SOLUTIONS THROUGH KNOWLEDGE
Health Research: Solutions Through Knowledge

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Regional Director’s Message

Shaping the research agenda and stimulating the generation, translation and dissemination of valuable knowledge is one of the six core agendas of the WHO. Health research is critical to improve the quality of care and health outcomes, and helps find appropriate solutions to everyday challenges in health-care settings.

This collection of seven case studies outlines how, over the decades, research has played a key role in transforming health policy, programmes and treatment options in the WHO South-East Asia Region, home to one-fourth of humanity.

Six decades ago, when WHO SEARO was formed, the Region faced a variety of challenges on the health front, many of them related to poverty, lack of basic infrastructure and medical expertise. Many member countries, some newly independent from colonial rule, found themselves in the throes of a severe resource crunch, low food production and rapid rise in population growth.

Over the years, through visionary political leadership, the dedication of thousands of health personnel and the participation of ordinary citizens, South-East Asia has overcome all these crises one by one. Through the process of nation building, framing of appropriate policies and setting up sound implementation mechanisms, the Region has also gone on to become the hub of global economic growth.

Playing a quiet and unassuming role in the background of this transformation has been research, carried out by both state-supported and private institutions, that has provided the knowledge and information needed. Working in tandem with global collaborators, often facilitated by the WHO, researchers in the Region have helped tackle a diverse range of health threats from tuberculosis and leprosy to pandemics like HIV and avian flu.

Over the years, the Region’s researchers have carried out valuable work in a wide variety of disciplines from virology and epidemiology to drug efficacy and disease prevention, adding to global medical knowledge in significant ways. Thailand’s 100% condom campaign, Sri Lanka’s Universal Health Care policies, Bangladesh’s experience with oral rehydration therapy and Indian research on short-course chemotherapy for TB stand out as examples of work in the South-East Asia Region that have had worldwide impact.
Investigations in the social sciences too have contributed immensely, particularly in understanding the dynamics of health-seeking behaviour, impact of literacy and gender empowerment or the cultural underpinnings of stigma and discrimination. Given the unique contexts and needs of individual member countries, implementation research has played a key role in bridging the gap between knowledge and action—as evident in Indonesia’s successful containment of avian influenza.

Another area where steady advances have been made is in surveillance of diseases and data collection. The Region’s health laboratories contribute in generating reliable information to develop strategies for disease prevention and control, updating treatment guidelines, improving disease detection and understanding their epidemiology.

Thanks to all these efforts, countries in the Region have seen drastic declines or even elimination of dreaded ailments such as mother-to-child transmission of HIV, leprosy, filariasis, yaws, neonatal tetanus, syphilis and the worst forms of undernutrition.

Despite such stellar achievements there is little room for complacency, as the changing demographic and economic profile of the Region brings with it new health problems. Non-communicable diseases are rapidly replacing communicable diseases as the major area of concern, with growing phenomenon like the ‘double burden of malnutrition’, affecting rich and poor alike.

This indeed is a time when much more needs to be done to get optimal results from research in the complex and constantly changing scenario of the South-East Asia Region. Some of the hurdles facing researchers in the Region include: weak health systems to support health research in some countries; absence of clear national policies on health research; lack of modern tools for data processing and management and lack of incentives to motivate and encourage researchers to improve their competencies, especially in areas like health economics and quantitative data analysis.

The challenges of health research in the Region are accentuated in particular by the 10/90 gap, wherein only 10% of the resources for research are available in parts of the world where 90% of the health problems persist. It is estimated that less than 3% of the global funding for researches go to developing countries and only 27% of all the researchers in the world are in developing countries.

The case studies presented in this booklet demonstrate how investment in research now helps save future costs in terms of lives saved, productivity gains and utilization of resources in the most efficient manner. Research is particularly relevant in the context of helping achieve the health-related goals among the new Sustainable Development Goals, which have been adopted recently to take over from the Millennium Development Goals.

Governments in both the South-East Asia Region and other parts of the world urgently need to work together with multilateral bodies like the WHO to find the funds needed to carry out cutting edge research that addresses the health problems of the Region. Knowledge indeed has the power to help heal the world but it can do so only if provided sufficient support from those in leadership positions and with the commitment to make the globe a better place.
The primary purpose of this document is to encourage greater investments in cutting-edge research that will lead to policy and programmes for effective transformation of the health landscape in the WHO South-East Asia Region.

At a more basic level, it also hopes to inspire a newer generation of researchers to take up the numerous health challenges faced by the Region’s populations and come up with the knowledge and expertise needed to overcome them.

The document attempts to achieve these objectives through a presentation of case studies showcasing research-driven health interventions, across the South-East Asia, over the last several decades. These transformative initiatives have saved millions of lives and contributed to significant gains in improving health in the Region.

This compilation is however not an attempt to extensively review ongoing research in each thematic area. Instead, it seeks to explain to a wider audience the complexity of health research work itself, that takes many pathways in pursuit of its goal of figuring out the what, why and how of a disease and the best means to tackle it.

It is these insights that ultimately have a genuine impact on health outcomes over a stretch of time. A case in point is kala-azar where, in the last two decades, painstaking research in a wide variety of fields have produced new diagnostic, treatment and case detection options leading to the possibility that the disease can finally be eliminated.

Partly as a result of the tremendous diversity of factors that impacts health and also due to growing specialisation within its own fold, the field of health research itself has today evolved into many branches. This includes, to name just a few, the basic sciences, epidemiology, translation, operations and implementation research.

The stories presented in this document are about basic laboratory science that help to understand the mechanisms of infection and disease or developing new diagnostics; interventions to prevent and control disease; surveillance and monitoring of the prevalence of disease; and implementation research to test the feasibility and acceptability of interventions. The role of communities and engaging communities in research is also a theme for focus.

The key health issues which are presented range from leprosy to pandemic flu, and include HIV/AIDS, tuberculosis, and kala-azar or “black fever”—also known as visceral leishmaniasis. Research on nutrition-related problems, as well as solutions to address them, is also examined with a special focus on the exciting new directions for investigation and action emerging in this field.

It is well understood that, along with generation of new knowledge in the basic sciences there is also a need to develop insights into the social, economic and cultural dimensions of health. As a result, health research has always involved disciplines
In many sectors that have bearing on health outcomes, such as, security and justice, education, finance, employment, gender, environment, infrastructure, housing and transportation.

In all these case studies, apart from the critical role of different branches of research, what has also been highlighted is the complexity of contexts in which health programmes have been carried out and the multi-sectoral nature of responses required to ensure that they are truly impactful.

For example: ill-health often afflicts those who are already poor due to their poor living conditions and lack of nutrition or sanitation facilities. As part of a vicious cycle, disease pushes them into further poverty and prevents them from transforming both their health and livelihood situations.

Again, poor health of children impedes educational attainment, reducing educational potential and abilities to pursue better opportunities in life. On the other hand, educational attainment, particularly of women, directly contributes to better outcomes on both the health and economic fronts, creating a productive society with engaged citizens.

The nutrition case study highlights the roles of multiple partners, ranging from the education sector to agriculture, fisheries, transport, food processing, finance, media, civil society and political leadership.

The avian influenza or H5N1 story, too, features research not in the laboratory, but in the live bird markets of Indonesia, where researchers sought to understand H5N1 epidemiology. Research found that critical sites of risk of H5N1 transmission were in the sale and slaughter zones of the bird market, which led to a further study to inform structural interventions and workflow modifications to minimize risk for contamination. The research on the live bird markets also prompted the Jakarta provincial government to issue a local regulation, which was critical in controlling the bird flu epidemic.

The critical issue of emerging drug resistance is also explored. In other words, what happens when the valuable medications we have no longer work? The detective story of identifying, then researching and addressing parasite resistance to anti-malarial treatment in the Greater Mekong Sub-region details not just the new technologies that make tracking such resistance possible but also the bold measures needed to eliminate malaria altogether from the Region.

Among the country examples, India features most prominently given its size and the tremendous burden of both communicable and, increasingly, non-communicable diseases. India has the largest capacity and infrastructure for research in the region, and the country plays a significant role locally, regionally, and globally, in generating evidence for health policies as well as programmes.

Overall, the following pages are a compelling mix of historical and contemporary developments in infectious and non-communicable disease research, medical research, social science, political science, ethics and economics, all rallying towards the common goal of improved health and well-being. Moreover, it places the research contributions of the South East Asia Region in the context of global health, while articulating how it has served—and continues to serve—the health needs and realities of the Region’s own vast and diverse population.
Muzaffarpur, a district adjoining Patna, the capital of the eastern Indian state of Bihar, is famous for its sweet fruits that flourish in the region’s rich, alluvial soil, washed in by the mighty Ganges.

For epidemiologists and health authorities though, the district is synonymous with the bitter harvest of kala-azar cases, a nasty, debilitating disease that has killed thousands of people in the last century.

Kala-azar, literally “black fever” when translated from Hindi, is known to medical doctors as visceral leishmaniasis (VL). Caused by the parasite Leishmania, transmitted into human blood by certain species of infected female sandflies, it is the second-most deadly parasitic killer in the world—only malaria is deadlier (Figure 1).

In the past decade, however, researchers in India, Bangladesh and Nepal, collaborating with each other as also with global partners, have developed and validated powerful new treatment, diagnostic, case detection and vector-control options, that have raised hopes for the Indian subcontinent to be rid of this dreaded disease forever. Between 2012 and 2015, the incidence of reported new cases have decreased by about 61% in India, 67% in Bangladesh and 46% in Nepal, taking them rapidly towards WHO’s target of regional elimination1 of kala-azar by 2020.2

**Burden of Kala-azar**

Worldwide, an estimated 200,000–400,000 new cases of kala-azar occur annually,3 of which Bangladesh, Bhutan, India and Nepal harbour an estimated 67%. In the South-East Asia Region, India has the highest number of people at risk of getting infected by kala-azar, an estimated 130.7 million people.4

The disease is however confined to a few states in the eastern part of the country with kala-azar being endemic in 34 out of 38 districts in Bihar, contributing 80–90% of the reported cases.5 Within Bihar, Muzaffarpur has the highest number of patients every year, mostly from the poorest communities.

Kala-azar on the Indian subcontinent and throughout South-East Asia has a unique epidemiological feature of being anthroponotic; humans are the only known reservoir of infection. The disease attacks the internal organs and can be fatal if left untreated. Symptoms include irregular bouts of fever, weight loss, enlargement of the spleen and liver, and anemia.
“In the past decade, researchers in India, Bangladesh and Nepal, collaborating with each other as also with global partners, have developed and validated powerful new treatment, diagnostic, case detection and vector-control options, that have raised hopes of the Indian subcontinent to be rid of this dreaded disease forever”

FIGURE 1: Life Cycle of Leishmania Parasite

1. **Sandfly Stages**
   - Sandfly takes a blood meal (injects promastigote stage into the skin)

2. **Human Stages**
   - Promastigotes are phagocytized by macrophages or other types of mononuclear phagocytic cells
   - Promastigotes transform into amastigotes
   - Amastigotes multiply in cells of various tissues and infect other cells

3. **Infective Stage**

4. **Diagnostic Stage**

Source: Centers for Disease Control and Prevention (CDC), United States.
Drug resistance

Kala-azar was first detected in the early twentieth century. Since the 1940s, pentavalent antimony compounds, such as sodium stibogluconate (SSG), had been in use for the treatment of kala-azar in India and were the drugs of choice because of their efficacy, cost and availability.

In the 1970s, however, reports of drug resistance emerged, particularly in endemic areas like north Bihar, and by the late 1990s only 35–38% patients responded to these antimony compounds.6

To overcome such resistance, sodium stibogluconate was given in increasing doses, with the treatment period increasing from six to thirty days. However, that meant patients were at higher risk of possible drug toxicity, which carries a risk of cardiac arrest. These drugs also could not be given orally and the patient had to be monitored closely in a hospital setting. In HIV-coinfected patients, the risk of treatment failure and relapse was high.

An alternative was available for people who were unresponsive to antimony compounds: Amphotericin B, an antifungal, macrolide antibiotic. Its anti-leishmanial activity had been detected in the early 1960s already.

Conventionally prepared as Amphotericin B deoxycholate, the drug had an excellent long-term cure rate of almost 100% when administered as a slow intravenous infusion over 4 to 6 hours, on alternate days, for 15 doses. But there was a problem. The treatment was accompanied by troubling side effects and toxicity, with many patients developing fever, chills and, occasionally, serious toxicity effects such as nephropathy, potassium deficiency and inflammation of heart muscles. In some cases, treatment appeared to be associated with the death of patients.

Pentamidine, another alternative to sodium stibogluconate, showed a cure rate of about 74% when given on alternate days for 15 days. It also had severe side effects among those patients, including onset of diabetes, hypo- and hyperglycemia and allergic shock.7 The drug was soon abandoned due to severe toxicity, which sometimes led to death.

By the early 1990s, the only available treatments were failing due to resistance, and researchers struggled to develop new, more effective and safe drugs. It was a frustrating period for health administrators, physicians and the population affected by kala-azar.

A new era in treatment

There were rays of hope emerging, however, when a series of multi-centre studies in Bangladesh, India and Nepal, actively identified potential new drugs for kala-azar and helped validate their safety and efficacy. According to Indian researchers, while in the 1990s they had nothing, today they are at a qualitatively different stage as far as treatment options for kala-azar patients are concerned (Figure 2).

Their first breakthrough came with the development of an oral drug for kala-azar, which vastly improved ease of administering treatment to patients, by eliminating parenteral therapy or prolonged hospitalization.

Miltefosine, originally developed as an anticancer drug in the 1980s in Germany, showed very good anti-leishmanial activity in animals and in vitro. Starting in 1997, Indian researchers

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carried out a series of clinical trials in collaboration with international counterparts, as well as the state-funded Rajendra Memorial Research Institute of Medical Sciences and Balaji Utthan Sanstan, a private trust in Muzaffarpur.

The phase I and II trials, aimed at finding an effective and safe treatment schedule for the drug, conducted in selected sites around Bihar, showed that a daily dose for 28 days in adults was well tolerated and would cure most patients. This led to a multi-centre Phase III study, in which a high cure rate of 94%, established miltefosine as the first orally effective anti-leishmanial agent, thus revolutionizing therapy. Importantly, the drug proved effective even in sodium stibogluconate-resistant cases.

“...There were rays of hope emerging, when a series of multi-centre studies in Bangladesh, India and Nepal, actively identified potential new drugs for kala-azar and helped validate their safety and efficacy.”

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In the late 1980s, researchers at the Max Planck Institute for Biophysical Chemistry and the University of Göttingen, demonstrated the anti-cancer properties of miltefosine, a compound from the phospholipid group alkylphosphocholine.

Around the same time as the discovery of its anti-cancer property, miltefosine was reported by a team at the London School of Hygiene and Tropical Medicine as having anti-leishmanial effect as well. Later, in 1992, new research was reported in which the compound was highly effective in lab studies against different life-cycle stages of different leishmania species and, in fact, more potent than the conventional sodium stibogluconate therapy by a factor of more than 600.9

In 1998, results of the first clinical trial in humans were reported from Indian patients with chronic leishmaniasis with high degree of success and safety.10 This in turn led to a unique collaboration for further studies between Indian scientists and the pharmaceutical company Zentaris GmbH11 in Germany, supported and coordinated by WHO’s Special Programme for Research and Training in Tropical Diseases (TDR).

Eventually, several successful Phase II and III trials led to the approval of miltefosine in 2002 as the first and only oral drug for leishmaniasis. Subsequently, the Indian Council of Medical Research (ICMR), supported by Zentaris and TDR, carried out a Phase IV operational trial in several districts of Bihar.

A downside of the drug, however, was that it could not be used in pregnant women, and females of child-bearing age were required to practice contraception for the duration of therapy and for 2 months after the therapy. Studies also found minor side effects such as mild gastrointestinal symptoms and temporary elevation of liver enzymes.

Another negative aspect concerned poor compliance of patients with the regimen and consequent rise of drug resistance. Despite all these drawbacks, miltefosine offered relief to kala-azar patients, who otherwise faced almost certain death in the absence of effective treatment.

Meanwhile, the development of safer and more effective formulations of amphotericin B to treat systemic fungal infections had led to the innovation of liposomal amphotericin B preparations. The lipids helped mask amphotericin B from susceptible tissues, thus reducing its toxicity. They also facilitated targeted drug delivery to the parasite, resulting in increasing efficacy.

The delivery of lower quantities of the drug in a more focused way made the treatment more efficient and safer. Many of the researchers who had helped with establishing miltefosine as part of the kala-azar treatment regime also played a key role in demonstrating the efficacy and safety of liposomal amphotericin B through a series of clinical trials in affected parts of eastern India.

In 2010, a WHO-appointed expert committee concluded that single-dose liposomal amphotericin B was the best available therapy for kala-azar in the Indian subcontinent as it was effective and safer than any other treatment. However, the drug was initially not considered viable for widespread use due to its high cost.

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11 Now known as Æterna Zentaris GmbH.
BOX 2: DOMESTIC RESEARCH CAPACITY

Apart from new drugs and diagnostics, research on a range of other themes has played a critical role in controlling kala-azar effectively on the ground in the Indian subcontinent. These include studies to improve indoor residual spraying of insecticides for better vector management, understanding the health-seeking behaviour of patients, developing training modules and treatment guidelines for health workers, mobilizing political support for national programmes and fostering regional cooperation.

Established in 1963, the Rajendra Memorial Research Institute of Medical Sciences (RMRIMS), Patna, has been one of the key centres involved in almost all the studies and clinical trials carried out in India over the last two decades on new treatment options for kala-azar, development of new diagnostic kits, innovations in vector control and novel methods of surveillance. The institute’s work goes beyond just research also as it offers treatment to regular kala-azar patients, as well as those with HIV co-infection and the difficult-to-treat cases of post-kala-azar dermal leishmaniasis, a complication characterized by different kinds of rashes in patients who have recovered from VL and are otherwise well.

“Effective diagnosis and treatment are necessary but not sufficient for eliminating kala-azar completely from the Indian subcontinent”, points out the Director of the institute, explaining the importance of implementation research in the institute’s overall focus and work plan.

As part of its kala-azar elimination strategy, India’s National Vector Borne Disease Control Programme (NVBDCP) has identified integrated vector management as a critical component, involving elimination of sandfly breeding sites, decrease in contact of vector with humans and lowering the density of the vector. Scientists at the institute are studying the behaviour of Phlebotomus argentipes—the sandfly species in India that transmits kala-azar—and insights gained are critical in developing appropriate strategies for vector control.

For example, one significant study comparing differences in kala-azar incidence between north and south Bihar revealed the unexpected insight that areas with low sandfly density as a result of insecticide use were more vulnerable to the disease than areas with a high sandfly density, pointing to the intriguing role of other factors such as Phlebotomus argentipes saliva and the patchy spraying of insecticide for vector control in the epidemiology of kala-azar.\textsuperscript{12} The institute is also a declared WHO reference centre for the leishmania parasite and manages a bank of sera collected from kala-azar patients for research purposes.

Researchers also developed an innovative bio-environmental intervention for controlling sandfly populations. This involved application of mud and lime plaster up to 1.22 metres in households in kala-azar endemic areas, a measure that helped stop sandfly breeding without much labour, supervision or use of expensive materials.\textsuperscript{13}


“More recently, the attention of global agencies as well as researchers on the Indian subcontinent is focused on testing short-course, combination therapies for kala-azar that can reduce costs, duration of treatment and risk of drug resistance while being safe and efficacious also”
and the inability of patients, mostly very poor, to pay for it.

All that changed thanks to a WHO brokered deal in 2011, under which the manufacturer of the drug in the United States agreed to donate free supplies for use in resource-poor countries. The drug is currently the first line of therapy used for kala-azar patients in Bangladesh, India and Nepal.

“Patients here call it the ‘ek din wali dawai’ or ‘one-day drug’ and it has transformed the entire treatment scenario”, says Anil Sharma, manager of the Kala-azar Medical Research Center in Muzaffarpur, a private trust, which treats hundreds of patients every year with the free or subsidized medicine they receive.

Low-cost and combination therapies

The search for treatment options even cheaper than that offered by miltefosine or liposomal amphotericin B has led researchers to test yet another promising drug, paromomycin, an antibiotic that possesses both anti-bacterial and antiprotozoal activity. At a cost of approximately US$ 10–20 for one adult treatment course, it is the cheapest anti-leishmanial drug available currently.

More recently, the attention of global agencies as well as researchers on the Indian subcontinent is focused on testing short-course, combination therapies for kala-azar that can reduce costs, duration of treatment and risk of drug resistance while being safe and efficacious also.

In 2014, a Phase III, randomized, study in Bangladesh showed that three short-course combination regimens with liposomal amphotericin B, miltefosine and paromomycin were non-inferior to liposomal amphotericin B alone for the treatment of kala-azar.

BOX 3: DETECTING KALA-AZAR—A TESTING AFFAIR

For decades, diagnosing kala-azar has been a tricky affair, given that it involved painful and risky procedures, time-consuming lab tests and many of its early symptoms mimicked those found among typhoid, tuberculosis and malaria.

Conventionally, kala-azar has been confirmed mostly through the demonstration of parasites in aspirate extracted from bone marrow, spleen or lymph nodes. Stained smears of aspirate, when observed under a light microscope, shows the leishmania parasite as round or oval shaped amastigotes.

In the past, efforts to use noninvasive methods of diagnosis by testing more accessible samples, such as serum or whole blood, for antibodies to leishmania antigens or for parasite DNA, had proved difficult. Among the drawbacks many of the methods shared were costs, extensive lab equipment, specific technical knowhow, stable power supply, and long incubation periods that could delay diagnosis.

A major breakthrough in developing a simpler test for kala-azar came in 1998 when Indian researchers, along with global collaborators, announced the rK39 rapid diagnostic test (RDT) that was suitable for use under field conditions. It required a tiny amount of blood, no laboratory technology, and was simple to carry out and read.

Studies carried out on suspected patients in Varanasi and Muzaffarpur showed that a positive K39 RDT was a highly sensitive and reliable indicator of active


kala-azar, used in conjunction with clinical diagnosis. One study in India, for example, found that the K39 strip test was 100% sensitive while the estimated specificity of the strip test was 98%.

Follow-up studies confirmed the high accuracy of the K39 RDT and led to its adoption as a diagnostic test in the VL Elimination Initiative on the Indian subcontinent. In recent years, the K39 RDT has been made even more user-friendly with researchers at the Rajendra Memorial Research Institute of Medical Sciences (RMRIMS) in Patna, replacing the use of blood with easier-to-obtain sputum and urine.

Challenges ahead

The target of eliminating kala-azar from the Indian subcontinent aims at maintaining the annual incidence rate below 1 kala-azar case per 10,000 population at upazila level in Bangladesh, subdistrict/block in India and district level in Bhutan and Nepal. By 2014, the elimination target was reached in all the endemic districts in Nepal, in 96% of the endemic upazilas in Bangladesh, and in 74% of the endemic blocks in India (Figure 3).

Despite such progress, there are still significant challenges facing affected countries in their efforts to steadily reduce incidence and provide treatment to all those who need it to ensure the elimination targets are met in a sustainable manner. This calls for further research on not just the basic science of drugs and diagnostics for kala-azar but also its epidemiology, etiology, social and behavioural aspects of patients and implementation of effective control programmes.

For example, the absence of precise knowledge of the incidence of the disease is a constraint in the planning of existing elimination programmes, and more research on the epidemiology of kala-azar is urgently required. According to some studies, the actual incidence of kala-azar in the Indian subcontinent is considered to be at least eight to ten times higher than the officially reported case numbers.

To get a better understanding of the human reservoir and what part asymptomatic infections play in transmission of kala-azar also requires longitudinal studies of patients, asymptomatic cases and their household contacts to identify biomarkers for disease progression and transmission.

There is also the rising number of cases of post-kala-azar dermal leishmaniasis (PKDL), which causes little or no clinical discomfort and for which patients rarely seek treatment. They, however, continue to be reservoirs for the leishmania parasites and can trigger new epidemics in future if left untreated.

Xenodiagnosis studies to establish whether post-kala-azar dermal leishmaniasis and

20 Upazila is a geographical region in Bangladesh used for administrative or other purposes. They function as subunits of districts.
asymptomatic infections transmit parasites to sandflies are necessary to understand disease transmission and to develop public health policy. Experts have also called for further research on a therapeutic vaccine to treat PKDL cases, which could represent a first step in the development of a prophylactic kala-azar vaccine in the long term.  

At another level, more implementation research is needed to establish how best to use existing treatments under field conditions and at a scale that will ensure a high rate of adherence and low rates of relapse. Studies are also needed to establish how best to carry out vector control and case detection in endemic villages, without placing an additional load on local health systems and using existing human resources and government infrastructure.

Again, a vast majority of the districts in the Indian subcontinent affected by kala-azar are along international borders. Research on demography, migration and population movements along the borders between Bangladesh, India and Nepal are required to help establish better coordination between health authorities of these countries.

Given the enormous progress that has already been made in recent years towards the elimination of kala-azar, a multidisciplinary collaborative effort between clinicians, public health specialists, basic science researchers, and patients and policy-makers from the affected countries could well see an end to this ancient disease on the Indian subcontinent and with that, also in all of South-East Asia.

“Despite such progress, there are still significant challenges facing affected countries in their efforts to steadily reduce incidence and provide treatment to all those who need it to ensure the elimination targets are met in a sustainable manner”

FIGURE 3: Percentage of Administrative Units (AU) achieving the target of eliminating kala-azar as a public health problem (2014)

<table>
<thead>
<tr>
<th>Country</th>
<th>Percentage of AU with incidence rate &lt;1/10000</th>
<th>Percentage of AU with incidence rate &gt;1/10000</th>
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<tr>
<td>Bangladesh</td>
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In September 2006, Indonesians switching on their television sets were pleasantly surprised to see Mohammad Farhan, a favourite talk-show host and comedian, on every domestic channel. This time though, Farhan was not just being funny. He was talking about avian influenza or ‘bird flu’—a deadly disease, with no effective cure, that had killed millions of poultry across the Region and was now claiming human lives in South-East Asia.

“Through comedy and simple storylines, we get people to take more care, like proper cooking, keeping chickens outdoors and getting to a doctor if you have flu,” said Farhan, in the 30-second public service ads sponsored by UNICEF. The highly pathogenic variety (HPAI) of the avian influenza virus\(^1\) or H5N1 HPAI spreads through close contact with chickens.

UNICEF & Indonesian Government’s ‘Tanggap Flu Burung’, or ‘Take Action on Bird Flu’, campaign itself was part of one of the world’s biggest mobilizations, in recent history, to contain an emerging epidemic that seriously threatened global health. While public communication was critical, at the heart of the monumental effort was painstaking research in a variety of fields—virology, veterinary science, epidemiology and public health—that provided crucial insights into the scale and speed of the response needed.

Getting the facts right

A key area of research that emerged initially, given the overall paucity of information about the avian influenza virus, was understanding the factors that were involved in its local, regional and global spread. One study\(^2\) reported that wild aquatic birds were the most likely source of low pathogenic avian influenza or LPAI viruses that converted to highly pathogenic avian influenza or HPAI viruses. The spread of the epidemic was then facilitated by migratory birds, infected with the new strains, seeding infection into local wild and domestic bird populations.

According to the study, after being seeded into one or more locations, the virus then spread within countries and, in some cases, to nearby countries through the movement of poultry. Other studies showed the critical role played by ducks, a major source of protein in many parts of South-East Asia, in the spread of H5N1 HPAI\(^3\) (Figure 1).

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\(^1\) The terms ‘bird flu’ and ‘H5N1 HPAI’ are used interchangeably throughout this text.

\(^2\) Morris RS, Jackson R. Epidemiology of H5N1 Avian Influenza in Asia and Implications for Regional Control. A contracted report for the Food and Agriculture Organization. EpiCentre, Massey University, Palmerston North, New Zealand; FAO. 2005.

Other studies, using phylogenetic analysis, helped track the clade or lineage of the virus to China from where it had spread to South-East Asia. Genetic sequencing techniques also confirmed the specific clade of H5N1 HPAI that had jumped the species barrier and was causing the avian flu outbreak among humans.

This information was critical to decide not just development of vaccines to prevent future outbreaks but also to study the potential of the virus to cause even greater harm in future. According to some estimates, if the virus were to undergo a mutation allowing for human-to-human transfer of infection, the epidemic could result in the loss of millions of lives worldwide.

Parallel to these research efforts, postmortem and clinical investigations carried out on H5N1 HPAI victims by histopathologists helped to develop the treatment protocols needed by physicians to deal with infected patients and cautionary messages for public health authorities to disseminate. For example, it was found that, early warning symptoms of bird flu infection often included high fever and malaise, cough, sore throat and muscle aches. The infection could progress quickly to severe respiratory illness such as difficulty in breathing, pneumonia and altered mental status or seizures.

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Other studies showed that the high mortality rate due to H5N1 HPAI in humans was due to the ability of the virus to damage alveoli leading to hemorrhage in the lungs of infected patients. The virus could also infect other organs, including the trachea, the intestines and the brain, and penetrate the placental barrier and infect the fetus. Improper regulation of key proteins in the body that influence the immune system of patients were found to be an important factor in making avian flu so deadly.

Role of live bird markets

Epidemiologists, in the meanwhile, helped to determine both the pathways by which H5N1 was transmitted from birds to humans as well as its virulence. A study conducted by Indonesian researchers on the first human cases of H5N1 HPAI infection in the country found that 76% of case patients had direct or indirect contact with poultry—whether appearing healthy, sick, or dead—during the two weeks preceding onset of illness.

The research team highlighted that a significant percentage of the cases had been identified in family clusters, with more than one third occurring in seven clusters of blood-related family members. Such cases, according to the study, suggested a possible genetic susceptibility to bird flu infection and implied that early administration of prophylactic medicine might prevent additional cases after an initial case patient is identified.

Research also focused on the importance of Indonesia’s live bird markets (LBMs), in spreading the H5N1 HPAI infection around the country. While such markets are ubiquitous in most South-East Asian countries and represent a major source of income and nutrition for local populations, they unfortunately provide the ideal conditions for the transmission and evolution of infectious disease pathogens.

The attention given to LBMs was particularly relevant to Indonesia, whose poultry industry was estimated to be growing at about 15% per year, with most of the growth occurring in small-scale commercial operations, with anywhere from 5000 to 30 000 birds being raised in open houses made of bamboo. The

Cholera, severe acute respiratory syndrome (SARS) and earlier avian flu outbreaks in the People’s Republic of China and Hong Kong, SAR of China. Their studies explained the epidemiology of H5N1 HPAI in LBMs, with a view to identifying control measures suited to the Indonesian context, with its poor infrastructure and limited regulatory capacities.

Among the issues addressed were the risk factors and transmission patterns for human infection, the critical points for H5N1 HPAI virus contamination in LBMs, and what control measures could work in the local setting.

For example, one study, sponsored by WHO, examined LBMs at 83 markets in three Indonesian provinces to identify sites commonly contaminated by H5N1 HPAI. Samples were collected to assess the extent of contamination and questionnaires that were used to ascertain the types of birds in the market, overall infrastructure and work practices. The results showed that 47% of markets were contaminated with the virus.

"Epidemiologists helped to determine both the pathways by which H5N1 was transmitted from birds to humans as well as its virulence"
The pandemic flu strain that spread throughout South-East Asia from 2003 was called Highly Pathogenic Avian Influenza A H5N1 or simply H5N1 HPAI. In 2009, the swine flu that caused global panic was termed Influenza A H1N1. What exactly do the letters and numbers in these names mean?

Essentially, there are three major types of influenza that infect humans, known as influenza A, B and C. While influenza A and B can both cause serious illness, influenza C viruses cause only a mild infection.

Each of these influenza strains, in turn, undergoes constant mutations in its genetic structure, sometimes creating flu variants against which humans have no immunity. When such strains spread rapidly, they can cause pandemics. However, as humans develop immunity to the new strains, their impact diminishes and they join the list of seasonal flus that occur annually. The seasonal influenza A strains currently circulating in humans are caused by constantly changing versions of H1N1 and H3N2 viruses from the past.

The letter ‘H’ refers to hemagglutinin (HA) and ‘N’ to neuraminidase (NA), both proteins, which are found on the surfaces of both influenza A and B viruses. While viruses use hemagglutinin to attach themselves onto receptors on the surface of cells in order to infect them, the neuraminidase helps these viruses to spread within the infected host.

Among influenza A viruses, there are 16 different types of hemagglutinin, from H1 to H16 and nine different types of neuraminidase, from N1 to N9. Each virus has one type of H, such as H1 and one type of N, such as N1. While there are many combinations of H and N seen in birds, widespread human infection has only been caused by a few.

For example, H1N1 was the strain responsible for the 1918 pandemic virus and the recent 2009 swine flu pandemic, while H2N2 caused the 1957 Asian flu pandemic, and the H3N2 resulted in the Hong Kong, SAR of China, pandemic in 1968.

While H5N1 and H7N9 strains can be transmitted directly from birds to humans, these viruses have not yet adapted sufficiently to spread from human to human. That could happen in the future though, if the virus either adapts through random mutations or if two different strains of influenza infect the same host and manage to swap and mix their genes.

The challenge now was to use this information for practical interventions that could prevent the transmission of the virus in these markets. The WHO research team, based on the insights gathered from their study, suggested structural interventions and workflow modifications to minimize risk for contamination in LBMs through daily removal of waste and segregation of poultry-related areas.

A follow-up research project, led by Gina Samaan of the Australian National University, identified five critical control points to reduce the risk of H5N1 HPAI virus contamination in markets in low-resource settings. The surveys they carried out assessed poultry workflow, market infrastructure, hygiene and regulatory practices and microbiological contamination with the H5N1 HPAI virus. The control points included reducing risk of receiving infected birds into the market; surface contamination by isolating slaughter processes from other poultry-related processes; and the risk of surface contamination in the sale zone of the market.

The insights into the role of LBMs were quickly translated into larger policy measures to deal with the avian flu epidemic in Indonesia and other countries in the Region. For example, the Jakarta provincial government issued a local regulation in 2007 on the control of LBMs.
raising and distribution of poultry, prohibiting live poultry trade in the territory of Jakarta. The regulation decreed that live poultry could not be transported into or out of Jakarta, and that all poultry must be marketed within the city as carcasses or poultry parts. The regulation stated that officials in Jakarta would close most of the poultry collection sites, live bird markets and slaughterhouses in Jakarta and relocate them outside the city within a period of not more than 3 years.

Converting the research into practice on the ground, however, has not proved easy. Studies on the knowledge, attitude and practices among LBM workers in Jakarta showed that, despite being given adequate information, that they had no detailed understanding of avian influenza. There was low perception of risk of contracting avian influenza, and low compliance with recommended precautionary measures.

The study pointed to the complex relation between knowledge and change in practices and called for better designed training and communication programmes aimed at the LBM workers to improve implementation of recommended biosecurity measures. The lack of adequate infrastructure on the ground and resistance from poultry traders to the plan to shift LBMs out of the city limits for fear of losing business were also identified as factors influencing the behaviour of workers.

Participatory surveillance

While research uncovered the epidemiology and clinical implications of the pandemic, global and domestic agencies helped to strengthen disease surveillance networks and on-the-ground efforts to improve biosecurity measures through good farming practices.

In December 2005, with the assistance of the Food and Agriculture Organization (FAO), Indonesia developed a National Strategic Plan to address the bird flu outbreak. The plan emphasized disease control activities ‘at source’, as well as strengthening underlying capacities for disease detection and outbreak response.

One of the novel initiatives developed, through collaboration between national and international agencies, was the Participatory Disease Surveillance and Response (PDSR) programme, which targeted the backyard poultry sector and engaged thousands of families that breed chicken for commercial or subsistence purposes across Indonesia’s many islands.

Starting off in early 2006 as a pilot programme in four Local Disease Control Centres (LDCCs) of Java, the project rapidly expanded throughout much of Indonesia. At its peak in mid-2008, there were 2123 PDSR officers in 31 LDCCs situated in Bali, Java, Kalimantan, Sulawesi and Sumatra. PDSR officers were either civil servants or people recruited on fixed-term contracts by local government, under the authority of the state agency in charge of livestock services.

Focusing on the village as its epidemiological unit, the PDSR programme used its large cadre across the country to build its own surveillance system for data collection, analysis and synthesis. The participatory disease searching and disease reporting ensured that the surveillance system was sensitive and timely, yielding valuable information for both local action as well as policy-making purposes.

“Apart from helping to deal with the ongoing avian influenza outbreak, the PDSR project has been praised for helping to build capacity at the level of local communities to deal effectively with epidemics in the future as well.”

According to one independent evaluation,16 the PDSR approach has “injected a new lease of life into the understanding of, and responsiveness to, the animal health constraints of many rural and urban communities” and “strengthened the capacity of local animal health services in Indonesia”.

The Indonesian Ministry of Health also set up the Integrated Surveillance for Avian Influenza (IS-AI) project to make detection and reporting of human cases in the community more efficient and improve information sharing and coordination between human and animal health sectors. The system incorporated immediate reporting of outbreaks to human health authorities, documentation of best practices in descriptive epidemiology and case management, contact tracing and intensive case finding, sample collection and rapid transport to laboratory.

The IS-AI project collaborated closely with the PDSR initiative, through its cadre of medical District Surveillance Officers (DSOs), who worked at the community level in the public health response to avian influenza.

Knowledge without borders

The response to the bird flu epidemic also saw the entire global research community flock together, supported by the UN and multilateral agencies, national governments, medical and health professionals and civil society — in an unprecedented fashion. New and existing networks of laboratories, surveillance systems and response mechanisms, established by international partners, played a crucial role in enhancing Indonesia’s capacity to detect and control the avian influenza outbreak.

Among the significant collaborative efforts that provided technical expertise, initiated research and facilitated sharing of evidence and information were:

- The Crisis Management Center for Animal Health, established by the United Nations., FAO and the World Organization for Animal Health (OIE), to respond rapidly to outbreaks or emergency events related to avian flu.
- The Global Avian Influenza Network for Surveillance (GAINS), launched by the United States- based Wildlife Conservation Society, which conducts wild bird mortality surveillance, avian flu sampling, local training, wild bird censuses and monitors key wild bird migration routes.
- OFFLU, an international network established by OIE and FAO, to support veterinary services in countries with limited capacity, in their efforts to reduce risks to animal and public health from animal influenza viruses.
- The Global Early Warning System (GLEWS) for major animal diseases, including zoonoses, that coordinates the alert mechanisms of FAO, OIE and WHO to help predict, prevent and control animal disease threats through information sharing, analysis and joint field missions to assess and control outbreaks.

**BOX 3: LESSONS LEARNT**

There are several important lessons that emerge from the national and global response to the H5N1 avian influenza outbreak.

The first lesson was the central importance of a well-functioning national-level disease surveillance system that can slot into an international early warning system. While Indonesia did not have such a surveillance mechanism initially, it managed to respond fast and build one with international help.

Secondly, the swift translation of surveillance data into a rapid institutional response is a key factor determining success or failure. Similarly, quick and close collaboration between policymakers and researchers in a variety of fields, from natural, social and management sciences, is crucial.

The third lesson was that top-down, bureaucratic action often flounders and fails to achieve compliance and buy-in. Addressing local social realities and community concerns is essential to achieve success.

In the Indonesian context, a fourth lesson was that using the response to build infrastructure, systems and surveillance mechanisms was a wise decision as it could help to detect and react decisively to future threats.

**Challenges ahead**

Thanks to the various counter measures launched by international and national agencies the total number of reported human cases and fatalities due to H5N1 HPAI went down from an annual high of 55 cases and 45 deaths in 2006, to 9 and 9 in 2012, and 3 in 2013, with no cases or fatalities recorded since 2014.

In poultry, the number of reported outbreaks also declined. The highest seasonal peak of over 426 outbreaks in village poultry was reported in May 2007, which declined to 121 by January 2013.17

That the H5N1 HPAI epidemic, despite initial fears, did not result in human losses on a very large scale, was at least partly due to the success

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of control efforts, cutting across national boundaries. Since the epidemic started in 2003, over 50 of the 63 countries affected by the virus have managed to eliminate it.

The cost of the epidemic turned out to be very high though. One estimate\(^\text{18}\) put the economic losses due to the H5N1 HPAI outbreak in South-East Asia at over US$ 20 billion. At the same time, it was calculated that if the outbreak had not been effectively contained and had spread worldwide, the potential cost to the global economy would have been nearly US$ 2 trillion\(^\text{19}\).

Despite many important achievements, there is little room for complacency as the H5N1 HPAI remains entrenched in several countries, and still has the potential to cause a pandemic that can overwhelm the globe’s health and governance systems.

In 2008, four specialized agencies – FAO, UNICEF and WHO, along with OIE – came up with a Strategic Framework\(^\text{20}\) based on evaluation of the Asian and global response to the H5N1 HPAI outbreak.

Important areas where further studies are required include development of vaccines for both human and animal health, dynamics of disease transmission, social and economic impact of bird flu and behaviour change communication strategies.

Significantly, the Strategic Framework endorses the concept of ‘One World, One Health’ that seeks to develop collaborations between and integrate health care for humans, animals and the environment (Figure 2). Given that many emerging infectious diseases are zoonotic and most of the recent outbreaks of new infectious diseases have had their origin in wild animals, it strongly emphasizes the need for interdisciplinary work and greater investment into research in this area.

There is little doubt that Asia’s H5N1 HPAI crisis was indeed a wake-up call about the threat from infectious diseases that emerge and re-emerge from the interface between animals and humans and the ecosystems they occupy. It is a warning the world would do well to heed.

**“Apart from long-term interventions to strengthen public and animal health systems, the Strategic Framework identifies research as a key area of focus to develop rational and targeted control programmes to tackle avian influenza.”**


On 7 June 2016, Thailand became the first country in Asia to eliminate mother-to-child transmission of HIV and syphilis by meeting targets set by the World Health Organization. Thailand was also the second country, after Cuba, outside the Organisation for Economic Co-operation and Development, to have reached this important public health goal.

Once among countries most affected by HIV in Asia, Thailand has become a model for the rest of the region in containing and reversing the HIV pandemic. Global knowledge-sharing partnerships, strong domestic research capacity together with efficient implementation of health programmes have been key to its success.
Thailand’s unique achievement of eliminating all cases of transmission of the HIV virus from mother to her child during pregnancy, labour, delivery or breastfeeding, is also an example of the excellent teamwork between its research community, policy-makers, public health practitioners and the government’s fiscal decision-making mechanisms.

**Evidence-driven policy**

The first case of HIV in a pregnant woman in Thailand was reported in 1988, and increasing HIV prevalence was detected among pregnant women in the early 1990s. Lacking antiretroviral drugs, Thailand’s public health sector focused at first on slowing HIV transmission through behaviour change. It offered family education and pre-marital counseling, and encouraged couples to take an HIV test before deciding to have children.

Then came a breakthrough in 1994, when a clinical trial, carried out by the National Institute of Health in the United States, confirmed the efficacy of AZT (zidovudine) for reducing the risk of HIV transmission from mother to child. The study showed that use of AZT could cut the transmission rate of HIV from mothers to their newborns from 24% to 8%.

Thailand was quick to act, using the evidence to shape domestic policy and programmes on prevention of mother-to-child transmission (PMTCT) of HIV. Thai health authorities first validated the research findings in a domestic trial, and then implemented the AZT intervention in pilot projects. The Thailand Ministry of Public Health (MOPH) and Siriraj Hospital, in collaboration with CDC Thailand/ Southeast Asia Regional Office, launched a trial of short-course oral AZT in 1996. The trial demonstrated an encouraging 50% reduction in mother-to-child-transmission.

During 1997–1999, the MOPH implemented pilot projects in northeastern and northern Thailand to provide HIV testing for pregnant women, administer AZT to those who were HIV-positive, and monitor the preventive effects. This then led to astute and timely policy changes that helped to scale up the intervention across the country.

In 2000, the MOPH announced the first national policy integrating PMTCT activities into routine maternal and child health services, including HIV testing for all pregnant women, antiretroviral therapy for PMTCT, and infant formula for babies born to HIV-positive mothers.

The same year, Thailand began a countrywide programme that provided short-course AZT for HIV-positive women as a routine part of antenatal care. The Thai government ensured sufficient resources by tripling the budget for PMTCT services, while drug costs were lowered by manufacturing generic versions of AZT locally.

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5 Regional Validation Committee. Elimination of mother-to-child transmission of HIV and congenital syphilis, Thailand validation. New Delhi: WHO Regional Office for South-East Asia, 2016.
By 2001, the coverage expanded rapidly, and two in three HIV-positive pregnant women were covered by PMTCT services. In that year, the government also guaranteed universal access to PMTCT services, integrating these into the new universal health coverage scheme. Consequently, by 2009, 94% of pregnant women were counselled and tested for HIV and 94% of HIV-positive pregnant women received antiretrovirals. By 2015, 99.6% of infants born to HIV-positive mothers in Thailand received antiretroviral prophylaxis.

Thailand also demonstrated its ability to swiftly adopt proven new technologies. In 2014, for example, Thailand switched from implementation of short course AZT to lifelong highly active antiretroviral therapy regardless of CD4 count, a regimen also known as WHO option B+. As a result of all these measures by June 2015, Thailand’s MTCT rate dropped to 1.9%, lower than the WHO’s elimination of MTCT target of <2% for non-breastfeeding populations (Figure 1).

FIGURE 1: Elimination of HIV and syphilis. Thailand, 2014 values and global targets

![Figure 1: Elimination of HIV and syphilis. Thailand, 2014 values and global targets](image)

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HIV and AIDS Data Hub for Asia-Pacific. Thailand country review. HIV and AIDS Data Hub for Asia-Pacific, Bangkok; 2012


The 100% Condom Use Campaign

Thailand’s success with eliminating mother-to-child transmission of HIV was not a one-off event and rested on earlier experience of using solid research, and informed rapid programmatic interventions to beat the larger HIV epidemic affecting its entire population. According to global health experts, if Thailand’s AIDS epidemic were as severe today as it was in the 1990s—or, had substantially worsened—the challenge of eliminating mother-to-child transmission would have been immeasurably greater.

The story goes back to the 1980s when the country was just waking up to the growing HIV epidemic within its borders. Within a few years after the first AIDS case in Thailand was reported in 1984, the Thai health ministry, based on strong epidemiological data, raised the alarm about the rate at which HIV was spreading.

Initially, the route of transmission had appeared to be limited to male sex workers (MSW) and their male clients and spread to injecting drug users (IDUs) but, by 1989, epidemiological data compiled by the health ministry affirmed that HIV outbreaks were also occurring among female sex workers (FSW). This transmission also risked spreading to the wives of the male clients of infected FSWs. In the absence of any feasible treatment for HIV at that time, health officials warned that behavioural change was the only option to prevent the deaths of millions of people.

“Thailand’s success with eliminating mother-to-child transmission of HIV was not a one-off event and rested on earlier experience of using solid research for programmatic interventions”

Surveillance and innovation

In its ability to first beat back the growing HIV epidemic and then eliminate mother-to-child transmission of HIV, Thailand has benefited much from its investments in developing a sound disease monitoring and data collection mechanism.

Thailand’s national sentinel serosurveillance system was established in mid-1989. In the first round of testing in 14 provinces conducted in June 1989, high infection levels were detected among sex workers in the country’s northern provinces, especially among sex workers in brothels. By June 1990, the surveillance system had been expanded to include all 73 provinces.

The epidemiological evidence collected was used to lobby the country’s political leaders in the late 1980s and early 1990s. Based on excellent implementation research, facilitated

14 Evaluation of the 100% Condom Campaign in Thailand, UNAIDS Case Study, UNAIDS, July 2000.
through pilot projects, evidence collection and analysis, the Thai health authorities decided to make 100% condom usage a precondition for commercial sexual encounters between female sex workers and their male clients.

‘No Condoms, No Service’ was the new slogan promoted by health authorities. Regular monitoring and mid-course correction mechanisms ensured the campaign was fine-tuned from time to time for greater impact.

In 1992, convinced by the success of these pilot projects, Thailand’s National AIDS Committee, chaired by the prime minister, decided to implement the “100% Condom Use Campaign” or CUP on a national scale. At its core, the programme included the distribution of condoms to brothels and other sex establishments, a media campaign to promote condom use and an enforcement programme to ensure compliance.

Expansion of the 100% CUP campaign nationwide brought about immediate results among groups vulnerable to HIV infection such as young recruits to the Thai military who visited commercial sex establishments. Studies also found a tenfold reduction in STI incidence and a fivefold reduction in HIV incidence among young Thai men between 1991 and 1993\(^\text{15}\) (Figure 2).

The 100% CUP campaign to ensure condom use and safe sex practices is credited with preventing an estimated 5 million Thais from becoming infected with HIV between 1989 and 2004. In 1991, the new annual HIV rates stood at 143,000, and a decade later, the number of new annual HIV diagnoses was less than 14,000.\textsuperscript{16} Thailand transformed itself from a country worst affected by the pandemic into a best practice model, offering valuable lessons on how to tackle HIV (Figure 3).

![Figure 3: Number of sexually transmitted disease (STD) cases in Thailand, 1970–2004](image)

**FIGURE 3:** Number of sexually transmitted disease (STD) cases in Thailand, 1970–2004

Lessons learnt

Thailand’s success in responding to the HIV epidemic would not have been possible without the emergence of firm and focused political commitment, the high public spending, the mobilization of sectors and partners well beyond the health ministry and the pragmatism that guided Thailand’s response and effective feedback from the field to policy-makers.\textsuperscript{17}

Researchers studying the condom use campaign also found that several important structural and even cultural factors played a key role ensuring effective interventions. First, Thailand’s sex industry was relatively well organized, with the Thai government maintaining a database of both “direct” and “indirect” sex establishments, which enabled officials to reach their owners to seek their cooperation.

Second, the campaign also saw authorities repealing a variety of repressive policies that, for example, insisted on the mandatory reporting of names and addresses of people with HIV and denied them anonymity or privacy. Health officials also took a pragmatic approach to the commercial sex industry. While on paper, sex work remained illegal, authorities encouraged condom use, and sex workers were screened weekly or biweekly for STDs, treated, and provided with free condoms.\textsuperscript{18}


As a result of this initiative, in a very short time, the campaign managed to increase condom use in brothels and massage parlours from 14% in early 1989 to more than 90% by June 1992. They became extremely effective in discouraging unprotected intercourse in establishment-based sex work.19

Another very significant factor in ensuring the success of the CUP and later also the programme to eliminate mother-to-child transmission of HIV was that Thailand already had a well-functioning health system and a good network of STI services, both for treatment and surveillance. The system had an adequate number of trained health workers, epidemiologists who provided essential treatment and advice to sex workers and their clients as well as statisticians who supplied decision-makers with crucial data both at the baseline and when the programme took effect.

Lastly, Thailand’s HIV campaigns benefited immensely from the fact that officials from different state sectors were able to work together smoothly without battling over turf or differences over strategy. Close collaboration between the research community, epidemiologists, statisticians on the one hand, and policymakers and practitioners, on the other, has also been crucial in the country’s successful HIV response.

**BOX 2: THE SONAGACHI EXPERIENCE**

Thailand’s 100% CUP campaign has not been without its critics, very often from feminists, human rights activists and sex workers’ groups themselves. They point out, for example20, that the 100% CUP affirms the stereotype that sex workers are the ‘vectors of disease’ and perpetuates the stigma and discrimination that hinder their ability to advocate for their rights.

According to them, in direct contradiction to current notions in global human rights discourse about the value of community participation in HIV programming, the creators of the 100% CUP never attempted to support collaborative efforts by sex workers to address the epidemic. This has failed to put sex workers’ rights and wellbeing at the centre of HIV/AIDS programme design.

An alternative to CUP’s top-down model comes from Kolkata, India, where the Sonagachi Project, a cooperative of over 60,000 sex workers, has adopted a participatory and community-led approach to bringing down HIV prevalence through safe sex campaigns. One evaluation of the Sonagachi model in 2000 found that compared with narrowcast clinical and prevention services alone, empowerment strategies can significantly impact a broader range of factors to reduce vulnerability to HIV and STDs.21

Initiated in 1992, the Sonagachi Project is recognized by UNAIDS as a “best practices” model for its use of a community development approach to empower sex workers to take individual and collective action to reduce their vulnerability.

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19 Chamratrithirong A et al. The success of the 100% Condom Promotion Programme in Thailand: survey results of the evaluation of the 100% Condom Promotion Programme. IPSR Publication No. 238. Institute for Population and Social Research, Mahidol University, 1999.


Challenges ahead

Despite Thailand’s historical success in controlling the HIV pandemic, there is little room for complacency today. Sustaining the country’s decline in HIV incidence will need reaching out to teenagers and young people with the sexual health information and services that they need to protect themselves and others against HIV and other sexually transmitted infections.

A 2014 survey, for example, showed that people under the age of 25 have lower levels of HIV knowledge and exposure to HIV testing and counselling than those aged over 25. According to other research studies, Thailand is experiencing a transition in sexual norms and practices, particularly among adolescents and young adults. An increase in the acceptance of premarital sex coupled with a decrease in condom use among youth and young adults has been identified as one of the threats to Thailand’s continued HIV prevention success.

Another cause for worry is that Thailand still has very high rates of HIV among people who inject drugs (PWID). In 2012, the HIV prevalence in this category stood at 25.2%, and declined to 19.0% in 2014. Although Thailand has a free needle and syringe distribution programme for PWIDs, the uptake is low. In 2014, the average number of needles and syringes distributed to the estimated total PWID was just 14, much lower than the country target of 88.

These trends call for designing a strategic response based on lessons from Thailand’s own sterling record in controlling the HIV epidemic and ending mother-to-child transmission of HIV. Carrying out high-quality research, systematic data collection and surveillance, adopting a multisectoral approach and developing partnerships for translating evidence into policies and programmes will once again be the key to ensure that the important gains made in the past are not slowly frittered away.

“According to other research studies, Thailand is experiencing a transition in sexual norms and practices, particularly among adolescents and young adults.”
Tuberculosis
DOTS AND BEYOND

In January 2012, when a large private hospital in the Indian metropolis Mumbai announced that they had detected 4 patients with extensively drug resistant TB or XDR-TB, it set alarm bells ringing around the world.1

While the more commonly found multidrug resistant TB or MDR-TB is defined as a strain of the disease resistant to first line drugs such as rifampicin and isoniazid, XDR-TB refers to resistance that extends to second-line fluoroquinolones, and to at least one of the second-line injectables such as amikacin, capreomycin and kanamycin.

India, home to a quarter of the world’s new TB patients detected annually, has been grappling with a rising number of MDR-TB cases over the last decade. The arrival of XDR-TB in any significant way would mean a sharp rise in the already high number of TB-related deaths in the world’s second-most populated nation.

Responding to the situation, a coalition of local and national state agencies together with NGOs and global health funders have put together an initiative that promises to not just beat TB in Mumbai but to evolve a model that can be used in other parts of India and perhaps throughout the developing world.

The initiative, called the Mumbai Mission for TB Control (MMTBC), operational since 2014, involves setting up a Private Provider Interface Agency (PPIA) to network private-sector physicians to enhance timely TB diagnosis and treatment. The project, focused on involving private practitioners operating in the city’s urban slum areas, is already showing results in terms of new case detection, early treatment and increased adherence rates.

These private physicians, from both the formal and informal sectors, are linked by PPIA field officers to nearby x-ray and sputum-testing facilities through vouchers, which the providers can give to patients for free or subsidized TB diagnostics at those facilities. Incentives for notification are paid to providers electronically, as are payments to diagnostic centres for laboratory tests. Once TB is confirmed, with state-of-the-art diagnostics, patients are referred to experienced chest physicians, who then manage their TB treatment using standard protocols.

Since inception, the PPIA network has engaged more than 1900 traditional medicine practitioners working in the slums of Mumbai and 850 qualified physicians working at 260 hospitals and clinics.2 Physicians in its network have initiated 14 000 TB patients on treatment, of which more than

4000 patients have successfully completed treatment. The project has further identified 1400 MDR-TB patients and guided them to public health facilities for treatment.

Apart from helping patients to get access to cheaper and better treatment, the initiative is popular with private physicians also as the scheme does not affect their regular revenues adversely. In addition, doctors have also welcomed being part of a larger network that helps provide quicker and more accurate diagnosis and treatment.

**FIGURE 1:** Projected trajectory of TB deaths and incidence rate by 2030 in South-East Asia Region

![Projected trajectory of TB deaths and incidence rate by 2030 in South-East Asia Region](image)

**BOX 1: COLLABORATION IS KEY**

The MMTBC project is an excellent example of global and local cooperation in the field of health, bringing the Government of India’s Central Tuberculosis Division, the World Health Organization, and the Bill & Melinda Gates Foundation together with the Mumbai municipal authorities and city-based NGOs.

The PPIA, which is part of the MMTBC, is implemented by PATH, a US-based international nonprofit organization working on delivering health care in Asia and Africa using innovative technologies and concepts. PATH, in turn, partners with two local community-based organizations—the Association for Leprosy Education, Rehabilitation, and Treatment and Maharashtra Janavikas Kendra—to engage private providers, including informal and formal practitioners, laboratories, hospitals, and chemists across Mumbai.

MMTBC has also roped in celebrities from Mumbai’s famous Bollywood or Hindi cinema industry to help propagate the message of need for timely and adequate care for TB among the city’s residents and physicians.
Research-driven policy shift

The MMTBC project, together with its PPIA platform, is a good example of policy-makers responding quickly to adopt new concepts; and of knowledge emerging from years of research in a variety of fields — ranging from drug and diagnostic development to epidemiological studies and implementation science.

For instance, one of the critical insights that lies in the backdrop of the project is about the very significant impact of the vast and unregulated private health-care sector on TB diagnosis, treatment and outcomes in the Indian context.

Nominally, all of India’s TB patients are entitled to free treatment and care from the state-sponsored Revised National TB Control Programme or RNTCP, which was launched in 1997 and is the world’s largest TB control programme. Using the WHO-recommended Directly Observed Treatment Short Course (DOTS) strategy, RNTCP has reached over a billion people in 632 districts around India and achieved a 55% reduction in the TB prevalence rate and a 58% reduction in TB mortality rate between 1990 and 2014.³

Despite such progress, India’s TB control programme still faces significant challenges including “diagnosis of TB and defining cure, detecting drug resistant TB, co-infection with HIV, suboptimal prescribing practices, and infection control”.⁴

Many of these problems exist because a sizeable section of new TB patients end up with the country’s vast and poorly regulated private health sector. A cross-sectional community-based survey⁵ in 30 districts around India, for example, found that nearly half of self-reported TB patients were missed by the official TB notification system in these districts. This was particularly true of rural populations, who accessed treatment from private providers.

The study highlighted the need for reviewing and revising the scope of the TB notification system. It also called for advocacy, communication and social mobilization activities focused on rural communities with low household incomes and involvement of their health-care providers.

Another study⁶ estimates the number of people with suspected TB accessing private practitioners at a staggering 2.2 million cases: more than twice the burden suggested by previous assumptions.


Such research evidence has helped shape India’s national health policies, with the Indian Ministry of Health and Family Welfare’s National Strategic Plan, 2017-25, advocating engagement with the private sector to improve services and not rely on public health facilities alone. To achieve their ambitious goal of providing quality TB care to all patients, Indian health authorities have also decided to extend provision of free treatment for TB patients in the private sector. A qualitative study of TB patients in South India showed that they preferred private practitioners, who provided DOTS for free as per the new government guidelines, over government facilities. This was because, according to patients interviewed, private practitioners were geographically closer and offered flexibility in timings for treatment. Patients could also consult practitioners immediately when they experienced some side effects after taking TB drugs.

**BOX 2: UNEVEN STANDARDS FOR TB CARE**

The problem with many private health providers in India, who include large numbers of those who practice traditional and other streams of medicine, is that they are often not trained or motivated enough to provide the quality of care needed by TB patients. Apart from delays in diagnosis that prolong tuberculosis transmission, poor counselling and lack of support for patients results in low treatment adherence that in turn has fuelled drug-resistant TB.

One study in Mumbai found that a majority of private practitioners were neither able to provide a correct prescription for treating TB nor had they been approached by the national TB programme, over the years, for training or awareness raising. It pointed out that strategies to control TB through public sector health services will have little impact if inappropriate management of TB patients in private clinics continues unabated, and recommended large-scale implementation of public-private mix approaches as a top priority. Ignoring the private sector, it warned, could worsen the epidemic of multidrug-resistant and extensively drug-resistant forms of TB.

In response to this situation, the WHO, to facilitate change in clinical practices based on research evidence, released the ‘Standards for TB Care in India’ (STCI), a set of guidelines that are based on international standards but adapted to the Indian context. The STCI, based on research of various factors affecting the TB situation in India, was developed by a large number of organizations and individuals, both within and outside of the Government of India in late 2012.

The document prescribes more than 26 standards with India-specific evidence touching upon themes including diagnosis, treatment, public health and social inclusion. Each standard prescribed is followed by a brief summary of the international and national evidence on which it is based, along with references to relevant research literature.

The STCI is expected to enhance quality of TB care in the private and other sectors in India and become an important tool for achieving the goal of universal access to quality TB care.

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1. Vijayashree Yellappa et al., Coping with tuberculosis and directly observed treatment: a qualitative study among patients from South India. BMC Health Serv Res. 2016.
New diagnostics

The MMTBC project has also taken full advantage of cutting-edge TB diagnostic technologies that have emerged in recent years and provide results far quicker than before, with implications for early treatment initiation and patient care. For example, the project has enabled over 8500 GeneXpert MTB/RIF tests, a new molecular test that apart from detecting the presence of Mycobacterium tuberculosis (MTB) DNA, also detects resistance to rifampicin (RIF).

Traditionally, TB has been diagnosed by looking for bacteria either through the use of the chest X-ray, through sputum smear microscopy, a technique that was developed a century ago or through culture of bacteria in the lab. Each of these TB tests has their own limitations, with sputum tests not being reliable enough, especially when patients are also HIV positive.

Although culture gives a definitive diagnosis, results usually take weeks rather than the hours taken by the GeneXpert test. Bacterial culture also requires trained personnel and expensive lab equipment.

The GeneXpert test was endorsed by WHO in December 2010 after rigorous assessment, with a recommendation and guidance for countries to incorporate the new test into their programmes. According to WHO, the new test could result in a three-fold increase in the diagnosis of patients with drug-resistant TB and a doubling in the number of HIV-associated TB cases diagnosed in areas with high rates of both TB and HIV.

India was among the countries where clinical validation studies of the new diagnostic were carried out, an engagement that has helped it adopt the technology more easily.

According to one study, treatment based on widespread use of GeneXpert diagnostic testing together with universal drug susceptibility testing to determine bacterial resistance levels could substantially impact MDR-TB in India. According to the study, achieving 75% access over 3 years among all cases being diagnosed for TB in the public sector alone could avert more than 180 000 cases of MDR-TB between 2015 and 2025.

M-Health

Another significant feature of the MMTBC initiative is its ‘M-Health’ approach, making creative use of mobile phone services to deliver health care. Under the project, patients for example receive “e-vouchers” for standardized TB medications, which they can redeem at no charge from private chemists, while call centres issue reminders to patients for follow-up visits via telephone calls and SMS.

Trained phone counsellors remind patients to collect their next lot of medicines, and also handhold some patients, helping them adhere to their TB drug regimens, thus lowering the chances of developing drug resistance. This digital system is in turn linked with the RNTCP, so that their programme staff also receive alerts and take action as necessary.

The MMTBC’s use of mobile phone technology is based on growing global research that shows the benefits of ‘M-Health’ in remote data collection, quality health-care delivery, diagnosis, monitoring and care, disease surveillance, health alerts and

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13 WHO has, however, also emphasized that conventional microscopy culture and drug sensitivity testing are still relevant to monitor treatment progress and to detect other types of drug resistance. The GeneXpert test cannot be used for treatment monitoring, as it detects both live and dead bacteria.
warning system and disease management. In October 2015, the number of mobile subscribers\textsuperscript{16} in India passed the one billion mark, and many experts feel that mobile phones and networks could revolutionize the Indian health sector, if utilized well. Several studies carried out in India have shown the willingness of mobile phone users, in both urban and rural areas, to receive health-related messaging.\textsuperscript{17}

**“The MMTBC’s use of mobile phone technology is based on growing global research that shows the benefits of M-Health”**

Getting the data right

By institutionalizing a close working relationship with private practitioners, projects such as the MMTBC initiative in Mumbai are also expected to boost notifications of new TB or relapse cases to the national health system.

Until recently, a lack of accurate estimates of TB prevalence, incidence or related mortality posed a major challenge for the Indian health authorities. Among the reasons was the difficulty in ensuring that private practitioners formally report the TB cases that they encounter.

The situation has improved considerably in recent years, thanks to changes in government policy and the introduction of new mechanisms that make it easier for health providers to report TB cases. Since May 2012, government policy has required mandatory notification of TB cases by all private doctors, caregivers and clinics via a new web-based reporting system known as Nikshay.

Developed by the Central TB Division of the Indian Ministry of Health and Family Welfare and the state-run National Informatics Centre, Nikshay is accessible via Android-based smartphones or a web portal, and it can be used by both public and private health-care providers throughout India.

Data reporting by the private sector has increased, and data quality has also improved dramatically. About 5000 TB cases are being reported to the system each day.\textsuperscript{18} The impact is so big that the increase in global TB notifications reported in the Global Tuberculosis Report 2016 was partially attributed to a 29% rise in notifications from India\textsuperscript{19} (Figure 2).

\textsuperscript{16}http://trak.in/tags/business/2016/01/05/indian-telecom-stats-1billion-mobile-subscriber-base/, accessed on 21 August 2016.
FIGURE 2: TB case notifications in India, 2000–2014

BOX 3: SEEDS OF HOPE

WHO’s Global Tuberculosis Report 2016\(^{21}\) describes the current state of research on new drugs, diagnostics and vaccines that promise to help achieve the targets set in the End TB Strategy.

- Four new diagnostic tests have been reviewed and recommended by WHO.
- Assessment continues of a next-generation cartridge called Xpert Ultra, which may replace the Xpert MTB/RIF cartridge.
- A new diagnostic platform called the GeneXpert Omni, intended for point-of-care testing for TB and rifampicin-resistant TB, is also in development. These will use the new Xpert Ultra cartridges.
- Nine anti-TB drugs are in advanced phases of clinical development for the treatment of drug-susceptible, multidrug-resistant TB. Of these, six are new and three are already approved or repurposed.
- There are also 13 vaccine candidates in clinical trials: eight in Phase II or Phase III trials, and five in Phase I trials. They include candidates for prevention of TB infection and candidates for prevention of TB disease in people with latent TB infection.

\(^{20}\) WHO SEARO. [http://searo.who.int/india/topics/tuberculosis/substantial_increase_in_tb_notification_in_india_2015.pdf?ua=1, accessed on 19 December 2016].

Taking research forward

Historically, India’s contributions to research have included large vaccine trials, randomized trials of short-course therapies, and operational research to improve programme efficiency. Indian companies and agencies are also actively engaged in TB drug discovery and development of diagnostics.

The MMTBC initiative in Mumbai is the most recent example of India’s strong record in operations and implementation research, and use of evidence to rapidly respond to new challenges, such as the emergence of XDR-TB in India.

Research is a key component of the End TB Strategy, which was adopted by the World Health Assembly in 2014 and endorsed by India together with other countries. The End TB Strategy aims to reduce the number of TB deaths by 90% by 2030 (compared with 2015 levels), cut new cases by 80% and ensure that no family is burdened with catastrophic costs due to TB.

The WHO launched a new Global Action Framework for TB Research in 2015 to foster high-quality national and global TB research needed to end the TB epidemic. The framework outlines steps and benchmarks for key stakeholders at global and national levels to advance research, particularly in countries carrying the greatest burdens of disease.

Recently, several leading Indian research institutions partnered with US-based entities to launch the Regional Prospective Observational Research in Tuberculosis for India or RePORT.

India. The new effort is designed to strengthen TB research capacity and infrastructure, and foster research collaboration within India and other countries.

However, despite all these important developments, much more needs to be done especially in the area of efficient utilization of new technologies, validating promising new drugs, speeding up vaccine trials and understanding the social conditions that foster the spread of TB or promote behaviour that undermines effective treatment.

Currently, there are also indications that funds available to Indian institutions for taking on the challenge of the massive TB burden faced by the country are less than adequate (Figure 3).23 Globally also, after a significant increase from about US$ 358 million in 2005 to about US$ 637 million in 2009, funding for TB research and development has remained more or less static24.

If India and indeed the world are to achieve the ambitious goals of the End TB Strategy, much greater investments, in both research and implementation, will be urgently needed from both domestic and international agencies.

FIGURE 3: TB funding gap in countries in the SEA Region (Figures are in US$)

*Gaps estimated by countries to implement National Strategic Plans. Actual gaps to meet SDG targets are unknown

Taking the Bite Out of Malaria

Eliminating a well-entrenched disease that has tormented humanity for millennia from a region as vast as the Asia-Pacific is a very ambitious goal indeed. And yet, as 18 Heads of State came together for the 9th East Asia Summit in Nay Pyi Taw, Myanmar, this is what they collectively pledged to do – eliminate malaria by 2030.¹

In the WHO South-East Asia Region, the most affected part of Asia-Pacific, over 1.3 billion people are at some risk of malaria, with about 231 million at high risk. About 7% of the estimated 438 000 malaria deaths globally in 2015 occurred in the South-East Asia Region.²

While these numbers are large enough on their own to justify a concerted push to eliminate malaria in the Region, for global public health experts, there were even more compelling reasons to applaud the call made by leaders at the East Asia Summit.

New research, over the last decade, in the Greater Mekong Subregion (GMS) – comprising, Cambodia, Lao People’s Democratic Republic, Myanmar, Thailand and Vietnam – had revealed an alarming increase in parasite resistance to artemisinin, the cornerstone of malaria treatment worldwide. If such resistance spreads to other parts of the world, in particular to Africa, which has the highest deaths due to malaria in the world, the consequences would be extremely dire.

According to the WHO World Malaria Report 2016,³ there were an estimated 212 million cases of malaria worldwide of which 90% of both cases and also deaths were in the WHO African Region alone. The WHO South-East Asia Region came a distant second accounting for just 7% and the Eastern Mediterranean Region for 2%. The vast majority of deaths – about 99% – are due to mosquitoes that harbour Plasmodium falciparum (P. falciparum) – the same parasite that was turning resistant to artemisinin-based therapies in the GMS region.

That is why public health experts believe, beyond country-level benefits, that the Asia-Pacific 2030 goal had weighty strategic importance, and millions of lives are at stake globally. Eliminating malaria in the Region will also eliminate the alarming artemisinin resistance that was first documented on the Thai-Cambodian border and prevent it from wreaking havoc in other parts of the world.

² World Malaria Report 2016.
“Eliminating malaria in the Region will also eliminate the alarming artemisinin resistance that was first documented on the Thai-Cambodian border and prevent it from wreaking havoc in other parts of the world”

Rolling back malaria

Despite the large numbers and tough challenges involved, the WHO South-East Asia Region has used a mix of good medical science research, epidemiology, targeted health interventions and efficient programme implementation to contain the spread and impact of malaria. Strategies have included improved use of malaria rapid diagnostic tests (RDTs), case management and mass campaigns for long-lasting insecticidal nets (LLINs) and indoor residual spraying (IRS).

In the last decade or more, this has led to a significant decline in the overall malaria burden in the Region. Between 2010 and 2015, while the number of new malaria cases decreased by 21% globally, South-East Asia recorded a 54% fall.

Even more impressive, two countries in the Region – Maldives and Sri Lanka – have already been certified by WHO to be malaria-free (Figure 1). While Maldives has no reported case since 1984, Sri Lanka has not reported any indigenous malaria case since November 2012. Bhutan, which is in the pre-elimination phase, had 104 confirmed cases in 2015.

Overall, reported malaria mortality fell by 89% from 2000 to 2015 in the SEA Region.⁵

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⁵ End In Sight: Accelerating the end of HIV, Tuberculosis, Malaria and Neglected Tropical Diseases In The South-East Asia Region. 2016. WHO SEARO.
Magic of artemisinin

For many years now, the threat of drug resistance has been the focus of considerable research, field work and intervention programmes developed in close cooperation with health authorities in the GMS region (Figure 2).

The use of artemisinin for treating malaria here was initiated by Chinese researchers who, in the mid-1970s, had unearthed worrying signs of resistance to other therapies in the then war-torn Cambodia. They confirmed, for example, that chloroquine, then the drug of choice to prevent and treat malaria, was no longer effective.

In response, Chinese researchers first introduced piperaquine and noted that patient recovery became significantly faster. Then they introduced artemisinin, initially as an injection, and found this new medicine to be “exceptionally effective against severe malaria.” Isolated from the plant *Artemisia annua*, or sweet wormwood, artemisinin and its derivatives are powerful medicines known for their ability to swiftly reduce the number of *Plasmodium* parasites in the blood of patients with malaria.

In neighbouring Thailand, chloroquine had been the first line drug against malaria for many decades, since the end of Second World War up to 1972. Then, sulfadoxine/pyrimethamine was introduced during the 1970s followed by quinine as an interim therapy for a few years and then mefloquine in 1985.

However, faced with rising parasite resistance and also inspired by the Chinese experience, Thailand in 1995 embarked on a dosage of artemunate-mefloquine, an artemisinin-based combination therapy (ACT).

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9 Artesunate is a semi-synthetic derivative of artemisinin that is water-soluble and may therefore be given by injection.

was the first use of ACT in the global response to malaria, and it endorsed the growing optimism about the magic of artemisinin in controlling malaria. Cambodia followed Thailand’s innovation and started malaria patients with ACT in 2000.\textsuperscript{11}

### Rise of resistance

Since the mid-1990s, ACT regimens have been considered the best treatment for falciparum malaria and energized programmes to control malaria around the world. Combination therapies, in general, are recommended as they tend to delay the development of microbial resistance.

However, since several ACT regimens are combinations of artemesunate and older antimalarial drugs, against which resistance already exists, there were always worries about possible drug failure. Most studies\textsuperscript{12} initially showed that ACT treatment efficacy remained high. But the trends observed along the Thai-Cambodian border were very troubling.

Patients receiving treatment with some ACT and artemisinin monotherapy were not clearing the parasite from their blood streams quickly enough. The parasite was becoming resistant to the most powerful antimalarial drug available.

Used in combination with other antimalarial drugs, the role of artemisinin is essentially to reduce the main parasite load during the first 3 days of treatment. Artemisinin is a very fast-acting drug, which means that within 12 hours of starting treatment, about half of the parasites in the body are removed.

The role of the partner drug(s) is to eliminate the remaining parasites. In patients who are infected with artemisinin-resistant strains of malaria, the artemisinin compound does not clear all parasites by the third day of treatment. However, patients are still cured as part of a longer treatment regimen, provided that they are treated with an ACT containing a partner drug that is effective in that geographical area.\textsuperscript{13}

The significance of artemisinin resistance is that it puts additional pressure on the partner drugs to kill the parasites, which may lead to resistance to these drugs too and consequent treatment failure.

Being the most powerful antimalarial available, a drop in artemisinin efficacy was of tremendous concern and required extensive scientific investigations for confirmation. By 2002, a study\textsuperscript{14} showed that in Pailin, Cambodia, an “unusually high proportion (14.3\%) of \textit{P. falciparum} malaria patients treated with artemesunate-mefloquine combination had treatment failure at Day 28,” and further, that about “10\% of the patients had not cleared parasites by Day 3”. In nearby Battambang Province, artemether-lumefantrine combination (Coartem\textsuperscript{\textregistered}) was also shown to have a high treatment failure rate.\textsuperscript{15} Since then, subsequent studies have confirmed the trend of artemisinin resistance along the Thai-Cambodian border areas.\textsuperscript{16}

\textit{“Being the most powerful antimalarial available, a drop in artemisinin efficacy was of tremendous concern and required extensive scientific investigations for confirmation”}
In January 2007, the formal response to the threat from artemisinin resistance began, when experts, convened by WHO, gathered in Phnom Penh, Cambodia, for what was to be the first of a series of urgent consultations. Data from therapeutic efficacy studies and in vitro studies were reviewed, and urgent action was deemed necessary.

Led by WHO, the multinational collaborative programme, Artemisinin Resistance Confirmation, Characterization and Containment project (ARC3), was initiated in November 2007. Scientists, donor agencies, national malaria control programmes and other stakeholders started working together aiming to “contain” artemisinin-resistant malaria, to preserve the life-span of ACT regimens (Figure 3).

Clinical trials\(^ {17} \) sought to gain more insight on artemisinin development; for example, to establish whether longer clearance times were the result of increased resistance to artemisinin compounds. Another study followed an additional line of inquiry: whether increasing the dose of artemisinin/ACT would overcome drug resistance without increasing toxicity.\(^ {18} \) And, a third trial aimed to demonstrate that ACT remained effective in an area further away from the Thai-Cambodian border.\(^ {19} \)

These studies played a critical role in understanding and also predicting the emergence of drug-resistance in an area, rather than having to wait for drug-resistance to emerge. The research results helped investigators to conclude that the percentage of patients who were still blood-smear positive on Day 3 following treatment with ACT could serve as a surrogate for predicting the emergence of artemisinin resistance in that endemic area.


BOX 1: GENETICS OF ARTEMISININ RESISTANCE

While health authorities pursued a strategy of containing drug-resistant malaria on the ground, in research labs, scientists were figuring out the genetics underlying the entire phenomenon of artemisinin resistance. Scientists compared thousands of parasite genomes from different areas of Africa and South-East Asia to identify the genetic variations that could lead to drug resistance.\(^{20}\)

Between 2012 and 2013, using whole-genome sequencing of an artemisinin-resistant parasite line from Africa and clinical parasite isolates from Cambodia, researchers zeroed in on Chromosome 13 of \textit{P. falciparum} as a location of a gene called kelch13 or K13, which is responsible for artemisinin resistance.\(^{21,22}\)

Mutations in the gene are associated with delayed parasite clearance both \textit{in vitro} and \textit{in vivo}. Although the exact mechanism is still to be fully understood, mutations in the K13 gene serve as a molecular marker for large-scale surveillance of the phenomenon of artemisinin resistance. Identification of the parasites with these mutations is also expected to enable researchers to target them with medicines or insecticides to stop them before they take hold and spread any further.

Urgent response needed

Meanwhile, medical scientists tracking the behaviour of the malaria parasite were reporting that drug resistance on the Thai-Cambodian border was worsening. In Pailin, 26% of patients treated with an ACT, called dihydroartemisinin-piperaquine, remained positive for malaria parasites on Day 3 in 2008 with the proportion increasing to 33% in 2009.\(^{23}\) Cure rates were found to be below 90%.

The situation was no better to the west of Thailand. Studies of ACT’s therapeutic efficacy revealed increased Day 3 parasite positive rates in several parts of eastern Myanmar during 2009 and 2010, especially when there were significant population movements. There was little doubt that artemisinin resistance had emerged in eastern Myanmar as well.

These findings led to WHO’s decision to expand regional cooperation in the battle against artemisinin resistance, through its Strategy for the Containment of Artemisinin Tolerant Malaria Parasites in South-East Asia, implemented from 2009 to 2011.

With funding from global donors and a team of international, regional and national specialists, the task was to devise a quick start-up to contain the spread of the artemisinin-resistant parasites from where it was first detected on the Thai-Cambodian border. Extensive research was undertaken to look at the clinical/parasitological characteristics of artemisinin resistance, including the search for its genetic markers.

The Tracking Resistance to Artemisinin Collaboration study\(^{24}\) also showed the extent of spread of AR in the GMS and beyond, and validated the utility of using the K13 genetic marker for tracing the spread of artemisinin resistance.

Drawing on these studies, in January 2011, WHO released the Global Plan for Artemisinin Resistance


\(^{23}\) Personal communication with Dr Chansuda Wongsrichanala, WHO, Thailand.

Containment (GPARC) to outline the actions required to deal with the threat of artemisinin resistance before they spread to areas of higher transmission. The urgency was increased by the fact that no other antimalarial candidates that offered the level of efficacy and tolerability comparable with ACT had ever been found.

It was also clear that efforts to contain and prevent artemisinin resistance at local levels were not enough. Expansion, intensification and better coordination were required to protect artemisinin efficacy through the global malaria community. It was deemed essential to get other endemic areas well prepared to prevent artemisinin resistance from taking hold.

Towards elimination

The idea of solving the problem of artemisinin resistance, through elimination of malaria from the Region, was first mooted in September 2014, by the WHO Malaria Policy Advisory Committee (MPAC). They pointed out that it was technically and operationally feasible at a reasonable cost, and in line with the elimination goals of GMS countries themselves.

The MPAC recommendation in turn was based on a report25 by the WHO Drug Resistance and Containment Technical Expert Group, which confirmed that, “Although great progress has been achieved in reducing the *P. falciparum* malaria burden in the GMS through aggressive malaria control measures, this progress is being threatened by the emergence of multidrug resistance”.

This was followed, in 2015, with the launch of the Strategy for Malaria Elimination in the Greater Mekong Subregion (2015–2030) to put into practice the strategic transition from containment of multidrug-resistant malaria to accelerated elimination of malaria in the GMS. A key focus of the strategy is to ensure post-elimination vigilance to prevent re-establishment of malaria in areas where transmission has been interrupted.

Endorsements from Member States for the ambitious plan were mobilized in May 2015 at a World Health Assembly event to launch the Elimination of Malaria in the GMS 2015–2030. According to WHO,26 it was agreed that the worsening multidrug resistance situation in the GMS posed a threat to regional and global health security and necessitated urgent action.

The goal of eliminating malaria throughout the Asia-Pacific region also fits well into the overall fight against malaria globally, which has become ambitious and bolder, envisaging a world free of malaria. The Global Technical Strategy for Malaria 2016–2030, endorsed by the World Health Assembly in 2015, has fixed targets of reducing both malaria mortality and case incidence globally.

The aim is to achieve a reduction of at least 40% by 2020, 75% by 2025 and 90% by 2030, compared with 2015 levels. The strategy also calls for elimination of malaria from at least 10 countries by 2020 and 35 countries by 2030.27

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26 Personal communication with Dr Chansuda Wongsrichanalai, WHO, Thailand.

Challenges ahead

Despite much progress in reducing malaria in the Region, the disease burden remains high among vulnerable and marginalized populations, especially those living in pockets such as underserved or difficult-to-access geographical areas including international borders, conflict zones and among tribal populations. Rejuvenated decisive efforts are needed to ensure that those most vulnerable are not left behind, and each malaria case is being detected and treated adequately.

Given the current large differences in the malaria burden and malaria programme stages in different countries of the SEA Region, the goal to eliminate malaria from the Region also calls for urgent intensified efforts for tackling malaria across national borders, through sharing of information and coordinated control and preventive measures.

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Another challenge to achieving the goal of elimination is that in some parts of the Region, such as India, there is widespread resistance among some mosquito vectors to insecticides such as DDT and patches of resistance to pyrethroids and organophosphates, such as malathion. Indonesia and Myanmar have reported resistance to pyrethroids, while in Myanmar, there is also confirmed resistance to DDT and organophosphates (Figure 4).

The resources needed for carrying out the various tasks involved in a campaign to eliminate malaria from the Region are considerable. According to the World Malaria Report 2016, annual investments in malaria control and elimination globally need to increase to US$ 6.4 billion per year by 2020 to meet the first milestone under that strategy of a 40% reduction in malaria incidence and mortality rates. Total funding for malaria control and elimination in 2015 was only US$ 2.9 billion, just 46% of the 2020 investment target.

In the GMS countries alone, according to a feasibility study produced for WHO in September 2014, malaria elimination would cost more than US$ 3 billion between 2015 and 2030. Total funding for malaria programmes in the South-East Asia Region in 2014 stood at just US$ 207 million, including from both domestic and global sources.

Progress in reducing malaria incidence and mortality between 2000 and 2015 was made possible by large increases in the financing of malaria control and elimination programmes. It is clear, the ambitious task of eliminating malaria by 2030 calls on the entire world to pitch in the resources needed to make this dream goal a reality.

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A vaccine to protect populations against leprosy has been a major goal of health authorities and researchers worldwide for many decades. Thus far, no viable vaccine has been discovered, for reasons ranging from lack of efficacy to safety concerns.

That is why, in late August 2016, when India announced the introduction of an indigenously developed leprosy vaccine, it made a splash in the global media. The vaccine, developed from a bacteria called Mycobacterium indicus pranii (MiP) by Indian researchers, will be administered on a pilot basis to leprosy patients and those living in close contact with them, in five districts of the country.

Though its numbers are on the decline, leprosy, a chronic disease caused by a slow multiplying bacillus, Mycobacterium leprae, affects hundreds of thousands of people around the globe every year, particularly those from poorer communities. Untreated, leprosy can cause progressive and permanent damage to the skin, nerves, limbs and eyes. Historically, patients have also been subjected to much social discrimination, because of the disfigurement it causes and lack of understanding about how it was transmitted.
“Trials have shown that the vaccine, if given to people in close contact with affected persons, could bring down cases by 60% in three years. It has also expedited cure rates if given to people with skin lesions”, said a senior official of the Indian Council of Medical Research (ICMR), announcing the vaccine pilot project in Chennai, in southern India. The vaccine, after clearing required clinical trials, has been approved by the Drug Controller General of India and the Food and Drug Administration in the United States of America.

Over the last two decades, more than 16 million leprosy patients have been treated, and elimination of leprosy as public health problem – defined as prevalence less than 1 case per 10 000 persons – was achieved globally in 2000. The number of people registered for leprosy treatment globally has decreased from 5.2 million in 1985 to 805 000 in 1995, 753 000 in 1999 and 174 608 at the end of 2015. The prevalence rate of the disease has also dropped by 99%, from 21.1 per 10 000 in 1983 to 0.29 per 10 000 in 2015 – a massive decrease (Figure 1 and 2).

However, prevalence rates – much higher than the elimination target of less than 1 per 10 000 – continue to be found within countries, in certain geographical areas where the disease is endemic.

FIGURE 1: Registered prevalence of leprosy

Number of cases registered (prevalence/10 000 population), first quarter of 2015

1[http://www.who.int/wer, accessed on 1 January 2017.](http://www.who.int/wer, accessed on 1 January 2017.)


“The creation of TDR represented a significant shift of focus of a highly distorted global health research agenda, where 90% of the resources invested in health research are directed against diseases that affect only 10% of the global population”
Multidrug therapy to the rescue

Although search for a leprosy vaccine has been ongoing since the 1960s, these efforts were overshadowed by the emergence of a revolutionary new treatment option that has helped contain this dreaded disease. Introduced in the 1980s by WHO, multidrug therapy (MDT) — a regimen of several antibacterial drugs — has boosted cure rates while drastically reducing the duration of treatment. It also replaced the earlier monotherapy for leprosy, which relied on a drug known as “dapsone”.

Already, at the time of its recommendation in 1982, MDT was heralded in an editorial in The Lancet as “one of the most important and stimulating contributions to leprosy control for well over a decade.”

The development of MDT was the outcome of an initiative by three United Nations organizations — UNDP, The World Bank and WHO — which, in the 1970s, created the Special Programme for Research and Training in Tropical Diseases, now called TDR. TDR was set up to conduct research on a selected set of tropical diseases, develop new tools to control them and train scientists in affected countries to play a role in finding solutions. Together with institutional partners in the developing world, TDR helped facilitate research on tropical diseases, which had no licensed vaccines, where drugs are losing their effectiveness, and existing solutions did not reach those who need them.

“The creation of TDR represented a significant first shift of focus of a highly distorted global health research agenda, where 90% of the resources invested in health research are directed against diseases that affect only 10% of the global population — a disparity now known as the ‘10/90 disequilibrium,’” said Carlos Morel, in a review of TDR’s achievements on its 25th anniversary.

Unsolved problems

While the prevalence of leprosy has declined considerably in the past decade, worryingly, the number of new cases of leprosy detected each year has not been falling significantly enough. The number of new cases detected reduced only marginally from 265,661 in 2006 to 210,758 in 2015.

Of new leprosy cases, 94% were reported from 14 countries with only 6% of new cases reported from the rest of the world. SEAR Member States accounted for 74% of the global new case load. India alone reported 127,326 new cases, accounting for 60% of global new leprosy cases, while Indonesia reported 17,202 new cases, 8% of the global case load.

According to WHO, some of the slow decline in new cases annually is due to the expansion of MDT services, which is reaching previously uncovered or poorly covered areas. However, it is also believed that the disease is still spreading from the reservoir of both treated and untreated leprosy-affected people, particularly in endemic areas. For example, it has been pointed out that approximately 8.9% of newly diagnosed cases of leprosy globally are among children, indicating continued spread of the disease.

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4 Later UNICEF too became one of the sponsors of TDR in 2003.
Disability as indicator of burden

While the overall burden of leprosy has reduced drastically in the last two decades, it remains a leading cause of peripheral neuropathy and disability globally. WHO grades leprosy patients according to disabilities of the eyes, hands and feet with grade-2 disabilities (G2D) being the highest, involving the most severe medical impact of the disease on the patient. According to many leprologists, leprosy is best understood as two conjoined diseases. The first is a chronic infection that elicits an extraordinary range of cellular immune responses in humans. The second is a peripheral neuropathy, whose course often extends many years beyond the cure of the infection and may have severely debilitating physical, social and psychological consequences.

G2D has been proposed as a more robust marker for mapping cases of leprosy than leprosy prevalence, which is defined as the number of patients diagnosed with leprosy and registered for treatment over the course of a year. G2D, it has been argued, is less susceptible to operational factors such as detection delay or inadequate duration of treatment. For example, large reduction in the number of people affected by leprosy has been possible, by simply striking off from the registers those who have completed their MDT regimen.

In the last decade, global leprosy programmes have focused on the reduction of disease burden measured in terms of new cases with visible deformities or G2D. The Global Leprosy Strategy 2016–2020 has endorsed three key targets for all national programmes: (i) zero G2D among children diagnosed with leprosy; (ii) the reduction of new leprosy cases with G2D to <1 case per million population; and (iii) zero countries with legislation allowing discrimination on the basis of leprosy.

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**FIGURE 2:** Trends in the detection of new cases of leprosy, by WHO Region, 2006–2015

**Source:** Weekly epidemiological record, World Health Organization, 2 September 2016. No 35, 2016, 91, 405–420

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BOX 1: CLASSIFYING LEPROSY

Leprosy is caused by infection with *Mycobacterium leprae* (*M. leprae*), which belongs to the family of bacteria known as Mycobacteriaceae, a genus of Actinobacteria. It is diagnosed through bacteriologic, clinical, immunologic and pathologic analysis. The Ridley-Jopling scale classifies leprosy into five forms: lepromatous leprosy (LL), borderline lepromatous (BL), mid-borderline (BB), borderline tuberculoid (BT) and tuberculoid leprosy (TT).

People who develop the disease manifest a variable pattern ranging from patients who have only 1 minor lesion with hardly any detectable bacilli (tuberculoid leprosy or TT) to those who have many bacilli and have lesions everywhere (lepromatous leprosy or LL). Others fall in between the spectrum TT, BT, BL, LL forms of leprosy.\(^{11}\)

In practice, however, a lack of available or dependable skin-smear or pathology services means that most field programmes use clinical criteria for classifying individual patients and selecting their treatment regimen. One such clinical system recommended by WHO uses the number of skin lesions and number of involved nerves to group leprosy patients into one of two simplified categories; multibacillary (MB) for typically five or more lesions and paucibacillary (PB) leprosy for less than five lesions.

\(^{11}\) Talwar et al. Making of a highly useful multipurpose vaccine. doi: 10.15761/JTS.1000117.


FIGURE 3: Number of relapse cases reported worldwide, 2006–2013\(^{12}\)
Relapse and resistance

Also a concern to public health authorities is the increase in the number of relapse cases among leprosy patients who have undergone WHO-recommended MDT therapy for lengthy periods (Figure 3).

Several factors may be leading to relapse, including inappropriate treatment due to misdiagnosis, whether the leprosy is multibacillary (MB) or paucibacillary (PB). Although the exact mode of transmission of the disease continues to be investigated, it is also believed that even people who have successfully undergone MDT treatment are carriers of small numbers of M. leprae bacteria, which lead to both relapse and spread of the infection.13

Perhaps the most worrying development is the emergence of drug resistance to the constituents of MDT – drugs such as rifampicin, clofazimine and dapsone. Resistance to dapsone, the first effective therapy for leprosy historically, has been reported since the late 1960s. Widespread treatment failure using dapsone therapy was the main impetus for WHO support for the development and promotion of MDT.

As for the other two drugs, there have been sporadic reports of resistance in recent years from countries as far apart as Brazil and India.15 According to WHO, however, data supporting the existence of clofazimine-resistant strains of M. leprae are still lacking.16 Isolated reports of resistance to rifampicin, the most effective of the three drugs in the MDT combination, have come mainly from areas where rifampicin was administered as monotherapy, either alone or in combination with dapsone, to dapsone-resistant patients.17

There is no room for complacency, though. Resistance to rifampicin could become a serious problem. While dapsone-resistance is widespread, many leprosy patients avoid clofazamine because of the skin discoloration it causes, which means that use of rifampicin effectively becomes monotherapy, thus raising the chances of drug resistance.

WHO has also called for more research to develop non-rifampicin-containing regimens for leprosy;18 and since the late 1980s, three additional anti-leprosy drugs have been identified for evaluation. However, none of them thus far have been established as a viable replacement for MDT.

As a result, the global search for a leprosy vaccine has intensified. It is hoped that an effective vaccination strategy would reduce new cases of leprosy.

“WHO has also called for more research to develop non-rifampicin-containing regimens for leprosy”

13 For MB patients, a combination employing rifampicin, dapsone and clofazimine is recommended over the course of 12 months, while for PB patients, only rifampicin and dapsone are provided over 6 months.
Leprosy vaccine research

The vaccine that has been the most investigated in the context of leprosy historically has been Bacillus Calmette–Guérin or BCG, which was discovered more than a century ago.

The degree of protection against leprosy afforded by the BCG vaccination, however, has varied considerably between studies, with systematic reviews indicating an overall protective efficacy of 26–41% in experimental studies and 61% in observational studies.19 Nevertheless, BCG vaccination, when given soon after birth or in childhood, is considered to have contributed to the decline in leprosy incidence observed in several populations, and is still considered relevant for leprosy control and research.20

One of the largest leprosy vaccine trials was carried out by a team of Indian researchers in southern India with more than 171 400 volunteers between early 1991 and mid-1993.21 A double blind, randomized, prophylactic trial of four potential leprosy vaccines: BCG alone; BCG/M. leprae; Mycobacterium w; and the Indian Cancer Research Center (ICRC) bacillus were compared with a placebo group.

In two surveys conducted in the 8 years following immunization, it was determined that BCG/M. leprae provided 64% protection, ICRC provided 65.5% protection, Mycobacterium w provided 25.7% protection and BCG alone provided 34.1% protection. The observed leprosy incidence rates of the original intake population were not sufficiently high enough to ascertain the protective efficacy of the candidate vaccines against the progressive and serious forms of leprosy.

“The global search for a leprosy vaccine has intensified. It is hoped that an effective vaccination strategy would reduce new cases of leprosy”

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22 Later renamed as Mycobacterium indicus pranii (MiP).
The sequencing of the \textit{M. leprae} genome, initiated in 1991 and completed in 2001, was a big step forward in understanding the characteristics of the pathogenic bacteria's genomic structures. Based on genetic analysis, for example, more than 20 subtypes of \textit{M. leprae} have been identified in different parts of the world, showing a strong association between geography and genotype.

The technique of whole genome sequencing (WGS), which was used to decipher \textit{M. leprae}'s genetic structure, has now been proposed as a tool for carrying out surveillance and outbreak investigation and genotypic antimicrobial susceptibility testing for leprosy. In recent years, costs of WGS have been coming down rapidly, making it viable for use in diagnostic and reference laboratories.

The \textbf{MiP story}

Typically, vaccines are produced by using the target pathogen itself in a killed or weakened form. However, due to the very long reproductive cycle of \textit{M. leprae}, researchers have investigated other cultivatable mycobacteria as potential candidates for producing vaccines.

One of these was the \textit{Mycobacteria MiP}, which was investigated further by researchers at the National Institute of Immunology, New Delhi, because it shared more common features with \textit{M. leprae} than other candidates.

Immunotherapy with killed MiP vaccine was attempted in patients with borderline-lepromatous (BL), or lepromatous leprosy (LL), who showed rapid clinical improvement and significant reduction in their bacterial burden. Skin lesions on a sizeable number of vaccinated patients also showed improvement.

A large-scale, clinical trial of the vaccine in 272 villages of Kanpur Dehat, Uttar Pradesh, between 1992 and 2001 involving over 24,060 people demonstrated sustained protective effect for household contacts of leprosy patients vaccinated. The vaccine recipients were followed by surveys conducted at 3, 6 and 9 years after the initial vaccination. Protective effect of the vaccine was found to be sustained for a period of about 7–8 years, following which there is a need to provide a booster vaccination to extend the protection.

The MiP vaccine showed a protective efficacy of 68.6% at the end of the first survey, 59% at the end of the second survey and 39.3% at the end of the third follow-up survey. Vaccine effects were noted maximally in children, compared with adolescents and adults, who constituted the most responsive group.
Clinical trials for the vaccine, to be produced by a private Indian pharmaceutical company, have also shown that, when administered along with chemotherapy, it expedites bacterial clearance and improves the healing of lesions. It also speeds up recovery of patients who do not respond to the standard WHO-recommended multidrug therapy (MDT) and in whom the leprosy bacteria persists even after long periods of treatment.

As part of the pilot project, ICMR and India’s National Leprosy Elimination Programme plan to inoculate leprosy patients who will also be given MDT. The patient’s family members and contacts will also be immunized with the vaccine twice at an interval of six months, with the expectation that their immunity would be boosted enough to avoid contracting leprosy when exposed to M. leprae.

If the MiP vaccination programme significantly brings down incidence of new cases of leprosy in areas where it is endemic, that will mean a real breakthrough towards the dream goal of eradicating leprosy altogether. If successful, Indian authorities plan to extend vaccination to more than 163 high-prevalence districts in the country.

Researchers in the field have pointed out that there are various aspects of leprosy that are yet to be fully understood or elucidated. For example, the precise mechanism of transmission of M. leprae is still unknown, and there are no practical tools for early diagnosis of clinically inapparent disease.

Further research in the areas of prevention, management of nerve function impairment and the underlying reactions is required to improve the treatment of neurological conditions and to prevent disabilities, especially given reports that show at the time of diagnosis, most newly identified cases have considerable neurologic disability. There are also cases of misdiagnosis or long delays in initiating treatment leading to irreversible nerve damage being reported among patients.

Operational, epidemiological and implementation research to improve sustainability and quality of leprosy services is also needed, which can help better understand the socioeconomic, environmental and behavioral factors that promote its transmission. For example, even though public campaigns have reduced some of the stigma associated

Challenges ahead

While the development of the new MiP vaccine for leprosy is indeed good news, experts point out much more needs to be done to build upon the success of MDT. There is concern about growing complacency among both state and private agencies worldwide due to the success of the MDT and various national leprosy programmes, and unfortunately it has led to a corresponding erosion of leprosy clinics, specialists and research.

“Researchers in the field have pointed out that there are various aspects of leprosy that are yet to be fully understood or elucidated”

with leprosy, it remains a major obstacle to self-reporting and early treatment, and more research is needed on how to deal with stigma in local cultural contexts.

There is also concern with current control strategies, which rely excessively on passive case detection and are unable to obtain accurate estimates of actual prevalence rates. Active case finding is essential as it can help find undocumented cases. For example, a large-scale active case finding study involving clinical examination of 17,862 residents in northwest Bangladesh indicates that true prevalence rates in the Region may be six times higher than those being reported by traditional methods.

All of these research initiatives will need far greater allocation of resources than currently available. As a group of leprosy researchers put it recently, “Unless extraordinary resources are provided for clinical and epidemiological research, leprosy will remain a disease that is eliminated but is far from eradicated. Such an approach might in fact stimulate interest among a new generation of researchers, and generate research funding from donors that hitherto appear reluctant to support leprosy research”.

“Unless extraordinary resources are provided for clinical and epidemiological research, leprosy will remain a disease that is eliminated but is far from eradicated”

It's a bright, sunny afternoon and a group of villagers in the Koraput district of eastern India's Orissa state has gathered under a cluster of trees, watching a street theatre group demonstrate how to carry a pregnant woman to the nearest health centre for delivery. In the same flow, the actors explain the importance of washing hands, growing vegetables at home and consuming pulses to ensure good nutrition.
The theatre performance is part of a unique attempt to create a cadre of ‘Community Hunger Fighters’ (CHF), who will take basic, evidence-based nutritional guidance into the homes of one of India’s most impoverished districts. Orissa has one of the worst records of malnutrition in India, with an estimated 22.17% of children in the state malnourished or extremely malnourished1 (Figure 1).

Overall, despite considerable improvements in food security in recent decades, India has a disproportionately large number of people, in particular women and children, suffering from chronic hunger. According to estimates made by the FAO,2 there were more than 194.6 million undernourished people in India in 2014–2016, the world’s largest number and representing almost a quarter of the globe’s undernourished population.

Among the adult population, surveys have shown that more than 36% of women and 34% of men in the age group 15–49 have a Body Mass Index below 18.5, indicating a high prevalence of nutritional deficiency.3

India’s score in the Global Hunger Index (GHI), a tool designed to measure and track hunger globally, regionally, and by country, stood at 28.5 in 2016,4 putting it in the ‘serious’ category, which includes countries most affected by hunger (Table 1).

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India: Detailed Global Hunger Index score for 2016

<table>
<thead>
<tr>
<th>Country data (in %)</th>
<th>Proportion of undernourished in population (%)</th>
<th>Prevalence of wasting in children under five years (%)</th>
<th>Prevalence of stunting in children under five years (%)</th>
<th>Under-five mortality rate (%)</th>
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<td>15.2</td>
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<td>4.8</td>
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</table>

**Community hunger fighters**

The Community Hunger Fighters (CHF) initiative was launched in October 2011, by the M.S. Swaminathan Research Foundation (MSSRF), one of South Asia’s leading research organizations working on agriculture and food security issues. The project involves training young rural men and women in basic principles of health, nutrition and hygiene, to be practiced personally and also to be disseminated to fellow villagers. Typical interventions taken up by the volunteers are improving access to safe drinking water, ensuring more toilets per household, supplementation of family diets through vegetable gardens and improving health status, particularly of women.

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A total of about 90 CHFs from 18 villages in the Kundra and Boipariguda blocks of Koraput district, both men and women, have been trained so far. Apart from individual health, the CHFs also inform villagers about a plethora of state-sponsored schemes they can take advantage of through collective action.

The scientists behind the project understand that people’s involvement is key to the success of the initiative. Participatory research with the community has helped in development of new approaches, methodologies and techniques and for identifying areas needing policy interventions.

A well-designed baseline survey on the extent and nature of malnutrition prevailing in the Koraput region allows researchers to accurately estimate the impact of various interventions undertaken. The action research project hopes to yield valuable insights into both the health and non-health causes of malnutrition, a major reason for death and disability worldwide.6

Given the complex set of factors that determine nutrition outcomes, even for MSSRF with its considerable experience, the challenge that the CHF project has taken on is huge.

**Nutrition specific and sensitive interventions**

The UNICEF conceptual framework,7 which the nutrition community has been using for programming for nearly the past three decades, identifies three levels of causes of undernutrition8 (Figure 2):

- Immediate causes operating at the individual level, such as the lack of adequate, safe, appropriate or timely food and due to infectious diseases.

**FIGURE 2: UNICEF conceptual framework for malnutrition**

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8 Undernutrition is the result of food intake that is continuously insufficient to meet dietary energy requirements, poor absorption and/or poor biological use of nutrients consumed. This usually results in loss of body weight. Undernutrition can be indicated both by anthropometric indices such as underweight, stunting and wasting and with missing micronutrients in poor quality diets.

Overnutrition refers to a chronic condition where intake of food is in excess of dietary energy requirements, resulting in overweight and/or obesity. Malnutrition refers to deficiencies, excesses or imbalances in intake of energy, protein and/or other nutrients and includes both undernutrition and overnutrition.
Underlying causes influencing households and communities, such as access to financial, human, physical, social and natural resources and to quality care and medical services, as well as water and sanitation facilities.

Basic causes around the structure and processes of societies, for example, climate change, trade, the rate and pattern of economic growth, food and energy prices and volatility, and land-use policies.

Following this framework, nutrition interventions and programmes are classified on the basis of the determinants they are supposed to address. Nutrition-specific interventions and programmes are interventions that focus on supplementation of dietary and key micronutrient intake such as vitamin A, zinc, iron, folic acid and vitamin B12 of mothers and children. They also include advocacy of optimal breastfeeding and complementary feeding practices and disease prevention and management.

Nutrition-sensitive interventions, conversely, include interventions and programmes that address the underlying determinants of mother and child undernutrition. These include education, agriculture, fisheries, transport, food processing, finance, media, civil society, as well as political leadership, to support and sustain improved nutrition at the macro-level.

**Community-based surveillance**

The MSSRF’s Community Hunger Fighters project in India is at least partly inspired by the experience of Thailand a few decades ago, when it managed to dramatically reduce the country’s malnutrition rates, through a participatory, community-based food and nutrition programme.

“Participatory research with the community has helped in development of new approaches, methodologies and techniques and for identifying areas needing policy interventions”
Instead of relying on a top-down approach by government agencies alone, Thai health officials, in the mid-1970s, decided to involve villagers directly in implementation of national policies aimed at combating malnutrition.

Throughout Thailand, two groups of villagers — a very large number of them women — were selected and made responsible for mass social mobilization. These included the Village Health Communicators, for delivering information such as appointment dates and simple health messages, and Village Health Volunteers, to provide leadership and perform simple care in addition to conducting nutrition and health education.

By 1986, 550,000 village primary health care volunteers and communicators were trained, covering almost every village in the country.9 These volunteers were involved in developing village action plans to be mostly implemented with local resources and requests made for additional government support, where needed.

FIGURE 3: Malnutrition trends for children under five years in Thailand; 1982–199210


BOX 1: DOUBLE BURDEN OF MALNUTRITION

Despite much progress, even today undernutrition and related diseases continue to be unacceptably high in the South-East Asia Region because of its vast population and high levels of poverty. Limited access to good nutrition, compounded with inflation in food prices globally has created food-insecure households and a high prevalence of undernutrition across all segments of the population.

For example, undernutrition still contributes to about 45% of preventable deaths of children under five years of age annually. Although the overall prevalence of stunting in SEAR countries has been reduced from 59% in 1990 to 32.9% in 2013, it translates to 60.8 million stunted children at present in the 0–5 year age group while 45 million are still underweight.

The SEA Region also accounts for more than 70% of the world’s malnourished children and lack of dietary diversification; and poor bio-availability of iron from plant-based diets have resulted in the highest levels of anemia in the world. Nearly half of the preschool children and pregnant women in the Region have low levels of plasma vitamin A.

And, despite legislation mandating universal iodization of salt, substantial proportion of households in these countries still use non-iodized salt. While breastfeeding and complementary feeding practices determine the nutritional status of young children, it is estimated that only one fifth to one third of children in Bangladesh, India, Indonesia and Nepal consume minimum acceptable diets.

It is also becoming increasingly clear in recent decades that countries in the SEA Region are experiencing what has been called by public health experts a ‘double burden of malnutrition,’ which refers to continued stunting of growth and deficiencies of essential nutrients along with the emerging issue of obesity. Both among the urban rich and poor populations, high intake of energy-rich foodstuff is responsible for rising overnutrition rates, together with the steep reduction in physical activity due to increased mechanization of transport and more sedentary occupational and household activity.

Increased rates of overweight and obesity have contributed to unprecedented rates of noncommunicable diseases (NCDs) in the Region, with 55% of all deaths attributed to NCDs. Among adult women, prevalence of overweight is now greater than underweight and ranges from 18% to 34% across South-East Asia. Of a total 13.7 million deaths in the South-East Asia Region during 2012, 6.8 million were due to NCDs, principally cardiovascular diseases, diabetes, cancer and chronic respiratory diseases.

There is also growing evidence that undernourished stunted children are at higher risk of noncommunicable diseases - resulting in a dual nutrition burden. Poor intrauterine growth, but relatively excess growth later has been found to be associated with metabolic endocrine abnormalities, risking diabetes in adult life.

The same data used for planning community action was also used for policy-making and programme planning at higher administrative levels. Activities undertaken by the village volunteers’ initiative also built on earlier government measures to increase food production, develop health infrastructure and improve literacy.

One evaluation of the community-led nutrition programme noted that, “It transformed ordinary villagers themselves into change agents, monitoring their own progress, negotiating funding and taking responsibility for the nutritional well-being of their own children as well as others in their community.”

As a result of the initiative, between 1982 and 1991, combined mild, moderate and severe malnutrition by weight-for-age in Thailand declined consistently from approximately 50.8% to 17.1%. For moderate and severe malnutrition combined, the decline went from about 15.13% to 0.77% during the same period (Figure 3).

References:

Global focus on nutrition

Maternal and child undernutrition accounts for 11% of the global burden of disease and inflicts productivity losses on individuals in more than 10% of lifetime earnings, and losses to gross domestic product as high as 2–3%. Again, chronic undernutrition, manifested often as stunting, affects one out of three children under five years of age in the developing world, with 80% of these children residing in just 22 countries.

A series of papers published in 2008 by The Lancet, the prestigious medical journal, called undernutrition one of the world’s most serious but least addressed health problems. The Lancet’s 2008 series gathered hard evidence to show the impact of malnutrition on both health outcomes in societies as well as national economic growth.

All this has led to a spurt of interest worldwide among governments, donors and civil society to take up the malnutrition problem urgently. For example, the Scaling Up Nutrition (SUN) movement, which started in September 2010, has now over 57 countries as members, including many from the South-East Asia Region, committed to the scale-up of direct nutrition interventions and the advancement of nutrition-sensitive development. In 2013, leaders of SUN member countries endorsed the Global Nutrition for Growth Compact, which outlines bold nutrition-related targets to achieve by 2020.

In 2012, the World Health Assembly resolution 65.6 endorsed a comprehensive implementation plan on maternal, infant and young child nutrition, which specified a set of six global nutrition targets to be achieved by 2025. The WHO Global Action Plan for the Prevention and Control of NCDs, 2013–2020, also includes two more nutrition-related targets.

In September 2015, world leaders meeting at the UN General Assembly adopted the goal of ending all forms of hunger and malnutrition by 2030 and making sure all people — especially children and the more vulnerable — have access to sufficient and nutritious food all year round as one of the Sustainable Development Goals.

“Researchers as well as policymakers in the South-East Asia Region are also looking at new nutrition-related questions that are being investigated by institutions in other parts of the world”


Priorities for action

With such renewed global attention to malnutrition, there has been naturally concern regarding prioritization of resources for interventions that will have the most impact and also be cost-effective.

Some of the ways to enhance efficiency of nutrition programmes, research studies show, include: improved targeting; stimulating public and community participation; strengthening nutrition goals and actions; and optimizing women’s nutrition, time, physical and mental health, and empowerment.

In 2008, a panel of economic experts comprising some of the world’s most distinguished economists declared that micronutrient interventions — fortification and supplements designed to increase nutrient intake — were the most effective investment that could be made worldwide, with massive benefits for a tiny price-tag. They were part of the third Copenhagen Consensus project that got more than 65 researchers to prioritize among a series of proposals to confront 10 great global challenges. According to the researchers, for less than US$ 700 million annually, it would be possible to eliminate vitamin A deficiencies in pre-school children, eliminate iodine deficiency globally and dramatically reduce maternal anemia during pregnancy.

Even more specifically, The Lancet 2008 series on maternal and child malnutrition called for a focus on the first ‘1000 days’ — the crucial period from conception to a child’s second birthday — in which good nutrition and healthy growth have lasting benefits throughout life. As a result, many development agencies around the world have revised their strategies to address undernutrition focused on the 1000 days during pregnancy and the first 2 years of life.

BOX 2: BANGLADESH BUCKS THE TRENDS

While the enigma of South Asia’s stubbornly high rates of child malnutrition despite rapidly growing economies has spawned many explanations, recent research shows that Bangladesh has emerged as a positive exception to this trend.

A 2013 study by the International Food Policy Research Institute (IFPRI) revealed the magnitude of Bangladesh’s remarkable progress. According to data from five rounds of the Bangladesh Demographic and Health Surveys, between 1997 and 2007, the country recorded one of the fastest prolonged reductions in child underweight and stunting prevalence in recent history at 1.1 and 1.3 percentage points reduction per year, respectively.

Bangladesh’s performance was just behind the much more celebrated case of Thailand in the 1980s and a little ahead of success stories in other parts of the world such as in Latin America. The data also showed that Bangladesh has lower stunting rates – at 41.3% – than India, which recorded 47.5% stunting in its 2005–2006 survey, despite India having higher mean incomes.

Researchers pointed to several possible reasons for Bangladesh’s achievements in curbing undernutrition. Two of the most important factors were pro-poor economic growth leading to accumulation of assets at the household level and swift growth of secondary education, especially for girls, who benefited from a state-sponsored stipend programme that dramatically expanded girls’ enrollment in secondary school. Maternal education has also been found to be closely tied to nutrition outcomes, along with women’s empowerment within the home.

An expansion of private and NGO-provided health care, as well as advances in community-based service delivery that compensated for the government’s small health-care budget have also contributed to the reduction in undernutrition. Improvements in infrastructure, especially sanitation, through government and community-led efforts in the 1990s, helped dramatically to increase the percentage of households with a toilet. All of this happened in the overall context of a rapid reduction of fertility rates, attributed to the very proactive family planning programmes launched in the late 1970s.

New directions for research

Given the wide range of factors involved in determining the nutritional status of individuals, from biomedical aspects of the human body to social systems in which they are embedded, it is not surprising that nutrition research today encompasses a very wide range of disciplines.

At the purely physiological level, for example, new findings in the fields of nutrigenomics, proteomics and metabolomics are helping to determine how specific nutrients interact with genes, proteins and metabolites to predict an individual’s health. Omics research provides information on how nutrients are digested, absorbed and metabolized — and their functions in the body, helping to create new nutritional and disease biomarkers.

In recent years, research on the human microbiome, or the complex ecosystem of diverse microbes that live in and on each person’s body and make up their microbiome, has thrown new light on issues related to the digestive metabolism, obesity and NCDs such as diabetes.

There is research underway on imprinting, which examines how exposures to dietary components during critical periods of development contribute to an individual’s long-term health and well-being. Another area of research is on biological networks, which provides a better understanding of an individual’s DNA and RNA make-up and how these impact metabolic responses to diet and food.

Beyond pure natural sciences, much research is also required in the social sciences, the economics of nutrition interventions and in implementation science. Some fundamental questions identified in these fields include:

- How can enabling environments and processes be cultivated, sustained and ultimately translated into results on the ground?
- How has high-level political momentum been generated?
- What needs to happen to turn this momentum into results?
- How can we ensure that high-quality, well-resourced interventions for nutrition are available to those who need them, and that agriculture, social protection, and water and sanitation systems and programmes are proactively reoriented to support nutrition goals?

Challenges ahead

For the South-East Asia Region, WHO has developed a ‘Strategic Action Plan to Reduce the Double Burden of Malnutrition in the South-East Asia Region 2016–2025’, which calls for creating an enabling environment that will facilitate the implementation of interventions focused towards both undernutrition and overweight and obesity. At the same time, it has outlined several emerging challenges that need more research and understanding to develop an appropriate response.

One of these is ageing, with undernutrition among the elderly being a significant and neglected public health problem. Older people are vulnerable to malnutrition due to physiological and functional changes that occur with age, lack of financial support and inadequate access to food.
Another emerging area for further study is the impact of climate change, which increases the incidence and severity of extreme weather events, affecting both rural and urban livelihoods and accelerating population displacement.

Researchers as well as policy-makers in the South-East Asia Region are also looking at new nutrition-related questions that are being investigated by institutions in other parts of the world.

In 2013, a series of research papers published by The Lancet, for example, identified adolescent girls as especially vulnerable to the effects of undernutrition, calling for a special focus on them from nutrition-related programmes. Studies also highlighted the importance of fetal growth restriction or being born small for gestational age, a phenomenon, which according to estimates, causes more than 800,000 neonatal deaths and 20% of stunting in children younger than 5 years worldwide.28

Another study, carried out for the World Bank in 2009,29 identified a more selective package of 13 highly cost-effective interventions that could improve family nutrition practices and supplement foods and micronutrients provided by families, whether through market purchases or through home production. The interventions suggested were meant to complement the multisectoral approach and delivered as part of broader public health programmes or, in the case of fortified foods, through private markets.

At another level altogether, global researchers have also looked at how to use economic incentives, investments in agricultural R&D and new communication technologies to deliver the best results in terms of nutrition outcomes on a large scale. Some, for example, have called for increasing global food production as they argue that lower prices are necessary to make food more affordable, and to provide a buffer against some of the negative consequences of climate change.30

According to them, increasing annual global public investment in agricultural research and development by US$ 8 billion to US$ 13 billion would mean that in 2050, taking global population growth into account, the prevalence of hunger would be 63% less in 2050 than it was in 2010. Researchers also call for drastically increasing production of fertilizers to reduce costs of imports in developing countries and helping small farmers produce more food through dissemination of critical information using mobile phone technologies.

Other researchers have focused on reduction of post-harvest losses worldwide, curbing which they say can increase food availability and reduce hunger drastically, particularly where it is needed the most — in South Asia and Africa. One study,31 for example, has suggested an additional one billion people could be fed if food crop losses were halved globally, although other research challenges the cost-effectiveness of measures needed to reduce such losses.

Given all that needs to be done and the world’s growing commitment to supporting all efforts to drastically reduce malnutrition everywhere, these are exciting times indeed for researchers working in the field. The biggest reward for them would be the satisfaction of knowing their contributions can help to not only ensure that millions do not go hungry but also that they survive and live to their fullest human potential.

Notes