. Human anthrax is considered more or less endemic in India and Indonesia due to consumption of infected meat or contamination of open cuts with infected material. Although anthrax is an old disease, penicillin still remains the drug of choice but there are reports of drug resistance. Traditional food habits and sociocultural behaviours are the major risk factors responsible for outbreaks of human anthrax. The key research priorities are as follows:

Basic and applied research

- Identifying risk factors associated with anthrax outbreaks in endemic areas
- Estimating the problem of drug resistance among human anthrax cases

Operational research

- Establishing a joint surveillance system for animal and human anthrax
- Developing a vaccination strategy for prevention of anthrax in the animal population
- Formulating effective risk communication strategies to change risky sociocultural behaviours in the anthrax belt
**Toxoplasmosis**

Toxoplasmosis is seen in almost all countries of the SEA Region but is a neglected disease. It is considered a public health problem in India, Indonesia, Thailand, Sri Lanka and the Maldives. Congenital and ocular toxoplasmosis has been reported from these countries but the magnitude of the problem is unknown. Drinking water contaminated with *T. gondii* oocysts is becoming an important source of human infection, which was earlier considered uncommon.\textsuperscript{11}

Early detection and treatment of *T. gondii* infection in the mother, fetus and infant can prevent or reduce the risks of ophthalmological and/or neurological damage.\textsuperscript{12}

**Basic and applied research**

- Studying environmental contamination with *Toxoplasma* oocysts, i.e. in the soil, harvested rain water and vegetables
- Conducting surveys of cat population dynamics, animal behaviour and food habits in endemic areas
- Improving diagnostic tests to identify people infected with *Toxoplasma*
- Developing new drugs and combination therapy for the treatment of congenital toxoplasmosis
- Studying toxoplasmosis in animal models to understand the etiopathogenesis, pharmacokinetics and possibility of vaccine development
- Assessing the therapeutic value of and conducting a cost–benefit analysis for prenatal toxoplasmosis screening

**Operational research**

- Conducting serosurveys/screening among women of childbearing age and newborn infants
- Studying the role of human sociocultural behaviour in toxoplasmosis transmission
Conclusion

Control of zoonoses is necessary to not only protect human health but also facilitate the production of and trade in livestock and livestock products. Prevention and control of the zoonoses need mutual understanding and close collaboration among various disciplines and sectors at the planning and implementation phases.

Identification of priority research areas on major zoonoses in the SEA Region is a first step which should be integrated into the list of existing regional and national health research priorities. Many of them may have global importance.

Risk assessment of zoonoses at the country level is essential to understand the zoonoses situation and identify key issues for risk management, risk communication, operational research, and develop appropriate strategies and public health intervention techniques. Multisectoral and multidimensional interventional research studies for zoonoses control should be encouraged. These should be backed by a strong surveillance system supported by state-of-the-art laboratories equipped to handle and diagnose dangerous pathogens such as Nipah virus, SARS and avian influenza. Research findings should be imparted through regular interaction and training of clinicians, public and animal health professionals, and major stakeholders. A network of laboratories needs to be established within countries and at regional and international levels so that laboratory diagnostic back-up facilities for emerging and re-emerging pathogens are available. Academic institutions representing medical, veterinary and wildlife sciences should be encouraged to participate in research projects.

References


13. Research priorities for public health laboratories for emerging infectious diseases

RL Ichhpujani* and Rajesh Bhatia**

Introduction

Laboratories play a critical role in the early detection and containment of emerging infectious diseases (EID).1 In the recent past, outbreaks of avian influenza, Nipah virus disease, severe acute respiratory syndrome (SARS), chikungunya, dengue fever, leptospirosis and Japanese encephalitis have highlighted the inherent weakness of the public health infrastructure to provide rapid and reliable diagnoses. Hence, several outbreaks remain undiagnosed and run their natural course leading to considerable morbidity, mortality and economic losses. This also damages the credibility of public health agencies. Laboratories are cost-intensive ventures but efficient laboratory services can provide accurate and timely data for analyses, information and consultation to protect and enhance the health of the people as well as prevent and control EID.

Health laboratories provide cross-cutting support to all health programmes. With a few exceptions, horizontally functional laboratories have provided the requisite support to all the vertical programmes. The infrastructure, equipment and technologies for the diagnosis of several diseases are similar and by switching reagents/consumables, these can be used to deliver a wide spectrum of services that support effective, safe and quality public health interventions in a cost-effective manner.

Health laboratories are increasingly being recognized as a vital component of the public health team, as they provide a wide range of laboratory expertise and services using state-of-the-art technologies. Laboratories can contribute considerably in the following areas:

- To develop better strategies for disease control and prevention
- To develop and update disease management guidelines
- To evaluate different treatments for a disease
- To improve disease detection and response capabilities
- To develop health risk policies

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Research gaps

All components of the EID programme benefit from efficient health laboratories. The components include early detection and confirmation of the aetiology of outbreaks, monitoring the trends and spread of infections, identification of new infectious agents, detection of agents of biological warfare/terrorism, verification of elimination and eradication of diseases, and environmental monitoring.

Laboratory diagnosis of almost all EID is done by isolating the causative agent, enzyme-linked immunosorbent assay (ELISA) or immunochromatographic assays, direct detection by immunofluorescence and/or identification through molecular biological tools, especially the polymerase chain reaction (PCR) test. While the equipment, physical infrastructure and competent human resources to run these tests remain the same and are now widely available in selected laboratories of Member States, disease-specific reagents or kits essential for confirming diagnoses are not easily available, especially for diseases that have a low prevalence in
developed countries. Isolation of new organisms requires comprehensive genetic characterization and comparison with existing species.

At the peripheral level, where sophisticated laboratory infrastructure and expertise are not available, field-friendly tests can play a vital role in rapid diagnosis and early containment of disease. Rapid diagnostic tests (RDT) can make a considerable difference in the management of an outbreak in developing countries. These are now becoming available for infections such as HIV, hepatitis B, influenza, dengue fever, malaria, etc. Most of these are still produced in developed countries and are expensive. Their ability to establish a reliable diagnosis also suffers because the antigens used in these RDT are obtained from strains not prevalent in South-East Asia. For several EID, these are not available at all or those that are available have an unacceptable sensitivity or specificity. There is an urgent need to undertake research in developing countries in several areas so that solutions to locally prevalent problems can be designed, developed and disseminated.

**Priority research areas**

**Enhancing the detection of causative agents**

Advances in the laboratory sciences have helped in identifying more than 30 new microorganisms in the past three decades. But for laboratory tools, the world would not have been able to identify HIV, hepatitis C, Nipah virus and many other viruses of public health importance. The continual discovery of new pathogens has highlighted that there may be a large number of organisms causing diseases in humans and animals which are yet to be discovered. These need to be identified to be able to respond to their challenge.

Some life-threatening viruses are not detectable with the current technologies during the early phase of the infection. These include HIV, hepatitis B and hepatitis C. Apart from the progression of disease, inability to detect them may be a pitfall in the collection of safe blood. Antibodies to HIV are usually detectable approximately 3–4 weeks after exposure using sensitive antibody immunoassays. Use of a p24 antigen assay can reduce the window period to approximately 16 days, and HIV RNA tests can detect infection 8–14 days after exposure (average 12 days).\(^2\,^3\)
The window period for HCV is greatly reduced using the nucleic acid testing (NAT) methodology. HCV antibody assays have a window period of around 70 days, which can be reduced to 8–12 days using HCV NAT assays. The window period for diagnosing HBV by detecting the hepatitis B surface antigen (HBsAg) is highly dependent on the performance of the HBsAg assay. Some of the newer HBsAg assays detect infection within a time-frame similar to that of some NAT tests. The window period for detection of HBV infection can be shortened from approximately 51 days to 31 days (depending on the tests used) using NAT methodologies instead of HBsAg assays. Tools need to be developed to further reduce or eliminate the window period.

A persistent challenge in control efforts for some diseases is the inability of the currently used tests to diagnose the condition of interest. It is estimated that as many as 3 million individuals who present every year with suspected tuberculosis actually have sputum smear-negative pulmonary disease or extrapulmonary disease. Currently available tools, especially those that are widely used in disease control programmes, need improvement.

Laboratory tests have limitations in detecting organisms that are present in small numbers. The currently used sputum smear microscopy examination can detect mycobacteria only if these are present in concentrations higher than 10,000/ml. The low sensitivity of the technology, which detects only roughly half of the active cases, is further compounded by its complexity. It is estimated that less than 45% of predicted incident smear-positive cases of tuberculosis are detected and notified to WHO. This is true for several other diseases where the existing technologies are not able to detect causative agents present in small numbers.

Areas where research should be targeted include:

- Detection of new pathogens that cause outbreaks and remain undiagnosed
- Identification of HIV, hepatitis B and hepatitis C during the window period and dengue antibody during first five days of clinical disease
- Increasing the sensitivity and specificity of detection by rapid or conventional methods and refining the existing diagnostic tools
- Detecting organisms that are present in small numbers in the clinical material.
Research priorities for public health laboratories for emerging infectious diseases

- Increasing stability of the organisms in the clinical material through cost-effective methods of sample collection, storage and shipment
- Developing combo tests for use in diagnosis of common syndromes to confirm/exclude the common causes of disease syndrome
- Formulating tests/diagnostic algorithms for genetically modified pathogens where the organisms have been deliberately modified to make them amenable to diagnosis by the currently available tests

Development of quality diagnostic tools for neglected diseases

Several diseases with considerable public health importance do not have diagnostic tools that can either differentiate these from diseases with similar clinical features or identify the presence of their causative agents in the clinical material. Some of these diseases are considered under the broad group of “neglected tropical diseases” (NTDs) and include yaws, schistosomiasis, lymphatic filariasis, Chagas disease, leishmaniasis, to name a few. Development of specific diagnostic tools for these will facilitate public health interventions for prevention and control.

Research should be targeted at:

- Developing diagnostic tools that can rapidly and reliably establish the diagnosis of NTDs.

Development of reliable rapid diagnostics for use in field settings

Most of the EID originate in peripheral areas where sophisticated laboratory infrastructure is not available. Malaria, Japanese encephalitis, Nipah virus, avian influenza are some examples of diseases that initially affect rural populations. Collection, storage and shipment of the clinical material are time-consuming and, if not done accurately, can compromise the integrity of the clinical material. The availability of rapid diagnostic test kits that are stable in diverse environmental conditions and do not require a high degree of expertise can be of great help in detecting these diseases at an early stage and instituting specific control measures.
Research should be carried out for:

- The development of rapid diagnostic tests for epidemic-prone diseases that can be used in peripheral health facilities by minimally skilled health functionaries.

**Tools to monitor the environment**

Detection of microorganisms in the environment or their unique metabolic/biochemical characteristics can yield critical information for understanding the epidemiology of EID. Several organisms such as Yersinia pestis and Bacillus anthracis can survive in the environment for years and their early detection can help to control these diseases during the early phase. Technologies to detect organisms or their products are also of immense use in defence against biological warfare.

Several diseases are being targeted for elimination/eradication. Eradication calls for evidence that the organisms causing these diseases are no longer surviving in the environment. Persistence of the polio virus in the environment is an indication that this disease requires additional efforts for its elimination.

**Expanding characterization of the causative agent of EID**

Genetic sequence-based identification and typing of microorganisms not only helps in confirming an aetiological diagnosis but also assists in epidemiological tracing of the infection, its virulence profile, pathogenic genes, antibiogram and typing of isolates. Complete genetic profiling of the organisms also helps in understanding their evolutionary profile and thus the disease.

Research should be aimed at:

- Full characterization of local isolates and correlation of the genetic composition with the phylogenetic and epidemiological features of microorganisms and diseases caused by them

**Increase the stability of diagnostic reagents**

The environmental conditions required for the storage and shipment of diagnostic reagents/kits are usually exacting, leading to their deterioration
whenever these are exposed to adverse conditions. In peripheral areas in developing countries, environmental conditions are not conducive to retaining the essential characteristics of diagnostic reagents/kits.

Research should address:

- The modification of existing diagnostic kits/reagents to enhance their stability so that they can withstand wide fluctuations in environmental parameters (temperature, humidity, light) and have a longer shelf-life. This would go a long way in strengthening diagnostic capacity in remote and peripheral areas.

**Development of diagnostics using locally prevalent microorganisms**

The majority of diagnostic reagents/kits are produced in developed countries using antigens that are prevalent in those countries. The kits are sold even in areas where the specific subtype of the pathogen that the test kit aims to detect is not in circulation. This has been observed to be the case with regard to HIV, hepatitis B, Japanese encephalitis and dengue fever, and leads to false-negative results. Either the antigenic epitope that is common to all subtypes of the pathogen should be used or geographical area-specific diagnostic reagents developed.

Research is required:

- To develop tools for testing new vaccines and drugs in a given setting to analyse their context-specific efficacy and safety.

**Determination of antimicrobial resistance patterns using rapid and real-time tests**

Specific antimicrobial therapy plays a critical role in the clinical management of a patient. In addition, it is an effective public health tool to cut short the transmission of disease. Determining the susceptibility of organisms, especially viruses, to the available drugs can provide a powerful intervention for the public health system. Currently, these analyses take a long time and are restricted to very few laboratories. This hinders the wide application of this tool.
There is a need for:

- Development of bedside technologies that can rapidly identify the causative agent(s) of disease as well as provide information on the types of antimicrobial agents that would be effective against the isolated agent.

**Development of environment-friendly technologies**

Laboratories handle a large amount of material that can contaminate the environment. Several inexpensive and effective systems for proper disposal of infectious waste have been developed.

Research should address the need for:

- Redesigning diagnostic technologies to make these more environment-friendly by using less toxic chemicals and reducing the use of animals in toxicity tests.

To undertake these research priorities, there is a strong and urgent need to encourage research and development (R&D) institutes in developing countries to develop reagents/kits/RDT for EID, facilitate transfer of technology to the private sector and ensure the availability of these reagents to other countries at an affordable cost. It is important to institute mechanism of developing a regular dialogue with diagnostic technology and test developers for accelerated diagnostic tool development, evaluation, demonstration and sustainable adoption of the test.

**References**


Developing countries in Asia are at high risk for new and emerging infectious diseases and have become hotspot for many zoonoses, drug-resistant pathogens and vectorborne diseases. Better understanding of the epidemiology of and the broader social, economic, cultural, environmental, ecological and political dimensions are some of the challenges for today's research in communicable diseases. Research is essential for the development of new tools and interventions, and should be geared towards the development of evidence-based policies and interventions to increase efficiency and effectiveness of programme development and management of health promotion and diseases prevention and control.

The need for research as a part of strategic information and evidence base for developing effective and efficient disease interventions, that contribute to the scaling up and sustaining of interventions that work, cannot be underestimated. Besides old challenges, research should address new challenges such as climate change and its impact on health.

This document is a compilation of views of several leading experts on research priorities in field of communicable diseases.