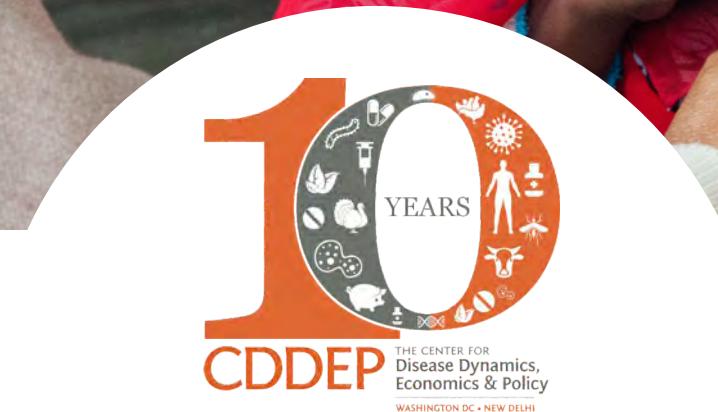


Infectious Diseases in the South-East Asia Region



2021

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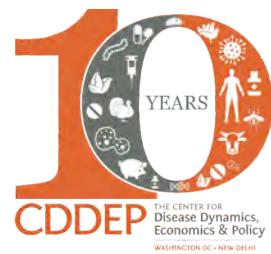
Related research and additional information on access to antibiotics and antibiotic use and resistance is available at www.cddep.org.

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Infectious Diseases in the South-East Asia Region

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Foreword

The emergence and spread of COVID-19 is yet another reminder of the vast social and economic impact communicable diseases can have. Throughout history communicable diseases such as HIV/AIDS, tuberculosis, malaria, neglected tropical diseases (NTDs) and enteric pathogens have taken hundreds of millions of lives, deepened poverty and inequality, reduced productivity and stymied economic growth. They have impeded sustainable development and been a barrier to the right of all to good health and well-being.

Though communicable diseases continue to burden countries in the WHO South-East Asia Region, progress against them has in recent years been strong. Between 2010 and 2018 the Region reduced the number of new HIV infections by an estimated 33% and the number of HIV-related deaths by 27%. Achieving the 90-90-90 targets remains a core priority, with community engagement and outreach, especially among key populations, central to the Region's strategy.

Momentum to tackle TB is unprecedented. Between 2015 and 2018, treatment coverage increased by around 20%. Average national investments in TB have more than doubled. Accelerating efforts to End TB by 2030 is one of the Region's eight Flagship Priorities. All countries are working to achieve the time-bound targets of the UN General Assembly's High-level Political Declaration on the Fight against TB.

Our progress against malaria continues. In 2018 the South-East Asia Region had an estimated 8 million cases and 11 600 malaria deaths – 69% and 70% fewer compared with 2010. This is the largest decline of all six WHO Regions. Countries in the Greater Mekong Sub-region continue to make strong gains, recording a 76% reduction in malaria cases and a 95% drop in deaths between 2010 and 2018.

The battle against NTDs is ongoing. Three NTDs – lymphatic filariasis, yaws and trachoma – have been eliminated from one or more countries in the Region. More are set to follow, as countries strive to achieve a set of new time-bound targets. Across the Region, lifting the NTD burden has become a measure of what it means to keep the promise and 'leave no one behind'.

Enteric pathogens are on the back foot. Since 2000, mortality due to diarrheal diseases in children under five years has dropped by 30%. Access to safe water, sanitation and hygiene continues to improve. Action across all sectors is needed to ensure our progress continues and our successes grow.

To achieve the Region's eight Flagship Priorities, contribute to WHO's triple billion targets, and hasten progress towards Sustainable Development Goal 3, more work is needed. This is especially true as the Region continues to respond to the COVID-19 pandemic. Previous disease outbreaks have shown that when health systems are overwhelmed, mortality from communicable diseases can dramatically increase. WHO will continue to support Member States in the Region to implement key guidance on maintaining essential health services and programmes as they directly respond to COVID-19.

Importantly, our onward journey will continue to be defined by the conviction that all people should have access to the services they need, without financial hardship – in other words, to achieving universal health coverage. Now more than ever, the old binary between vertical and horizontal programming must be done away with in favor of a smarter approach focused on integrating primary level services while staying in 'mission mode' where we must. Making real progress is not simply a biomedical pursuit: it must be biosocial.

As research and development advances, and new therapies and tools are developed, we must ensure that affected populations can access them. The Region's focus on increasing access to quality medicines, vaccines, diagnostics and devices will help ensure that happens. We must apply innovative thinking to policy development and the many ways we can chart game-changing progress.

There is much that is of public health interest in this book, and I am certain the many voices and perspectives contained herein will stimulate discussion, especially on communicable diseases in India. India accounts for around 70% of the Region's population, and one-sixth of humanity. The book's focus reminds us how important India's continued progress is, both for the Region and the world.

In addition to the wealth of information the following chapters provide, they highlight the historic opportunity we have to make rapid and lasting gains against communicable diseases — an observation that will continue to inform the COVID-19 response. As the battle against the pandemic continues, so too must our progress against communicable diseases, for which WHO will continue to pull out all stops in support of our Member States, partners and the Region's near 2 billion people.

Dr Poonam Khetrapal Singh
Regional Director
World Health Organization SEARO

Overview

The South-East Asia region continues to bear a significant proportion of the communicable disease burden worldwide. South Asia has the third largest HIV epidemic globally and the highest burden of TB, accounting for more than a quarter of the global burden. The second highest incidence of malaria, amongst all WHO regions, occurs here, and India bears the third-highest proportion of malaria cases globally. Malnutrition makes the South-East Asian population particularly vulnerable to neglected tropical diseases (NTDs) alongside emerging infectious diseases from the arbovirus infections, dengue, chikungunya, and Japanese encephalitis, and the continuing concern of a pandemic influenza outbreak. Furthermore, drug-resistant infections cause 58,000 deaths in newborns every year, in India alone, and continue to threaten the effectiveness of life-saving antibiotics across the region.

The Center for Disease Dynamics Economics & Policy (CDDEP) has commissioned a series of background papers to inform national and regional strategies on communicable diseases presented in this volume. While the primary focus is on India, the papers cover cross-boundary challenges, in communicable disease control, in the South and South-East Asia region. They indicate the emphasis on communicable diseases relative to other sources of disease burden in the region. In addition, the papers document overall trends in disease-related health and economic burden in the region and the projected share of the burden associated with communicable diseases.

Covid-19 has disrupted the control of other infectious diseases in myriad ways, hindering routine vaccination programs, impeding the distribution of bed nets against malaria, and reducing TB services, among others. With the rollout of vaccines against the novel coronavirus and the ebbing of Covid-19, it will be essential to devote our full collective attention to the control of infectious diseases that have long plagued this region and continue to constitute a significant proportion of the avertable disease burden.

Isabel Frost
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The Center for Disease Dynamics, Economics & Policy



Tuberculosis

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Tuberculosis (TB) is one of the oldest infections in humans (1), and today is a leading cause of death due to infectious disease (2). Inextricably linked to poverty, TB affects mostly low- and middle-income countries, in turn disproportionately affecting the poorest in these countries. Significant developments in recent years signal increasing recognition of TB as a major global health problem. The End TB goals, launched by WHO in 2015 (3), have set ambitious targets for reductions in incidence and mortality by 2025. The recent UN General Assembly included, for the first time, TB as the subject for a high-level meeting (4). In the WHO South-East Asia (SEA) Region, which accounts for the largest share of global TB burden, a ministerial meeting in 2017 was an important step in mobilising political commitment for TB control in the region (5). Meanwhile, India's most recent national strategic plan set out a bold and ambitious vision for TB elimination, with support at the highest political level in the country (6).

There remains much to be done, to translate these ambitions into real and measurable progress (7). TB is a complex disease: it is not yet vaccine preventable in the same manner as measles or influenza, but most cases are curable. Current control efforts are therefore focused on early detection and effective treatment of TB (8). However, even these goals can be hard to implement, particularly in countries (as is typical in the SEA region) with complex and fragmented healthcare systems, where many healthcare providers do not participate in nationally coordinated TB programmes (9,10). Moreover there is a limit to what treatment alone can achieve (11,12), and ultimately there is a need for improved primary prevention of TB: whether through controlling transmission, or through preventing the progression from latent TB to active disease. Current 'preventive therapy' strategies are valuable (13), but only a first step: current recommendations are restricted to specific risk groups (those with HIV, as well as all-age household contacts of diagnosed TB cases). For widespread impact on incidence or mortality, in future there will be a need for new 'population' preventive approaches, that are unrestricted to any specific subpopulation. Such measures might involve not just biomedical tools, but also the wider 'social determinants' of TB (14), including factors such as malnutrition.

Nonetheless, important scientific progress in recent years offer promising signs for advances in TB control efforts. New, safer, more effective options are emerging for the treatment of drug-resistant TB (15,16), and are the leading edge of an active drug development pipeline (17). Recent phase IIb trial results raise the prospect of a vaccine that could halve the risk of developing active disease among those with latent TB (18). There have been important advances in the delivery of TB services as well, with new approaches for engaging the private healthcare sector in India yielding unprecedented contributions from this sector to TB notifications, and currently being scaled up across the country (10,19). Such gains need to be sustained and accelerated, across the spectrum from scientific to programmatic innovations, in order to achieve real declines in TB burden in future.

In the present paper, we set out some of the relevant background of tuberculosis epidemiology and control, with a focus on the WHO South-East Asian Region. We begin with an overview of the natural history of TB, identifying critical features such as the distinction between latent infection and active disease. We then identify some key aspects of routine activities by TB control programmes today, before discussing the epidemiology of TB in the SEA region. All of this serves as context, for a discussion of the progress and shortfalls of TB control efforts in the SEA region over the last two decades. Using results from a recent prevalence survey in India, we assess the gaps in TB control that remain. We then move on to discuss recent scientific and programmatic developments in TB control, that may be important in addressing these gaps, in order to accelerate current, slow declines in TB burden over the next two decades.

Background

Latent TB infection

It is estimated that almost a quarter of the world's population has latent TB infection (LTBI), and that countries in the SEA region alone account for 35% of these infections (20), despite accounting for 25% of the world's population.

LTBI arises from a complex interplay between infecting TB bacilli and the host's immune response (1). Although macrophages play an important role in clearing many different types of infection, TB is an example of a pathogen that has subverted this immune function, essentially to infect macrophages and avoid sterilisation (21). The immune system recruits other immune cells to the site of infection, to form a 'granuloma', or sites where which infection is contained (22). Latent TB infection does not present outward signs of disease, nor is it possible to transmit infection to others. By itself, therefore, latent TB infection is not a direct cause of morbidity or mortality. However, the granuloma is a dynamical equilibrium between immune function and still-viable bacilli (21-23). Adverse changes to the immune system, that shift this balance in favour of the bacilli, can lead to the 'breakdown' of latent infection, to active disease: that is, uncontrolled bacterial replication that progressively causes disease, can be transmitted to others, and left untreated, can kill.

There are a variety of immunosuppressive factors that are known to precipitate the breakdown of latent infection to active disease (24-25). On a global level the most prominent risk factor is HIV coinfection (2,26). However HIV plays a less prominent role in the SEA region, where instead other factors such as malnutrition are gaining increasing recognition as key drivers (27-29). We discuss these risk factors in further detail below, in the context of potential strategies to improve the prevention of TB disease.

Unfortunately there is no gold standard for the diagnosis of latent TB infection (30,31). Amongst countries in the SEAR region, as well as other high-burden settings, the conventional approach has been the 'tuberculin skin test' (31). However, recent years have seen shortages of the raw material ('purified protein derivative', or PPD) used in these tests (32). Moreover, these tests cannot distinguish latent TB infection from BCG vaccination, nor from exposure to environmental mycobacteria, challenges that can become increasingly important as TB transmission drops below 1% annual risk of infection – for example, as is currently the case in India (33). An alternative approach is using serological assays such as interferon gamma release assays (IGRA) (34). Similarly to TSTs, these tests detect immune correlates of infection rather than infection itself. However, they are considerably more costly than TST (35), a major challenge in their widespread deployment in high-burden, resource-poor settings. It must be noted that none of these tests are prognostic of which individuals are most at risk of developing active disease.

Active TB

Most forms of active TB are pulmonary, that is involving infection and disease of the lung. However, it is estimated that around 15 - 20% of TB cases are extrapulmonary, most commonly in the lymph nodes, the pleura, and in bone and joint tissue (36,37). Extrapulmonary TB, while not infectious, can be difficult to diagnose, and as a result can be more likely to lead to mortality (36).

A recent systematic review estimated a case fatality rate of 50% for untreated TB (38) (notably, comparable to that of Ebola), with the average duration of untreated disease being three years. The remainder of cases spontaneously resolve disease over this time, 'self-curing' without intervention. However, survivors are liable to recurrence of disease, whether through relapse of existing infection, or exogenous reinfection (39-41).

In practice, diagnosis of TB is typically informed by three different approaches: (i) bacteriological confirmation using sputum samples from patients with suspected pulmonary TB, (ii) radiological evidence (i.e. chest X-rays), and (iii) clinical evaluation. International guidelines place an emphasis on the first of

these methods (42), in order to promote TB detection while minimising the risk of individuals without TB being unnecessarily being initiated on TB treatment.

Culture is the gold standard for sputum investigation, and involves cultivating the organism in solid or liquid media, in laboratory conditions. Although highly sensitive and specific for TB, this method is costly and, in the case of solid culture, can take weeks to provide a diagnosis. Reliant as it is on sufficient laboratory capacity, culture also does not lend itself to deployment in peripheral health settings. Instead, the most widely used diagnostic tool in routine TB diagnosis is smear microscopy, whereby sputum samples are prepared and investigated under a microscope for signs of tuberculosis bacilli. Smear microscopy is cheap, widely implemented, and can offer diagnosis more rapidly than culture. However, it has poor sensitivity and can miss up to half of culture-positive TB cases. As a result of this shortfall, current TB programmes distinguish 'smear positive' and 'smear negative' diagnoses of pulmonary TB. As discussed below, new diagnostic tools may offer considerably improved sensitivity amongst smear negative cases of TB, who may otherwise escape detection through smear microscopy.

An added complication is that not all active, infectious TB is symptomatic. Community prevalence surveys in Asia and elsewhere reveal a sizeable proportion of prevalent cases (40 - 79%, depending on the setting), that do not report symptoms, despite having lung pathology as indicated by X-ray and presenting sputum that is bacteriologically positive for TB (43). While, as described above, the use of X-ray is not favoured as a stand-alone diagnostic test for TB, it is increasingly being considered as a potentially helpful adjunct, as a screening tool to help identify those without apparent symptoms, who would nonetheless be eligible for sputum investigation(44).

There are other potentially important complexities: for example, while the dichotomy between latent infection and active disease described here is convenient for presentation, it is potentially a false one. There is evidence for a continuum between latent and active forms of TB (45), including the potential for transmission before the onset of disease (46). It is hoped that current and future research will shed light on these complexities, and their implications for TB control.

Principal tools in TB control

As background, here we discuss 'conventional' approaches to routine TB control, comprising core activities of TB programmes in the SEA region over the last two decades. This background serves to contextualise the discussion of more recent innovations and strategies in TB control, that we discuss in further detail, below.

In the 1970s, India was home to a major vaccine trial that contributed to the wide deployment of the BCG vaccine, a live-attenuated TB vaccine (47). The BCG vaccine continues to be deployed in routine immunisation programmes in the SEA region and elsewhere, and has had an important impact in reducing the burden of severe childhood tuberculosis (48). Nonetheless, for TB to be a vaccine-preventable disease in the same manner as (for example) measles or rubella, there is a need for a vaccine that can offer durable, effective protection in adults against either infection, or the development of active disease (49). While there is evidence that BCG may offer some protection against infection (50), this performance is highly variable across settings, including a study in India suggesting no protection at all (51,52). One possible explanation for this variation is pre-vaccination exposure to environmental mycobacteria (52). As a result of all these considerations, the BCG vaccine is today largely deployed to protect against severe disease, rather than to control transmission.

On the other hand, most cases of TB are curable, with affordable chemotherapy. Standard, first-line regimens involve 6 months daily treatment with combination treatment, including isoniazid and rifampicin as core drugs. This regimen is well-tolerated and inexpensive (53). TB treatment has therefore been a cornerstone of TB control efforts since the launch of the DOTS strategy in the 1990s, which aimed to ensure the availability of high-quality TB services, through nationally coordinated TB programmes worldwide (54,55). DOTS has had a considerable impact in averting deaths 9 (56,57). As discussed below, although these measures have surely improved patient outcomes, more now needs to be done to achieve reductions in TB incidence.

A critical challenge to treatment-based TB control strategies is the emergence of drug resistance, specifically rifampicin resistance (RR-TB) and multi-drug-resistance (MDR-TB, resistant to both isoniazid and rifampicin) (58). Such forms of resistance pose serious challenges: diagnosing drug resistance is more challenging than diagnosing TB, meaning that many patients are initiated on inappropriate, first-line therapy. For decades, the drugs used for second-line treatment have been highly toxic, with a regimen lasting for upto 24 months, and costing upto a hundred times as much as first-line treatment (59,61). These regimens have also shown poor treatment outcomes, compared with first-line treatment of drug-susceptible TB (62,63). We discuss below some recent important, developments that help to address some of these challenges. Such developments notwithstanding, the management of drug-resistant TB inflicts a disproportionate financial burden on TB programmes.

Tuberculosis in the South-East Asian Region

Despite accounting for 26% of the world's population, in 2019 the SEA region accounted for an estimated 44% of TB incidence worldwide (27) the largest share amongst the six WHO regions. Figure 1 shows the distribution of TB burden amongst the different countries in the region, illustrating a wide disparity between countries: on the one hand are India, Indonesia and Bangladesh, which together account for 89% of TB burden in the region. On the other hand, Sri Lanka is one of the lowest-burden countries in the region, with an annual incidence of 64 cases per 100,000 population, contributing <1% to regional incidence.

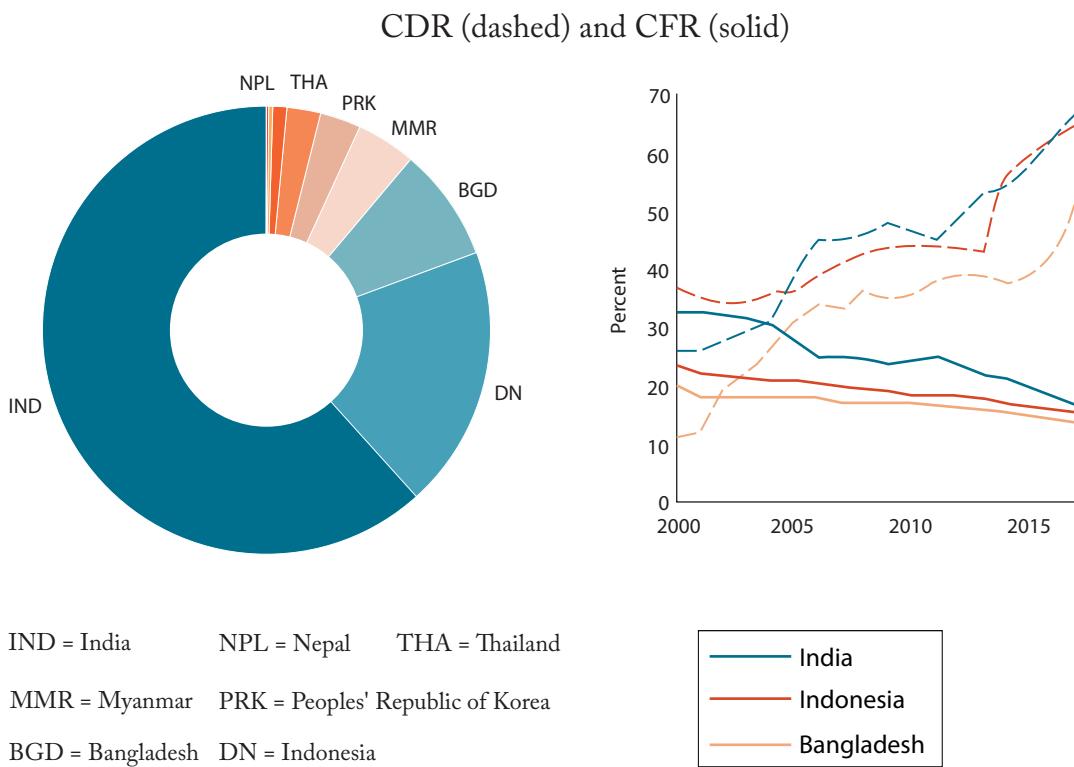


Figure 1. Summary of TB in the South-East Asian Region. Left-hand panel: Proportion contribution of each of the 11 countries to overall TB incidence in the region, as estimated in 2019. For clarity, only the countries with the largest burden are labelled. Right-hand panel: trends over time in the three highest-burden countries in the region (India, Indonesia and Bangladesh), in case detection rate (CDR, shown in dashed lines) and case fatality rate (CFR, shown in solid lines)

Data source: World Health Organization. Global Tuberculosis Report 2020. 2020. (27)

Routine programmatic performance

Table 1 illustrates some key indicators for the performance of national TB programmes in the SEA region, including first-line treatment success rates, and the case detection rate, or the proportion of estimated incident TB cases that are reported to public health authorities. Amongst TB patients managed by national TB programmes, treatment success rates have reached or are approaching the 85% target set by the DOTS strategy. Case detection is clearly a greater challenge: as discussed below, a major challenge is the sheer number of TB patients that are managed by the private healthcare sector, but not notified.

TB services in the SEA region have largely been delivered through vertical TB programmes that are 'passive', in the sense that they are contingent on a TB symptomatic presenting for care. Figure 1 suggests that – while TB patients managed by this system have significantly improved outcomes compared to the pre-DOTS era, there is a need to considerably expand the coverage of TB patients that can benefit from these quality TB services (as measured by the 'case detection rate' in Fig.1).

The role of HIV coinfection

Although HIV is a major driver of TB on the global level, in SEA it is not the driving factor for TB epidemiology that it is, for example, in sub-Saharan Africa: in 2019, HIV/TB coinfection accounted only for roughly 3% of TB incidence in the region (27). Nonetheless there is some variation across countries (Thailand's TB epidemic is the most affected, with an estimated 10% of incident TB cases being HIV coinfected) as well as within countries (India's southern states - Andhra Pradesh, Telangana, Karnataka and Tamil Nadu - account for 60% of known HIV/TB coinfections in the country (64)).

Table 1. Performance of national TB programs in SEAR countries, 2017

Country	Case detection rate (best estimate)	Treatment success rate, first-line (new cases)	Treatment success rate, second-line	Proportion RR/MDR-TB among new cases	Proportion RR/MDR-TB among previously treated cases
Bangladesh	67%	94%	78%	1.6%	29%
Bhutan	80	95	91	13	33
DPR Korea	77	—	72	2.2	16
India	65	69	46	2.8	12
Indonesia	53	86	47	2.4	13
Maldives	80	83	—	1.7	18
Myanmar	68	88	79	5.1	27
Nepal	70	91	69	2.2	15
Sri Lanka	62	85	76	0.5	4.1
Thailand	74	83	60	2.2	24
Timor- Leste	54	89	50	3.3	18

MDR = multidrug resistant; RR = rifampicin resistant.

Table 1. Summary indicators of TB programmatic performance amongst SEAR countries. Dashes indicate that no data exist. All numbers given as percentages, and refer to 2019.

Data source: World Health Organization. Global Tuberculosis Report 2020. 2020. (27)

Drug resistance

Table 1 shows estimated levels of rifampicin- and multi-drug-resistance (RR/MDR-TB) amongst different countries in the region, using two indicators: the proportion of new cases (i.e. those without prior TB treatment history) having rifampicin- or multi-drug-resistance, and similarly the proportion amongst previously treated cases. Rates of drug resistance amongst new cases are an indicator of the extent to which drug resistance is transmitted, rather than acquired through first-line treatment: in the SEA region, although only 2.5% of new cases have RR/MDR-TB, this must be seen alongside the fact that 70% of the total estimated burden of RR/MDR-TB is amongst new cases. Recent modelling work suggests that the majority of RR/MDR-TB incidence is through transmission, rather than through primary acquisition (65).

Table 1 summarises key programmatic indicators for the management of RR/MDR-TB. Second-line treatment success rates are substantially lower than for first-line treatment, reflecting the expense, toxicity and poor effectiveness of current second-line regimens. Moreover, control of RR/MDR-TB depends as much on early recognition of drug sensitivity status, as on treatment outcomes (66). On the regional level in 2019, 65% of new cases and 82% of previously treated cases were tested for rifampicin resistance.

Even if drug resistance accounts only for a small share of overall TB burden, its management nonetheless consumes a disproportionate amount of programmatic TB spending, owing to the cost of second-line treatment, as well as the clinical and staff challenges of managing such poorly tolerated, long regimens. For these reasons, despite only accounting for 4% of TB incidence in 2019, the management of RR/MDR-TB accounted for over 13% of overall programmatic expenditure, in the SEA region (27). Therefore reducing the burden of drug resistance in SEA will have important budgetary as well as public health implications.

Private sector

Many countries in the region have a sizeable private healthcare sector that manages TB, but does not notify their patients to public health authorities (10). In India the private sector is vast, disorganised and difficult to regulate (67-69). There is widespread evidence of generally poor quality of TB care in this sector (69-71), resulting in delays in diagnosis. Moreover, a general lack of patient support for treatment adherence means that many patients do not complete their 6-month regimen. The problem is exacerbated by the fact that the private sector is a first port-of-call for most TB symptomatics, meaning that this sector dominates TB care in India (72). Other countries in the region face similar challenges: the dominant role of the private sector in these and other countries in the region is a major contributor to the 'missing millions' of incident TB cases that are never notified to public health authorities (19). As a result of these pressing challenges, the need for effective engagement with the private sector forms a key role in India's recent national strategic plan (NSP) (73), as well as NSPs in other countries in the region. Below we discuss ongoing and potential future mechanisms for effectively delivering these interventions.

Assessing priorities for TB control in the SEA region

In light of the complexity of TB control, there is a need to identify the largest 'gaps' in TB service provision. Although routine surveillance data can offer some insights, a major limitation is that it only speaks to the cases that are notified. In this respect, TB prevalence surveys can offer helpful insights.

Figure 2 shows results from a 2011 prevalence survey in Gujarat state, the first statewide TB prevalence survey in India (74). In this figure, the denominator is the number of TB cases who were either sputum-bacteriologically positive (and thus presumably infectious), or on TB treatment at the time of the survey. The left-hand chart shows the proportions at different stages in the care cascade. The figure illustrates, for example, that 11% of prevalent cases had visited a healthcare provider for their symptoms, but had not yet initiated TB treatment (green segment). Roughly, this represents the proportion of prevalent TB cases that are undergoing the 'diagnostic delay': they would benefit from initiatives to improve the quality of diagnosis and treatment initiation within existing, passive TB services (i.e. those services that are contingent on a TB case presenting for care).

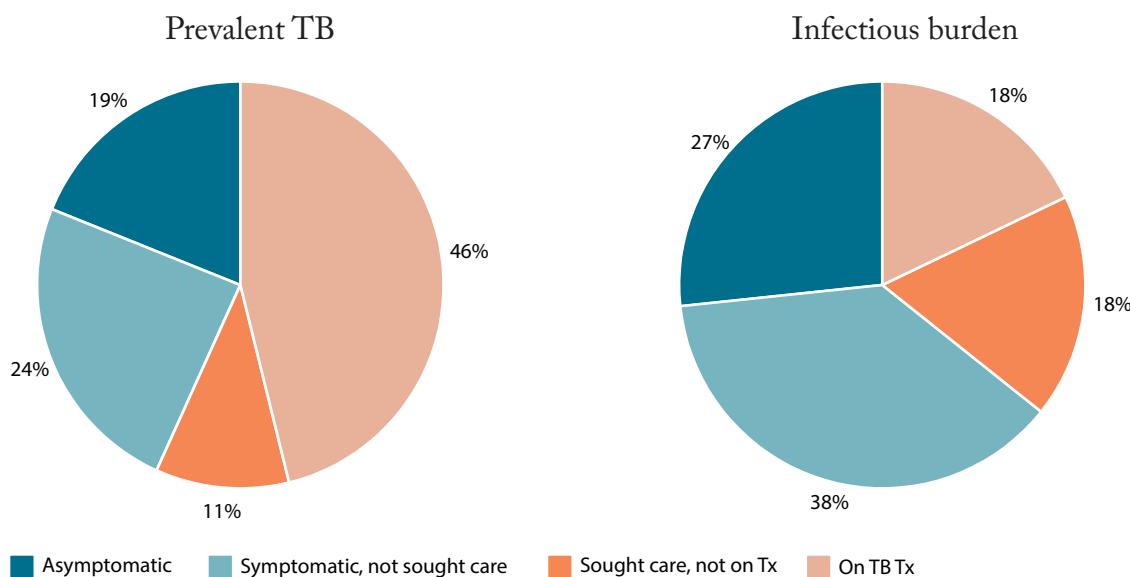


Figure 2. Distribution of cases from 2011 Gujarat prevalence survey, by stage in the TB cascade. Denominator is the number of TB cases that were either bacteriologically positive, or on TB treatment at the time of the survey. Left-hand panel: breakdown of prevalent TB cases by the stage in the TB cascade, from asymptomatic, bacteriologically positive TB to those on TB treatment (regardless of bacteriological status). Right-hand panel: the relative contribution of each stage in the cascade, when weighted by transmission potential. We use bacteriological status as a simple proxy for transmission potential, as described in the text.

Data source: Chadha VK, Anjinappa SM, Dave P, Rade K, Baskaran D, Narang P, et al. Sub-national TB prevalence surveys in India, 2006–2012: Results of uniformly conducted data analysis. *PLoS One*. 2019 Feb 22. (74)

However, the figure also highlights important limitations of passive TB control: a quarter of TB cases had not yet presented for care, despite reporting symptoms in the survey (light blue segment). These cases may be regarded as TB cases 'outside' the health system, who cannot be reached by any improvements in passive diagnosis or treatment. Moreover, almost a fifth of prevalent cases were sputum-bacteriologically positive, and thus presumably infectious, but did not report symptoms in the survey (dark blue segment).

However, this picture does not account for variations in infectivity. For example, those with symptoms severe enough to prompt careseeking may contribute more to transmission, than those already on TB treatment, who are more likely to be bacteriologically negative. Here we adopt a simple proxy for infectivity: to every TB case in the denominator, we apply a weighting according to bacteriological status, assigning

values of 0, 0.24 and 1 respectively, for those who are culture negative; culture positive but smear negative; and smear positive. These weightings represent assumptions that (i) culture-positive, smear negative TB cases are 24% as infectious as smear positive TB cases (75), and (ii) culture negative TB cases are not infectious (here, only amongst those on TB treatment). We refer to the sum of weighted prevalence as the 'infectious burden'.

The right-hand side of Figure 2 shows results from this analysis, illustrating that symptomatics who have not presented for care account for almost 40% of overall infectious burden, while 'asymptomatics' contribute almost 30%. This picture highlights the fact that – while routine service delivery is undoubtedly important – there is a critical need to extend TB services to those infectious TB cases that remain 'outside' the health system (blue segments in the chart).

Aside from the limitations of our simple proxy for transmission, we note also that this is only a cross-sectional picture, and does not directly quantify the losses at each step of the TB care cascade, nor the delays. Moreover Gujarat is a relatively prosperous state in India, and so this picture may not be generalisable to other states, or indeed to other countries in the region. Indeed, a national prevalence survey is currently underway in India, that will extend these results to the country level in India. Additionally, it is important to note that these results do not speak to two important aspects of TB control: (i) drug resistance. As noted above, even though RR/MDR-TB does not account for a major share of TB burden, its control will have important budgetary implications that will make available resources for other TB control activities. (ii) TB prevention. The figure's scope is limited to the distribution of prevalent, infectious TB burden in the community, and therefore only speaks to gaps in detection and treatment.

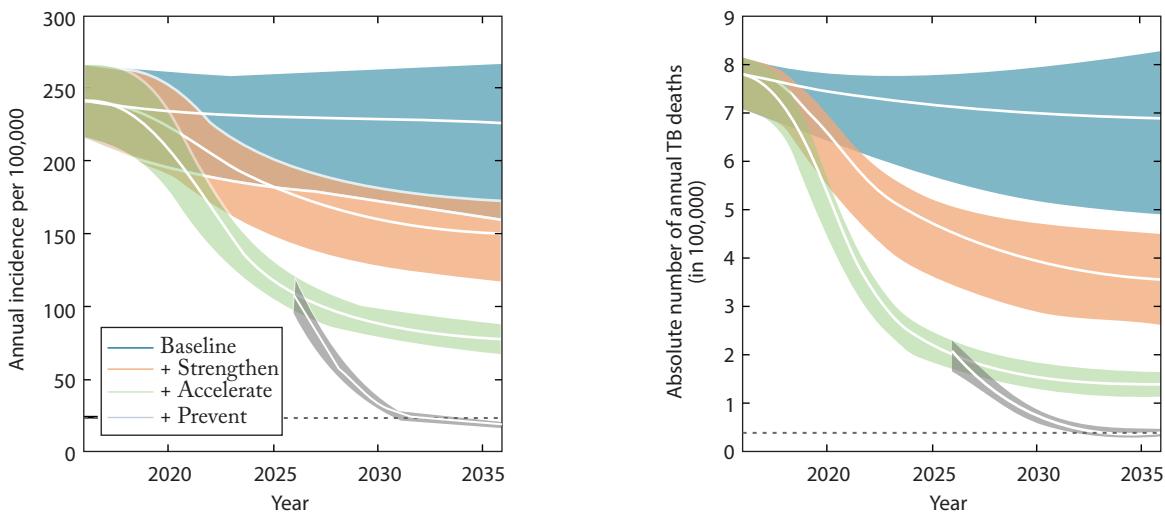


Figure 3. Simulated impact of combined measures to control TB in the SEA region. Dashed line shows the 2035 End TB targets. The 'strengthen' package of interventions includes adherence support for improved treatment outcomes; comprehensive private sector engagement; and improved tools for routine TB diagnosis. The 'accelerate' package includes active case finding; contact investigation; and generation of demand for TB services. The 'prevention' package includes additional interventions, which we assume to be available by 2025, for primary prevention of TB: these could include preventive therapy amongst those most likely to develop TB, or a new transmission-blocking vaccine. All of these measures are discussed in further detail in the following section.

Data source: World Health Organization. Regional Office for South-East Asia. Bending the curve: ending TB in the WHO South-East Asia Region. 2017. (76)

The importance of preventive measures is illustrated by Figure 3, which shows the results of modelling analysis conducted for all 11 countries in the SEAR region, in support of a regional ministerial meeting in 2017 (76). The figure illustrates three illustrative scenarios, modelling these separately for each of the 11 countries in the region, and aggregating to the regional level. The red shaded area shows the impact of measures to optimise basic TB services, wherever symptomatics seek care (that is, addressing the yellow and green segments of Figure 2). This is a critical foundation, that can reduce cumulative incidence by 18% between 2019 and 2035. The green area in figure 3 illustrates additional measures to accelerate the detection of TB (that is, addressing the light blue segment of Figure 2). Such measures could have an important impact in bringing down TB burden, achieving an incidence reduction of 42%. Given the aggressive interventions being modelled in both packages, this curve illustrates what could be achieved through curative interventions alone. However, these measures still fall short of the End TB targets. Ultimately it will be important to move towards more prevention-based approaches in TB control (orange curve). In the following section, we discuss emerging and potential future strategies for achieving the impact shown in each of these stages.

Addressing gaps: new and emerging strategies for TB control

In SEA and elsewhere, control efforts over the past two decades have arguably had greater success in managing than in controlling TB (77). In this section we assess the new strategies that may be brought to bear on combating TB in the South-East Asian Region. Figures 2 and 3 set the context by highlighting that there is a need to fill all gaps in the care cascade, ensuring (i) that all incident TB cases are able to undergo relapse-free cure, and (ii) that there are effective measures in place, for prevention of TB. In the present section we discuss some of the key interventions acting at different stages of the cascade, starting from the 'end' of the cascade (treatment outcomes) and working our way upstream (to early case detection, and ultimately prevention).

Improving treatment outcomes

First-line treatment

A recent systematic review (78) estimates that under programmatic conditions in India, there is 86% recurrence-free survival at 1 year following treatment completion. However, a recent retrospective analysis of clinical drug trial data suggests that there is more to recurrence than treatment completion (79). In particular, current first-line regimens appear not to be very 'forgiving' of missed doses, with as few as 10% missed doses increasing the post-treatment hazard rate by up to twofold.

In recognition of these challenges, there is increasing attention to new approaches for maximising the quality of treatment implementation. The DOTS strategy originally called for daily supervision by a healthcare worker – this approach is increasingly debated, owing to the considerable programmatic and ethical challenges involved (80,81). Indeed, these concerns are likely to be amplified with the prospect of future TB interventions dramatically increasing the numbers of patients on TB treatment. Alternative mechanisms for adherence support include technology-based approaches, such as 99DOTS, currently being implemented in India and in other settings (82). Under this platform, patients register their self-administration of daily treatment by calling a telephone number embedded in the drug packaging. Although unanswered, each call is logged by a call centre, and offers a way of monitoring patient treatment. Similarly, 'medical event reminder monitors' are boxes containing TB drugs that issue audio alerts when they have been unopened for longer than a day (83). Despite their potential role in supporting treatment adherence, but there is a need for further work to address their impact on relapse-free survival (82).

Social support mechanisms may also prove valuable in maintaining and improving treatment outcomes. India has recently launched a 'Nikshay Poshan Yojana' initiative, involving direct benefit transfer to those undergoing TB treatment (84). As implementation of the scheme progresses, it will provide valuable insights into the potential impact of such mechanisms for facilitating treatment adherence. Amongst other approaches, earlier work in Bangladesh highlighted the potential value of empowering the local community to undertake core treatment support functions (85).

Second-line treatment

Recent years have seen notable progress in the drug development pipeline: first, the introduction of a shortened, second-line regimen based on the new TB drug bedaquiline (86). This regimen is 9 months in duration, significantly shorter than current, 24-month regimens. In a recent study in South Africa, this regimen demonstrated significantly reduced mortality amongst patients with RR/MDR-TB (16). Second, early trial results have offered promising results for the performance of another new regimen, for treatment of extensively drug-resistant TB (XDR-TB), or cases who are resistant even to current second-line treatment (15). Although XDR-TB is typically even more challenging to manage than RR/MDR-TB, early trial results suggest that it may offer outcomes comparable to those of first-line treatment. Other new regimens in the TB drug development pipeline may soon enter advanced clinical trials (17).

In the context of new WHO guidelines (87) for the management of RR/MDR-TB, it is hoped that coming years will see a corresponding shift at the country level, to these and potentially other new, safer, more effective regimens. For maximum impact on drug resistance, such shifts need to be accompanied by an expansion in drug sensitivity testing at the point of TB diagnosis (discussed below), thus allowing TB patients to be initiated on appropriate treatment at the outset of treatment.

Improved diagnostic tools

In recent years a major development in TB diagnosis has been the emergence of rapid molecular diagnostic tests. GeneXpert (or simply 'Xpert'), developed by Cepheid, is a cartridge-based nucleic acid amplification (CB-NAAT) test that is playing a central role in efforts to modernise TB diagnosis worldwide (88-90). GeneXpert can provide TB diagnosis with superior sensitivity and specificity to smear microscopy – approaching that of culture – and within a matter of hours. Being a cartridge-based test, it does not require the same amount of training as culture.

However, performance of any new technology depends not only on the characteristics of the technology itself, but on the health system in which it is deployed. In the case of Xpert, despite its much-improved sensitivity in comparison with microscopy, programmatic demonstration studies replacing the latter with the former yielded only modest improvements in overall notifications (91,92). A key reason is that clinical diagnosis of smear negative patients plays an important role in TB diagnosis, so that Xpert merely serves to shift the proportion of diagnoses having bacteriological confirmation, rather than increasing the overall number of diagnoses (93). Another challenge is that current Xpert tests are more expensive than smear (90). For routine TB diagnosis, the replacement of smear by Xpert as a primary tool for diagnosis, may be challenging to justify in cost-effectiveness terms.

Nonetheless there are two important areas in which high-performance, high-cost rapid diagnostics such as Xpert will be important. First, Xpert is able to test for genetic markers of rifampicin resistance at the same time as providing a TB diagnosis. It therefore lends itself as a tool for drug susceptibility testing, potentially to be used subsequent to a diagnosis using conventional diagnostic algorithms. For this reason, and for several national TB programmes in the region, Xpert is at the centre of strategic planning to achieve universal drug susceptibility testing: that is, that every patient initiating TB treatment should do so with their drug sensitivity status being known, at least for rifampicin resistance.

The second key value of tests such as Xpert is in active case finding (ACF) in the community, where there is a significantly lower prevalence of TB than amongst those presenting for care (we discuss ACF in further detail below). In settings like India, TB prevalence is typically around 5% and 10% respectively, among these two populations (43,91,94). Thus, test specificity is as important as sensitivity. Even if each Xpert test should cost more than smear, this cost differential could be more than outweighed by the cost of treating false-positive TB cases as a result of imperfect specificity (87). Moreover, unnecessary TB treatment contains heavy and avoidable societal costs (95). For case detection at the community level, it is therefore important to deploy the test or algorithm with the greatest possible specificity (96).

Truenat (97) is another molecular diagnostic platform, developed in India, and recently incorporated in WHO guidelines for TB diagnosis (98). If such tests can perform at least as well as Xpert, and at lower cost, they could open new options for the use of molecular diagnostics in routine TB services (for example, as a primary diagnostic tool that is prioritised for symptomatics with previous TB history). Looking further into the future, however, there would be immense value in sensitive, cheap point-of-care diagnostics that can be used routinely and widely at primary care level (99). Such diagnostics may be qualitatively different from current approaches, and indeed may not be sputum-based: for instance, breath tests could be much more feasible for wide deployment in primary care settings, than sputum-based tests (100). Another possibility is urine-based tests for TB, an active area of current research (101,102). Although current urine tests perform best in very sick patients with HIV coinfection (102), in future improving their sensitivity in HIV-negative patients could open new opportunities for their deployment in primary care settings in the region.

Private sector engagement

In India, early attempts to engage with the private sector met with arguably limited success, owing partly to weak collaboration between the public and private sectors (103-106). However, recent years have seen the introduction of a new mechanism, involving 'public-private support agencies' (PPSAs). Piloted in Mumbai, Patna and elsewhere, PPSAs act as agencies that could engage with private providers on behalf of the public sector (19,107). Crucially allowing private providers to retain and manage their TB patients, PPSAs offer support for private providers to notify these cases, as well as offering patient vouchers for subsidised access to high-quality diagnostic services, and free, publicly funded TB treatment. As a result of these and other measures, in 2017 private providers accounted for 21% of total TB notifications in India, an unprecedented contribution (64) that subsequently grew to 34% by 2019, as a result of fresh initiatives to scale up private sector engagement across the country (108).

The challenges posed by the private sector are not unique to India, and indeed are typical of countries in the region. In general, efforts to engage the private sector would have at least one of three objectives: (i) facilitating the private sector to notify TB to public health authorities, (ii) improving the standard of diagnosis in the private sector, and (iii) improving the quality of TB treatment support, all in line with international and/or national standards of TB care.

Considering these aims in turn: while notification alone may not directly impact incidence, it is an important step for two reasons. First, it allows routine surveillance to more accurately capture a country's TB burden, providing critical data for monitoring and planning. Second, notification acts as a 'gateway' for other interventions, for example the tracing of household and social contacts of notified TB cases, to identify those who would be eligible for followup investigation. The incidence impact of any such interventions can only be maximised with comprehensive notification of TB, whether from the public or private sectors.

Next considering the standard of TB diagnosis in the private sector, India's 2011 ban on serology had important success in reducing the use of this inaccurate test for TB (109). However, private providers in India and elsewhere maintain a reliance on radiographic (X-ray) approaches for diagnosis of TB, as well as empirical treatment using broad-spectrum antibiotics (70). In this environment, facilitating the timely uptake of more accurate diagnostic tools such as smear or Xpert could help to reduce the 'diagnostic delay' shown in Fig.2. The IPAQt initiative, which introduced Xpert to the private sector in India through a network of private laboratories, was an important first step in improving the quality of TB diagnosis in the private sector: nonetheless more remains to be done, to change provider diagnosis behaviour, and to drive further demand for these tests.

Finally on treatment outcomes, in settings like India there is a general lack of adherence support in the private sector. For a 6-month regimen in which patients often have symptomatic relief within a matter of weeks, treatment interruptions are therefore thought to be common (69,110,111). Current initiatives in the region aim to address these issues by implementing the measures described above ('Improved treatment outcomes'), as an integral part of their activities for private sector engagement.

Overall, the relative priority of these different aims may differ, depending on the local context. For example, in settings where the quality of TB care in the private sector is considered to be comparable with that in the private sector, the focus of private sector engagement may be on notification.

Accelerating case detection

In this section we consider interventions to reach the prevalent TB cases that, at a given time, have not yet presented for care: as suggested by Fig.2, this population can amount to a substantial share of overall infectious TB burden. However, this is also an area with a pressing need for more systematic evidence.

Active case finding (ACF)

We denote as 'active case finding' any measures for diagnosing TB that are not contingent on a symptomatic presenting for care, and that instead aim to diagnose TB at the community level. Such measures may involve community-based screening for TB, for example with mobile diagnostic units (112–114). Although an earlier systematic review did not find clear evidence for the population-level impact of ACF, this was partly due to a lack of systematic studies from South Asian countries (115).

Screening for TB needs to be carefully focused: even in a high-burden setting like India, the prevalence in the general population is less than 1% (43%). As a result, country planning for ACF has often identified specific target populations that bear a disproportionate burden of TB. Prisoners are sometimes considered as a priority group: although their rates of TB are certainly higher than the rest of the population, their small population size, and their relative isolation, means that they may only have a very weak effect on population-level TB incidence. If ACF is to be deployed as a tool for incidence declines, therefore, there is a need also to include sizeable populations that are epidemiologically relevant to country-level burden. Urban slums are one important example: India's national strategic plan calls for sustained active case-finding in these and other vulnerable populations (6). Current programmatic efforts across the country are exploring ways of implementing these activities in practice.

Contact investigation

Another population bearing a disproportionate burden of TB is household contacts of TB cases. For example, studies in India and elsewhere suggest that there is a 3–5% co-prevalence of TB amongst household contacts of notified TB cases, considerably higher than the community prevalence, of <1%. Contact investigation of households has therefore been proposed as a method of case-finding. However, it is possible that even further gains could be achieved through not just surveying contacts at the point of diagnosing the index case, but also in following up these contacts over time: that is, an 'incidence-based' rather than 'prevalence-based' approach. Such an approach was demonstrated in a recent study in Vietnam, which followed up contacts of index cases over a two-year period, to identify 1788 TB cases per 100,000 contacts (98).

Generating demand for TB services

Alongside the programmatic activities described above, it must also be noted that patient-centred approaches may be equally effective, at reducing the size of the light-blue segment in Fig.2. In particular, the large size of this segment suggests a substantial 'patient delay', before a TB case presents for care for the first time. However, it is not clear what drives this delay. One hypothesis is that, with TB disproportionately affecting the poor, careseeking may also incur important opportunity costs, for example lost wages for daily wage labourers (98). If true, then social protection programmes for TB patients, although often intended to support patients on TB treatment (such as the social support mechanisms mentioned above), may have the positive secondary effects of encouraging symptomatics to come forward for care. Such effects are, as yet, only hypothetical: nonetheless, given their potential importance for declines in TB incidence, further evidence for the impact of such 'demand generation' measures could be of immense value in future interventions in the region.

Prevention

Modelling analysis has consistently shown that it will not be possible to end TB as a public health problem with curative measures alone (11,116). Even with the most timely and effective treatment, there will remain a large pool of latent TB infection that will continue to generate incidence for at least a generation. Ultimately, there will be a need for wide-scale prevention of TB: whether preventing latent infection from developing into active disease, or preventing transmission (117). In this section we assess some possible approaches to prevention: although tools currently exist, we are not yet at the stage where TB transmission can be prevented on a population level.

Preventive therapy

Treatment of latent TB infection, with a view to preventing the development of active disease, is known as 'preventive therapy'. One conventional PT regimen, 'Isoniazid Preventive Therapy' (IPT), consists of 6 months of daily treatment with isoniazid, and can reduce the risk of developing TB disease by 60 – 90% (118). Recent years have seen significant advances in the development of new regimens that are shorter and just as effective. For example, the 3HP regimen uses a combination of drugs to reduce the treatment duration by 3 months, with just once-weekly treatment (119). Further regimen development is raising the prospect of a one-month regimen (120). Simplifying and shortening regimens in this way can be valuable for PT, particularly as these regimens often need to be administered to healthy individuals with no outward symptoms of TB.

However, a major challenge in the deployment of PT is that it is not possible to predict which individuals with LTBI would benefit from it: that is, who would go on to develop active disease in the absence of preventive therapy. Given that these individuals account only for an estimated 10% amongst HIV-negative LTBI, universal treatment of people with LTBI is not recommended. Instead, WHO recommendations concentrate on specific risk groups who are particularly at risk of developing TB (121). This includes HIV-infected individuals with LTBI who, as described above, face a considerably higher risk of developing active TB disease than those without HIV. More recently, WHO guidelines have expanded to include all-age (not just paediatric) household contacts of TB cases. As described earlier, a recent study in Vietnam (122) suggested an eightfold higher incidence of TB amongst household contacts, than in the general population. Preventive therapy may therefore have a powerful effect in addressing this excess risk of TB disease. Indeed, recent modelling work suggested that full coverage of eligible populations could reduce annual incidence rates in SEAR by almost 10% by 2030, compared to 2015 .

Despite its potential impact, uptake of preventive therapy has been slow (123). It is possible that new, simplified and shortened PT regimens may help to address some of these challenges. The search for prognostic 'biomarkers', to predict who would be most likely to develop active disease, continues, with some promising signs from a recent study in S Africa and The Gambia (124). If successful, these technologies could enable real reductions in incidence by preventive therapy.

TB vaccination

As described above, the widely-deployed BCG vaccine is more effective at protection children from the severe form of TB, than from preventing infection. Efforts at developing a truly transmission-blocking vaccine are complicated by the fact that TB immunity is only incompletely understood; in particular, by the lack of immune correlates of protection, as well as the lack of good preclinical animal models (125).

Ongoing vaccine development explores a range of vaccine strategies, ranging from BCG 'boosters', to candidates replacing BCG altogether (126). In a study in 2013 in South Africa, the MVA85A vaccine – a new, viral vectored formulation – showed less-than-anticipated protection, highlighting the difficulties in both developing and trialling a new TB vaccine (127). More recently, however, early phase IIb results from another trial have shown promising results from the M72/AS01E vaccine, a subunit vaccine administered with an adjuvant (18). The results are only preliminary, the study population was limited to those already with LTBI, and further work is needed to build on this proof-of-concept. Nonetheless, the potential for a 50% reduction in developing active disease could have important implications for reducing TB incidence in future, and raise hope for a vaccine that could be deployed to block TB transmission.

Social determinants and modifiable risk factors

We discussed in section 1 the different risk factors that are known to increase the risk of LTBI developing into active disease. Modifiable risk factors may offer an opportunity for TB prevention – an important example is malnutrition in India (29). Both undernutrition and diabetes are thought to promote the risk of developing active disease threefold. Undernutrition in particular, as a result of its sheer prevalence, is thought to mediate a substantial proportion of TB burden in the country (28). However, the evidence shows that this elevated risk could be reversed with appropriate nutritional support (128,129). Other potentially important areas for risk reduction include smoking and second-hand smoke exposure (130,131), and the role of organic cooking material in indoor air pollution (132). In all of these factors, collaborative activities between tuberculosis and other health programmes could therefore have a profound effect on tuberculosis burden, in India and elsewhere (133).

Conclusion

It seems paradoxical that a curable disease such as TB should still cause over 1.2 million deaths a year worldwide. While TB control efforts over the last two decades have succeeded in improving the outcomes of TB disease, they have arguably had less impact on its causes in high-burden settings with only modest impact on incidence. Now, at a time of increasing political recognition of the challenge posed by TB, there is a pressing need to translate these ambitions into sustained, effective improvements in TB control.

In this context, here we have reviewed TB epidemiology and control, as relevant to the WHO South East Asian region. This account is necessarily a broad but shallow overview; with a focus on transmission, we note that there are important aspects of TB burden that we have not had space to cover here, for example the burden of paediatric TB. Nonetheless, a key message of this paper is that TB is not just a biomedical problem, but also one embedded in sociocultural issues (including careseeking behaviour and social determinants) and dependent on health systems. These complexities mean that the future of TB control in the region must involve a broad, holistic approach. For example, alongside the development of new technologies, there is also a need to understand how best to deploy these technologies in the complex health systems that are typical in the region. Moreover, it is likely that patient-centred approaches will become as important as technological innovation: for example, in understanding the behavioural drivers of careseeking, and how these drivers might be affected by interventions such as social protection programmes.

This review has not addressed the recent challenges to TB programmes raised by COVID-19, challenges that emerged following the time of writing. Current data from countries in the Region highlights the major disruptions that anti-COVID lockdowns have had, on routine TB services. These disruptions can last longer than the lockdowns themselves; modelling suggests that the associated increases in incidence and mortality can last longer still, on the order of years. In order to mitigate these adverse long-term consequences, there is a pressing need to ensure that TB programmes, in the Region and elsewhere, can be brought 'back on track' as quickly possible.

There are undoubtedly many challenges ahead, in developing and delivering the innovations that are so badly needed. At the same time, important scientific and political developments over the last five years provide reason for optimism. Ending TB in the South-East Asian Region would not only benefit millions in the region; it will also have profound, long-lasting implications for the global burden of TB.

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Malaria

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Malaria, an age-old disease, has crippled vulnerable populations in tropical and subtropical climates of the globe for centuries. Only in the past two decades have the morbidity and mortality ascribed to this dreaded disease declined, thanks to political will and commitment, which in turn attracted the financial resources necessary to fund wide-scale malaria prevention, diagnosis, treatment, surveillance, and associated research. Encouraged by the success of these efforts, the health sector has proposed area-based strategies and targets for the elimination of malaria by 2030. Achieving this goal will require coordination with other sectors that have direct or indirect effects on the social determinants of malaria.

Background

Biology

Malaria in humans is caused by parasitic alveolates of phylum Apicomplexa and genus *Plasmodium*. It is believed to have evolved in humans from parasites infecting apes in Africa (1). Today, eight *Plasmodium* species, either singly or in combination, are known to cause malaria in humans. Four (*P.falciparum*, *P.vivax*, *P.malariae*, and *P.ovale*) are established human malaria parasites with the ability to sustain independent human-to-human disease transmission through anopheline mosquito vectors; the other four (*P.knowlesi*, *P.cynomolgi*, *P.simium*, and *P.brasiliianum*) still require a zoonotic spillover to be able to cause human infections through anopheline mosquitoes (2–5).

Human malaria is clinically characterized by a febrile illness with tertian (every 48 hours; *P.falciparum*, *P.vivax*, and *P.ovale*) or quartan (every 72 hours; *P.malariae*) periodicity and associated chills and rigor. However, these classic symptoms of malaria are infrequently observed now: a substantial proportion of persons infected with *Plasmodium* parasites may not show any signs or symptoms of malaria and cannot be detected using conventional diagnostics (microscopy or rapid diagnostic tests). Rather, low-density infections are identified through highly sensitive methods, such as nucleic acid amplification-based tools (6, 7). Clinical features of malaria are determined not only by parasite factors—for example, the species of parasite (*P.falciparum* is known to cause a severe and fulminant disease) and the parasite virulence factors (switching of *var* and *rif* genes-derived expression of *PfEMP1* (8–10) and rifins (9, 11)—and the age and previous malaria exposures of the human host, but also by the complex interplay between the parasite and the human, leading to parasite sequestration and immune evasion (12–14). Depending on such host-parasite interactions, malaria manifests as an uncomplicated febrile illness, just like any other viral fever, presenting with paroxysms of low-grade fever, chills, and muscle aches coinciding with hemolysis of parasite-infected red blood cells and then progressing to high fever, sweating, and exhaustion, or as a severe, often fatal disease presenting with severe anemia and signs and symptoms of multiorgan failure, sometimes including cerebral malaria. Severe malaria is believed to be associated with parasite sequestration and subsequent microvascular occlusion due to sequestered parasites in the capillaries of vital organs (14–17).

The natural history of malaria follows that of any infectious disease involving a classic epidemiological tetrad of agent, host, environment, and time, which either singly or in combination determine the occurrence of disease (18). *Plasmodium* species have two hosts: humans (secondary hosts) and female *Anopheles* mosquitoes (primary or definitive hosts and also the vectors of the disease). Recent advances in comparative genomics are enabling scientists to better understand the evolutionary relationships between

humans and *Plasmodia* species (19, 20). It is believed (and debated) that human malaria parasites have originated from a bird parasite that descended as *P.falciparum* in humans and *P.reichenowi* in chimpanzees (21).

Parasite determinants

Plasmodium parasites are the most direct and absolute determinants of not only the clinical course of the disease but also its transmissibility (together with vectoral determinants). The parasite-related factors that determine the clinical diagnosis (presence of infection and disease), prevention, and success of treatment or cure (absence of infection and disease) in humans include the presence of parasite species known to cause human malaria, the density of infection, or parasitemia (22–24), the developmental stage of the parasite, the virulence (cytadherence properties) of the parasite strain (25), its susceptibility to antimalarial drugs, *hrp2* and *hrp3* deletions (26–28), its tendency to undergo a dormant stage associated with clinical relapse (29, 30), its multiplication rate and duration of erythrocytic stage (31), the number of merozoites per hepatic and erythrocytic schizonts, and antigenic variations in the immunogenic epitopes. For successful transmission of the parasite to mosquitoes, the gametocytogenic potential (commitment to gametocytogenesis) (32), number, density, timing of appearance in peripheral blood, maturity stage, sex ratio (33), vitality, and functionality (fecundity) of the gametocytes are the main determinants, in addition to the availability of female *Anopheles* mosquitoes near the infected host (34–36).

Human determinants

Human malaria parasites are transmitted by the bites of sporozoite-infected female *Anopheles* mosquitoes. The establishment of infection is determined by many host factors, including age, immunity (repeated exposures to *Plasmodium* lead to premunition (37) or nonsterilizing protection (38), and thus to asymptomatic infections in high endemic areas (39, 40)), and both genetic and acquired factors that affect malaria severity (41). The genetic factors that predispose a human host to severe malaria have been identified as presence of sickle cell disease and human blood group B. The conditions and genomic loci that protect from severe malaria include Haemoglobin AS (sickle cell trait (42–44)), Haemoglobin C, Thalassaemia, Glycophorins A and B, and blood group O (45). Although the exact mechanisms conferring protection have not yet been pinpointed, parasite growth inhibition appears to be a central phenomenon in mitigating symptoms of severe malaria (41, 44, 46). Predisposition to clinical severity in malaria has been attributed to certain acquired factors like pregnancy and early postpartum period, malnutrition, HIV status, and hyposplenism.

In addition, two more genetic defects that may protect a human host from *P.falciparum* severity (G6PDd) and *P.vivax* infection (Duffy antigen negativity) are worth a mention. The A allele of X-linked Glucose-6-phosphate-dehydrogenase (G6PD) enzyme deficiency appears to protect male hemizygotes and female heterozygotes from cerebral malaria but at the same time makes male hemizygotes and female homozygotes more susceptible to severe anemia in malaria (41, 45, 46). A reticulocyte surface receptor (Duffy antigen receptor for chemokines, or DARC) that binds critically to the Duffy binding protein (DBP) ligand of parasites *P.vivax* and *P.knowlesi* has been demonstrated to be indispensable for parasite invasion (and hence subsequent establishment of red blood cell infections) into the host reticulocytes (47, 48). However, evidence increasingly shows the dispensability of DBP in parasite invasion because individuals with Duffy-negative red cell genotype are shown to be infected with *P.vivax* in Africa (49–56).

Social determinants

Malaria has been bidirectionally linked with virtually all social determinants of general health—poor education, poverty, migration to an endemic area, war, other humanitarian emergencies—in such a way that the presence or exacerbation of one predisposes the other (57). All these determinants contribute significantly not only to morbidity and mortality in malaria-endemic areas but also to vulnerability to malaria (the probability that malaria parasites will be imported) in areas from which malaria has been eliminated. Increased vulnerability is an established risk factor for the reintroduction of malaria in a malaria-free area or country (58).

That explains why and how malaria has inextricable linkages with many of the Sustainable Development Goals (SDGs), set by the UN General Assembly in 2015 (59, 60). For example, poverty (addressed by SDG1) traps the most disadvantaged people into sickness, suffering, and poverty; hunger (SDG2) has enormous bidirectional linkage with agriculture production; health and well-being (SDG3) show the highest return on investment; education (SDG4) and sickness absenteeism in schools are affected by malaria; gender equity (SDG5) allows women to be more productive when free from caring for family members with malaria; water and sanitation (SDG 6) addresses the stagnant water where mosquitoes breed; climate (SDG13) has huge potential effects on the number of cases; and partnerships (SDG17) are critical for defeating malaria (57–59, 61).

Entomological determinants

Although some 40 species of *Anopheles* mosquitoes are established vectors of malaria and abundantly distributed all over the world, the efficacy of malaria transmission in a region is largely determined by the locally prevalent mosquito species (62, 63). For example, the predominant malaria vector in tropical Africa is *A. gambiae* (64), and on the Indian subcontinent, *A. culicifacies* (65, 66). The efficiency of a mosquito as a malaria vector (vector competence) depends on its longevity, which affects the development of the parasite inside the insect (the extrinsic incubation period); critical density; the degree of the parasite's affinity for human versus other animal hosts (anthropophilism); and gametocyte and sporozoite inoculation rates (67). Malaria is said to be stable when longevity and anthropophilism are high enough and sufficient malaria cases exist in the population, even if the critical vector density required to sustain the basic reproduction rate (R_0) of malaria over one is low (67). The extrinsic incubation period, or the sporogony period (68, 69), of *Plasmodium* is the time taken by the parasite from its ingestion by the mosquito in the blood meal (as gametocytes) to the development of infectious sporozoites in the mosquito salivary glands. It is believed that a decrease in this period, which is thought to be due to global warming, potentially increases the possibilities of malaria transmission more than a corresponding increase in vector competence and/or density (70).

Environmental determinants

Since human *Plasmodium* parasites are maintained in nature by passive transmission between humans (secondary hosts) through mosquito vectors (definitive hosts), the burden of disease in humans is a true reflection of—and is in direct correlation with—the number of parasite-transmitting *Anopheles* mosquitoes in the environment. The environment, in turn, has a pivotal role in the epidemiology of malaria because the majority of the mosquito life cycle (egg-larva-pupa-adult) depends on bodies of water (71). The availability of water is a potential population bottleneck, particularly in dry seasons (72–74). Environmental conduciveness for vector-borne malaria transmission will thus be determined by the natural (local climate, vegetation, rainfall, altitude, relative humidity, and temperature) and human environment (41). Climate change therefore has implications not only for transmission dynamics in malaria-endemic areas and estimated malaria-related mortality (75, 76), but also for predicting areas that could become malaria-endemic because of their increased receptivity, defined as the ability of an ecosystem to allow transmission of malaria (77–80) and reduced extrinsic incubation period (70). Of particular concern are those future neo-endemic areas that had been malaria-free for decades whose populations are malaria-susceptible because of a lack of premunition (37, 81).

Effects on the poor

Malaria damages and in turn is aggravated by hosts' socioeconomic status, at both family and population levels (57, 60, 82). Growth rates of per capita gross domestic product (GDP) are lower by up to 1.3 percentage points in malaria-endemic countries than in malaria-free countries (83). The effect is so pronounced that malaria control and elimination are inextricably linked to achieving the SDGs (59, 60) (see "Social determinants," above). Of the SDGs directly associated with malaria, the one having most direct and considerable influence on malaria is the goal of eliminating poverty, which is both a cause and an effect of malaria. Efforts to eliminate malaria are considered to be cost-effective public health approaches because they can break the malaria-poverty cycle (57, 60). A disproportionately higher burden of malaria cases and related deaths is observed in the world's poorest populations (84). An estimated 60% of malaria deaths occur among the poorest 20% on the globe—a higher imbalance in distribution than for other diseases (85, 86).

An episode of malaria is estimated to incur a direct health-related cost of \$2.67 on the infected individual, in addition to such indirect costs as an average 3.4 days of lost productivity. The caregiver, too, loses two to four days of work each time a dependent family member is struck with malaria, causing extra economic burden to the household (60). Poorer households also spend a higher proportion of their annual income on healthcare for malaria—about one-third of average annual income versus one-20th for households that are economically better off (86, 87). This economic loss is compounded if the patient is a female and the family breadwinner (86, 88).

Because the brunt of malaria falls on the poorest of the poor, all approaches to reduce malaria directly raise the health and socioeconomic standing of this segment of society (60, 89, 90). Researchers have substantiated the finding that countries with successful malaria elimination and eradication efforts are associated with less work disability, higher incomes, and noticeable financial growth compared with neighboring nations where malaria is still a problem (83, 89–92). Research on malaria and poverty has been published piecemeal, however; explicit and in-depth research exploring the causal links and their mitigation have been scant in the past decade (93). Since the relationship between poverty and malaria is multidimensional and involves multiple players and stakeholders, mitigation efforts demand multidisciplinary research and coordination with agriculture, housing and urban development, social justice, women's empowerment, and other sectors (57, 59–61, 93, 94).

Malaria in the South-East Asia region

The World Malaria Report 2018 estimates a total of 219 million malaria cases worldwide (95% CI 203 million–262 million) in 2017, which is a little more than an 8% decline from the 2010 estimates. However, it is also a 1% increase in the malaria burden estimates for 2016 (95), indicating suboptimal and ill-sustained control efforts during the past few years. The WHO South-East Asia region (SEAR) was second only to the Africa region in contributing to the burden of malaria cases in 2017, being home to 5% of the total malaria cases estimated in 2017 (Figure 1). Fifteen countries in the African region and one country, India, in SEAR were responsible for 80% of the world's malaria burden. However, India had 24% fewer estimated malaria cases in 2017 than in 2016. Of the total malaria deaths in 2017, India and 17 African countries accounted for 80%.

Whereas worldwide malaria incidence was stagnant, at 59 per 1,000 population, from 2014 to 2017, SEAR demonstrated a 59% decrease in malaria incidence from 2010 to 2017—the best record of all the WHO regions. The region also showed the largest decline (54%) in the number of malaria deaths across the world over that seven-year period (95). Four SEAR countries (Bhutan, India, Myanmar, and Timor-Leste) reported a more than 20% reduction in estimated malaria cases since 2016; Nepal, however, reported a more than 20% increase.

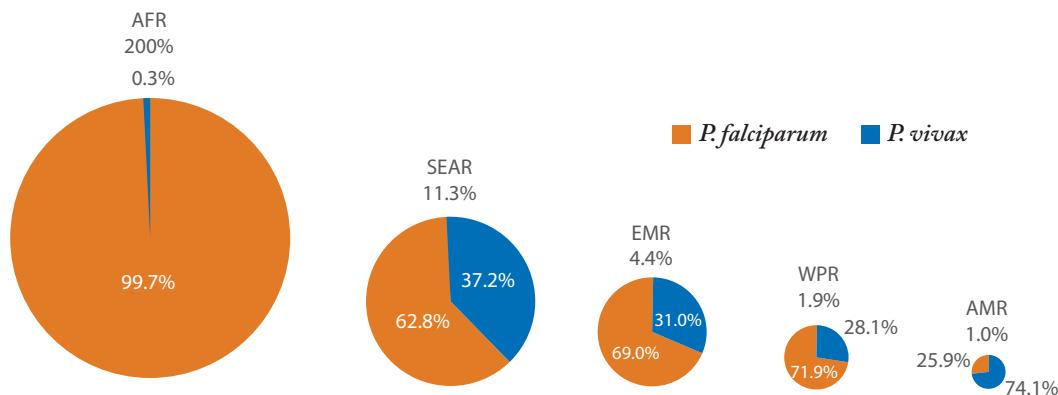
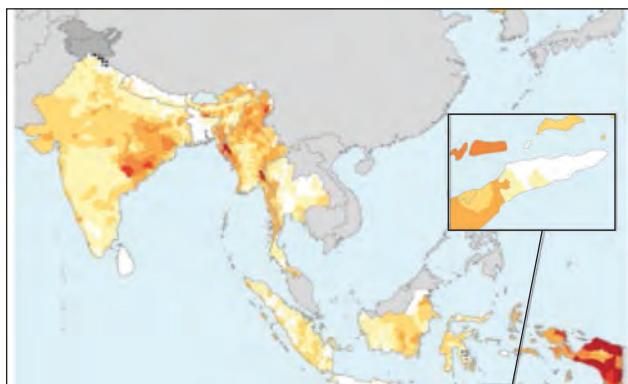


Figure 1. Estimated malaria cases (millions) by WHO region, 2017. The area of the circles is shown as a percentage of the estimated number of cases in each region. Source: The World Malaria Report 2018 (95).

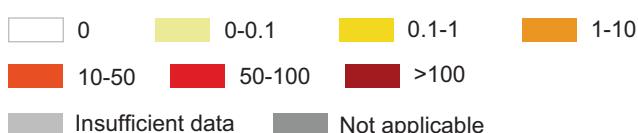
AFR: WHO African Region; AMR: WHO Region of the Americas; EMR: WHO Eastern Mediterranean Region; SEAR: WHO South-East Asia Region; WHO: World Health Organization; WPR: WHO Western Pacific Region; *P. falciparum*: Plasmodium falciparum; *P. vivax*: Plasmodium vivax.

In 2017 SEAR had 1.6 billion people at risk for malaria, with 1.23 million confirmed malaria cases (a 54% reduction from 2010) and 299 reported deaths (an 88% decrease from 2010) (95). The wide discrepancy between estimated and reported malaria cases (10.7 million, 95%) and deaths (19,401, 98% deficit) points to the probable lacunae in the sensitivity of existing surveillance system in the region, which may be one of the greatest roadblocks to elimination by 2030. One reason for these surveillance gaps is the meager involvement of the private sector in reporting malaria cases to the government system: in India, for example, testing and reporting rates from public sector healthcare centers are exceptionally high (nearing 100%), but fewer than 20% of febrile children under five years are brought to public clinics, and thus official surveillance may miss four-fifths of such patients (95).

Confirmed malaria cases per 1000 population, 2017



Two countries contributed almost all the malaria burden...



Share of estimated malaria cases, 2017

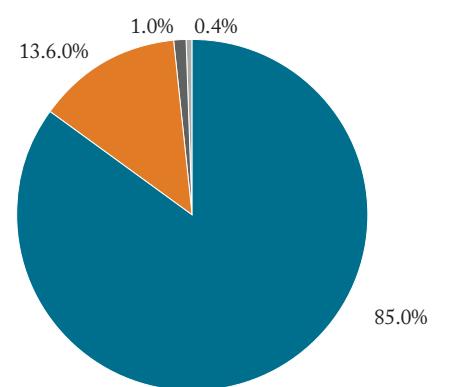


Figure 2. Distribution and share of estimated malaria cases within SEA region countries. Source: The World Malaria Report 2018 (95). India and Indonesia contributed most of region's malaria burden.

Of the 11 SEAR countries, only Maldives and Sri Lanka have been certified as “malaria eliminated.” Bhutan, Nepal, Democratic People’s Republic of Korea, and Timor-Leste have nationwide malaria elimination programs; the remaining countries—Bangladesh, India, Indonesia, Myanmar, and Thailand—have subnational programs. Of the estimated 11.3 million cases, India (85%) and Indonesia (13.6%) contribute almost all (98.6%) of this burden (Figure 2). *P. falciparum* contributes more than 50% of the malaria burden in Bangladesh, Timor-Leste, Myanmar, Indonesia, and India (in decreasing order), and the other SEAR countries have *P. vivax* as predominant species. With current efforts, all countries except India and Indonesia are on track for reducing the case incidence by 40% or more by 2020.

Certain population groups deserve special mention in malaria epidemiology as high-risk and particularly vulnerable: children under five years of age, pregnant women, HIV/AIDS patients, nonimmune migrants, mobile populations, and travelers. Among all ages, children under five were the most vulnerable population; 61% of all malaria deaths across the world occurred in this age group in 2017. However, the proportion of deaths in under-five children continues to decline, with a drop of 12 percentage points between 2010 and 2017. Young children and pregnant women were also identified as being highly vulnerable to anemia attributed to malaria in 2017.

Gender norms and dynamics—what the local society expects as a specific gender role— influence vulnerability to malaria. Female gender may affect the risk of infection and access to promotive, preventive, diagnostic, and therapeutic healthcare services, with ramifications for the distribution of malaria morbidity and mortality (96), poverty and its aftermath, and decreased autonomy (97), particularly in patriarchal societies like India (98) and other SEAR countries. Although the World Malaria Report addresses data needs by geographic region, gender- and age-disaggregated data, such as the burden of malaria (by sex and age), the number of people treated for malaria (by sex and age), and the number of insecticide-treated bed nets distributed (by sex) are missing (88, 94, 99).

Disability-adjusted life-years (DALYs) are one indicator for quantifying the total burden of a disease, both fatal and nonfatal, on a population. DALYs for a particular disease or health condition are calculated by

adding the estimated number of years of life lost due to premature mortality and years of life lived with disability, both attributed to the disease or health condition in question (100–102). Data from the Global Burden of Diseases estimation study (2016) reveal that the all-age DALYs attributed to malaria declined by 7% between 1990 and 2016, with a steeper decline (27%) between 2006 and 2016. The corresponding declines in age-standardized DALY rate per 100,000 due to malaria were even sharper, 15% and 31%, between 1990 and 2016 and between 2006 and 2016, respectively. These declines in malaria DALYs simply reflect the downward trend of disease burden in terms of years of healthy life lost due to malaria (101). What is promising for malaria DALYs is that the Global Burden of Diseases figures for 2016 are lower than for 2015, reflecting better malaria control specifically in SEAR. Outside Africa, notable reductions in estimated cases, years of life lived with disability, and DALYs were observed in three SEAR countries—India, Myanmar, and Indonesia—plus Pakistan (101, 102).

Priorities for malaria control

Despite intensified efforts to eliminate the disease, malaria not only remains a major cause of morbidity and mortality but also shows early signs of rebound. Recent data from the World Malaria Report 2018 (95) demonstrate both the positive and the negative results of the elimination efforts, putting the entire health community at the crossroads of success and failure. Evidence of resurgence jeopardizes not only the malaria elimination goals outlined in the Global Technical Strategy 2016–2030, but also the Sustainable Development Goals that are intertwined with malaria in the South-East Asia region (58, 59).

According to the World Malaria Report 2018, more countries are now on track for eliminating malaria, in line with the goals of the Global Technical Strategy 2016–2030. With existing tools, malaria elimination certainly appears achievable by 2030: more than 50% of the endemic countries (47 of 87) have fewer than 10,000 malaria cases reported to public health surveillance systems, and more than half of them (24 of 47) have fewer than 100 reported cases (95, 103). Ethiopia, India, Pakistan, and Rwanda demonstrated substantial declines in 2017. However, the success has been punctuated by a few pivotal downfalls. The report shows that we risk losing the gains achieved in the past two decades of malaria elimination endeavors. The malaria community has missed two of the critical 2020 milestones of the Global Technical Strategy: reducing malaria incidence and deaths by at least 40% from 2015 levels. With 219 million cases (3.5 million more than in 2016) and 435,000 deaths in 2017, the picture is clouded.

Despite intensified efforts and political will, insufficient access and uptake of malaria interventions still cripple the public healthcare systems of the nations where it matters the most. Stagnant funding dedicated to malaria elimination and the inertia of the status quo in some of the high-burden states is compromising the goal.

A new strategy, “High Burden to High Impact,” is intended to put the derailed malaria elimination efforts back on track (95). This initiative emphasizes sustained political will and commitment to reduce malaria deaths; best possible global guidance, policies, and strategies; strategic information; and concerted country responses. Two interventions are increasing and ensuring funding and targeting of resources (with emphasis on domestic funding), and rectifying healthcare system inefficiencies in line with the Sustainable Development Goals (transformation to robust systems with quality services).

Developing new tools, along with improving existing tools, is also critical. The emerging resistance of parasites and mosquitoes to first-line approaches of artemisinin-based combination therapy and pyrethroid-based insecticides threaten malaria elimination efforts (103). Approaches include new tools for vector control (bed nets incorporating combinations of a pyrethroid and synergist piperonyl Butoxide and/or insect growth regulator pyriproxyfen, and paratransgenic Wolbachia-infected mosquitoes), diagnosis, treatment, immuno-prophylaxis (point-of-care hrp2-independent kits, G6PD tests, tafenoquine, mass drug administration, focal/mass screening and treatment, sporozoite- and PvDBPII-based vaccines), and research on basic host-parasite-vector biology and their interactions (103–112).

Population-based interventions

Indoor residual spraying

Indoor residual spraying is recommended for vector control in malaria-prone and affected areas (113). In India, use of this intervention is based on information collected at state, district, and subdistrict levels. The country's National Vector Borne Disease Control Programme distributes the insecticides and dispensing pumps to district malaria teams. Different mechanisms are used, and the quality of spraying, management, and results are monitored by the service providers on regular basis.

Nets and sprays are sometimes misused for purposes other than malaria control. Such activities hamper progress, escalating the costs of achieving the goals, and also increase the likelihood of the emergence of insecticide-resistant vectors and drug-resistant parasites.

Source reduction

Source reduction refers to destroying mosquitoes' breeding places. This method, usually directed by civil engineers and carried out by municipal agencies, supports other efforts to reduce the malaria burden and prevents the spread of other vector-borne diseases as well (74, 114). Source reduction methods that prevent mosquitoes from laying eggs include filling open land, covering drainage systems and surface drains, using environmentally safe garbage collection and disposal mechanisms, and building sanitary landfills (115). The methods are socially acceptable and economically feasible and even have financial benefits; they boost the general well-being of communities and overall environmental health.

Entomological surveillance

Entomological surveillance collects information about the vectors (their distribution, behavior, and biting habits) and changes in response to an intervention. Vectors' presence, density, and susceptibility to insecticides are observed in different areas and across different time periods to generate knowledge about possible methods of vector control (116). In India, entomological surveillance is conducted by the National Health Mission, which has both rural and urban components, and by the National Vector Borne Disease Control Programme and National Institute of Malaria Research during the transmission season in malaria-affected areas.

Population-based screening and testing

Where the burden of malaria has fallen to very low levels, population-based treatment strategies (rather than case-based treatment) can clear the residual parasites and achieve malaria elimination. These strategies include mass drug administration, mass screening and treatment, mass fever treatment and others.

Mass drug administration includes providing curative doses of a recommended antimalarial drug to the entire population under observation, without screening for the presence of malaria parasites in the blood or symptoms of malaria in the target population.

Mass screening and treatment require the entire population to be screened for parasitemia (or parasite antigens) by a malaria diagnostic test; only those who test positive receive the curative dose. This approach uses rapid diagnostic tests to detect malaria infection in a large population in the remote locations of endemic areas. Multiple rounds have been used to treat and prevent malaria infection (117). The strategy provides a significant amount of information on the epidemiology and burden of the disease, and it supports further implementation of the current strategies.

Focal screening and treatment, a variant of mass screening and treatment, targets a restricted, defined population—a household, a village, or a malaria hotspot (Figure 3).

Mass fever treatment screens for the presence of fever rather than the presence of parasites in a large population to determine whether people should be treated with a curative dose of an antimalarial.

Mass treatments tend to clear blood stage residual parasites and offer the additional advantage of treating low-density parasitemias—those below the threshold of clinical manifestation that nevertheless contribute to the parasite-transmissible load in the community. These are effective tools for eliminating malaria in areas that have achieved a very low incidence of parasitism.

Mass drug administration has not yet been recommended for malaria by WHO because of insufficient epidemiological evidence for its overall benefits and the anticipated risk of promoting drug resistance in the target population.

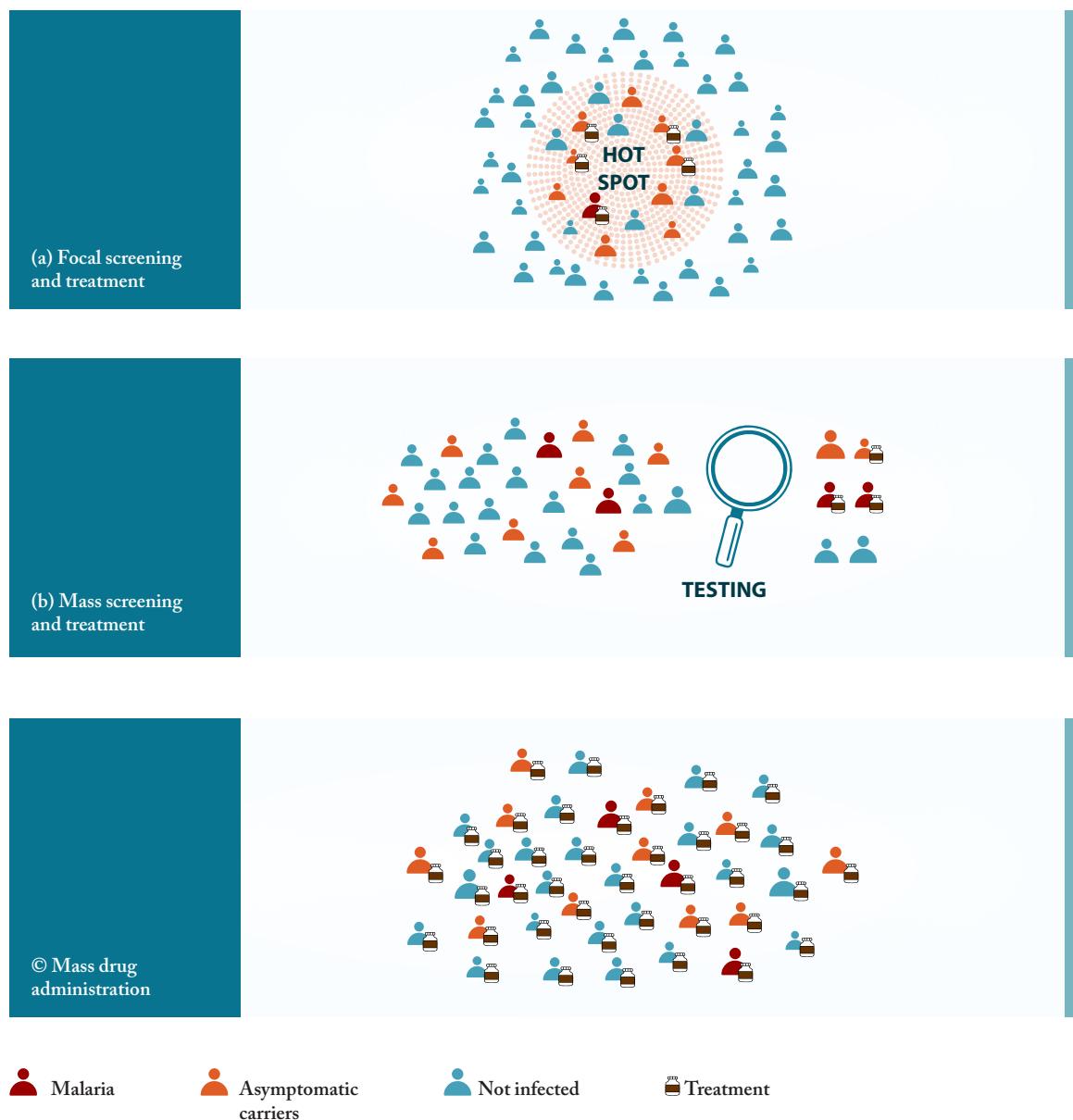


Figure 3. Schematic diagram of population-based screening and testing approaches. Mass drug administration is conducted without prior screening. Grueninger H and Hamed K (2013); Source: (165).

The challenge for mass and focal screening and treatment is the diagnostic accuracy of the detection methods. The strategies could supplement routine passive case detection and be useful for liquidating the foci in hard-to-reach areas. However, today's microscopy and rapid diagnostic tests are limited in their ability to detect low-density infections (<50 parasites/ μ l). Moreover, mass screening and treatment are resource intensive (118). A diagnostic tool with higher sensitivity, such as polymerase chain reaction, needs to be tested for this application. The focal approach is operationally more feasible, but because it is not delivered simultaneously across the entire area sustaining malaria transmission, it is unlikely to contribute significantly to elimination efforts (118).

Funding for diagnosis and treatment

For reduction of malaria prevalence and burden in malaria-prone areas with large at-risk populations, early diagnosis and treatment can limit the severity and spread of the disease. Early diagnosis of malaria parasites in SEAR is accomplished with rapid diagnostic test kits and blood smear microscopy. Microscopy, the standard in malaria diagnosis, is labor- and time-intensive and requires qualified technical staff to make and interpret the blood slide. It is therefore being replaced by rapid diagnostic tests, especially in remote areas. In India, early diagnosis of malaria is generally done by accredited social health activists or other skilled health workers under the direction of a local community healthcare center or primary healthcare center medical officer, and infected individuals are then treated according to national policy. Early diagnosis can be more efficient if done by village health workers, who are the primary link in India's malaria elimination program (119). Informal and often unqualified health practitioners in the private sector are the first point of contact for most rural and semi-urban Indians.

Table 1. National antimalarial drug policy in SEAR countries for *P. falciparum* and *P. vivax*

WHO region Country/area	<i>P. falciparum</i>			<i>P. vivax</i>
	Uncomplicated unconfirmed	Uncomplicated confirmed	Severe	Treatment
Bangladesh		AL	AS+AL;QN	CQ=PQ(14d)
Bhutan		AL	AM;QN	CQ=PQ(14d)
DPR Korea				CQ=PQ(14d)
India	CQ	AS+SP+PQ;AL	AM;AS;QN	CQ=PQ(14d)
Indonesia		DHA=PP+PQ	AM+AS;QN	DHA+PP+ PQ(14d)
Myanmar		AL;AS+MQ; DHA=PPQ;PQ	AM;AS;QN	CQ+PQ(14d)
Nepal	CQ	AL+PQ	AS;QN	CQ=PQ(14d)
Thailand		DHA=PPQ	QN+D	CQ=PQ(14d)
Timor- Leste		AL+PQ	AM;AS;QN	CQ=PQ(14d)

CQ = chloroquine; PQ = primaquine; DHA = dihydroartemisinin; PP+PQ = piperazine; d = days; AS = artesunate ; AL = artemether-lumefantrine; QN = quinine; D = doxycycline. Source: *The World Malaria Report 2018* (95).

In India, malaria is diagnosed and treated at three levels: primary care (as home-, school-, or worksite-based management), secondary care (district hospitals), or tertiary care (specialty hospitals, referral centers, and medical colleges). Most schools and worksites are not equipped to deal with any kind of disease, so patients first visit a primary healthcare facility or, in Bangladesh, Gonoshasthya Kendra (120). District hospitals have intensive-care units for severe or complicated malaria cases in both malaria-endemic and nonendemic areas (121, 122). Malaria patients who cannot be managed by primary or district hospitals are referred to tertiary facilities, which have life-support systems, skilled medical and paramedical staff, blood banks, sophisticated laboratories, and teams of experienced doctors and residents. Case reports are prepared at this level for research publication and to track malaria events (123).

The private sector also provides healthcare in India. Urban areas have a high concentration of private healthcare providers, whereas in rural areas, government health services predominate. Malaria control programs must be coordinated to succeed, but lack of trust and cooperation characterizes the relationship between the private and public systems.

Not all staff in remote areas have sufficient training. Delayed diagnosis, misdiagnosis, and wrong treatment are some of the factors responsible for development of drug-resistant malaria, which is becoming a major issue for malaria elimination efforts.

Costs and benefits of interventions

The financial and other burdens of malaria diagnosis and management fall to public healthcare delivery systems, which provide free services. Of the many factors that influence the cost-effectiveness of interventions, time and money are the major constraints, especially in densely populated SEAR countries. The time that healthcare personnel spend on malaria cases comes at the expense of providing other services, and some patients seek alternative providers at their own, out-of-pocket expense. Dedicating teams of healthcare providers to malaria cases would require additional funds and also involve a reorientation of healthcare delivery systems (124). Supplies for the diagnosis of malaria—rapid diagnostic test kits, microscopistic glass slides, microscopes—require a robust logistic chain and quality assurance.

Malaria control and elimination are not a one-time investment; rather, they need sustained financial commitment. Reducing the disease burden of malaria in endemic regions warrants a more sensitive surveillance system with more detailed investigations, which constitute yet another financial burden. Sustained use of insecticide-treated nets, indoor residual spraying, vaccines, and larvivorous fishes are additional costs.

Malaria reduces infected individuals' productivity, which affects household economic stability and leads to poverty. Conversely, besides reducing the morbidity and mortality rates of malaria, interventions increase the productivity of individuals and their countries, strengthening the economy and making funds available for other health issues or other sectors, such as infrastructure. Because malaria is linked to many socioeconomic and behavioral determinants of health and social development, its elimination would drastically improve social, demographic, and economic indicators.

Once elimination is achieved and sustained by prevention-of-reintroduction activities, malaria control programs could be ramped down (125). The earlier the goal is met, the higher the cost savings and the greater the advantages: this is the “early elimination bonus.”

Intervention cost-effectiveness

Malaria control and elimination are the second most cost-effective public health interventions, after the universal immunization of children: US\$5–\$8 for each malaria case averted (126–128). It has been roughly estimated that eliminating malaria worldwide by 2030 would cost US\$101.8 billion, with an additional investment of \$673 million each year for continuing research (60, 61). More robust evidence for estimating intervention cost and cost-effectiveness or cost-benefit analyses for malaria elimination are scanty or lacking, but it is anticipated that the intervention costs will decrease by up to 25% after the disease has been eliminated and is in the prevention-of-reintroduction phase (129–134).

Though the cost may appear high, the benefits are disproportionately higher. Return-on-investment (ROI) analyses evaluate the efficiency of investments in terms of a ratio of the return (gains achieved through increased revenue and/or decreased costs) to the investment (financial and nonfinancial resources) (135). The ROI of malaria is US\$6.75 per capita GDP for every \$1 invested (136). The gains include both direct and indirect financial gains: reductions in worker absenteeism; increased productivity in agriculture, business, and industry (137–140); reductions in social inequality and thus more cohesive societies and safer cross-border movements of people; reductions in school absenteeism and increased literacy (141); increases in household prosperity; equity and women's empowerment; and improved health security and public healthcare systems, particularly in countries where malaria patients have overburdened public systems (142–147).

Elimination would save more than 10 million lives if the WHO Global Technical Strategy 2030 malaria goals are achieved, which translates, in monetary terms, to more than US\$4 trillion of additional capital. The returns will in turn drive the achievement of related SDGs, thus breaking the vicious disease-poverty cycle. Achieving the targets of malaria elimination as set by the WHO Global Technical Strategy for malaria

would cost approximately US\$24 billion in 2020, \$36 billion in 2025, and \$42 billion in 2030. The costs include further scaling up of proven interventions, targeted surveillance systems, and further investment in research and development to discover innovative tools and approaches. The effective gains expected from the investment would be 1.6 million, 4.2 million, and 4.5 million lives saved, plus 0.4 billion, 1.3 billion, and 1.3 billion malaria cases averted, respectively (60, 61, 125, 148).

Annual per capita costs for malaria elimination are front-loaded: they gradually diminish to a plateau once elimination has been achieved. The costs for sustaining malaria elimination in Sri Lanka, for example, are approximately threefold than the per capita costs when the disease was rampant (131).

Elimination of malaria is estimated to produce an incremental benefit of US\$0.7 trillion by 2020, \$2.3 trillion by 2025, and \$4.1 trillion by 2030 through increased productivity at work and school, stronger public healthcare systems, and greater household prosperity in general. The total return on investment by 2030 is 40:1 overall and 60:1 for malaria-struck countries like Africa (60, 61, 140, 148), a return that is considered phenomenal (149).

The costs of malaria resurgence, on the other hand, would prove disastrous, based on historical examples from India and Thailand in mid and late 1960s and also according to the World Malaria Report 2018. The reasons: the number of cases shoots up rapidly, increased vulnerability due to loss of premunition generates more severe cases, and drug and insecticide resistance is likely to rise (131, 150, 151). Malaria resurgence would not only wipe out the gains achieved thus far but also incur huge humanitarian and economic costs. A reversion to the 2007 levels of malaria burden would cost US\$1.2 trillion in lost economic production, involve 2 billion additional malaria cases and 18 million additional cases requiring admission to public hospitals, cause 3.7 million additional deaths, result in the loss of 1 billion working days per year, and incur US\$5.2 billion in direct costs to hospitals and households (60, 61, 148, 152, 153).

Research and development agenda

The favorable cost-benefit and cost-effectiveness ratios and high returns on investment suggest that the world has a unique opportunity to end malaria forever. Complacency now would not only preclude malaria elimination but also allow a near-future and very rapid rebound. Smart use of existing tools—intensified surveillance, prompt diagnosis, accurate and effective treatment, efficient vector control—could end malaria by 2030. Walking the last mile requires an intensified research and development (R&D) effort.

Investment in R&D

The World Malaria Report 2018 acknowledges that steep escalations in investments towards malaria research and development are needed to meet the target. The US\$588 million spent in 2016 was 15% short (61, 95). Allocation of funds and their balanced application to malaria research sectors are one critical challenge (95). Commitments from government, philanthropists, and other stakeholders for both financial and nonfinancial resources are required to support new methodologies and tools that could provide better disease burden and mortality estimates (103) and sustain activities related to malaria elimination.

Determining the true burden of malaria depends on inputs from government and formal and informal nongovernmental health sectors. The epidemiological data must be collected on a continual, regular basis; ideally, real-time data would enable microplanning for elimination efforts (103). Public healthcare systems' data suffer from multiple flaws. First, the approach is passive, looking at care-seeking behavior, which for countries like India are inadequate. Second, the private sector does not collect data, and hence the results do not represent the true caseload. Third, cases may be underreported even in public sector databases. Consequently, the World Malaria Reports present only disease estimates that incorporate correction factors (63, 154).

To upgrade the disease monitoring systems, representative demographic surveillance sites could serve as models, with burden and transmission modeling systems, mobile technology, drone-based ecological surveys, and improved electronic data monitoring, capturing, reporting, and sharing systems and platforms that connect scientists, researchers, program implementers, policymakers, the public, and other stakeholders (103).

Screening and treatment topics

Research is also needed to identify new tools for early and point-of-care diagnosis, early treatment, transmission-blocking drugs and vaccines, vector control, access of services to vulnerable populations, and timely identification of parasite and vector resistance. Research efforts should focus on *P. vivax*, which demands special attention because of its typical pathophysiology (unique liver stage development), clinical course (presence of relapses), diagnosis (biomarkers for hypnozoites, G6PD deficiency), treatment (radical cure, compliance for complete treatment), and epidemiology (early and asymptomatic transmission potential). Climate change is another topic: it could significantly affect the postelimination landscape of malaria, and the predicated changes in climate could open new avenues for malaria epidemiology in terms of generating newer vector ecology, new malaria endemic foci, and altered receptivity for malaria and other vector-borne diseases.

Screening and therapeutic approaches that merit further research include population-based interventions (see “Population-based screening and testing,” above), interventions targeted to vulnerable groups (pregnant women and children), and clinical and vaccine trials for advancement to registration. In parallel, clinical therapeutic efficacy studies to monitor resistance to artemisinin and its partner drugs should be a priority in representative malaria endemic sites, particularly where the risk is high because of proximity to resistance foci or high cross-border travel involving such sites (155).

Certain blood schizonticidal agents are now in the advanced stages of development. Examples include Artefenomel (OZ439) / Ferroquine; KAF156/Lumefantrine, Cipargamin (KAE609), DSM265 etc. (108). Single exposure radical cure and prophylaxis (SERCaP), for example, Artefenomel (OZ439) / Ferroquine will be a major achievement. Single-dose Tafenoquine in particular could be pivotal for the radical cure of *P. vivax* and prevention of relapses because of its high efficacy and circumvention of treatment adherence (as with primaquine), but a G6PD test is required prior to administration (156). Although the pipeline of antimalarials under development appears robust, resistance to artemisinins is a concern. Hence, we need to use the choices carefully, and also make use of the evidence generated.

The efficacy of antimalarials should be monitored regularly (157), and the evidence generated should be considered for changes in drug policy. As per the WHO malaria treatment guidelines, the first-line treatment should be changed if the failure rate is more than 10% (118).

Vector and parasite biology

Research topics include vector resistance to existing insecticides, paratransgenesis and development and release of genetically modified mosquitoes, innovative mosquito control approaches, and identification of new vectors, especially in relation to climate change. In the field of parasite biology, the priorities are molecular signatures of drug resistance, clinical relapses (in *P. vivax*), new parasite species implicated in causing human malaria, parasitic determinants of hepatic invasion and dormancy, and identification and clinical advancement of new drug and vaccine targets.

Epidemiological work should focus on the transmission potential of a population in terms of basic reproductive number, or R_0 , and the effectiveness of population-based transmission-blocking approaches. Volunteer infection studies (formerly known as controlled human malaria infection studies) should be ethically and scientifically promoted as a way to assess the effectiveness of interruption of transmission and chemoprevention (158–162).

Social, policy, and advocacy issues

Because malaria is interlinked with achievement of the SDGs, research is needed on social and socioeconomic policy issues that relate to malaria: mainstreaming of marginalized populations; mitigation of civil unrest, wars, and natural disasters; access to migratory populations (particularly cross-border migrants); disease-related surveillance of international travelers (especially from endemic countries to countries at risk of reintroduction); care-seeking behavior for vector-borne diseases; integration of the private healthcare sector (both formal and informal) into malaria programs; vulnerability reduction; and improvement of land-use planning. Two other important topics are education and communication methods, and behavioral change communication.

Conclusion

Malaria can be eliminated with available tools (163). Proof comes from Sri Lanka and Maldives, which have achieved elimination despite transmission-favorable conditions (6, 164).

The World Malaria Report 2018 identifies inadequate investment as a major constraint in achieving the malaria elimination targets as proposed by the Global Technical Strategies 2016–2030 (61, 95). Continuous mobilization and optimization of resources, involving strategic planning, advocacy, communication, and negotiation with donors and policymakers are needed to narrow and then close the resource gap.

Efforts to eliminate malaria should go beyond SDG3 (good health and well-being). To achieve success, the malaria elimination efforts should be coordinated with work on related SDGs, particularly SDG1 (no poverty), SDG6 (clean water and sanitation), SDG8 (decent work and economic growth), SDG10 (reduced inequalities), SDG11 (sustainable cities and communities), SDG13 (climate action), and SDG17 (partnerships).

Years of committed efforts could be overturned by even short-term complacency. The world needs to see concerted and committed country-owned actions driven by best possible evidence and policies. With country-led initiatives focusing on sustainable development and commitment, we can now keep the promise and realize the dream of a malaria-free world.

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Enteric pathogens and typhoid

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The gastrointestinal tract is the commonest portal of entry for a variety of pathogens, but not all of the pathogens are causally associated with disease in all patients. Among the pathogens that infect enterocytes, or at least use them as a portal of entry, one major group comprises those that cause systemic infections after entering into the body through the gastrointestinal tract; diarrhea, if ever present, is not a major feature of infection. This group includes many enteroviruses, including poliovirus and coxsackieviruses, hepatitis A and E viruses, and some adenoviruses, as well as bacteria such as *Listeria monocytogenes* and *Salmonella enterica* subspecies *enterica* serovar *Typhi*. The second group comprises pathogens that infect the small or large intestine and cause noninflammatory or inflammatory diarrhea or dysentery. These pathogens include the viruses that cause mainly acute watery diarrhea, and bacteria and parasites that may cause acute or chronic diarrhea or dysentery. In this chapter, we consider only diarrheal disease and the enteric fevers.

The gut is not a sterile site, is continually exposed to the external environment through food and water and has its own rich microbial ecosystem. Assessment of the burden of enterically transmitted infections has always been challenging, for a number of reasons, including the difficulty of detecting and characterizing potential agents of disease, distinguishing colonization from disease-causing replicative infection, and estimating the damage caused by the acute infection as well as the long-term effects on growth, nutrition, and resilience (1). Further, it can be difficult in a health policy context to judge the comparative importance of risks, through infection of the gastrointestinal tract to other illnesses and their outcomes, in groups that vary in multiple sociodemographic dimensions. Synthesis of information for policy requires integration and validation in a framework that brings together and analyzes the limited, sometimes contradictory information that is available on a population's health and disease conditions. How that population's health changes over time must be tracked so that the information stays relevant for health policy and planning purposes.

Background

Diarrhea results from the reversal of the normal net absorptive status of water and electrolyte absorption in the gastrointestinal tract. In acute infectious diarrhea, such a derangement is best exemplified by the production of an enterotoxin that induces secretion. In other forms of diarrhea, tissue damage and inflammation may result in malabsorption and bloody diarrhea. Syndromically, diarrhea may be acute watery diarrhea (also known as acute gastroenteritis), with three or more watery stools a day that may result in rapid dehydration; persistent diarrhea, which lasts 14 days or longer and can be associated with fat or carbohydrate malabsorption, nutrient losses, and wasting; and bloody diarrhea, which is due to cellular damage and associated with inflammation.

Acute gastroenteritis is among the most common illnesses affecting humans and causes the most harm at the extremes of age, severely affecting children and the elderly. The spectrum of disease can range from asymptomatic infections to severe diarrhea and/or vomiting with dehydration, which can be fatal. Diarrheal disease continues to be a major cause of mortality in young children, particularly in developing countries.

Persistent diarrhea has a decreasing incidence but is associated with malnutrition, either preceding or resulting from the illness itself (2). Persistent diarrhea was reported to be associated with higher mortality in several countries, including India, Pakistan, and Bangladesh (3–5), but recent studies have found that the proportion of diarrheal episodes that are persistent has declined in parallel with the rapid decline in diarrheal mortality (6).

Bloody diarrhea, or dysentery, may range from diarrhea with visible blood in the stool or severe disease with frequent small-volume, bloody mucoid stools with tenesmus and fever. This is due to mucosal damage and inflammation, with fecal blood and white blood cells detectable by microscopy. Fever and altered metabolism lead to loss of protein, carbohydrates, and fats.

Unlike enteric infections that result in the symptom of diarrhea with or without associated vomiting and fever, typhoid, also known as enteric fever, has protean manifestations that can make diagnosis challenging. Typhoid presents as an undifferentiated fever, with malaise and diffuse abdominal pain. Untreated typhoid may progress to delirium, intestinal hemorrhage, bowel perforation, and death. Even with treatment, a small number of patients may become carriers (7). Nontyphoidal salmonellae causes infections in humans and animals, which may be asymptomatic or result in disease. In humans, infections can occur as localized sepsis or spread beyond the gastrointestinal tract to result in bacteremia and vascular and neurological complications.

Diarrhea and typhoid are caused by infections that are transmitted directly or indirectly from the stool of one individual to the mouth of another; this is termed feco-oral transmission. The organisms differ in their infectious dose, with stomach acid playing an important role in determining the survival of pathogens. For example, *Shigella* is resistant to low pH and has a low infectious dose of a few hundred or thousand organisms, whereas *Vibrio cholerae* is easily killed by acid and requires millions of organisms to cause illness. Other factors that influence transmission include the ability to survive in the environment and the ability to infect multiple species (e.g., *Campylobacter* in cattle and poultry).

Causes of enteric infectious diseases

Prior to 1972, the etiology of most episodes of gastroenteritis was unknown, and cases were attributed to a multitude of causes, including teething, weaning, diet, old age, drugs, and malnutrition as well as infections. Intensive investigation of enteric infections in the past three decades has resulted in the discovery of many new viral agents, filling in the “diagnostic gap” in diarrheal disease. Since the 1970s, with the identification of rotavirus, astroviruses, enteric adenoviruses, noroviruses, and other caliciviruses, it has become increasingly clear that viruses cause a significant proportion of the enteric illnesses that did not earlier have a defined etiology. Although more than 100 pathogens are known to cause diarrhea, most laboratories test for a limited number of agents because the conventional methods for identification and characterization are cumbersome and time consuming. Enzyme-Linked Immunosorbent Assay (ELISA)-based methods, developed in the 1980s and 1990s, expanded the range of testing, and more recently, extensive molecular testing has become available, at least in the research setting. In addition, the ability to identify and quantify virulence genes and their products has led to new approaches to epidemiology and attribution of disease . Molecular methods also allow distinction between organisms that appear to be identical by conventional testing. An example is *Escherichia coli*, which is a commensal organism in the gut and is detected in culture: five pathotypes of *E. coli* cause watery and bloody diarrhea, and distinguishing these pathogens from nonpathogenic *E. coli* requires either complex tests, including evaluation in animals, or molecular testing.

Based on clinical findings and the location of the infection, it is also possible to consider potential etiologies (Table 1).

Table 1. Etiology of diarrheal disease, based on symptoms

Clinical observation	Location	Likely cause
Few, voluminous stools	Diarrhea of small bowel origin	<i>Vibrio cholerae</i> , enterotoxigenic <i>Escherichia coli</i> , <i>Shigella</i> (early infection), <i>Giardia lamblia</i> , <i>Vibrio parahaemolyticus</i>
Passage of many small-volume stools	Diarrhea of large bowel origin	<i>Shigella</i> , <i>Salmonella</i> , <i>Campylobacter</i> , diarrheagenic <i>E. coli</i> , <i>Yersinia enterocolitica</i> , <i>Entamoeba histolytica</i>
Tenesmus, fecal urgency, dysentery	Colitis	<i>Shigella</i> , <i>Salmonella</i> , enteroinvasive <i>E. coli</i> , enterohaemorrhagic <i>E. coli</i> <i>Campylobacter</i> , <i>E. histolytica</i> , <i>V. parahaemolyticus</i> (rare)
Predominance of vomiting	Gastroenteritis	Viral agents (rotavirus, norovirus) or intoxication (<i>Bacillus cereus</i> , <i>Staphylococcus aureus</i>)
Predominance of fever	Mucosal invasion	<i>Shigella</i> , <i>Salmonella</i> , <i>Campylobacter</i> , enteroinvasive <i>E. coli</i>

Data source: Farrar J, Hotez P, Jungmans T, Kang G, Lalloo D, White N. Manson's Tropical Diseases - 23rd Edition. 2014.

Children exposed to enteric pathogens risk entering a vicious cycle: gut inflammation impairs the absorption and processing of micronutrients, with consequences of growth faltering and impaired immunity, making the child more prone to enteric infection (10). How and which factors interact is unclear, in part because this concept has been based on observational studies of only individual or a subset of components, given the difficulties of studying all interactions among hosts, pathogens, and the environment over time.

In addition to the bidirectional interaction between infection and nutrition, another research focus is the condition known as environmental enteropathy/environmental enteric dysfunction (EE/EED). The small intestine is characterized by gut inflammation and permeability barrier disruption and malabsorption without diarrhea. EE/EED is mainly seen in children in low-income countries and is believed to be due to continual exposure to fecally contaminated food, water, and fomites (11). Because there are no acute symptoms, it has not been seen as a priority, but it is recognized that EE/EED contributes to growth faltering, low efficacy of oral vaccines, and poor neurocognitive development. Much recent work has sought to unravel its complex pathogenesis, but effective diagnostic methods or possible interventions remain unclear.

More detailed studies are contributing to deeper exploration but are again limited by the duration of follow-up, which can make longer-term consequences of acute or repeated infections difficult to assess. In addition, the tools for modeling and analytic frameworks that go beyond the traditional modeling framework, in which one or more factors are assessed in response to a collection of independent covariates, are needed. Graphical models derived from expert opinion allow experts to describe a web of factors that covary not in isolation but in different combinations, which can then be validated against empirical evidence (12).

Typhoid is caused mainly by *Salmonella enterica*, subspecies *enterica* serovar *typhi*, and to a lesser extent, related serovars paratyphi A, B, and C, which are known as the typhoidal salmonellae and are exclusively human pathogens. The nontyphoidal salmonellae, comprising more than 2,000 serotypes, are an important cause of foodborne illness and cause gastroenteritis and related disease in humans and animals. Typhoid fever and paratyphoid fever continue to be important causes of illness and death, particularly among children and adolescents in the South-Central and South-East Asia regions; nontyphoidal salmonellae appear to be more important in Africa (13).

Risk factors

Diarrhea is more prevalent in the developing world in large part because of the lack of safe drinking water, sanitation, and hygiene (WASH), as well as poorer overall health and nutritional status. The Joint Monitoring Programme's 2017 update report has estimated that worldwide, 2 billion people use drinking water from a source contaminated with feces, and 2.3 billion people do not have access to safe sanitation, mostly in the poorest households and rural areas; 90 percent of the people who practice open defecation live in rural areas (14).

Unsafe food containing bacteria, viruses, and parasites causes enteric and systemic infections and is increasingly recognized as a problem. Urbanization and changes in consumer habits, including travel, have increased the purchase and consumption of food outside the home. Globalization has resulted in consumer demand for a wider variety of foods, resulting in complex global food chains. Climate change brings new risks associated with safe food production, storage, and distribution. Food safety and security also threaten the nutritional status of the most vulnerable people. When food supplies are insecure, people tend to shift to less healthy diets and consume foods that may pose health risks. Food safety, and the potential for typhoid carriers in the food industry, are major factors affecting the transmission of typhoid (15).

In children, an important risk factor for gastrointestinal infection is the reduced rate of breastfeeding. The effects of breastfeeding on infant and child morbidity and mortality, particularly diarrhea, derive from observational studies dating back to the 1960s and 1970s, but the findings have also been supported by more recent studies, including a random-effects meta-analysis of 18 studies; it showed greatest protection conferred by exclusive breastfeeding among infants from birth to five months of age and by any breastfeeding among infants and young children six to 23 months. Specifically, not breastfeeding resulted in an excess risk of diarrhea mortality compared with exclusive breastfeeding among infants up to five months of age (relative risk, RR, 10.52) and to any breastfeeding among children aged six to 23 months (RR 2.18) (16).

Malnutrition has a bidirectional relationship with diarrhea. It reduces immunity and makes children susceptible to infections, including diarrhea, but it can also be a result of persistent or severe diarrhea. Childhood malnutrition is prevalent in low- and middle-income countries. In India, stunting was estimated at about 38%; in the South-East Asia region (SEAR) as a whole, stunting was 32% in 2015 (17).

Among micronutrients, zinc deficiency is associated with an increased risk of gastrointestinal infections, as well as impaired immune function and stunting. Dietary deficiency of zinc is especially common in low-income countries because of a low dietary intake of zinc-rich foods (mainly foods of animal origin) or inadequate absorption caused by its binding to dietary fiber and phytates often found in cereals, nuts, and legumes (18, 19).

Disease burden

In the past decade, studies conducted in less developed countries in Asia, Africa, and Latin America have collected data on children hospitalized with diarrhea and those with less severe diarrhea in the community, using standardized testing and analytic methods to better describe the etiology of diarrheal disease (6, 20). Recently, data from the Global Enterics Multi-Site Study (GEMS), which used a case-control approach and a definition of moderate to severe diarrhea to identify and test samples from cases and controls, have been reanalyzed using quantitative molecular methods (21). The study defined moderate to severe diarrhea in a case-control design in children under five years of age. Table 2 lists the top pathogens, based on the retesting. Table 2 also includes a reanalysis with quantitative approaches of community-based cohorts known as the Etiology, Risk Factors, and Interactions of Enteric Infections and Malnutrition and the Consequences for Child Health and Development, or MAL-ED study (22), in which birth cohorts were followed for diarrhea of any severity and asymptomatic infection up to two years of age.

Table 2. Top 10 pathogens by attributable fraction in GEMS and MAL-ED studies

Global Enteric Multicenter Study (GEMS) (20)		Malnutrition and the Consequences for Child Health (MAL-ED) Study, (1)		
Mirzapur, Bangladesh	Kolkata, India	Dhaka, Bangladesh	Vellore, India	Bhaktapur, Nepal
Rotavirus	Sapovirus	Adenovirus 40/41	Shigella	Rotavirus
Shigella	Rotavirus	Shigella	Sapovirus	Sapovirus
<i>Campylobacter jejuni/C. coli</i>	Adenovirus 40/41	Rotavirus	Rotavirus	Shigella
Adenovirus 40/41	<i>Campylobacter jejuni/C. coli</i>	ETEC	ETEC	Norovirus
ST-ETEC	Astrovirus	Sapovirus	Astrovirus	ETEC
Norovirus GII	Cryptosporidium	Astrovirus	Adenovirus 40/41	Astrovirus
Astrovirus	ST-ETEC	Norovirus	<i>Campylobacter jejuni/C. coli</i>	<i>Campylobacter jejuni/C. coli</i>
Cryptosporidium	Norovirus	<i>Campylobacter jejuni/C. coli</i>	Norovirus	Adenovirus 40/41
Sapovirus	Shigella	Cryptosporidium	tEPEC	Cryptosporidium
<i>Vibrio cholerae</i>	tEPEC	tEPEC	Cryptosporidium	tEPEC

ETEC = enterotoxigenic *Escherichia coli*; ST-ETEC = Stable toxin-producing enterotoxigenic *E. coli*; tEPEC = typical enteropathogenic *E. coli*.

Few comprehensive efforts have been made to collect and validate burden-of-disease estimates across different diseases, conditions, and geographies, but in the past decade, the Global Burden of Disease framework has begun to provide morbidity and mortality data to estimate prevalence and incidence and track trends over time. For enteric infection mortality, a Bayesian hierarchical modeling platform that evaluated a wide range of covariates and model types on the basis of vital registration and verbal autopsy data is used (23). Incidence of infection is modeled using a compartmental meta-regression tool that relies on population representative surveys, healthcare data, and multicountry, multipathogen research studies. In the most recent report of data for 2016, diarrhea deaths and episodes were attributed to 13 pathogens by use of a counterfactual population attributable fraction approach, yielding estimates that in 2016, diarrhea was the eighth leading cause of death among all ages, with 1,655,944 deaths (95% uncertainty interval (UI), 1,244,073–2,366,552), and the fifth leading cause of death among children younger than five years, with 446,000 deaths (95% UI 390,894–504,613). By etiology, rotavirus caused the greatest number of deaths, with 128,515 deaths among children younger than five years (95% UI 105,138–155,133), and 228,047 deaths among all ages (95% UI 183,526–292,737).

In 2016, for the first time, detailed data on India became available through a collaboration with the Indian Council for Medical Research, and hence data on the burden of diarrheal disease mortality and morbidity at the level of states can be analyzed. In 2016, diarrhea contributed to 7.94% (95% UI 5.45%–12.47%) of total deaths and 4.64% (95% UI 3.54%–6.58%) of total disability-adjusted life-years (DALYs) for all ages. In under-five children, diarrhea accounted for 7.64% (95% UI 6.56%–8.87%) of deaths and 7.19% (95% UI 6.18%–8.31%) of DALYs. There was a difference by gender, with 10.36% (95% UI 5.9%–18.91%) of all deaths in women and 5.98% (3.51%–10.71%) of all deaths in men attributed to diarrhea. Table 3 summarizes deaths and DALYs attributed to diarrheal disease, typhoid, and paratyphoid by age and gender in India, and Figures 1 and 2.

Table 3. Burden of diarrheal disease and enteric fever in India, by age and gender, 2016

Cause	Age group	Gender	Deaths		DALYs	
			Percentage of total deaths	Annual percentage change	Percentage of DALYs	Annual percentage change
Diarrheal diseases	< 5	Male	9.04 (6.98%-11.24%)	-5.73%	8.52% (6.64%-10.59%)	-5.67%
		Female	10.79 (9.05%-12.7%)	-6.03%	10.22% (8.62%-12.02%)	-5.97%
		Both	9.91 (8.54%-11.32%)	-5.9%	9.36% (8.1%-10.68%)	-5.84%
	5-14	Male	9.19 (4.47%-18.35%)	-4.46%	5.21% (3.1%-9.17%)	-3.87%
		Female	11.82 (6.26%-21.38%)	-4.86%	6.28% (3.8%-10.29%)	-4.37%
		Both	10.57 (6.65%-17.31%)	-4.7%	5.77% (4.01%-8.68%)	-4.17%
	15-49	Male	2.47 (1.05%-5.16%)	-3.32%	2.4% (1.55%-4.1%)	-2.49%
		Female	4.09 (1.9%-8.11%)	-3.4%	2.97% (1.95%-4.81%)	-2.59%
		Both	3.11 (1.85%-5.22%)	-3.36%	2.67% (1.97%-3.86%)	-2.54%
	50-69	Male	3.49 (1.51%-7.55%)	-3.05%	2.85% (1.46%-5.81%)	-2.82%
		Female	5.89 (2.82%-11.44%)	-2.44%	4.21% (2.25%-7.67%)	-2.22%
		Both	4.55 (2.76%-7.84%)	-2.7%	3.48% (2.28%-5.71%)	-2.48%
	70+	Male	7.96 (3.51%-15.99%)	-2.44%	6.17% (2.95%-12.45%)	-2.58%
		Female	12.33 (6.32%-21.77%)	-1.92%	9.14% (4.84%-16.07%)	-2.12%
		Both	10.23 (6.3%-16.23%)	-2.1%	7.71% (4.93%-12.02%)	-2.29%
Typhoid and paratyphoid fever	< 5	Male	1.21 (0.58%-2.18%)	-3.43%	1.11% (0.53%-2%)	-3.44%
		Female	0.96 (0.45%-1.79%)	-3.17%	0.89% (0.41%-1.65%)	-3.18%
		Both	1.09 (0.51%-1.99%)	-3.31%	1% (0.47%-1.8%)	-3.32%
	5-14	Male	21.64 (13.07%-31.91%)	-4.31%	9.29% (5.35%-14.27%)	-4.33%
		Female	17.03 (10.08%-26.58%)	-4.16%	7.36% (4.14%-11.8%)	-4.18%
		Both	19.22 (11.52%-29.06%)	-4.24%	8.28% (4.81%-12.86%)	-4.26%
	15-49	Male	1.47 (0.75%-2.5%)	-2.95%	1.07% (0.55%-1.81%)	-2.97%
		Female	1.89 (0.95%-3.16%)	-2.57%	1% (0.5%-1.71%)	-2.58%
		Both	1.64 (0.83%-2.73%)	-2.79%	1.03% (0.53%-1.78%)	-2.8%
	50-69	Male	0.094 (0.047%-0.16%)	-3.93%	0.076% (0.039%-0.13%)	-3.98%
		Female	0.11 (0.054%-0.19%)	-3.84%	0.077% (0.039%-0.14%)	-3.91%
		Both	0.099 (0.05% 0.18%)	-3.9%	0.077% (0.039-0.13%)	-3.97%
	70+	Male	0.023 (0.013%-0.036%)	-3.72%	0.022% (0.013%-0.035%)	-3.82%
		Female	0.022 (0.013%-0.034%)	-3.6%	0.02% (0.012%-0.032%)	-3.75%
		Both	0.022 (0.013%-0.035%)	-3.66%	0.021% (0.013%-0.033%)	-3.8%

Data abstracted from the Institute of Health Metrics and Evaluation Viz Hub.; DALY = Disability Adjusted Life Year

Geographic distribution of diarrhea morbidity in India

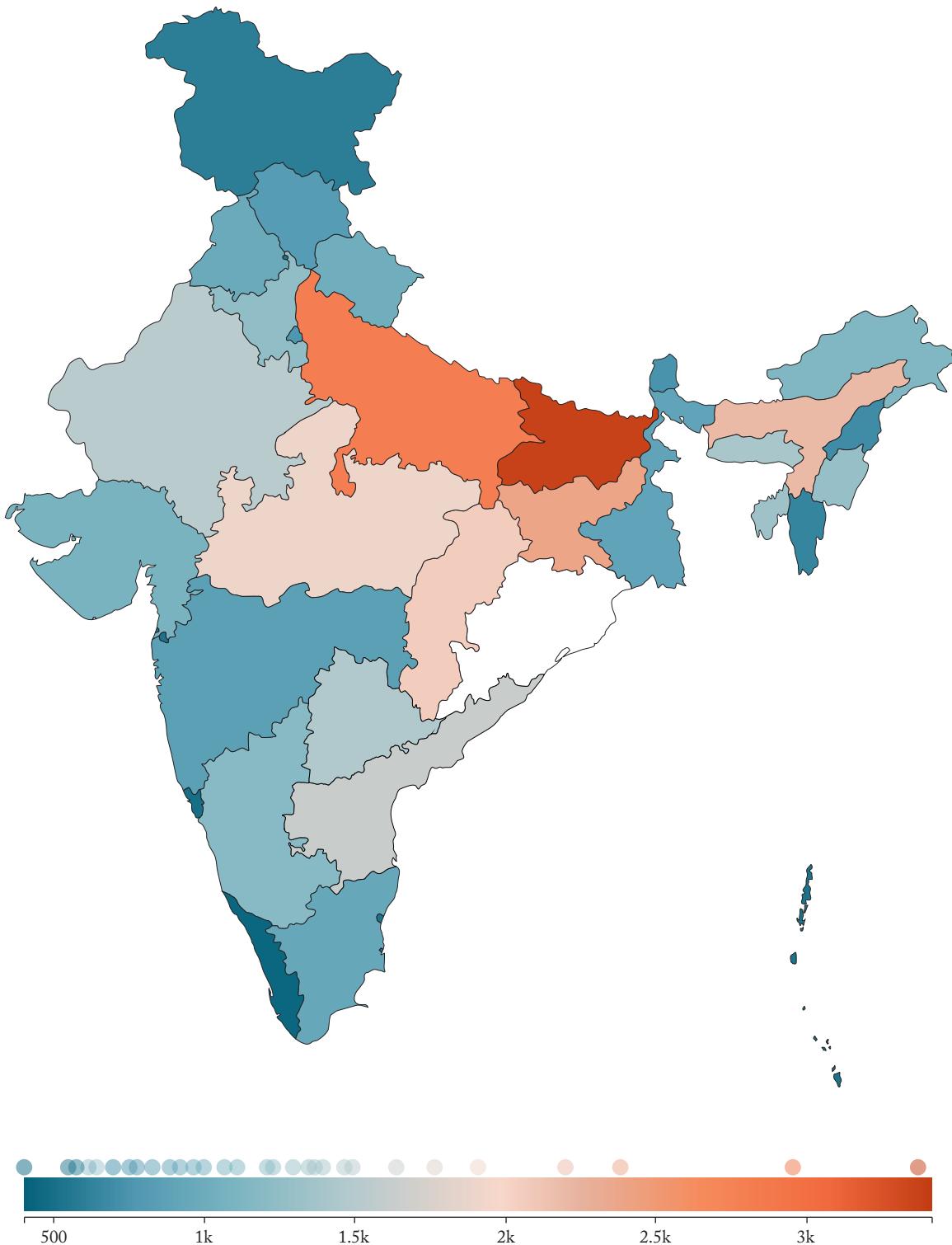


Figure 1. Diarrheal diseases, Both sexes, All ages, 2016, DALYs per 100,000; Data abstracted from the Institute of Health Metrics and Evaluation Viz Hub.; DALY = Disability Adjusted Life Year

Geographic distribution of typhoid morbidity in India

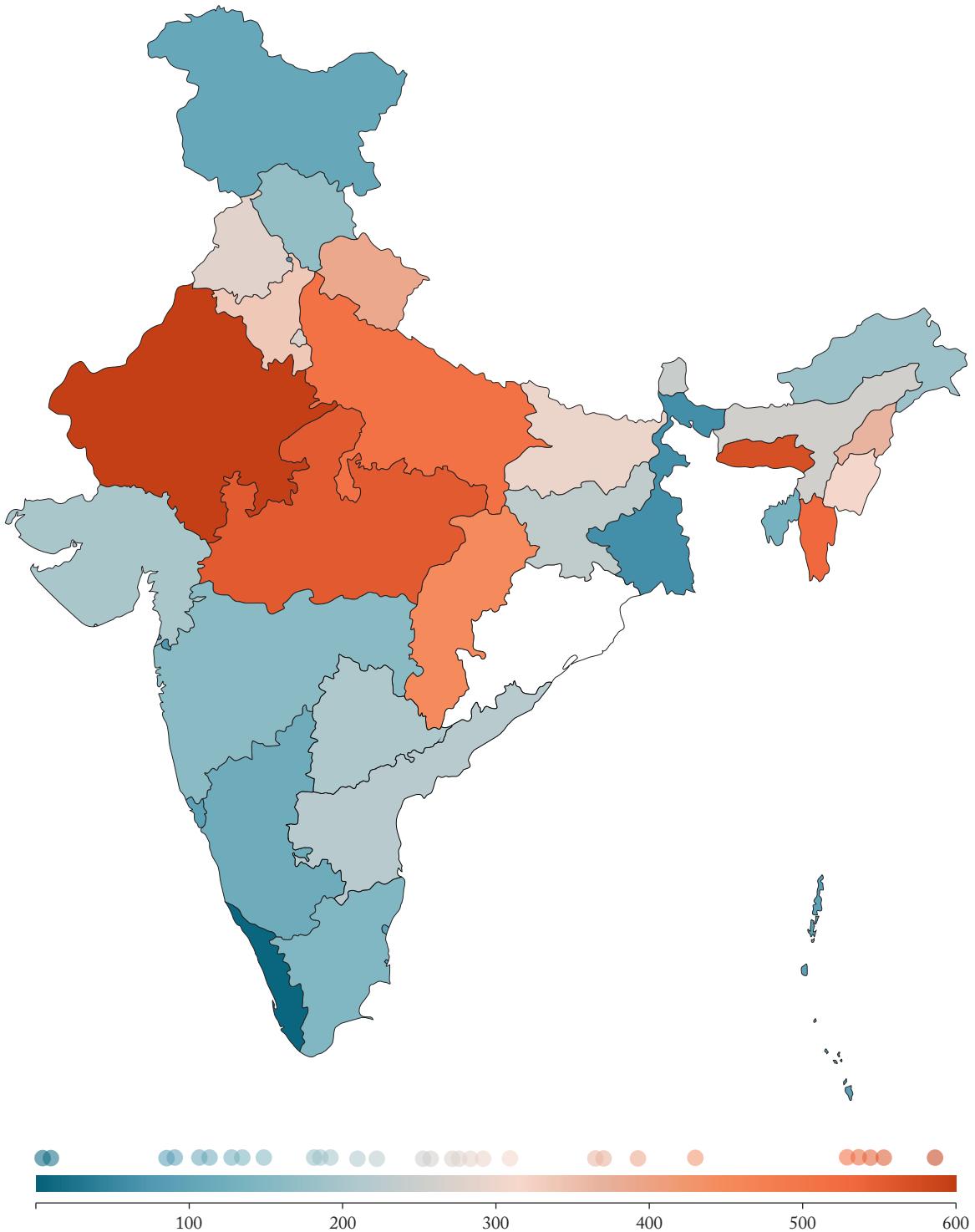


Figure 2. Typhoid fever, Both sexes, All ages, 2016, DALYs per 100,000; Data abstracted from the Institute of Health Metrics and Evaluation Viz Hub.; DALY = Disability Adjusted Life Year

In 2015, the World Health Organization (WHO) Initiative to Estimate the Global Burden of Foodborne Diseases published the first estimates of global foodborne disease incidence, mortality, and disease burden in terms of DALYs, based on work done by the WHO Foodborne Disease Burden Epidemiology Reference Group over several years (15). The estimates included 31 foodborne hazards causing 32 diseases, of which 11 were diarrheal disease agents (one virus, seven bacteria, three protozoa), seven were invasive infectious disease agents (one virus, five bacteria, one protozoan), 10 were helminths, and three, chemicals. It is estimated that the 31 hazards caused 600 million (95% UI 420 million–960 million) foodborne illnesses and 420,000 (95% UI 310,000–600,000) deaths in 2010. The most common infectious causes of foodborne illness were norovirus and *Campylobacter* spp. Foodborne diarrheal disease agents caused 230,000 (95% UI 160,000–320,000) deaths, and the most common cause of death was infection with nontyphoidal *Salmonella enterica* which causes both diarrhea and invasive disease. Other major infectious causes of foodborne deaths included *Salmonella Typhi*, *Taenia solium*, and hepatitis A virus. The global burden of foodborne disease by these 31 hazards was 33 million (95% UI 25 million–46 million) DALYs in 2010. Almost 40% of the foodborne disease burden was among children under five years of age.

SEAR had the second-highest burden per population, after Africa, with diarrheal disease the leading cause of foodborne disease burden. The main causes included enteropathogenic *E. coli*, enterotoxigenic *E. coli*, *Salmonella Typhi*, and *Vibrio cholerae*, with the helminths *Opisthorchis* spp., *Paragonimus* spp., and *Clonorchis sinensis* also important as foodborne pathogens (15).

With pathogens that are not necessarily eliminated by good hygiene, diarrheal disease affects all ages and occurs in all locations, but there is a strong relationship between poverty, poor environments, and the number and severity of diarrheal episodes, especially in young children. Poverty is associated with environmental conditions that facilitate the spread of disease, such as poor housing, crowding, dirt floors, lack of safe water and food, lack of toilets, and close interaction with domestic animals that may carry human pathogens. Poverty also affects feeding, if mothers are unable to breastfeed for the recommended six months or breastfeed too long because weaning foods are unavailable, if complementary feeding is inadequate and inappropriate, and if, after weaning, diets are deficient in energy and micronutrients. Illness places high metabolic demands on the body, and among children with a high incidence of disease, nutritional recovery between episodes may not occur (10). The situation is likely to be compounded by the lack of accessible, adequate, and affordable healthcare.

For diarrhea specifically, much of the medical treatment occurs outside the formal medical system, with care accessed through a range of traditional healers, the informal sector, and pharmacies that offer syndromic and frequently inappropriate drug therapy. Further, since an etiologic diagnosis is rarely made, the inappropriate use of antibiotics is a concern for all classes of society but particularly for the poor, who may be at greater risk because they cannot afford and complete a course of treatment, thus creating the environment for antibiotic resistance to emerge. The high out-of-pocket expenditure on healthcare is a concern and likely exacerbates poverty (24).

Control of enteric pathogens and typhoid

Alignment of goals and indicators with the 17 Sustainable Development Goals (SDGs) adopted by all United Nations member states in 2015 increases the likelihood of targeted policies and investments. The main goals for 2030 applicable to diarrheal diseases and enteric fevers are SDGs 3 (health and well-being), 6 (water and sanitation), and 2 (food security and nutrition).

Under SDG 3, target 3.2 aims to end preventable deaths of newborns and children under five years of age, with all countries aiming to bring neonatal mortality to 12 or fewer per 1,000 live births and under-five mortality to 25 or fewer per 1,000 live births by 2030. This is given further specificity for diarrheal disease by the Global Action Plan for Pneumonia and Diarrhoea, which sets a target of no more than one death due to diarrhea per 1,000 live births by 2025 (25).

Further, under SDG target 3.3, countries are working to end epidemics of major diseases, including waterborne diseases. SDG 3.9 aims to substantially reduce deaths and illnesses from hazardous chemicals and from air, water, and soil pollution and contamination. Safe water, sanitation, and hygiene will help reduce maternal mortality and end preventable deaths of newborns and children, as called for in SDG targets 3.1 and 3.2.

Under SDG 6, targets 6.1 and 6.2 use as indicators the proportion of the population using safely managed drinking water services and sanitation services and safely treated wastewater; 6.2, which aims to end open defecation, recognizes the need for special attention to women and girls and those in vulnerable situations.

SDG 2 aims to end hunger and achieve, by 2025, the internationally agreed targets on stunting and wasting in children under five years of age, and to address the nutritional needs of adolescent girls, pregnant and lactating women, and older persons, all of which are related to reducing the susceptibility to diarrheal disease and its consequences.

Table 4 summarizes the targets relevant to diarrheal disease for countries in the South-East Asia region.

Table 4. SEAR targets, status, and tools

2030 target	Current status	Tools
Diarrheal mortality less than 1 per 1,000 live births in children under 5 years; incidence of severe diarrhea reduced by 75% in children under 5, compared with 2010	SEAR: 9% of deaths in children <5 due to diarrhea in 2016; 8.6% of DALYs lost in children <5 due to diarrhea (11.11% in 2010)	Education, behavior change, WASH, ORS, zinc, point-of-care diagnostics, vaccines
Stunting reduced by 40% in children under 5 years compared with 2010	SEAR: 32.9% stunting in 2015 (38% in 2010)	Education, behavior change, WASH, appropriate management of diarrhea, vaccines
90% full-dose vaccination coverage, with 80% coverage in every district	SEAR: measles, less than 90% coverage; rotavirus, less than 20%; cholera and typhoid vaccines not introduced	Evidence-based decision making on vaccination and immunization
90% access to appropriate diarrhea case management, with 80% coverage in every district	India: approximately 30% appropriate management*	Education, behavior change, primary healthcare, improved facilities

Table 4. SEAR targets, status, and tools

2030 target	Current status	Tools
At least 50% coverage of exclusive breastfeeding during first 6 months of life	India: 54.9% of children breastfed (higher in Bangladesh)	Education, behavior change, support of mothers
Universal access to toilet that safely contains excreta	India: 59% of child stools appropriately disposed*	Education, behavior change, WASH, total sanitation programs
Improved drinking water sources at all healthcare facilities and homes	India: 89.9% of households have improved sources*	Education, behavior change, water safety, monitoring
Universal access to handwashing with soap and water at all healthcare facilities and homes	20%–50% access, depending on location and source of data	Education, behavior change, water safety, monitoring
Outbreaks: Respond to outbreaks within 48 hours Reduce outbreaks by 30%	India: acute diarrheal disease and foodborne disease outbreaks are most common outbreaks†	WASH, chlorination and other point-of-use disinfection, rapid response, improved laboratories, appropriate case management, vaccines, education
Food safety: Establish food safety standards in all countries, reduce foodborne disease mortality by 50%	India: acute diarrheal disease and foodborne disease are most common outbreaks†; SEAR second- highest (after Africa) for foodborne disease mortality	Food industry standards, local hygiene standards and monitoring, diagnostics for food contamination, education

*As reported by National Family Health Survey-4 (India).

†As reported by World Health Organization. Strategic Plan for Food Safety Including Foodborne Zoonoses 2013–2022, 2013 and WHO Estimates of the Global Burden of Foodborne Diseases, 2015.

‡As reported by WHO, UNICEF. Global Nutrition Targets 2025 – Breastfeeding Policy Brief (WHO/NMH/NHD/14.7) 2014

§As reported by United Nations. SDG Indicators 2019

As reported by World Health Organization. Roots for Resilience: A Health Emergency Risk Profile of the South-East Asia Region, 2017

DALY = disability-adjusted life-year; ORS = oral rehydration solution; WASH = water, sanitation, and hygiene.

Water, sanitation, and hygiene

The United Nations' Global Analysis and Assessment of Sanitation and Drinking Water (GLAAS) covered 10 of the 11 SEAR countries, with a total population of 1.8 billion, in its 2013–2014 reporting cycle. Overall, access to improved drinking water and sanitation services in the region was 92% and 49% (in 2015), respectively. More than 330 million people gained access to improved drinking water sources and nearly 250 million people gained access to improved sanitation in the 2005–2015 time period. The GLAAS strategy includes creating an enabling environment and developing sustainable financing to better align with the SDGs (26).

A 2018 report by the UN Joint Monitoring Programme, Progress on Drinking Water, Sanitation and Hygiene: 2017 Update and Sustainable Development Goal Baselines, presents the first global assessment of safely managed drinking water and sanitation services. About three in 10 people worldwide, or 2.1 billion, still lack access to safe, readily available water at home, and six in 10, or 4.5 billion, lack safely managed sanitation (14).

WHO's guidelines set out four principal recommendations:

- Sanitation interventions should ensure that all communities have access to toilets that safely contain excreta.
- The entire sanitation system should undergo local health risk assessments to protect individuals and communities from exposure to excreta, whether from unsafe toilets, leaks in storage, or inadequate treatment.
- Sanitation should be integrated into local government-led planning and service provision to ensure efficiency and sustainability.
- Greater investment and coordination by the health sector in sanitation planning is required to protect public health.

Hand hygiene reduces the transmission of enteric pathogens, but education and access to soap and water have been limiting factors, particularly among impoverished populations. A Cochrane review (27) found that handwashing promotion reduced the incidence of diarrhea in daycare centers and schools by approximately one-third in high-income settings, and may prevent a similar proportion in low- and middle-income settings. Further, community-based trials in low- and middle-income settings demonstrated a reduction in the incidence of diarrhea by approximately one-third following hand-washing promotion and was also effective in reducing incidence in a hospital-based trial in patients with a high risk of diarrhea.

A recent meta-regression analysis (28) of 135 studies, mainly conducted in low- and middle-income countries, showed that compared with a baseline of unimproved drinking water, point-of-use filter interventions with safe storage reduced diarrhea risk by 61% (RR 0.39; 95% confidence interval, CI, 0.32,0.48); high-quality piped water, 75% (RR 0.25; 95% CI 0.09, 0.67); and continuously available piped water to premises, 36% (RR 0.64; 95% CI 0.42, 0.98), respectively compared to a baseline of unimproved drinking water. Further, sanitation interventions reduced diarrhea risk by 25% (RR 0.75; 95% CI 0.63, 0.88), and interventions promoting handwashing with soap, 30% (RR 0.70; 95% CI 0.64, 0.77).

Breastfeeding and nutrition

Exclusive breastfeeding means the infant receives only breast milk, no other liquids or solids—not even water—with the exception of oral rehydration solution (ORS) and syrup or drops of vitamins, minerals, or medicines. The current WHO recommendations are exclusive breastfeeding for six months and then continued breastfeeding as complementary foods are introduced, up to 24 months of age. Exclusive breastfeeding has many proven benefits to both the infant and the mother. Breast milk contains all the nutrients an infant requires in the first six months of life, protects against respiratory infections and gastrointestinal infections, and decreases exposure to potentially contaminated food during a period of vulnerability in early childhood. Continued during diarrheal episodes, exclusive breastfeeding also diminishes the adverse effect on nutritional status. It has also been associated with a higher intelligent quotient (IQ) in children. In a systematic review and meta-analysis of 17 studies, a random-effects model found that breastfed subjects had a higher IQ (mean difference of 3.44 points; 95% CI 2.30, 4.58). However, studies that controlled for maternal IQ showed a smaller benefit from breastfeeding (mean difference of 2.62 points; 95% CI 1.25, 3.98) (29).

Those data underpin the campaign to promote exclusive breastfeeding for the first six months of life by increasing both the initiation and the duration of exclusive breastfeeding. The strategies include the following:

- “baby-friendly” hospital policies and actions to encourage breastfeeding, including early initiation and feeding on demand, and to discourage teats and bottle feeding;
- counseling and education provided by peers or health workers;

- mass media and community education; and
- mothers' support groups.

A meta-analysis by WHO of 23 studies of the effects of exclusive, partial, and no breastfeeding on diarrheal morbidity, hospitalizations, and mortality showed that differences could most clearly be identified when comparing exclusive with no breastfeeding; effect sizes were smaller for exclusive versus partial breastfeeding. Breastfeeding decreased diarrheal morbidity (RR 0.46, 95% CI 0.28, 0.78), risk of hospitalization (RR 0.28, 95% CI 0.16, 0.50), and diarrheal mortality (RR 0.23, 95% CI 0.13, 0.42). The greatest protective effect was seen in younger children, and there was little or no protection beyond infancy (30). Recent reviews indicate that promoting “kangaroo mother care” significantly increases breastfeeding in healthy neonates and decreases mortality, including that due to infections, in preterm neonates in developing countries (31, 32).

Complementary feeding practices

Complementary foods should be introduced at six months of age, and breastfeeding should continue for up to two years. Lack of appropriate, adequate, and timely complementary feeding in children six to 11 months increases rates of malnutrition, contributing to setting up a cycle where repeated infection leads to increasing nutritional deterioration, impaired immune function, and greater susceptibility to infection. Interventions to decrease infection or improve nutritional status are necessary to break the cycle (33).

Whether improved complementary feeding has a direct effect on enteric infections or typhoid is unclear, but interventions to prevent malnutrition, whether improved complementary feeding or dietary diversification, supplementation, and education, have benefits, particularly in food-insecure populations (34). Vitamin A supplementation has been recommended for young children in areas where deficiency is prevalent to prevent diarrhea, respiratory infections, and all-cause mortality, and although prevalence of deficiency has declined in many parts of the world, rates in South Asia are still high (35). Cochrane reviews recommend supplementation in children six months to five years of age, but not in neonates or infants one to six months of age (36–38). Preventive zinc supplementation also reduces incidence of diarrhea (RR 0.87; 95% CI 0.81, 0.94) and had a nonsignificant effect on diarrhea mortality in a systematic review (39).

Food safety

Diseases that people get from eating contaminated food cause illness, disability, and deaths around the world, as revealed by the first-ever WHO Estimates of the Global Burden of Foodborne Diseases (40). Foodborne diseases, especially those caused by bacteria, viruses, parasites, and fungi, are preventable, and education in safe food handling is critical for prevention, including to contain antimicrobial resistance.

WHO developed the Five Keys to Safer Food Programme to assist member states in promoting safe food-handling behaviors and educate all food handlers, including consumers, about tools that are easy to adopt and adapt. The program explains the basic principles of preventing foodborne diseases by keeping the environment and food clean, separating raw and cooked food, cooking food thoroughly, storing food at safe temperatures, and using safe water and raw materials.

The management of foodborne disease requires both prevention and rapid detection and response. Surveillance systems that can rapidly detect food safety events and outbreaks and monitor trends in priority foodborne pathogens are needed, particularly to track circulation and variation of human pathogens and to monitor antimicrobial resistance. Such systems have been established in developed countries but are lacking in most of the developing world. WHO has recently considered the use of whole genome sequencing for foodborne diseases to increase the speed of detection and response and to develop more targeted responses (40).

Vaccines

Rotavirus vaccine

Rotavirus was once the leading cause of severe gastroenteritis in children under five years of age worldwide, resulting in approximately 40%–60% of diarrheal hospital admissions and approximately half a million deaths. Beginning in 2006, the United States and then many countries in the Americas and Europe, as well as Australia, adopted rotavirus vaccines as part of their routine childhood vaccination programs. Two orally administered, live attenuated rotavirus vaccines, Rotarix® (GlaxoSmithKline Biologicals, Belgium) and RotaTeq® (Merck Vaccines, USA), have been introduced in more than 90 countries worldwide. Many studies unequivocally demonstrate the benefits of rotavirus vaccines in reducing the burden of severe childhood gastroenteritis and mortality (41).

After the vaccines were licensed and introduced, WHO recognized a need to prove their efficacy in less industrialized countries, where other oral vaccines have been less effective than in developed countries, and recommended that trials be conducted. After trials in several Asian and African countries demonstrated a vaccine efficacy of 50%–70%, WHO in 2009 recommended that all countries include rotavirus vaccines in their national immunization programs, particularly those with high child mortality due to diarrhea (42). The most recent estimates indicate that because of the vaccine and other interventions, global mortality from rotavirus gastroenteritis has been cut in half (recently estimated at 120,000–215,000), and the number of rotavirus acute gastroenteritis hospitalizations is estimated to have fallen by 38% (43). Recent vaccine effectiveness studies in Africa have demonstrated marked reductions in morbidity and mortality (44, 45).

The uptake of rotavirus vaccination in sub-Saharan Africa and the Americas has been high, but few Asian countries have introduced it nationally, despite their well-characterized burden of rotavirus disease. Two studies have demonstrated the effectiveness of the vaccines as partial introduction in routine programs in Asia, with 41.4% (95% CI 23.2%–55.2%) effectiveness against acute rotavirus diarrhea in Bangladesh (46) and 88% (95% CI 76%–94%) overall vaccine effectiveness for hospitalized rotavirus diarrhea in Thailand (47).

The reasons for delayed vaccine introduction in Asia likely vary by country but may include multiple hurdles to availability of evidence, prioritization and decisionmaking, planning, and introduction. In India, an indigenous Indian vaccine (Rotavac) was evaluated in phase 3 clinical trials and demonstrated 53.6% efficacy (95% CI 35.0%–66.9%) against moderate to severe rotavirus diarrhea (48). The vaccine was licensed in 2014 and introduced into the national program in 2016, initially in four states and with another six states in further phases. A second rotavirus vaccine made in India (Rotasiil) was licensed in 2017 and has been introduced in one state (49). Both vaccines are WHO prequalified and cost less than the vaccines made by GlaxoSmithKline and Merck. Gavi, the Vaccine Alliance, has supported vaccine introduction in multiple countries in Africa and South America, and introductions are pending in Asia; constraints due to supply issues could be addressed by deploying the Indian products.

Some questions regarding the performance of rotavirus vaccines remain to be addressed. One is the duration of protection, particularly in the second year of life, since the Bangladesh effectiveness study showed that vaccine-induced protection appeared to wane from 45.2% in the first year of life to 28.9% during the second year, with the latter estimate not reaching statistical significance (46). This study did not identify any measurable indirect protection, despite its having been designed to capture such effects. Further, the effectiveness of the vaccine in malnourished infants is unknown, an important gap because studies in Africa have shown rapid waning of vaccine effectiveness in stunted children (50).

Oral cholera vaccines

Although endemic cholera is primarily a disease of children, adult morbidity and mortality can be significant, especially during epidemics. Cholera mortality is due to rapid and profound dehydration, but oral or intravenous rehydration, if administered in time and in adequate volume for replacement, has a

dramatic effect on survival. Access to care and appropriate case management can reduce the cholera mortality rate to well below 1%.

However, access to acute care is frequently a limitation for remote populations and overburdened healthcare systems, making a cholera vaccine an attractive option for disease prevention in conjunction with water safety and sanitation improvements and behavioral interventions. A live attenuated vaccine is available but expensive and is used mainly for travelers. WHO's prequalified whole-cell oral vaccine with recombinant B subunit (Dukoral) is not widely available in Asia, although it was extensively evaluated in Bangladesh. Bivalent whole-cell oral cholera vaccines that target *V. cholerae* O1 and O139 are made in India (Shanchol) and South Korea (Euvichol) and are prequalified, and other Asian countries, including Vietnam and Bangladesh, have vaccine manufacturers.

The inactivated vaccines evaluated in vaccine trials in India had effectiveness of 69% (95% CI 14.5%–88.8%) with two doses over two years of follow-up (51). In Bangladesh, when evaluated with and without behavioral interventions, protective effectiveness of two doses was 37% (95% CI 13%–55%; P=0.005) in the vaccination group and 45% (95% CI 16; 9%–67%) in the vaccination and behavioral change group of individuals older than one year (52). The short-term effectiveness of a single dose of Shanchol was estimated at 80% (95% CI 61%–100%) following a campaign in South Sudan in 2015 in individuals older than one year (53). In another study using a single dose, with follow-up for two years, protective efficacy was 52% (95% CI 8%–75%) against all cholera episodes and 71% (95% CI 27%–88%) against severe cholera episodes in participants aged five to 14 years. For participants 15 years or older, vaccine protective efficacy was 59% (95% CI 42%–71%) against all cholera episodes and 59% (95% CI 35%–74%) against severe cholera. In participants younger than five years, the vaccine did not show protection against all cholera episodes (protective efficacy –13%, 95% CI –68%–25%) or severe cholera episodes (–44%, 95% CI –220%–35%) (54).

Based on those data, WHO has recommended the use of killed whole-cell cholera vaccines in areas with endemic cholera, in humanitarian crises with high risk of cholera, and during cholera outbreaks (55). Gavi has recently expanded support for the use of the vaccine not just for outbreaks and humanitarian crises but also for endemic use, which opens up many opportunities for endemic SEAR countries.

Measles immunization

Measles is known to predispose to diarrheal disease, secondary to measles-induced immunodeficiency. Measles immunization has been estimated to decrease diarrheal episodes by 1%–4%. In Bangladesh, although immunization coverage has increased significantly, lack of measles immunization has been shown to be associated with diarrhea (56).

Typhoid vaccine

For decades, two typhoid vaccines have been widely available, Ty21a (oral) and Vi polysaccharide (parenteral) vaccines. Recently, WHO has prequalified and recommended a Vi tetanus toxoid (Vi-TT) conjugate vaccine, Typbar-TCV, as the preferred vaccine for all ages, and funding support is available from Gavi for eligible countries.

Although the Ty21a (five trials) and Vi polysaccharide (six trials) vaccines had been widely evaluated and found effective, questions concerned the duration of protection, efficacy in younger populations, and need for booster doses, causing WHO to prefer the typhoid conjugate vaccine, even though Vi-rEPA vaccine and a Vi-TT that is not prequalified (Pedatyph) were the only ones evaluated for efficacy in field trials. Administration of two doses of the Vi-rEPA vaccine in a trial in Vietnam prevented 50%–96% of typhoid cases during the first two years after vaccination (year 1: 94%, 95% CI 75%–99%; year 2: 87%, 95% CI 56%–96%). Two doses of the PedaTyph vaccine in India gave 94% protection (95% CI –1%–100%), according to a small study (57). Vi-TT (TypBar TCV), a WHO-prequalified vaccine, has been evaluated for efficacy in a human challenge study, although in a nonendemic group (58). More field trials are needed to evaluate vaccine efficacy (59), and some trials in Africa and Asia have begun.

Healthcare management

Primary care

WHO and UNICEF updated their guidelines for managing diarrheal disease in all children in 2004 (60), and WHO updated the guidelines for integrated management of childhood illness in 2005 (61). Measures to treat diarrhea in primary care include the following:

- rehydration with ORS, which is absorbed in the small intestine and replaces the water and electrolytes lost in the feces;
- zinc supplements, which reduce the duration of a diarrheal episode by 25% and are associated with a 30% reduction in stool volume; and
- nutrient-rich foods, including breast milk, to break the vicious circle of malnutrition and diarrhea.

Another recommendation involves vitamin A supplementation: once for infants and every four to six months for children 12–59 months of age in populations where the prevalence of night blindness is 1% or higher in children 24–59 months of age, or where the prevalence of vitamin A deficiency (serum retinol 0.70 μmol/l or lower) is 20% or higher in infants and children 6–59 months of age (62).

District hospitals

For diarrheal disease, immediate assessment of dehydration and prompt rehydration are critical. Intravenous fluids are required in case of severe dehydration or shock. In children with collapsed veins, other means, such as intraosseous access, may be necessary. Consultation or referral is required for management of persistent diarrhea, when there is blood in stool, or if there are signs of dehydration.

For enteric fever, WHO's previous Integrated Management of Adolescent and Adult Illness guidelines for health workers at first-level facilities (district hospitals) recommended ciprofloxacin (62). Because of the high rate of fluoroquinolone resistance and the wide prevalence of the H58 haplotype, which is resistant to previously used antibiotics, the antibiotic of choice in the region is now azithromycin. Treating any fever without known etiology as enteric fever is a major reason for the misuse of antibiotics. Although sensitivity to older drugs, such as chloramphenicol, has been reported, the known side effects preclude their wide usage (63). The emergence of an extensively drug-resistant strain in Pakistan is also a matter of concern (64).

Higher-level facilities

Children with severe dehydration plus other clinical symptoms, electrolyte disturbances, or shock may need to be managed in higher-level facilities, including those that can provide intensive care. In such settings, survival is generally higher if patients present early in illness.

The bulk of enteric fevers can be managed in outpatient or first-level referral facilities, but neurological symptoms and ileal perforation are known complications requiring higher-level care. Appropriate therapy depends on local antimicrobial susceptibility patterns and may include cephalosporins, but as stated above, azithromycin is currently the oral drug of choice. Supportive therapy, early recognition, and prompt surgery improve survival and outcomes.

Cost-effectiveness of prevention and treatment

Cost-effectiveness studies can focus on different components of the prevention, recognition, and management of illness. Studies of vaccination for prevention find that the cost of the vaccine and its delivery, the burden of disease, and the efficacy of the vaccine affect estimates of cost-effectiveness. However, use of the vaccine can reduce disease in unvaccinated individuals, as when the incidence of rotavirus gastroenteritis in older children and adults fell after rotavirus vaccination was introduced for infants in the United States (65), or reduce a nontarget disease, as seen with the reduction in febrile seizures in rotavirus-vaccinated children. The analysis of cost-effectiveness is thus complicated, particularly when such indirect effects are seen in some settings and not others (66, 67).

Etiology for appropriate evidence-based management of illness is rarely established in primary care because of the lack of point-of-care tests, and it is also rarely done in first-referral units because of the lack of resources and the expense of testing, which is frequently greater than the cost of empiric therapy. For diagnostics, the multiplicity of causes of diarrhea is a challenge for designing and evaluating diagnostic strategies. For enteric fever, the sensitivity of available tests, such as blood culture, is low, and serological tests like the Widal test, which has very low specificity, are used instead, making the evaluation of cost-effectiveness of strategies difficult.

Cost-effectiveness analyses for management of illness are influenced by the cost of the illness, and since diagnostics are rarely used for either enteric infections or enteric fever, and antibiotics in SEAR tend to be cheap generics, the cost of illness is usually orders of magnitude lower than in the industrialized world. Disease burden and consequently cost-effectiveness of interventions are strongly influenced by the case fatality ratio, which for both conditions has fallen in the past two decades with greater access to healthcare.

The treatments that are available (rehydration, zinc, and appropriate antibiotics) are generally effective, but their supply chains may be complicated, driving down their use. Inappropriate antibiotic use is common and increases the measured direct cost of illness but does not contribute to good outcomes, and it may result in the development of resistance.

The effect of environmental interventions on specific disease conditions, even though mediated through the environment, can be difficult to evaluate because of the challenge in determining exposure, the potential for nonlinear effects, and the uncertain dose-response (68).

Interventions related to water, sanitation, and hygiene can significantly raise social and economic conditions. Privacy for women changes their station in society, for example, and not having to walk to water sources allows girls to go to school and women to contribute to family income.

Other, more directly health-related interventions also contribute to greater potential educational achievement through lowered illness and improved cognitive development, which leads to economic benefits.

WASH

Large-scale investments in piped water and sanitation infrastructure are challenging in resource-limited countries. Particularly for water, approaches can be difficult to develop, given the dangers of depleting or contaminating groundwater. The costs of investment in piped water and sanitation in India have been recently estimated by Nandi *et al.* (69). For piped water, the average per capita investment cost ranges from US\$89 (sensitivity range \$62–\$116) to \$203 (sensitivity range \$142–\$264) across wealth quintiles. For sanitation, the average per capita investment costs are US\$91 (sensitivity range \$64–\$118) to \$429 (sensitivity range \$300–\$558).

The health benefits of WASH can be converted to a common money metric, but these estimates are

frequently crude, relying on limited measurements of cost or value. These estimates are further complicated by the noncomparability of studies that were conducted at different times, with different base years and effects, and with all or only some components of WASH. Interventions focus on technology options or tools to change WASH practices, better provision of services, and a stronger enabling environment with better policies, processes, and resources.

In 2017, UNICEF India reported results from a study on the economic benefits of sanitation in the country. With a total sample of 18,376 respondents, representing 10,068 households across 12 states, it found that rural households in India, living in open defecation-free environments, on average benefited by US\$780 from averted deaths, time saved, and deferred medical costs; the estimated economic return on investment for every dollar invested in sanitation was 430% (unpublished).

Breastfeeding, nutrition, and food safety

The World Breastfeeding Costing Initiative has estimated a cost of US\$130 per live birth to implement the WHO and UNICEF Global Strategy for Infant and Young Child Feeding (70), but this included maternal allowances. For India, the World Bank estimates a cost of US\$5.13 per child for implementation of infant and young child nutrition counseling, along with \$10 million for promotion of breastfeeding activities (71). The attributable economic burden of inadequate breastfeeding is estimated to be US\$7 billion for disease and an additional \$7 billion for cognitive losses, making breastfeeding a cost-effective intervention, with every dollar invested in breastfeeding giving a return of \$35 (72).

UNICEF estimates that 19.9% (95% CI 19.4%–20.4%) of children six to 23 months of age in India meet the criteria for minimum dietary diversity (73). The data on effectiveness of both nutrition education and complementary feeding strategies appear promising (34), particularly in food-insecure populations, but outcomes are not always standardized and rarely include cost-effectiveness. A 2005 WHO review, based on data from 2000, indicated that provision of supplementary food, nutritional counseling, and growth monitoring in the poorer SEAR countries, following immunization, appropriate management of diarrhea, and micronutrient supplementation, was expensive but had the potential to avert 16 million DALYs per year with incremental cost-effectiveness ratio of 44 384\$ per DALY averted (74).

Although research is now moving beyond description of contaminating microorganisms to quantitative microbial risk assessment (75), few studies have addressed interventions for food safety in SEAR, and none have examined cost-effectiveness of either processing or education on health outcomes.

Vaccination

Several cost-effectiveness studies have examined the potential benefits of adding rotavirus vaccine to the national immunization programs of some SEAR countries. This modeling has varied by approach, inputs of vaccine efficacy, estimated herd protection, vaccine costs, outcomes assessed, and rate of discounting, but in all scenarios, vaccine introduction was predicted to be cost-effective or very cost-effective. Table 5 summarizes individual country studies (multicountry studies, including countries outside the region, are not included).

Table 5. Summary of cost-effectiveness analyses of rotavirus vaccine introduction for SEAR countries

Country (reference)	Approach	Type of evaluation	Price of vaccine /dose	Unit	ICER	Threshold	Conclusions
Indonesia (76)	Regression equation	CUA	\$7	\$/DALY	\$120	\$1,560	Very cost-effective
India (77)	Markov model	Cost-effectiveness analysis	\$5.8	\$/life yr gained	\$165	\$570	Very cost-effective
Thailand (78)	Decision tree model	CUA	\$7	\$/DALY	\$370	\$3,070	Very cost-effective
India (79)	Excel based model	CUA	\$0.5	\$/DALY	\$21.41	\$1,017	Very cost-effective
Thailand (80)	Decision tree model	CUA		\$/DALY	\$3,938	\$3,841	Very cost-effective
India (81)	Agent based model	CUA	Incorporated	\$/DALY	Cost saving (out-of-pocket included) \$70.89	GDP per capita	Very cost-effective
India (82)	Decision tree model	CUA	\$1	\$/DALY	\$139	\$1,490	Very cost-effective
Indonesia (83)	Excel based model	CUA	\$5.17	\$/QALY	\$155	\$3495	Very cost-effective
Bangladesh (84)	TRIVAC model	CUA	With (without) Gavi pricing	\$/DALY	\$82 (\$871)	GDP per capita (cost-effective)	Very cost-effective
India (85)	Dynamic simulation model	CUA	\$1	\$/DALY	\$56	GDP per capita	Very cost-effective
Bangladesh (86)	Decision tree model	CUA	\$1	\$/DALY	\$740	GDP per capita	Very cost-effective

GDP = gross domestic product; DALY = disability-adjusted life-year; ICER = Incremental Cost Effectiveness Ratio; QALY = quality-adjusted life-year; CUA = Cost utility analysis

Very few studies have explored the cost-effectiveness of adding oral cholera vaccine to national immunization programs in SEAR countries, in part because recommendations for use have not been clearly defined to fit with routine immunization, and the disease burden is uncertain because of poor reporting. Table 6 summarizes the available studies.

Table 6. Summary of cost-effectiveness analyses of oral cholera vaccine introduction							
Country (reference)	Approach	Type of evaluation	Price of vaccine /dose	Unit	ICER	Threshold	Conclusions
India, Bangladesh, Indonesia, Mozambique (87)	Static model, including indirect protection	Cost-effectiveness analysis	\$0.6	\$/DALY	\$331–\$3,400 with indirect protection	GDP per capita for each country	Cost-effective only if indirect protection included and for younger groups
Bangladesh (88)	VICE model	Cost-effectiveness analysis	\$1.85	\$/DALY	\$592 for hot spots to \$3,113	\$2250	Very cost-effective to not cost-effective, depending on strategy
Bangladesh (89)	Dynamic model, including herd protection	Cost utility analysis	\$0.77–1.40	\$/DALY	\$591–\$823 for 1–14 years	GDP per capita	Very cost-effective

DALY = disability-adjusted life-year; GDP = gross domestic product; ICER = Incremental cost effectiveness ratio; VICE = visitors, industry, community and environment

For the older polysaccharide and the new conjugate typhoid vaccines, cost-effectiveness analyses conducted in SEAR are summarized in Table 7. For typhoid vaccines, approaches have included campaigns, routine vaccination, school-age vaccination, school and preschool vaccination, or a combination of such approaches. Depending on the models, the drivers of cost-effectiveness include vaccine costs, case fatality rates, the disease incidence, the presence of carriers, and the vaccination strategy.

Table 7. Summary of cost-effectiveness analyses of typhoid vaccine introduction

Country (reference)	Approach	Type of evaluation	Price of vaccine /dose	Unit	Economic evaluation	Threshold	Conclusions
India (90)	Static model	Cost-benefit analysis	\$0.75–\$3	\$/case	\$6.70–\$83 per case averted, depending on strategy	—	Societal cost benefit for all strategies
India, Indonesia, Vietnam, Pakistan (91)	CHOICE	Cost-effectiveness analysis	\$0.60–\$5	\$/DALY	\$147–\$3,779 per case averted, depending on location	GDP per capita	Cost-effective or very cost-effective in India, Indonesia, and Pakistan; depending on strategy, not in Vietnam
India (92)	Static model	Cost-benefit analysis	\$1.11	\$/DALY	\$147–\$454 per case averted, depending on strategy	\$1,045	Cost-effective or very cost-effective in moderate endemicity, depending on strategy; cost-saving in high-endemicity setting

DALY = disability-adjusted life-year; GDP = gross domestic product; ICER = Incremental cost effectiveness ratio.

Implementation of control strategies

The WHO program for control of diarrheal diseases was established in 1980 and integrated first with control of acute respiratory illness and then with the Integrated Management of Childhood Illness program, which seeks to build primary care and referral systems for acute disease in children. These programs required the establishment of tiered training, reporting, referral, and monitoring systems involving staff at multiple levels of the healthcare system. Diarrhea treatment units have served as training units and aided research into case management. Partner agencies, such as UNICEF and PATH, have engaged with national and state governments and WHO to promote education, behavioral interventions regarding hygiene and sanitation, improvement in water supply, and complementary feeding and nutritional assessments.

The current Global Action Plan for Prevention and Control of Pneumonia and Diarrhea seeks to engage multiple stakeholders in improving financing, policymaking, and service delivery. The Triple Billion Targets endorsed in the 71st World Health Assembly in May 2018 are supported by metrics for universal healthcare coverage. The United Nations Commission on Life-Saving Commodities for Women and Children addresses delivery systems for critical products, like ORS and zinc, that could considerably improve diarrhea control. The Global Vaccine Action Plan, endorsed by the World Health Assembly in 2012, calls for delivery of vaccines as part of the package of complementary interventions for control of diarrhea, among other diseases. The integration of behavior change with WASH interventions can have health benefits beyond reducing diarrheal disease, but implementing—and sustaining—any intervention to improve health outcomes is complex because strategies typically need to be multifaceted and adapted to the local context and healthcare system. Further, the strategies involve different levels of care and multiple participants—patients, providers, and organizations.

The incidence of severe diarrheal disease has declined, and diarrheal disease mortality continues a downward trajectory—improvements attributed to increased use of oral rehydration, improved nutrition, increased breastfeeding, better supplemental feeding, maternal education, measles immunization, and improvements in hygiene and sanitation. But morbidity continues. In India, the National Family Health Survey–4 reported that about half of all children with diarrhea had received oral rehydration solution, and about 20% had received zinc, in the prior two weeks. These figures indicate considerable room for improvement. Targeted and mass media interventions showed improvements during the period of study (94), but their incorporation into routine processes and their sustainability are not optimal. Better prevention and primary and secondary care are essential to reduce disease and improve case management.

One success story in India over the past few years involves rotavirus vaccine, which is now provided to almost half the Indian birth cohort of 27 million, with plans for further scaling up. Other SEAR countries, including Nepal, Myanmar, Thailand, and Bangladesh, have made plans for its introduction, largely with Gavi support.

The prevention and management of diarrheal disease are based on simple principles, and the tools for its prevention and treatment are available and are being implemented, resulting in declines in mortality in the past three decades. However, the remaining disease burden affects the poorest and most vulnerable, not just with severe disease but also with long-term consequences for growth and development. Addressing this equity issue requires multisectoral interventions, along with better primary care in all parts of the region.

Interventions still tend to be top-down, vertical programs. For example, food safety interventions require the engagement of stakeholders beyond the health sector, but they are not often a priority at the local level, with small vendors. Micro- and macronutrients prevent deficiency and aid in recovery from disease, but supply and delivery constraints exist, particularly for zinc, which forms part of the diarrhea management package. Age-appropriate complementary feeding and nutritional supplements for malnourished children are also important for managing diarrhea and its consequences, but although midday meals and school meal programs have begun to address the nutritional needs of older children, the reach and quality of supplementation and feeding programs for younger children are variable.

For typhoid, the healthcare system continues to rely on the easy availability of antibiotic treatment instead of focusing on prevention through safer food and water. No standardized treatment guidelines for typhoid are available, treatment is empirical in most parts of SEAR, and in many countries, access to antibiotics does not require a prescription. The increasing rates of antibiotic resistance make this approach a matter of concern.

Oral rotavirus vaccines have decreased efficacy in children living in poor environmental conditions—the very children who need prevention the most. Cholera and typhoid vaccines have not yet been introduced into the national immunization programs, although there are plans for introduction of a locally manufactured oral cholera vaccine into parts of Bangladesh.

Research agenda

A consultation of more than 150 experts, using the methods of the Child Health and Nutrition Research Initiative, conducted a systematic review and in 2013 published research priorities for the next 15 years (95). More recently, interventions for diarrhea and to prevent the consequences of diarrheal disease have also been reviewed (96, 97). Table 8 highlights the priorities that such reviews have identified.

Table 8. Priority research topics

Area	Research focus
Epidemiological research: etiology, burden of disease, and consequences	Effect of coinfections on disease and response to treatment Cognitive deficits associated with diarrheal disease and stunting; duration and consequences Effect of acute, prolonged, persistent, and recurrent diarrhea on growth of children and on adult height
Epidemiologic research: risk factors	Mechanisms (at gut and immunologic level) by which malnutrition and various micronutrient deficiencies increase risk of severe diarrhea Role of vitamin D deficiency in diarrhea risk Effect of nutritional imbalances on frequency and quantity of acute diarrheal disease
Epidemiological and clinical research: prevention and treatment	Biomarkers of “gut health” (e.g. gut barrier function, inflammatory biomarkers) that identify children at risk of chronic enteropathy Role of short-chain fatty acid delivery to colon in enhancing sodium and water absorption, reducing fluid secretion, and facilitating mucosal repair Role of enteral glutamine in local and systemic immune responses Utility of targeting NKCC, K channels, and Na-coupled transporters in diarrhea therapy Microbiome modification to prevent diarrhea and promote gut absorptive capacity Causes of poor efficacy of live oral vaccines in low- and middle-income countries
Product development: diagnostics	Affordable point-of-care diagnostics for diarrhea (including cholera alone, combination of viral pathogens, viral pathogens alone, Cryptosporidium, and Giardia) Sensitive test for typhoid in blood or stool, point-of-care test for typhoid, point-of-care tests to detect water contamination, and tests for food contamination
Product development: treatment	Safe and effective antisecretory (or transporter targeted) agents Anticryptosporidial therapy Combination ORS and zinc or calcium therapy to reduce duration of diarrhea

Table 8. Priority research topics

Area	Research focus
Product development: vaccines	<p>Better rotavirus and cholera vaccines (oral, parenteral)</p> <p>Combination typhoid-paratyphoid-nontyphoidal Salmonella vaccines</p> <p>Shigella vaccines (mono- and multivalent) ETEC vaccines</p> <p>Campylobacter vaccines (for humans, animals, poultry)</p>
Operational research: intervention delivery	<p>Strategies to improve availability and uptake of effective interventions for diarrhea (e.g. 2009 WHO 7-point plan)</p> <p>Nutritional diversity to enhance appropriate diarrhea management</p> <p>Caregiver demand for ORS and zinc, particularly in remote areas</p> <p>Evaluate effect of community-led total sanitation approach on decreasing diarrhea risk</p>
Operational research: evaluation of strategies and tools	<p>Benefits of waterless hand sanitizer use on diarrhea risk in household and school settings, particularly in water-constrained areas</p> <p>Better food safety in households</p> <p>Effect of interventions to support mothers (e.g. reduce maternal depression, strengthen maternal coping, problem solving for child health) on diarrheal disease outcomes</p> <p>Low cost, sustainable health education packages through community involvement (community motivation steps) to mothers to prevent diarrhea and assess effects on children's cognition and school achievement</p>
Operational research: monitoring and evaluation	<p>Factors that drive care-seeking behavior during childhood diarrheal disease</p> <p>Attributes of successful and sustainable childhood diarrhea programs</p> <p>Test indicators to determine effectiveness of Integrated Management of Childhood Illnesses and Integrated Community Case Management in reducing diarrhea burden</p> <p>Effectiveness (in terms of supply-demand and cost of alternative distribution networks) of zinc and ORS, in particular in rural or remote areas</p> <p>Best monitoring indicators to assess full process of program implementation (e.g., access, availability, sales of product, compliance with full 10–14 day course, geographic coverage, equity, knowledge of providers and caregivers)</p>
Strategic research	<p>Integration of health education services in government and NGOs healthcare facilities, cost-effectiveness for developmental outcomes</p> <p>Strategies and messages that convey advantages of ORS and zinc (compared with antibiotics or other drugs) to healthcare providers</p> <p>Stages of behavior change to tailor effective messages</p> <p>Most effective mix of WASH interventions in different epidemiological settings Measurement of vaccine benefits after introduction to influence decision-making for future vaccines</p>

Conclusion

As the decline in diarrheal disease deaths demonstrates, today's interventions to prevent or treat diarrheal diseases and typhoid have proven their efficacy, but to meet the Sustainable Development Goals of health and equity, they need to be expanded to universal coverage. In addition, new products, tools, and strategies will enhance the efficacy of interventions—for example, point-of-care sensitive and specific diagnostics, treatment strategies based on the pathophysiology of the infection, prevention of water and food contamination, more effective sanitation, improved performance of oral vaccines, and development of new vaccines. The looming threat of increasing antimicrobial resistance makes investment in approaches that decrease the use of antibiotics a necessary and urgent driver of better prevention and management approaches.

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Antimicrobial resistance and hospital-acquired infections

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Antimicrobial resistance (AMR) occurs when infections that could once have been treated with drugs no longer respond to treatment. This is a growing issue worldwide, but it particularly affects South-East Asia, where limited water, sanitation, and hygiene (WASH) services facilitate the spread of infection while widespread over-the-counter availability of antibiotics has led to their overuse and selection for resistance (1).

In India, more than 58,000 deaths a year may be attributable to just two common resistant organisms: extended-spectrum beta-lactamase producers and methicillin-resistant *Staphylococcus aureus* (MRSA) (2). In Thailand, 19,000 deaths are caused by multidrug-resistant bacteria each year, and on a population basis, this figure is approximately three to five times greater per capita than the number of such deaths in the European Union or the United States (3). Worldwide, 214,500 neonatal sepsis deaths have been attributed to resistant pathogens, including 56,500 in India (4).

Rising resistance will cause the most harm for those living in poverty, and it has the potential to set back developing countries' healthcare systems by raising the costs of treating common infections (5).

In India and Nepal, 67% of healthcare expenses are paid for out-of-pocket (6,7). In India alone, estimates of the population that will be pushed into poverty each year by such medical expenses range from 46 million households (7) to 57 million people (6). Also in India, up to 80% of out-of-pocket medical expenditure is spent on medicines, including antibiotics (6). In Nepal and Timor-Leste, 77.1% and 70% of out-of-pocket payments are spent on medicines, respectively (6). India is in the process of rolling out universal health coverage in the form of Ayushman Bharat (6), which aims to provide funding for secondary and tertiary care to 100 million of the poorest families. India's Jan Aushadhi scheme is an initiative to provide high-quality, affordable generic medicines (7). However, the issues of access to antibiotics must be addressed in tandem with appropriate use to prevent the emergence of resistance that would render these treatments ineffective and burden the nascent universal healthcare system with higher treatment costs.

We discuss the current situation with antimicrobial resistance and antibiotic consumption in the South-East Asia region (SEAR), which comprises 11 countries: Bangladesh, Bhutan, Democratic People's Republic of Korea, India, Indonesia, Maldives, Myanmar, Nepal, Sri Lanka, Thailand, and Timor-Leste. We then consider possible solutions for the region as part of the global response to AMR.

Background

The South-East Asia region's dense population and lack of clean water, sanitation, and hygiene infrastructure create the conditions for the emergence and spread of resistant strains. Increasing population density has been associated with an increase in antimicrobial resistance in the Chaophraya River basin in Thailand (8). Dense populations combined with rising antibiotic consumption in urban areas have been found to correlate with increased resistance (9). Antibiotic use also drives resistance: inappropriate prescribing (10,11) and over-the-counter access without a prescription (12) all contribute to antibiotic misuse, as does the use of antibiotics to promote growth in livestock (13). Because the region's growing population requires rapidly expanding food sources and the demand for meat increases with people's incomes, antibiotic consumption in agriculture is rising (14).

Some developing countries have expanded healthcare coverage without adequate infrastructure to prevent infections at the most basic and effective level—through access to clean water, nearby or onsite sanitation facilities, and provisions for, and education in, basic hygiene practices (15). The resulting dependence on high levels of antibiotic use is not sustainable and leaves nascent healthcare systems vulnerable to increasing resistance. As in much of the world, noncommunicable diseases are on the rise in SEAR, and antibiotics will be essential to support their treatment, including prophylaxis for surgery and during chemotherapy.

The mass movement of people within and outside the region—whether because of cultural practices, forced migration of refugees, or global travel and trade—also facilitates the spread of AMR. During the pilgrimage season, for example, mass bathing in the Ganges for religious ceremonies has been associated with levels of the resistance gene *blaNDM-1* that are 20 times higher than normal (16). Studies suggest that much of the multidrug-resistant tuberculosis found among Tibetan refugees in India may be explained by the administration of counterfeit medications and delays in treatment (17). The emergence of multidrug-resistant genetic elements, in the form of *New Delhi Metallobeta-lactamase-1*, from South Asia and its subsequent global spread (18) have shown the potential of this region to be a source for AMR (19). Similarly, multidrug-resistant typhoid appears to have originated in South Asia and spread to Africa (20), Europe (21,22), and other parts of Asia (23).

AMR is a one-health issue that involves the well-being of humans, animals (including livestock, poultry, and aquaculture), and the environment (24). Solutions need to involve all these sectors in preventing infection, reducing antibiotic use, and fortifying surveillance systems (13). Interventions to directly reduce infections are essential at all levels, including environmental cleaning and infection prevention and control in hospitals, adequate vaccination coverage, food safety, and improved access to clean water, adequate sanitation, and hygiene facilities in the community (1). Surveillance of AMR provides clinicians with the information needed to effectively treat bacterial infections. The availability of cheap diagnostic tests would also help clinicians improve the appropriateness of treatment. The large pharmaceutical manufacturers in the region have produced relatively inexpensive medicines, including generics, improving access through affordability throughout Asia and in the rest of the world. However, strong regulatory structures are needed to ensure the quality of antibiotics (25).

Prevalence and epidemiology of drug resistance in South-East Asia

Data from Thailand and India (Figures 1–4) indicate that resistance is emerging even to antibiotics of last resort. Carbapenem resistance, has been found in some bacteria in Bangladesh: 2.3% and 13.5% of *E. coli* and *Pseudomonas* spp. were resistant to imipenem, and 13.3% and 33.9%, respectively, were resistant to meropenem (26).

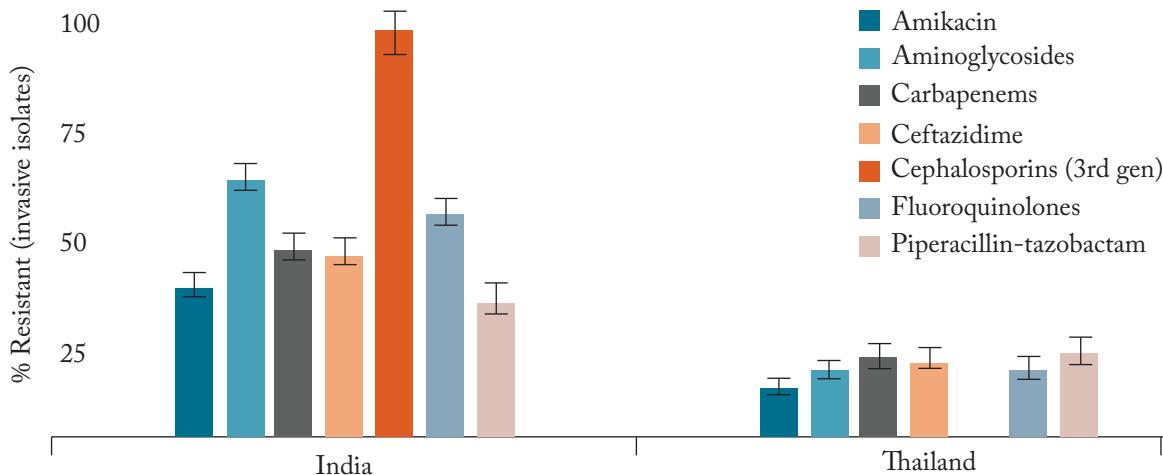


Figure 1. Antibiotic resistance of *Escherichia coli* isolates from India and Thailand in 2015.

Data source: Center for Disease Dynamics, Economics & Policy (27).

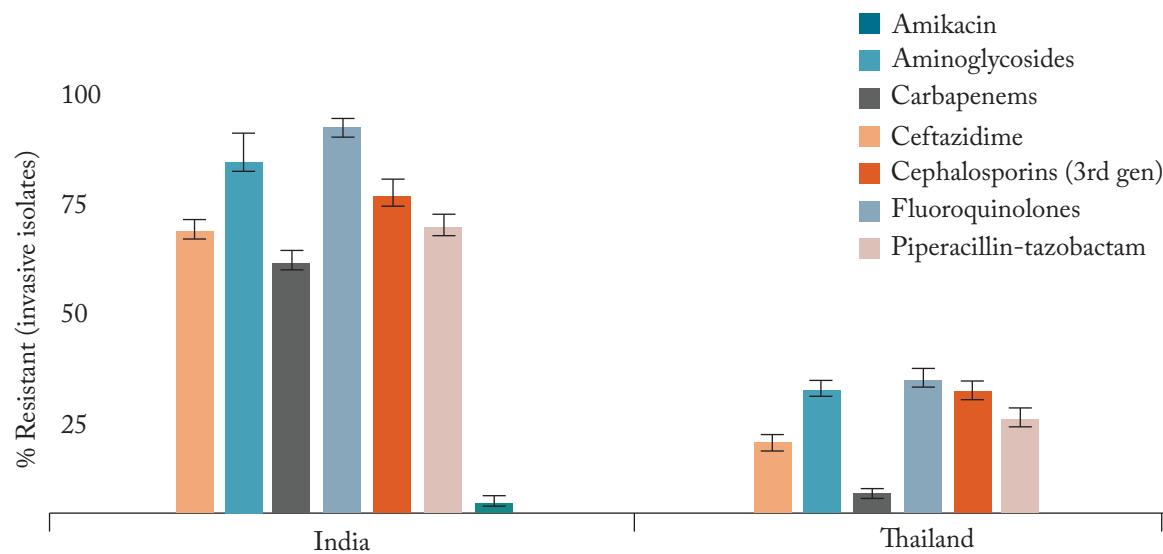


Figure 2. Antibiotic resistance of *Klebsiella pneumoniae* isolates from India and Thailand in 2015 (data for polymyxins were not available for Thailand). Data source: Center for Disease Dynamics, Economics & Policy (27).

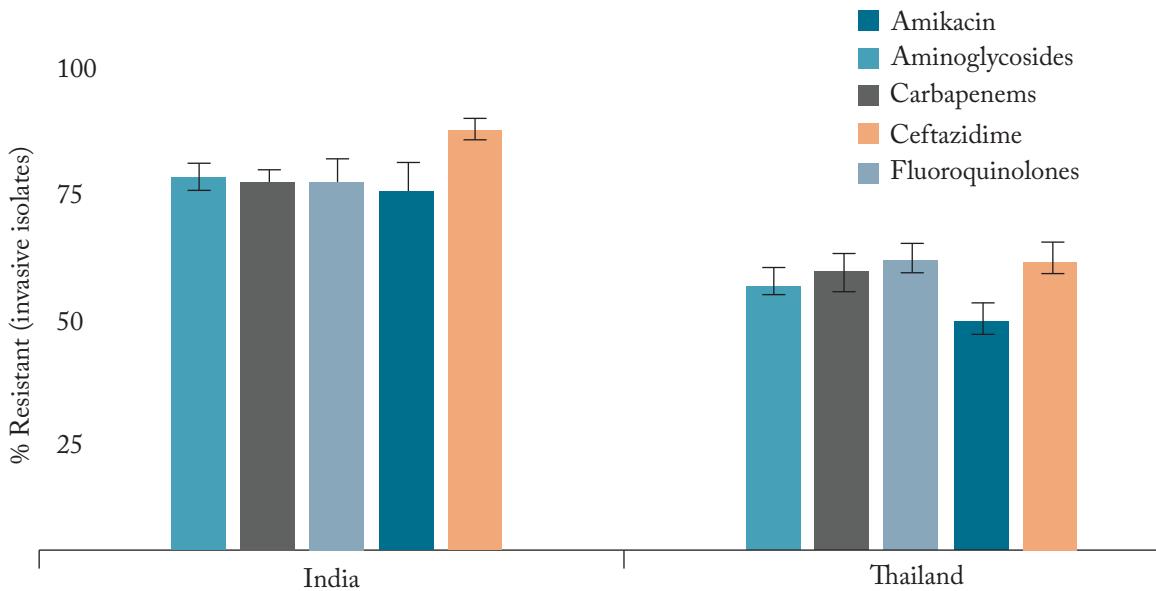


Figure 3. Antibiotic resistance of *Acinetobacter baumannii* isolates from India and Thailand in 2015. Data source: Center for Disease Dynamics, Economics & Policy (27).

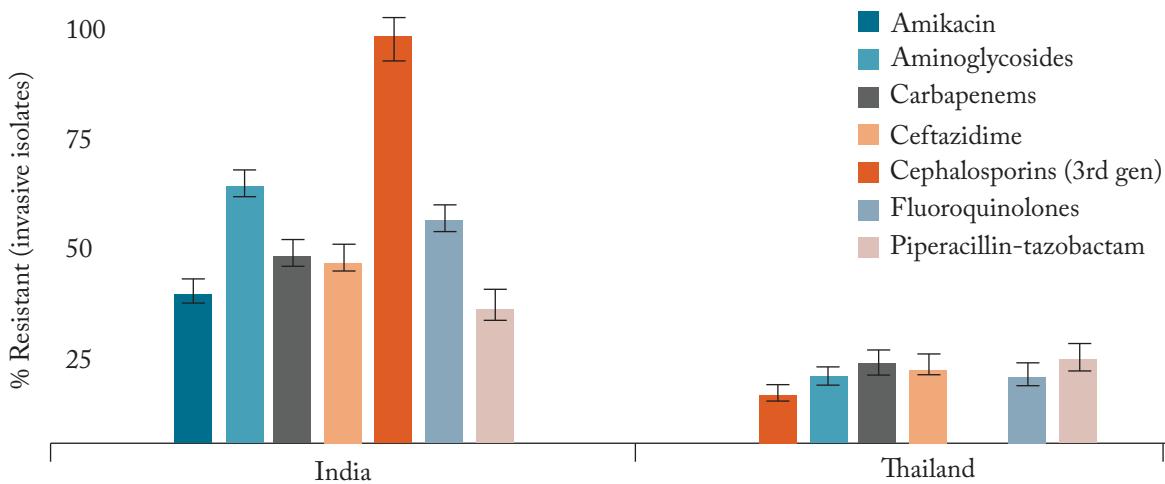


Figure 4. Antibiotic resistance of *Pseudomonas aeruginosa* isolates from India and Thailand in 2015 (data for cephalosporins are from 2013 for India and were not available for Thailand). Data source: Center for Disease Dynamics, Economics & Policy (27)

Hospital-acquired infections

The prevalence of multidrug-resistant (MDR) organisms in healthcare settings is increasing. The ecology of bloodstream infections (BSI) in intensive-care units (ICUs) in India is different than in Western countries. Gram-negative bacilli (GNB) (49%) are the leading cause of BSI in these settings, followed by gram-positive cocci (GPC) (33%) and fungi (18%) (28,29). In the West, GPCs are the most common cause of hospital-acquired infections (HAIs) (30). The most common single isolate in the intensive-care unit (ICU) of a tertiary hospital in northern India was coagulase-negative *staphylococcus* (20.3%), normally considered a skin contaminant, followed by *Candida* spp. (17.5%) (29). Non-albicans *Candida* spp., particularly *C.*

tropicalis, are now a leading cause of HAIs. This could be attributed to the increasing exposure to multiple antibiotics, in-dwelling catheters, previous surgery, parenteral nutrition, immunocompromised hosts, and increasing life spans. The distribution of *Candida* spp. responsible for BSI is shifting to non-*albicans* species. *C. albicans* accounted for only 15.3% of *candida* BSIs, whereas *C. tropicalis* accounted for 25% (29).

The device-associated infections in ICUs at Sir Ganga Hospital in 2018 were catheter-associated urinary tract infections (CAUTI) (1.8%–5.2%), ventilator-associated pneumonia (VAP) (2.7%–5.4%), and central line-associated bloodstream infections (CLABSI) (1.8%–5.6%) (Figure 5). However, these figures are lower than the overall (pooled mean) infection rates per 1,000 device-days seen in the International Nosocomial Infection Control Consortium study from 43 countries (28). This hospital has been part of the AIIMS-ICMR-CDC national network surveillance for urinary tract infections (UTI) and CLABSI surveillance and the antimicrobial stewardship program since 2017. The above rates may be difficult for India's public sector hospitals, the majority of which do not have national accreditation, to achieve.

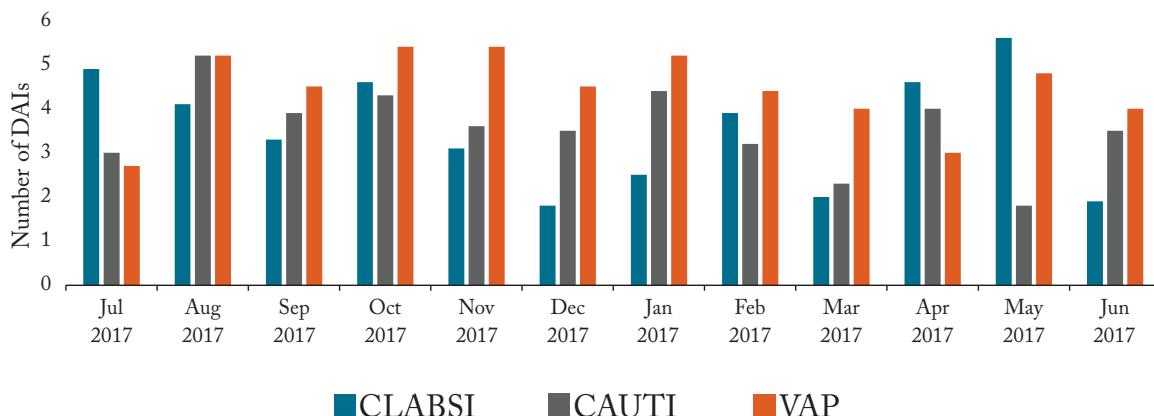


Figure 5. Device-associated infections (DAIs) in Intensive Care Units at Sir Ganga Hospital; CLABSI = central line-associated bloodstream infection; CAUTI = catheter-associated urinary tract infection; VAP = ventilator associated pneumonia. Data source: Personal communication, Chand Wattal, Sir Ganga Hospital, New Delhi, India

As in the rest of the world, India is experiencing an increase in antimicrobial resistance in GNB. India has transitioned from multidrug-resistant to pan-drug-resistant bacteria within the span of a few years. Over the past decade, AMR in *Enterobacteriaceae* has increased; there have been significant increases in resistance in *K. pneumoniae* to cefotaxime (75%–97%), carbapenems (2.5%–52%), ciprofloxacin (64%–84%), and piperacillin-tazobactam (55–84%); and antibiotic resistance in *E. coli* has been observed to cefotaxime (64%–75%) (31). A significant increase in resistance has also been observed in *A. baumannii* to fluoroquinolones (32%–86%), aminoglycosides (29%–88%), and carbapenems (0%–74%), and in *P. aeruginosa* to aminoglycosides (30%–65%) (32). Resistance to colistin was not seen in these studies; however, colistin resistance is emerging in *K. pneumoniae* (10%–13%), *E. coli* (0%–2%), and *A. baumannii* (4%–6%) (33), making them effectively untreatable with available drugs.

Community-acquired infections

Rates of resistance are often different at hospital and community levels (130). The prevalence of MRSA was estimated to be 67.4% in Asian hospitals in 2011 (35). However, community-acquired MRSA was an average of 25.5% across the eight countries in the study, the lowest rate being in Thailand (2.5%) and the highest in Sri Lanka (38.8%) (35). In two hospitals in Bhutan, *N. gonorrhoeae* was resistant to ciprofloxacin (85.1% of isolates), penicillin (99.2%), tetracycline (84.8%), and nalidixic acid (99.7%) (36). In Bangladesh, India, and Pakistan, 83% of fatal bacterial neonatal infections were susceptible to penicillin, ampicillin,

gentamicin, or a combination of these drugs (37). Surveillance is often at the level of large tertiary hospitals, which have facilities for microbiological testing; however, surveillance is also needed at the community level to inform prescribing.

Risk factors and interventions

Antibiotic consumption is an important cause of emerging resistance (32). Consumption in Indian healthcare settings is higher than in Western countries and contributes to the high prevalence of AMR in the region (32). Consumption in one North Delhi hospital increased from 158 defined daily doses (DDDs) per 100 bed-days (BDs) to 319 DDDs/100 BDs from 2000 to 2009. The largest relative increase in antibiotic consumption was seen for carbapenems ($p = 0.022$), followed by β -lactam-inhibitor combinations ($p = 0.033$); consumption of third-generation cephalosporins, fluoroquinolones, and aminoglycosides showed no significant difference (32). However, in 2017, after an effective antimicrobial stewardship program was implemented, antibiotic consumption in the same hospital decreased to 152.9 DDDs/100 BDs (38,39). This suggests that much of the increase in hospital prescribing was inappropriate.

The Center for Disease Dynamics, Economics & Policy tracks trends in antibiotic consumption, but data are not available for all countries in the region. Of countries for which data are available, in 2015 total antibiotic sales in DDDs/1,000 population were highest in Thailand, at 6,682, and lowest in Indonesia, at 3,022 (Figure 6) (27). The breakdown of sales data by antibiotic class shows large variation among countries (Figure 7). Thailand consumes a relatively higher amount of broad-spectrum penicillins, and India and Bangladesh consume high levels of cephalosporins. This suggests consumption may not be based on stewardship guidelines that promote appropriate use. Data for one year (2007–2008) from private retail pharmacies in West Delhi showed that fluoroquinolones, cephalosporins, and extended-spectrum penicillins were the most-consumed antibiotics, both by percentage and by total DDDs/1,000 patients, and that consumption of macrolides decreased while consumption of cephalosporins increased (40) compared with 2004 (41).

The World Health Organization (WHO) uses the AWaRE classification to categorize antibiotics as Access (those that should be widely available to treat common infections), Watch (those whose use should be limited to prevent resistance from emerging), and Reserve (those saved as a last resort for cases where other antibiotics have failed) (42). Comparison of the proportion of child-appropriate formulations of the antibiotics sold in each country by AWaRe classification shows that India and Bangladesh use a far lower proportion of antibiotics from the Access category than Indonesia, Thailand, and Sri Lanka (Figure 8). This may be due to a combination of poor antibiotic stewardship and differences in resistance profiles. In India, between 2010 and 2014, consumption of faropenem—an antibiotic in the carbapenem class, often considered drugs of last resort—increased by 150% (43).

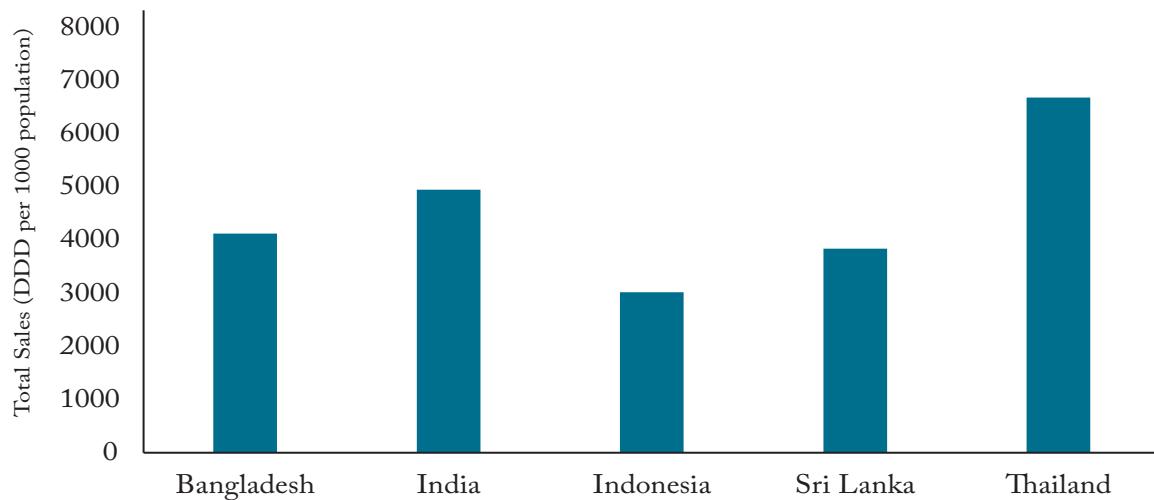


Figure 6. Total antibiotic sales in Defined Daily Doses (DDD) per 1,000 population in 2015 in selected SEAR countries for which data were available. Sales data from hospital or retail sectors are shown for all countries except Bangladesh and Sri Lanka, for which data come from the retail sector. Source: (27).

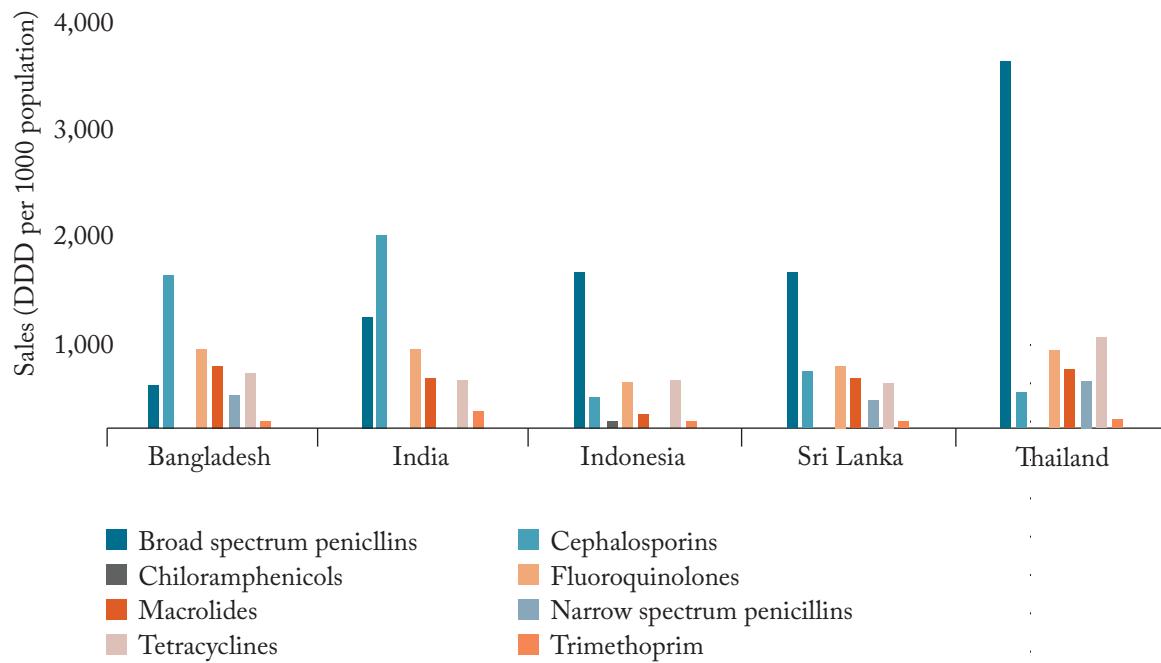


Figure 7. Antibiotic sales in defined daily doses (DDDs) per 1000 population in 2015 for selected antibiotics in selected SEAR countries for which data were available. Sales data from hospital and retail sector are shown (data from retail sector only for Bangladesh and Sri Lanka). Source: (27).

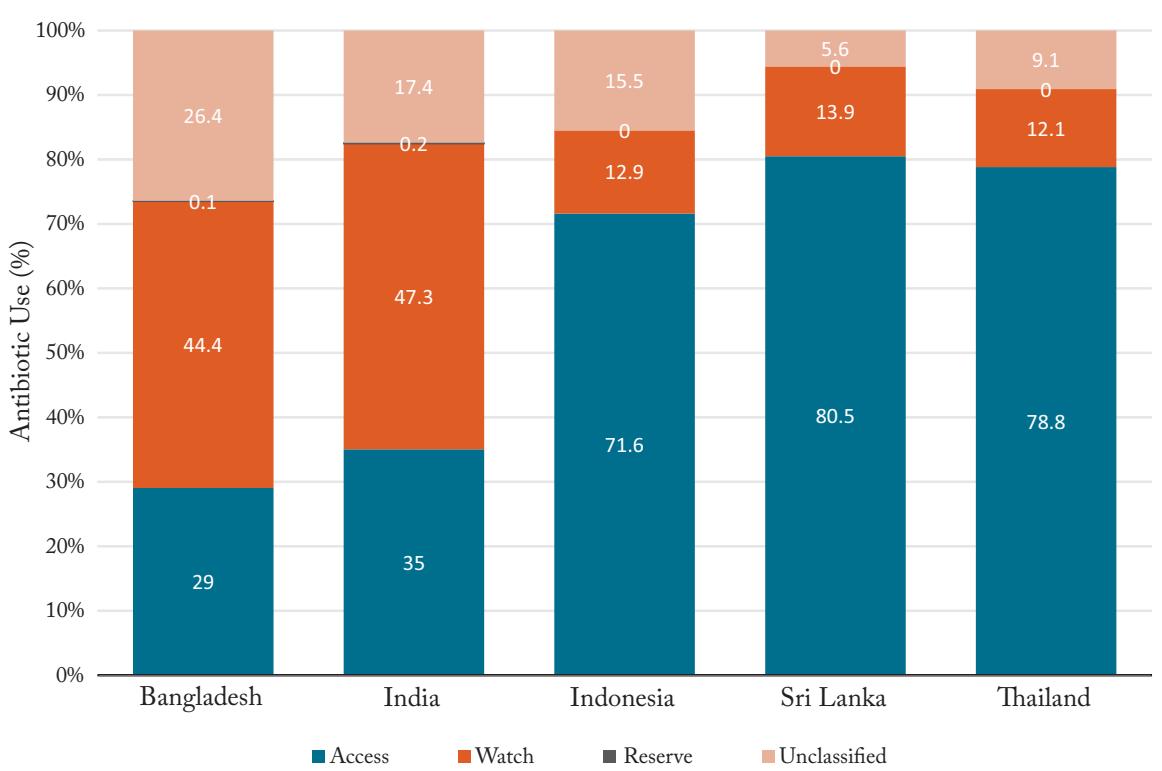


Figure 8. Percentage antibiotic use of child-appropriate oral formulations by WHO AWaRe grouping (42). Only core Access antibiotics are included in Access group. AWaRe=Access, Watch, Reserve. Data source: (44).

Trends in consumption by antibiotic class also vary among countries. In India, consumption of cephalosporins is increasing and in 2009 overtook that of fluoroquinolones, which in turn were eclipsed in 2012 by broad-spectrum penicillins (Figure 9). In Bangladesh, consumption of cephalosporins remains lower than in India but is increasing and has overtaken that of fluoroquinolones (Figure 10). In Sri Lanka, broad-spectrum penicillins are the most-consumed antibiotic class; far fewer cephalosporins are consumed than in India and Bangladesh (Figure 11). In Indonesia, consumption of broad-spectrum penicillins is higher than that of other antibiotics but has fallen below consumption of the same drug class in Thailand (Figure 12). In Thailand, broad-spectrum penicillin consumption has exceeded use of all other antibiotics since 2000 (Figure 13).

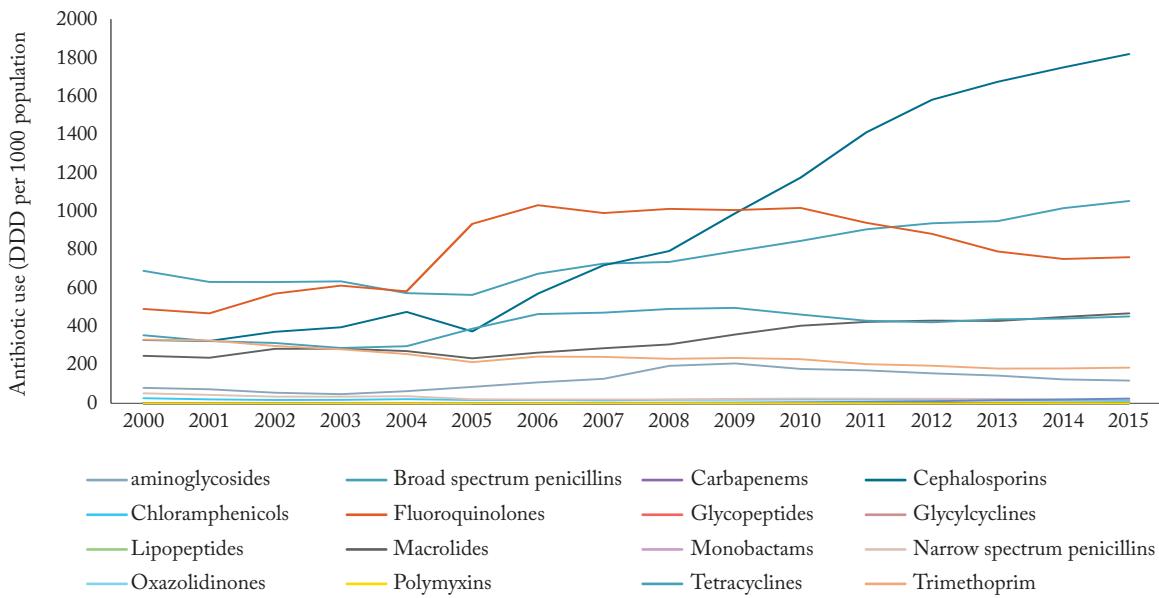


Figure 9. Antibiotic use in India, 2000–2015, in defined daily doses (DDD) per 1,000 individuals. Sales data from the hospital and retail sectors are shown. Source: (27).

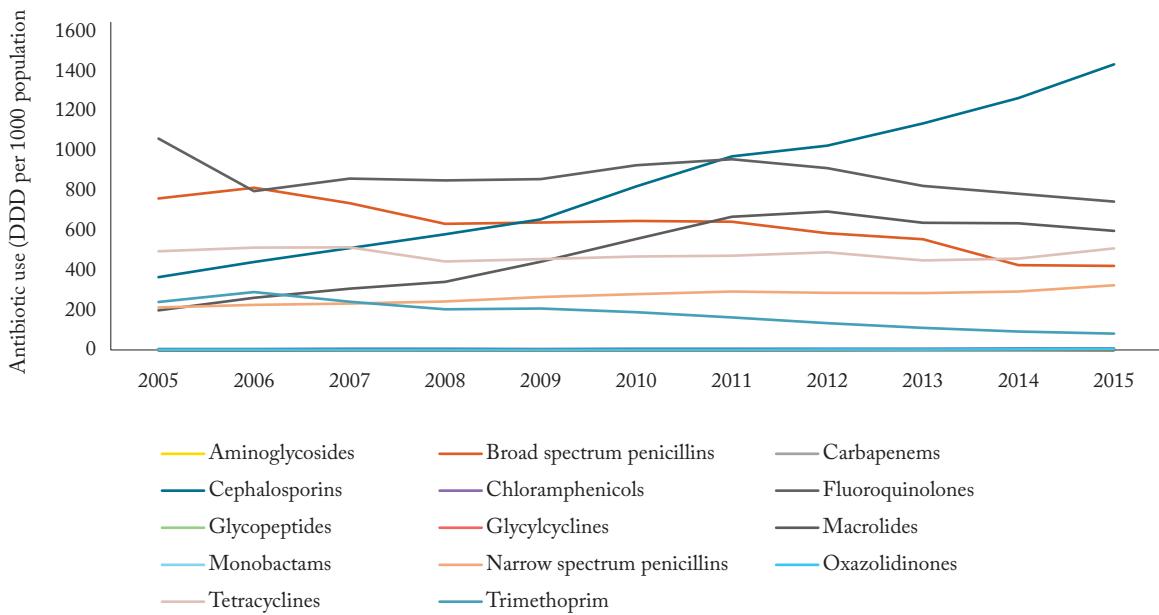


Figure 10. Antibiotic use in Bangladesh, 2005–2015, in defined daily doses (DDD) per 1,000 individuals. Sales data from the retail sector are shown. Source: (27).

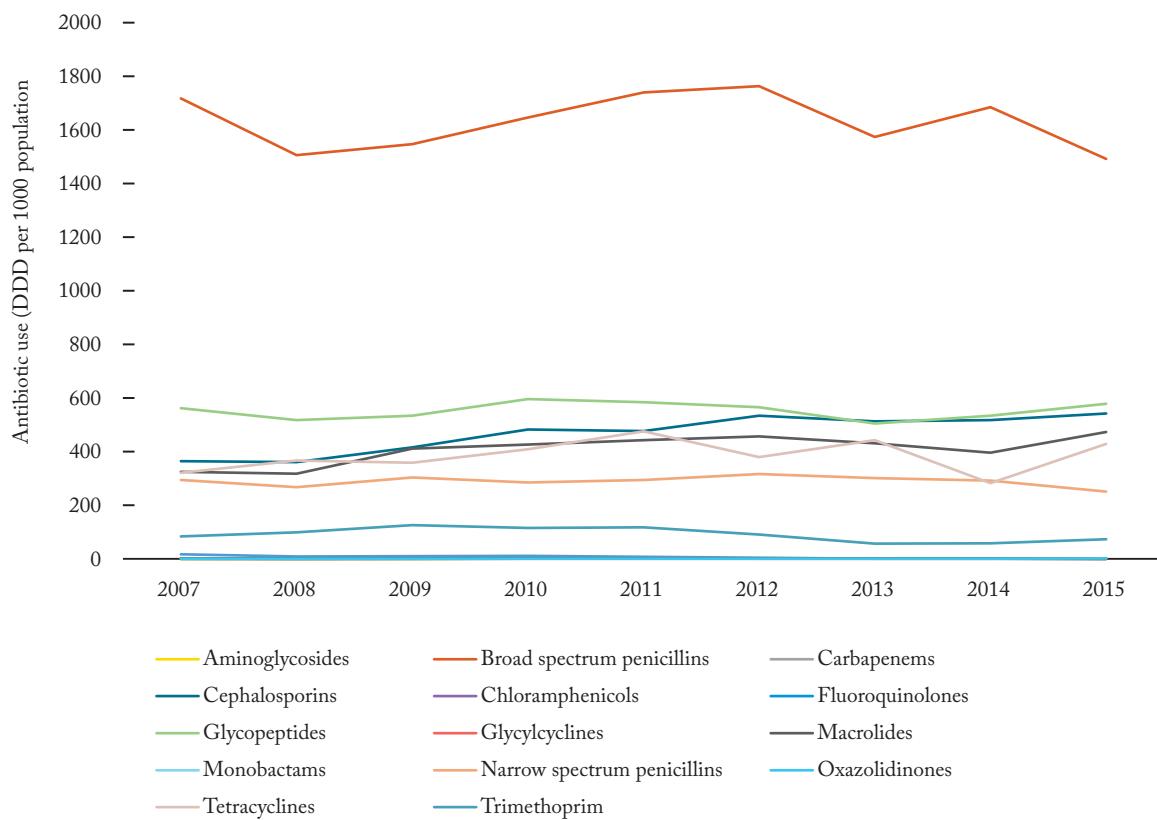


Figure 11. Antibiotic use in Sri Lanka, 2007–2015, in defined daily doses (DDD) per 1,000 individuals. Sales data from retail sector are shown. Source: (27).

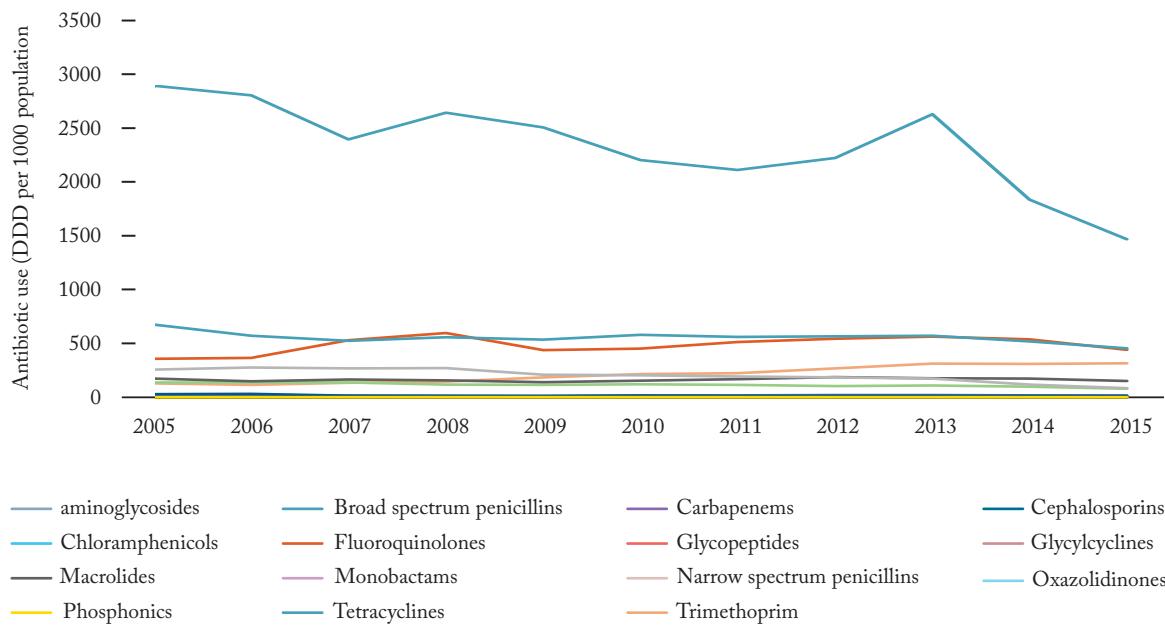


Figure 12. Antibiotic use in Indonesia, 2005–2015, in defined daily doses (DDD) per 1,000 individuals. Sales data from hospital and retail sectors are shown. Source: (27).

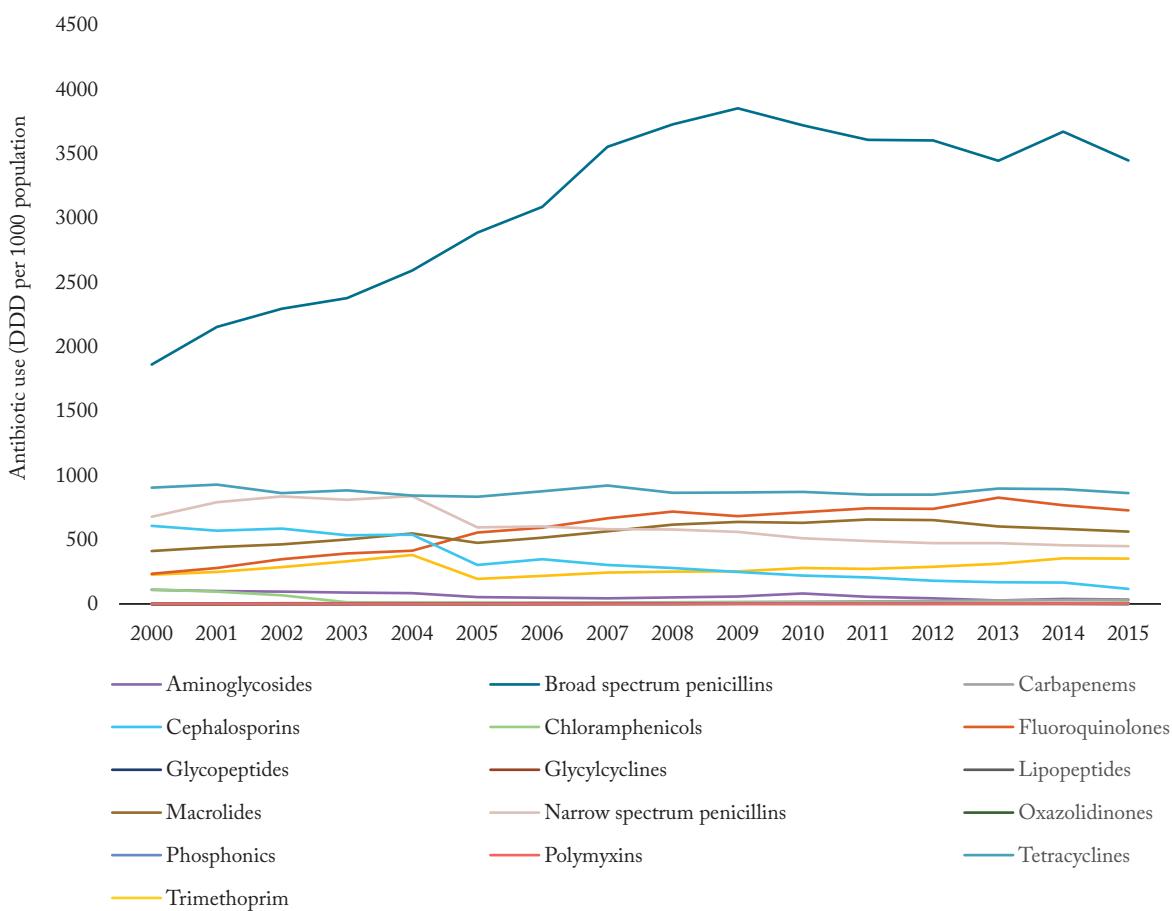


Figure 13. Antibiotic use in Thailand, 2000–2015, in defined daily doses (DDD) per 1,000 individuals. Sales data from hospital and retail sectors are shown. Source: (27).

One driver of inappropriate prescribing is the lack of stewardship programs and guidelines. Clinicians often prescribe broad-spectrum antibiotics even when narrow-spectrum agents would be as effective. Broad-spectrum antibiotics are active against a greater range of bacteria and select more strongly for resistance. Physicians receive regular visits from pharmaceutical sales representatives (45), who incentivize prescribing (43). In addition, irrational fixed-dose combinations (FDCs) of two or more antibiotics are often given, despite a lack of evidence of that such combinations increase effectiveness. Increases in antibiotic sales in India have been driven by FDC sales, which rose by 38% versus 20% for single-drug formulations (46). In 2011–2012, FDCs accounted for 34% of total sales in India (47). Of 118 FDC antibiotics sold in India, 64% had no regulatory approval (46). Antibiotics are sold over-the-counter across all SEAR countries except Bhutan (1), and self-prescribing is common. In India, for example, one in 10 interviewees was found to self-medicate with antibiotics, despite attempts to curb this practice with the “red line campaign” and schedule H1 (48). More than 70% of primary healthcare continues to be delivered by practitioners who lack formal training (49) and have limited knowledge of when antibiotics are an appropriate treatment.

Bacterial and viral infections have similar clinical presentations, and physicians often prescribe antibiotics because they lack rapid diagnostic tests. The last mile of connectivity for diagnostics is a big challenge in semirural and rural India, and the use of point-of-care tests in these settings is limited. However, in many lower- and middle-income countries, C-reactive protein and procalcitonin are used as surrogate markers of bacterial infection in the absence of culture facilities or positive cultures. Syndromic diagnostic tests are rare because of cost constraints. However, film array assays can indicate the presence of multiple organisms, including bacteria, fungi, parasites, and viruses.

Substandard and counterfeit antimicrobials can increase antibiotic resistance through underdosing, prolonging the time during which infections can spread and increasing treatment failure, necessitating treatment with second-line antibiotics (50). Of the 10% of falsified medicines worldwide, 50% are estimated to be antimicrobials, and of these, 78% are found in Asia or Africa (51). One worldwide literature review found that India had the greatest variety of reported substandard or counterfeit antimicrobials (50). Widespread ciprofloxacin resistance in India has been related in part to poor-quality ciprofloxacin (51). The Indian National Drug Survey (2016–2018) found that 3.16% of the drugs tested were not of standard quality and 0.0245% were spurious (25).

Lack of safe water, sanitation, and hygiene increases both the transmission of resistant bacteria and the burden of viral and bacterial disease, for which antibiotics are often consumed, selecting for resistance. Resistant infections may be treated with a second course of antibiotics, further increasing selection for resistance. In India alone, 40% of the population continued to practice open defecation in 2015 (52), and 50% of people across South Asia lacked access to basic sanitation services (53). Viral pathogens, against which antibiotics are ineffective, cause 70%–80% of diarrhea, yet in India, an estimated 29%–82% of diarrhea cases are treated with antibiotics (54). Improved WASH infrastructure and access in India could result in 590 million fewer diarrheal cases treated with antibiotics by 2020 (54). India's Swachh Bharat Mission to increase sanitation coverage is predicted to avert more than 300,000 deaths due to diarrhea and protein-energy malnutrition before its end date in October 2019 (55). SEAR is WHO's poorest-performing region for treating healthcare waste: fewer than half of facilities have a system to safely collect, dispose of, and destroy such waste, compared with 60% in the Africa region (56).

Many healthcare facilities in the region are under resourced and lack healthcare workers with adequate training in antimicrobial stewardship and prevention of hospital-acquired infections. WHO recommends a ratio of one doctor to every 1,000 people. In India this ratio is 1:10,189, which implies a deficit of 600,000 doctors (57), and the country has just one nurse for every 483 patients, a deficit of 2 million nurses (58,59). Patients often rely on informal healthcare providers, especially in rural areas. India is providing training to health workers who are unregistered and may be unqualified (60).

Antimicrobial stewardship efforts in Asia demand innovation and better use of existing human resources through skill building and task-sharing initiatives. In public sector primary-care facilities, antibiotic use is very high: up to 67% of all outpatients are given antibiotics. For upper respiratory tract infections, which are mostly of viral origin, antibiotic use ranges from 20% up to 100% of patients, with very few stewardship efforts to limit inappropriate antimicrobial use. Surveys in New Delhi have shown that more patients receive antibiotics in private clinics than in public sector primary-care settings (40).

Similarly, more patients are prescribed antibiotics for acute diarrhea and upper respiratory tract infections by private general practitioners than by public sector caregivers (10,11). The easy availability of antibiotics in the region indicates a need to strengthen hospital drug and therapeutics committees, update and implement national standard treatment guidelines (61), and train health staff—pharmacists, nurses, and doctors—in antimicrobial stewardship (62). Policy initiatives are needed to regulate over-the-counter availability of antibiotics while ensuring access to medicines. Innovative stewardship initiatives are needed in the primary healthcare system as well as in tertiary hospitals to develop synergies and help identify opportunities (62).

Hospital-acquired infections occur because of poor care of invasive devices and failure to follow international guidelines. HAIs, including CAUTI, VAP, surgical site infections (SSIs), and CLABSI are often not recognized early; the delay in treatment facilitates their spread. Many healthcare institutions in India do not have the infrastructure or human resources for microbiological investigation. Clinical microbiology facilities are needed to support the treatment of and provide the diagnosis for UTI, VAP, SSI, and CLABSI. Institutions cannot afford automated blood culture systems that facilitate the monitoring of CLABSI. The international guidelines for diagnosing bloodstream infections call for three sets of six bottles for blood cultures—unaffordable for many hospitals. Hospitals also lack trained staff to deliver the central-line care bundles or endotracheal tubes necessary for preventing VAP. Training of healthcare workers, from doctors to ward staff, does not adequately address prevention of HAIs.

Vaccination reduces AMR by directly reducing the transmission of resistant infections and by lowering the burden of disease requiring antibiotic treatment (63). Pneumococcal conjugate vaccine could avert 11.4 million days of antibiotic treatment for bacterial pneumonia in children under age five every year. This would almost halve the amount of antibiotics used for such cases across the 75 countries in the analysis (4). All countries in SEAR except Thailand have introduced Hib-containing vaccines in national immunization programs, and the pneumococcal conjugate vaccine has been introduced in five of the 11 countries. The rotavirus vaccine is given in two countries, however, Nepal, Bangladesh, Myanmar, Timor-Leste, and Indonesia are planning its introduction (64).

Environmental contamination with antibiotics is yet another driver of resistance. India is the second-largest global supplier of active pharmaceutical ingredients (65). Competition to supply lucrative pharmaceutical markets can lead to lapses in environmental standards. Samples taken from drinking water in Hyderabad, India, were contaminated with antibiotics, and the concentration of ciprofloxacin in a local lake was higher than would be seen in the blood of a patient on antibiotic treatment (66). Contamination in areas where the antibiotic manufacturing industry operates has been shown to increase selection for bacteria that are highly resistant, even to last-resort antibiotics like the carbapenems (67). This contamination can take multiple forms; resistant genetic elements which can be transferred between pathogens, resistant bacteria, and the antibiotic drugs. The pharmaceutical industry lacks standards to ensure the safety of manufacturing waste (68).

Research and development agenda

Prevention of HAIs begins with understanding their pathogenesis and epidemiology, risk factors, and burden across healthcare settings and cultural contexts. This knowledge will be helpful in developing strategies for prevention and containment (69). All countries in the region have national action plans to combat antimicrobial resistance. Although India, Indonesia, Bangladesh, and Thailand are international pharmaceutical manufacturing hubs (70), only a few countries in the region have policies to foster research and innovation in AMR (71).

Antibiotic product development and alternatives

Though the region has a large pharmaceutical production capacity, companies' research and development (R&D) budgets for drug discovery are shrinking. In India (72), for example, research in AMR has focused mainly on its epidemiology and the mechanism of resistance (effectiveness of routinely used antimicrobials, spread of resistant pathogens, and acquisition of AMR) (71). Research into alternatives to antimicrobial treatment has been insufficient. Over the past 10 years, major pharmaceutical companies in India have increased their R&D expenditure almost 40-fold, for example, but pharmaceutical companies and academic laboratories have focused on chemical modification of existing antimicrobial compounds rather than on discovering new therapeutic agents (73).

Collaborative projects to address AMR are being undertaken in the region. In India, following the declaration of the national action plan for AMR, several jointly funded research projects have been announced with Norway (74) and the United Kingdom (75). These projects involve research for new antibiotic molecules, innovative regulatory approaches to improving antibiotic use, and improved diagnostics and diagnostic approaches to detect resistance in humans, animals, and the environment.

The region will require innovative mechanisms to improve antibiotic research. In India, the government aims to establish a pharmaceutical innovation hub by 2020 and establish its global presence by launching one of every five to 10 drugs discovered in the country at the global level (76). To promote Start-up India and Make in India, the government has set up a facilitation unit, called First Hub, to address queries of researchers, entrepreneurs, academics, and incubation centers.

On the global front, the Global Antibiotic Research and Development Partnership, a not-for-profit R&D organization, is developing new antibiotic treatments while seeking to ensure sustainable access. Initiated through a collaboration between WHO and the Drugs for Neglected Diseases initiative, this partnership has received seed funding and pledges from the governments of Germany, the Netherlands, South Africa, Switzerland, and the United Kingdom, in addition to the medical humanitarian organization Médecins Sans Frontières; sites in South-East Asia, including India, are part of its clinical trial research network (77).

India's ministry dedicated to Ayurveda, Yoga and Naturopathy, Unani, Siddha, and Homeopathy (AYUSH) supports work on alternative herbal, ayurvedic therapies.

Diagnostics

The availability of a rapid, cheap diagnostic test that can differentiate between viral and bacterial infection in primary point-of-care facilities would improve clinical management and reduce inappropriate antimicrobial use. The cost of a test is often higher in South-East Asia than the cost of an antibiotic, and tests are often not available or promoted. Recent studies in Asian countries have demonstrated that rapid C-reactive protein tests are an inexpensive way to reduce inappropriate use in healthcare facilities that lack laboratories (64% antibiotic prescriptions versus 78% with routine tests). Concurrent use of two point-of-care rapid tests (urine dipstick and microscopy) improved antimicrobial prescribing in adults with urinary tract infections with improved sensitivity (99% versus 57%) but a lower specificity (47% versus 89%) – .

Rapid and easy-to-use diagnostic tests, including in vitro diagnostics, to detect whether an antibiotic is indicated, and if so, which antibiotic, have the potential to be a profitable market in the human, animal, and plant sectors (12).

Vaccines

In 2018, a typhoid conjugate vaccine manufactured in India by Bharat Biotech was prequalified by WHO, and this will be a useful tool in controlling drug-resistant typhoid (79). The vaccine is currently licensed in India and Nepal as a single, intramuscular dose. It has been shown to elicit a robust immune response in infants as young as six months of age, and it provides longer-lasting protection and requires fewer doses than the polysaccharide vaccine. It can also be administered to children younger than two years, allowing for delivery through routine childhood immunization programs and better protection for younger children in affected areas. As part of a clinical trial, its use is being piloted in a city in India (69).

One-health strategies

Operational models are needed to implement one-health strategies to combat AMR. Alternatives to antimicrobials in agriculture would encourage farmers to drop antibiotic use. Targeted R&D investments by governments and industry are vital for finding vaccines that could replace antibiotic use in animals (80). The ViPARC study for piloting veterinary interventions to reduce antimicrobial use by chicken farmers in Vietnam is a useful pilot approach that could be scaled up in the region (81). A similar study on intensive poultry farming in southern India was initiated in 2018 to understand the drivers of antibiotic use and resistance in poultry (82).

Behavioral research

Detailed studies are needed to understand how antimicrobials—seen as wonder drugs—are used in practice. Topics for research would include the repeated irrational behaviors underlying prescribing by healthcare professionals, demand by the public, and use by farmers. Behavioral studies have been conducted in New Delhi with pharmacists (12), primary care doctors (83), and schoolchildren and teachers (84) on their knowledge of antibiotics and antimicrobial resistance. One behavioral study in New Delhi found that patient pressure, profit, lack of follow-up, physician workload, lack of diagnostic facilities, and pressure to use near-expiry medicines can all drive antibiotic use for acute diarrhea and upper respiratory tract infection in children (85). Implementation research on challenges for prescribing antimicrobials without diagnostic testing may contribute to reducing their indiscriminate use.

Next steps

Research efforts in AMR thus far have been fragmented. Interdisciplinary research—across human and animal health and the environmental sciences—and improved communication and collaboration among sectors are critical for success in combating AMR. Researchers need to coordinate their work and share their results in a timely way to guide clinical decisions, interventions, and policies. Sustainable yet innovative approaches would increase investment and incentivize public-private partnerships for product development. Alignment of biological, engineering, and medical sciences would improve opportunities to develop disruptive innovations in antimicrobial diagnostic and therapeutic agents.

The Asia-Pacific countries' R&D agenda to limit the emergence and spread of AMR (86) has identified the following needs for further research:

- basic and molecular microbiological research to advance the development of novel therapeutics, including antimicrobials, adjunct treatments, combination therapies, and vaccines, and to support the redevelopment of existing antimicrobials;
- rapid and point-of-care diagnostic technologies to reduce inappropriate and unnecessary antibiotic use;

- improved understanding of how resistance develops and can transfer between species and settings, including across healthcare settings, between animals and humans, in food processing, and in the environment;
- health services research to identify and refine best-practice antimicrobial stewardship and infection prevention and control approaches; and
- social research on messaging that promotes behavioral change to support improved prescribing practices and rational use of antimicrobials.

Addressing gaps

Antimicrobial resistance poses a multidimensional challenge at the level of planetary health, including social, economic, and environmental dimensions that encompass the food production system as well as human and animal health (87). The one-health concept captures this scope by recognizing the interdependence of human health, agriculture, animal health, and the environment: it seeks to improve health and well-being through the integrated management of disease risks and contain AMR at the interface between humans, animals, and the natural environment.

Global Action Plan

WHO's Global Action Plan on antimicrobial resistance (GAP-AMR), adopted at the World Health Assembly in 2015 by member states, takes a one-health approach (13). The plan was developed through a tripartite collaboration of the UN Food and Agriculture Organization (FAO), Office International des Epizooties (OIE, World Organization for Animal Health), and WHO. All member states committed to prepare and align their national action plans (NAPs) on AMR by 2017. All 11 countries in SEAR have prepared their plans, though some countries have yet to detail the activities required to achieve their objectives (88).

The GAP-AMR identifies five strategic objectives:

1. to improve awareness and understanding of antimicrobial resistance through effective communication, education, and training;
2. to strengthen the knowledge and evidence base through surveillance and research;
3. to reduce the incidence of infection through effective sanitation, hygiene, and infection prevention measures;
4. to optimize the use of antimicrobial medicines in human and animal health;
5. to develop the economic case for sustainable investment that takes account of the needs of all countries and to increase investment in new medicines, diagnostic tools, vaccines, and other interventions.

National action plans

The SEAR nations are all low- and middle-income countries with high burdens of AMR. The issue has been declared a priority, and AMR has been a focus for the region since 2014.

A tool was developed by the South-East Asia Regional Office, with indicators and scoring for each focus area of the GAP's specific objectives, to conduct AMR situation analyses in 2016. The same tool is intended to be used at regular intervals, ideally every two years, for reporting on the development, implementation, monitoring, and evaluation of the plan for each country. To develop their plans, the countries' ministries of health worked with other ministries (agriculture, animal husbandry, education, environment) and professional councils in multisectoral core committees. For the five objectives of GAP-AMR, most countries were already creating their programs, and some were in the initial implementation phase. Available data, however, were fragmented and mostly from the human sector. Thailand, for example, had good information on antibiotic use in the human sector. Data on all five objectives were less available for the agricultural sector, and work on the program needed to be started. Sri Lanka had some livestock regulations in place. The environmental sector had not been surveyed for most of the focus areas.

All SEAR countries have prepared NAPs on AMR (88):

- Bangladesh: Antimicrobial Resistance Containment in Bangladesh, 2017–2022
- Bhutan: National Action Plan on Antimicrobial Resistance, 2018–2022
- DPR, Korea: National Strategic Plan on Antimicrobial Resistance, 2018–2020
- India: National Action Plan on Antimicrobial Resistance (NAP-AMR), 2017–2021
- Indonesia: National Action Plan on Antimicrobial Resistance, 2017–2019
- Maldives: National Action Plan for Containment of Antimicrobial Resistance, 2017–2022
- Myanmar: National Action Plan for Containment of Antimicrobial Resistance, 2017–2022 (Draft)
- Nepal: National Antimicrobial Resistance Containment Action Plan Nepal, 2016
- Sri Lanka: National Strategic Plan for Combating Antimicrobial Resistance in Sri Lanka, 2017–2022
- Thailand: Thailand's national Strategic Plan on Antimicrobial Resistance, 2017–2021
- Timor-Leste: National Action Plan on Antimicrobial Resistance, Timor-Leste, 2017–2020

The UN Environment Program (UNEP) signed a memorandum of understanding in May 2018 to facilitate joint action to combat health threats associated with interactions between humans, animals, and the environment. UNEP is working alongside WHO, FAO, and OIE to combat AMR.

Roadmap for national action plans

The greatest challenge after developing the NAPs on AMR is involving all three sectors in making the plans operational. The rapid rise in AMR and its containment are complex, multifaceted issues with social, cultural, and behavioral components that must be woven into the one-health approach. The involvement of multiple stakeholders means that the approach to address AMR must be carefully considered. Unlike other disease priorities, for which governments have often taken a vertical approach, AMR is a health issue that needs innovative, multisectoral approaches. Each country needs technical support in addition to financial support from international organizations. Good governance and monitoring and evaluation systems must be integral to the plans.

Elements of successful NAPs

1. The top governance of the multisectoral core working group should be at the prime minister's office or equivalent for each country. The core working group should have representation from ministries or departments of health, agriculture (livestock, poultry, aquaculture, food safety), environment, education, information (communications, broadcasting), and customs (import and export), as well as representatives from pharmaceutical companies, the food-processing industry, social and cultural stakeholders, academia, research, and non-governmental organizations. This nodal center should have two or three dedicated personnel from different specialties who have worked in the AMR field. A nodal center is advantageous for budget planning and disbursement to the stakeholders, collaboration between national and international agencies, and coordinating work involving different sectors. For example, for surveillance of antimicrobial consumption or resistance, members of a committee representing the human, animal, and environmental sectors can work as a team and learn from each other, saving time and resources.
2. The NAPs should fully include the environmental sector as an integral part of a one-health approach.

This sector's involvement is essential for Objective 4, optimum use of antimicrobials in the human, animal, and environmental sectors. Specific activities and regulations for the environmental sector include regulation (drugs, water quality standards), industry (drugs in the effluent, high-use facilities, sewage, hospitals), farming (agricultural run-off, food production), and—particularly important in SEAR, where some countries have large pharmaceutical industries—drug manufacturers (standards for antibiotic residues in effluents).

3. Each country should set measurable outcomes for each objective for each five-year block to 2030. For example, by 2022, morbidity caused by AMR will be reduced by $x\%$, antimicrobial consumption in humans and animals will fall by $y\%$, and public knowledge about the appropriate use of antimicrobials will increase by $z\%$. This approach has been taken by Thailand in its NAP.
4. Countries should consider developing “smart regulation”—innovative, less prescriptive approaches that promote compliance. Gunningham et al coined the term ‘smart regulation’ ‘to overcome the inefficiencies of traditional regulation on the one hand, and the pitfalls of deregulation on the other’(90). Targets could include appropriate use of antibiotics, regulations for the food and pharmaceutical industries, the environmental sector, infection prevention for communities and hospitals, education and training, and surveillance systems for antimicrobial use and resistance.

Box1: Smart regulation in the South-East Asia region

SEAR countries need to pilot innovative regulatory approaches moving beyond the top-down regulatory approach and the reliance on legal threats and penalties to shape behavior. “Smart regulation” refers to “regulatory pluralism that embraces flexible, imaginative and innovative forms of social control”(90, 91). A current Indo-UK collaborative multi stakeholder project aims to identify potential softer and innovative approaches for appropriate use of antibiotics based on the concept of Smart regulation (92). This is characterized by the involvement of multiple regulatory actors and the use of multiple policy instruments to achieve effective and efficient regulation. Thus, it can employ a mixture of regulatory models (command-and-control, self-regulation, co-regulation, volunteerism) and various regulatory instruments (subsidies, taxes, grants, penalties) with the objective of enhancing regulatory efficiency.

5. Each country should make a strategic plan for each objective with three categories: priority areas of action, gaps and challenges, and next steps. Each sector's research priorities should be identified and agreed upon. Funding organizations need to work more closely with the sectors, academics, researchers, and industries to identify gaps that could be addressed through a national approach. Much work, some undocumented and unpublished, has been undertaken to address AMR over the years. The AMR strategic plan should provide a way for information, achievements, and results to be made publicly available. Transparency would allow stakeholders to identify areas for collaboration and avoid duplication.
6. The nodal center in the prime minister's office should have annual meetings at which the core group and subcommittee members present their work and confirm that a one-health approach is in place.
7. A large international conference in SEAR would facilitate knowledge sharing and networking among academics, researchers, consultants, policymakers, and other stakeholders.

Conclusions

Antimicrobial resistance poses an increasing threat to the South-East Asia region and the rest of the world (3,13). Improvements in WASH facilities would greatly decrease the number of infections treated with antibiotics and thereby reduce AMR (54), as would better vaccination coverage (63). AMR is a one-health issue that requires the involvement of all sectors, including the environment (8, 66), agriculture (13), and human health (12). Surveillance is needed to track the rising number of resistant infections in both community and hospital settings (43) and inform appropriate prescribing. Higher consumption is an inevitable and essential consequence of improving healthcare systems, but this expanded access needs to be balanced with appropriate use if it is to be sustainable (1). Differences between the quality of care and prescribing in the public and private sectors need to be addressed (10,11), and stewardship is needed at both community and hospital levels. Substandard medicines continue to substituted for quality antibiotics in South-East Asia (51) and contribute to AMR (50). Innovative regulations that are specific to the country context are needed for an effective and sustained response to the threat of AMR.

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HIV/AIDS and sexually transmitted infections

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HIV/AIDS has been a medical catastrophe ever since it was first identified in June 1981 by the US Center for Disease Control and Prevention. Nearly four decades later, the world continues to face the human tragedy of HIV/AIDS. This epidemic started to spread rapidly in the 1980s and 1990s in Asia and Africa because of biological and behavioral synergies with conventional sexually transmitted infections (STIs). As of today there is still no cure for HIV infection, and no vaccine that is globally accessible.

In 2015 the United Nations' Sustainable Development Goals (SDGs) set forth specific targets to be achieved by 2030 (1). The overarching goal of SDG 3 (2) is to ensure healthy lives and promote well-being for everyone at all ages (including universal access to HIV prevention services, sexual and reproductive health services, drug dependence treatment, and harm reduction services) (3). Target 3.3 is to end AIDS as a public health threat by 2030, and Target 3.8 is to achieve universal healthcare coverage, access to quality healthcare services, and access to safe, effective, quality, and affordable essential medicines and vaccines. Other SDGs relate to the HIV and STI response as well. SDG 4, for example, addresses education and includes targets for comprehensive sexual and reproductive health education and life skills; SDG 5 promotes gender equality, with targets for sexual and reproductive health and rights and the elimination of violence and harmful gender norms and practices; SDG 10 aims to reduce inequalities through protection against discrimination and the empowerment of people to claim their rights and enhance access to HIV services; and SDG 16 seeks peace, justice, and strong institutions, reducing violence against certain populations and people living with HIV (4).

The focus of national HIV/AIDS programs in the South-East Asia region (SEAR) of the World Health Organization (WHO) is achieving the following targets by 2030 (4):

- zero new HIV infections;
- “90-90-90,” meaning that 90% of those who are HIV positive in the country know their status, 90% of those who know their status are on treatment, and 90% of those who are on treatment experience effective viral load suppression;
- elimination of mother-to-child transmission of HIV and syphilis;
- elimination of stigma and discrimination; and
- reduction of new STI infections by 80%.

Background

Both genetic and environmental risk factors are involved in spread of HIV/AIDS and sexually transmitted infections.

Genetic factors

Some HIV-infected individuals live symptom-free for long periods of time, but many progress rapidly to AIDS and death. Studies suggest that HIV types and subtypes, their tropism, and host immunity all affect the risk of HIV transmission and disease progression. HIV is categorized into two types, HIV-1 and HIV-2, each with many genetically distinct subgroups. Research on these variants is sparse, however, primarily because individuals with different subtypes are spread throughout the world (5). Tests to diagnose HIV and monitor the viral load must therefore be sensitive to the full range of subtypes, and although these tests exist, they are not readily available in all settings. HIV-1 is the more common and more infectious strain of the virus. It comprises one major group, M, and minor groups N, O, and possibly a group P. Within group M, which is responsible for most of the global epidemic of HIV, are nine genetically distinct subtypes: A, B, C, D, E, F, G, H, J, and K (5). Different subtypes can combine their genetic material to form a hybrid virus, known as circulating recombinant forms. The recombinant forms that have mucosal affinity can penetrate more easily through vaginal, anal, or oral mucosa. Despite repeated high-risk behavior, some individuals never get infected with HIV. The resistance of these highly exposed seronegative individuals has several possible explanations: (i) the resistance may be due to mutations in co-receptors used by HIV to establish infection; (ii) when HIV infection does become established, some individuals appear able to mount a particularly vigorous and effective immune response that overcomes and clears the infection; (iii) genetic factors, for example the homozygous LILRA3 deletion is associated with higher susceptibility for HIV disease and with faster disease progression (5).

Environmental factors

HIV/AIDS is a socioeconomic and behavioral problem. The stigma and discrimination associated with HIV/AIDS and STI prevent many individuals from seeking testing and treatment. Poverty and cultural issues also play an important role. Providing the public with scientific knowledge and information is critical for prevention and treatment of HIV/AIDS.

Disease burden

WHO's SEAR comprises 11 countries, of which five account for the majority of the HIV burden: India, Indonesia, Myanmar, Nepal, and Thailand. No cases have been reported from Democratic People's Republic of Korea, and the remaining five countries—Bangladesh, Bhutan, Maldives, Sri Lanka, and Timor-Leste—together represent less than 1% of the total HIV burden in the region (6). India, with its large population, bears the third-highest burden of the HIV in the world, after South Africa and Nigeria. Figures 1–3 show recent status and trends in HIV prevalence in India.

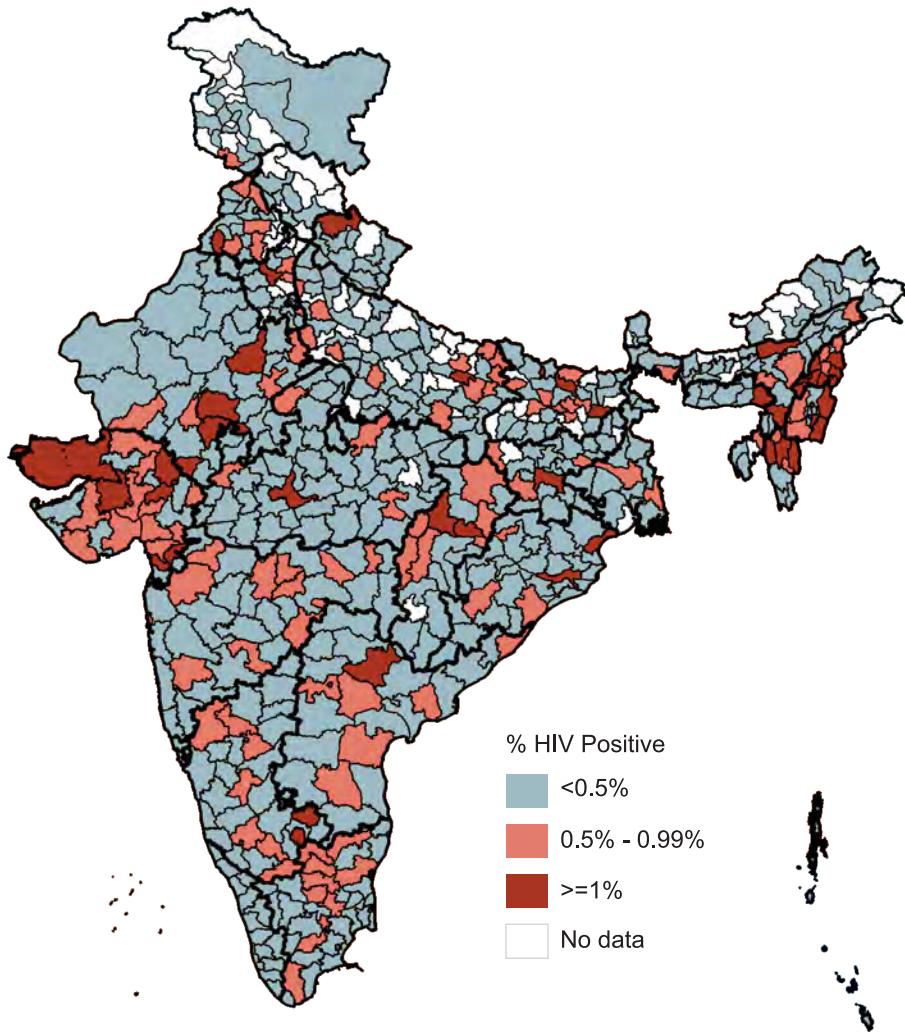


Figure 1. HIV prevalence in India, by district, Health Systems Survey (HSS) 2014–2015 .

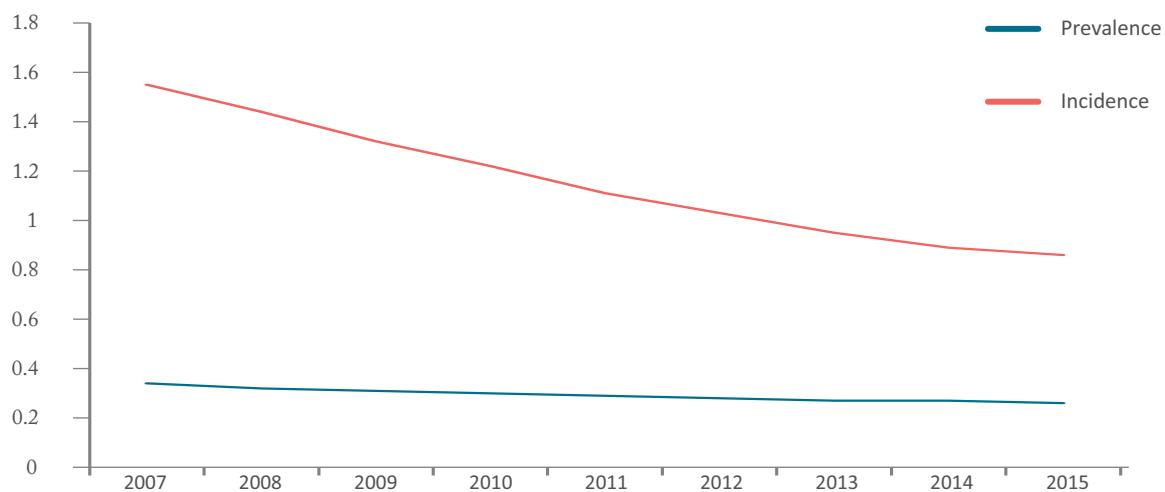


Figure 2. HIV incidence and prevalence in India, 2007–2015. Data source: National AIDS Control Organization, MoHFW, Government of India. HIV Facts & Figures

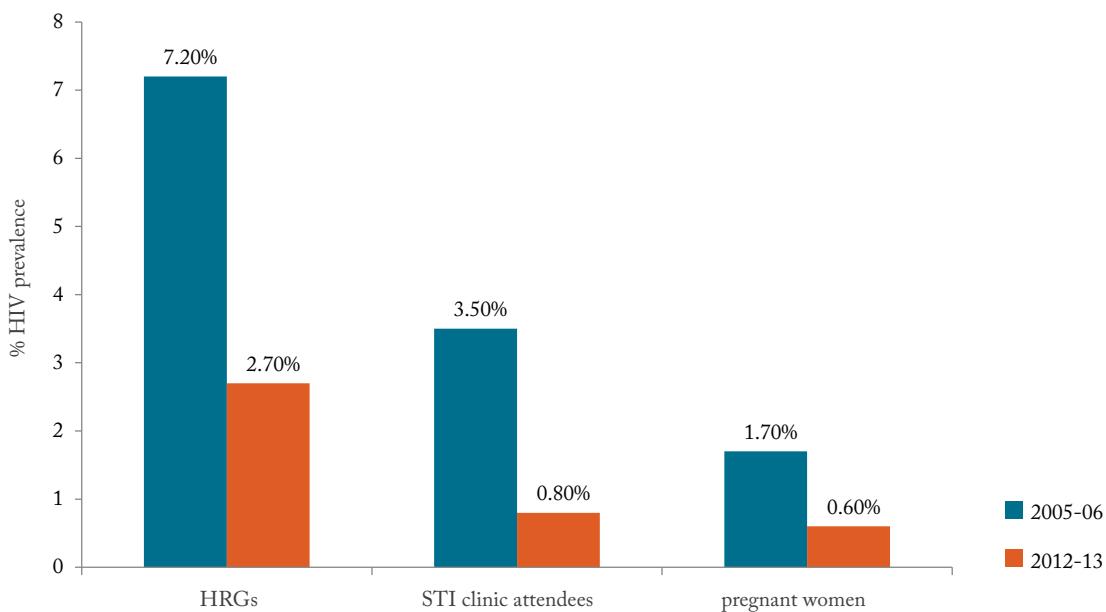


Figure 3. HIV prevalence among high risk groups and pregnant women in India, 2005–2013; HRG = high risk group; STI sexually transmitted infection. Data source: National AIDS Control Organization, MoHFW, Government of India. HIV Facts & Figures

Some states of India, especially those with high migration related to shipping industry employment, have higher rates of HIV-infected men (Figure 4). Examples include northern Bihar, western Gujarat (Alang), and eastern Andhra Pradesh (Vizag). Injection of drugs is a contributing risk factor in the spread of HIV infection mainly in the north and east—Punjab, Uttar Pradesh, Bihar, Delhi, and Uttarakhand. Risky community practices, such as sexual orgies, frequent exchange of sex partners, or “community customs” like nag panchmi (a night on which Hindus worship the snake God every year), are also risk factors (6). The state of Manipur has an adult HIV prevalence rate of 1.15% and thus is the only state in India with a generalized epidemic. Many of the formerly high-prevalence states, such as Andhra Pradesh, Karnataka, Maharashtra, Mizoram, Nagaland, and Tamil Nadu, have seen steady declines in the estimated number of new HIV infections. These states have a comparatively more robust public healthcare infrastructure and addressed the HIV epidemic relatively early. However, a rising trend in annual new HIV infections among adults is noticed in otherwise low-prevalence states and union territories, including Assam, Chandigarh, Chhattisgarh, Gujarat, Sikkim, Tripura, and Uttar Pradesh.

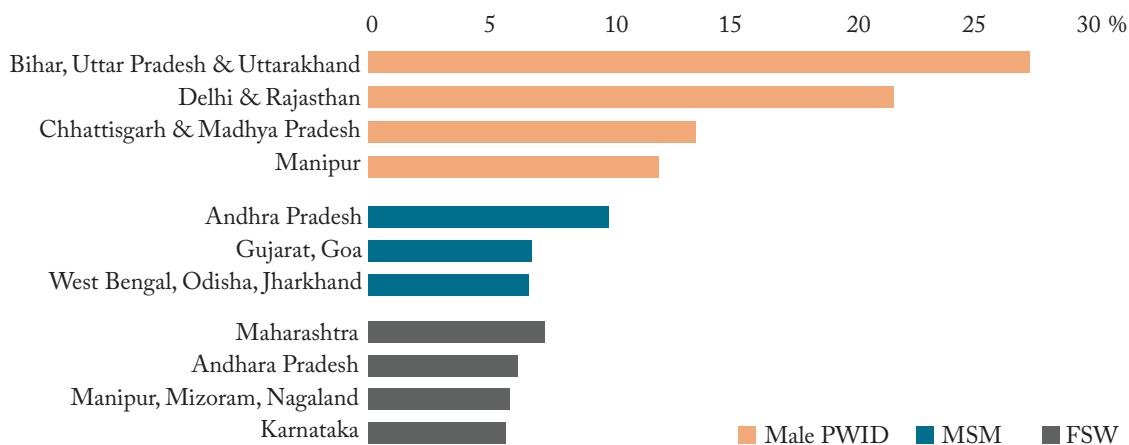


Figure 4. HIV prevalence in select states of India, by population, Integrated Biological and Behavioral Surveillance (IBBS) 2014–15(6); FSW = female sex workers; MSM = men who have sex with men; PWID = people who inject drugs.

Gender disparities

Biological, sociocultural, and economic factors render women and young girls more vulnerable to HIV/AIDS and STI. Lack of education and empowerment that leave women unable to say no to unwanted or risky sex, early marriage of girls, a patriarchal society with male dominance, gender discrimination (preference for a son over a daughter in India), domestic violence, the poor status of women (especially those from the Dalit community), the sex trade and trafficking: all these factors mean that many women face economic hardship and are more vulnerable to prostitution and transactional sex in which they have little power to negotiate safe sex (7). Evidence from the 2016 National Family Health Survey (6) and National AIDS Control Organisation (NACO) (8) shows that women are highly vulnerable to HIV/AIDS and STIs. Table 1 ranks six SEAR countries according to the prevalence of STI, and Figure 5 shows the seroprevalence of syphilis in India and Indonesia.

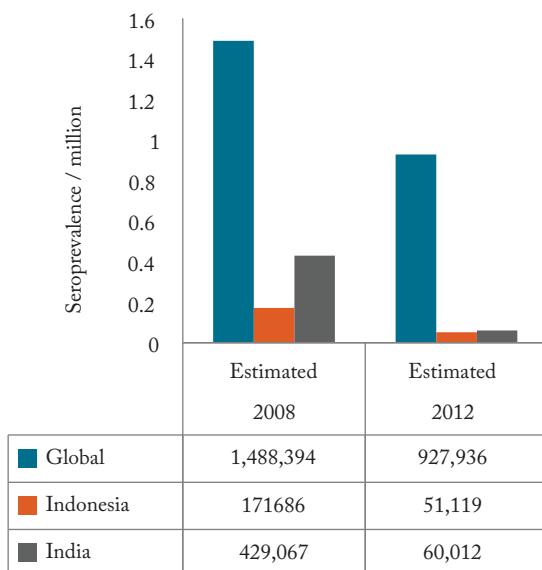
Table 1. STI prevalence and trends in 6 SEAR countries (9,10)

Country	Year	Total GUD/100,000	Male GUD/100,000	Female GUD/100,000	Male UD/100,000	Rank
Timor-Leste	2014	69.9	36.2	104.5	314.2	1
Bhutan	2012	52.6	35.7	73.0	278.1	2
India	2014	14.6	19.2	9.8	210.0	3
Maldives	2014	18.9	7.4	35.2	5.0	4
Myanmar	2014	2.6	3.5	1.8	5.0	5
Indonesia	2014	1.2	1.1	1.3	12.1	6

Source: WHO (2015) Report on global sexually transmitted infection surveillance (9, 10).

GUD = Genital Ulcer Disease (in males and females); UD = Urethral Discharges (in males); STI = sexually transmitted infection; SEAR = South East Asia Region.

Maternal Syphilis



Adverse pregnancy outcomes

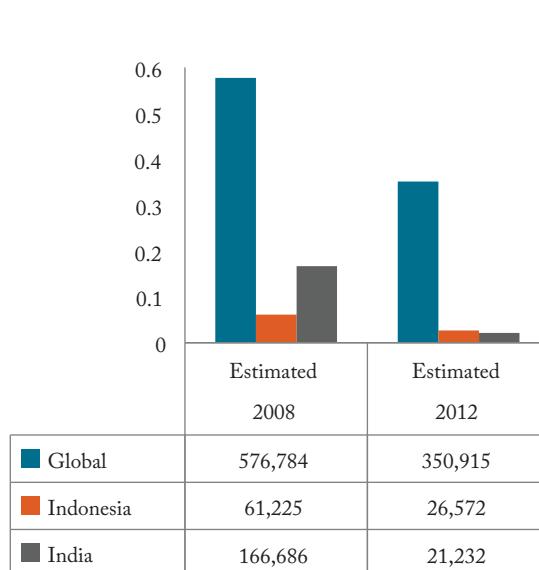


Figure 5. Syphilis seroprevalence and adverse pregnancy outcomes in India and Indonesia, 2008–2012 (10).

Effects on the poor

Mortality and morbidity are measured in disability-adjusted life-years (DALYs), these are the years lost due to morbidity or mortality compared with the average life expectancy. Although HIV/AIDS has received significant attention in high-burden countries, it has never been India's dominant health problem and thus it has been challenging to sustain HIV/AIDS programs. The contribution of HIV/AIDS to India's total disease burden may be relatively small, but it had a remarkably high share of the world's total HIV/AIDS burden in 2010: 11.4% of global DALYs (11).

Low socioeconomic strata of society are more vulnerable and have a higher risk of contracting HIV/AIDS and STI because of the lack of education, health literacy, and information about HIV/AIDS and its prevention. Poor people also have less access to screening and treatment services for HIV and STI, and poor families bear a heavy financial burden from expensive medical treatment. Chronic illnesses push almost 1% of middle-class families annually below the poverty line in SEAR (12).

Priorities for HIV/AIDS and STI control

The HIV/AIDS and STI interventions are of two types, population based and personal.

Population-based interventions are cost-effective for sex workers, people who inject drugs, men who have sex with men (13), prisoners, patients with STIs (14), and refugees and immigrants—all high-risk subpopulations whose HIV prevalence is five to 10 times higher than in the general population (15). Inconsistent use of condoms with multiple sex partners is widely prevalent in most SEAR countries. Reasons include poor HIV treatment literacy, poor health-seeking behaviors, gender-based violence, and poor adherence to antiretroviral therapy (ART) (14).

Personal interventions are equally cost-effective and take the form of care and support services (16–21). Effective management of HIV/AIDS in the primary care setting requires the coordination of interventions at clinics, community support for those clinical services, and individual patients' adherence.

Primary care at clinics, home, schools, and worksites must be convenient—before or after work. Clinics offer multidisciplinary care teams, provider-patient relationships, counseling and emotional support (18–21), confidentiality, and health literacy, and they help counter stigma and discrimination (18, 21). Home-based primary care involves health literacy training of family members about infection control. School-based primary care addresses the adolescent population, with early intervention to avoid high-risk behaviors, school anti-HIV clubs, and education about how HIV is transmitted and how to prevent transmission. Workplace-based care encourages self-management of health issues, addresses workplace discrimination, promotes a nonjudgmental and supportive environment at work, and provides easy access to male and female condoms.

District hospitals (21–23) offer secondary care: HIV screening tests and access to free ART medications. However, ART is frequently associated with reactions to antiretroviral (ARV) drugs. Whereas other infectious diseases usually respond to short-term clinical interventions, the long-term nature of ART has made HIV infection a chronic disease. Laboratory tests for HIV/AIDS are frequently abnormal because it is a multisystem disease. Patients are often at high risk for other medical conditions. Hematologic complications include anemia, neutropenia (due to HIV's effect on stem cells), and thrombocytopenia (due to direct HIV killing by HIV). Liver disease is common because of concurrent viral hepatitis, especially Hepatitis C Virus (HCV), in many cases and because all ART is potentially hepatotoxic. Abnormal renal function is caused by HIV infection of the kidneys resulting in nephrosis and end-stage renal disease. Abnormal renal function of any etiology is a contraindication for nucleosides in ART. A range of medical resources, including providers with subspecialties or superspecialties and laboratory expertise, must be in place (22).

Tertiary care (21–23) provides assessment and initial management after HIV diagnosis is confirmed, screening for tuberculosis (TB), behavioral and psychological assessment, social support, and nutritional assessments, plus education about HIV/AIDS transmission, risk reduction, and treatment options. Investigations include baseline Hb, blood profile, and HIV viral load to determine ARV drug failure. At the patient's second visit, within two to three days, adherence counseling is done and the client is initiated on ART. Subsequent monthly or annual visits include more tests—HB, blood profile, HIV viral load—and questions about any side-effects of ARV.

Table 2. Global strategy for prevention and control of sexually transmitted infections, 2007–2015, by WHO region

	Africa	Americas	Eastern Mediterranean	Europe	Asia	Western Pacific
Countries surveyed (countries responding)	47 (26)	35 (18)	22 (13)	54 (30)	11 (10)	29 (11)
Countries with surveillance systems (percentage)	20 (43%)	16 (46%)	10 (45%)	30 (56%)	9 (82%)	10 (34%)
Countries conducting gonococcal AMR monitoring in past 5 years (percentage)	10 (21%)	10 (29%)	2(9%)	19 (35%)	7 (64%)	4 (14%)
Countries conducting etiological studies in past 5 years (percentage)	4 (9%)	9 (26%)	4 (18%)	0 (0%)	3 (27%)	4 (10%)
Countries with national STI guidelines or recommendations updated since 2006	33	25	11	19	9	12
Countries with national strategy or action plan for STI prevention and control (percentage)	19 (40%)	16 (46%)	9 (41%)	22 (41)	9 (82%)	11 (38%)

AMR = antimicrobial resistance; STI = sexually transmitted infection.

Source: WHO (2015) Report on global sexually transmitted infection surveillance 2015.

Cost-effectiveness of interventions

Several factors influence the cost-effectiveness of interventions, including poverty, nutrition, access to medical care, and psychosocial barriers. Interventions for addressing the HIV/AIDS–environmental linkages (24), such as facilitating policy and systems-level change, strengthening community institutions, and encouraging sustainable, environmentally friendly livelihoods, provide benefits that go beyond health (25). The strengthening of healthcare systems that is driven by HIV/AIDS programs has improved the entire health sector. For example, disease surveillance, procurement and supply chain management, and health literacy are becoming integrated. All the social determinants of health—from poverty, gender equality, and socioeconomic status of households to education, safe drinking water, pollution control, and waste management—will improve if HIV/AIDS interventions are successful (24, 26). These interventions should give more emphasis to the human right to health and to empowerment through access to information, as well as healthcare services. Community-based approaches will empower communities to achieve meaningful results. Healthcare programs that improve HIV/AIDS indicators have also driven intersectoral health indicators that had been long neglected. For example, the declining socioeconomic indicators due to avoidable morbidity and mortality are gradually rising again. To normalize HIV/AIDS and STIs in communities, psychosocial counseling and community support are vital areas to strengthen—but without draining resources from other health programs.

Positive preventive interventions produce the desired outcomes (27). People living with HIV should be in their best possible state of health, both physically and mentally. This can be achieved by overall improvement of sexual health in communities. People must be fully aware of preventive measures to avoid the further spread of infection and unintended pregnancies. Active participation of people living with HIV in policymaking is needed. Psychological counseling for HIV patients will improve their coping mechanisms and prevent depression. Fighting the stigma and discrimination associated with HIV/AIDS will also help improve the overall happiness index of HIV patients. Networking between people with varied sexual orientations and needs is one of the positive outcomes of HIV/AIDS epidemic.

In dealing with any epidemic it is important to strike the right balance among prevention, treatment and care, and control. Evaluating the cost-effectiveness of strategies to combat HIV/AIDS and STI in SEAR is a first step, and in turn, that requires information on prevalence and trends (28–32). Funding can then be guided by the estimates of the relative cost-effectiveness of pilot interventions. Prioritizing interventions targeted to populations at higher risk will offer the best value for money, especially in countries with concentrated epidemics.

It is important to identify and characterize circumstantial issues (community beliefs, norms, local acceptability) that affect the selection of interventions. For example, many Africans practice “dry sex,” using herbal desiccants in the vagina to ensure tightened mucosa and increase friction and pleasure for the male (32), whereas SEAR sexual practices generally involve using oil and moisturizers or anal penetrative sex. Eliminating the duplication between different interventions—for example, psychological support offered through counseling and support provided through peer support groups—can improve cost-effectiveness. Cost savings can be gained by closing down any “negative” interventions, those that cost more than they deliver in benefits.

General community interventions (27, 28) comprise information, education, and communication (mass media campaigns); voluntary male medical circumcision; condom promotion and social marketing; school-based sex education; efforts to combat fear-based stigma and discrimination; and wider access to voluntary counseling and testing services in the community. The more focused community interventions consist of STI screening, treatment, and counseling, with special emphasis on adolescents and young adults, easy access to treatment that reduces sexual transmission and vertical transmission (from mother to child), promotion of breastfeeding substitutes for HIV-infected mothers, promotion of contraceptives to prevent unwanted pregnancies among infected mothers, blood safety practices, and sterile injections in medical practice.

Whether an intervention is good value for money is determined by analysis of its cost-effectiveness in reducing the disease burden. Interventions need to be adequately funded, but that may not be feasible if the number of interventions is large and the budget is limited. Then it becomes appropriate to focus on fewer interventions that address high burdens, even if interventions that affect smaller disease burdens are more cost-effective. For example, health campaigns for the general population in India cost US\$1,372 per HIV

infection averted, which is a huge amount to spend on preventing one HIV infection (33). However, these campaigns maintain a basic level of HIV information in communities while interventions for high risk groups are implemented. HIV prevention is clearly valuable: it promotes long-term health benefits and can avert downstream HIV care costs. However, this objective is stymied by limited HIV budgets. Prevention consumes resources today to deliver benefits that will not appear for many years, making it difficult for policymakers to commit to the upfront investment. A prevention intervention can be simultaneously cost-saving over a lifetime horizon and yet economically infeasible today. Most HIV/AIDS and STI control programs focus on care and treatment because of the immediate gains in reduced morbidity and mortality.

The cost-effectiveness of HIV/AIDS and STI interventions is shown in Table 2 (33–44).

Table 3. Cost-effective interventions for HIV/AIDS and STI in SEAR

Intervention	Metric	Unit cost (US\$)	Reference
Health campaign in general population, Vietnam	Cost per HIV infection averted	1,982	(33)
Health campaign in general population, Vietnam	Cost per DALY averted (each year of morbidity or mortality)	248	(33)
Health campaign in general population, India	Cost per HIV infection averted	1,372	(34)
Adolescent and school intervention, India	Cost per HIV infection averted	450	(37)
VCT, general population, India	Cost per DALY averted	69	(34)
VCT-HRG, India	Cost per HIV infection averted	104	(38)
VCT-HRG, India	Cost per DALY averted (each year of morbidity or mortality)	10.7	(38)
Blood safety, Asia	Cost for averting 1 HIV-infected unit of blood	20–121	(34)
Voluntary circumcision, Africa	Cost per HIV infection averted	174–2,808	(39)
Pre-exposure prophylaxis, South Africa	Cost per DALY averted (each year of morbidity or mortality)	2,700	(40)
Social marketing of condoms, global	Cost per HIV and STI averted	55.4	(41)
Adult ART, India	Average cost per DALY averted (year of morbidity or mortality) using test-to-treat plan	131–241	(42)
Adult ART, Vietnam	Average cost per DALY averted (year of morbidity or mortality) when CD4<500	290	(42)
Prevention of mother-to-child transmission, Plan B-plus, Vietnam	Cost per HIV infection averted	114	(43)
STI syndromic treatment, South Africa	Cost per STI averted	85	(44)
Maternal syphilis elimination	Average cost per DALY averted (year of morbidity or mortality)	11	(35,36)

STI = sexually transmitted infection; ART = antiretroviral therapy; DALY = disability adjusted life year;
VCT = voluntary counselling and testing; HRG = high risk group.

The medical interventions generally had higher unit costs. In 2013, WHO released updated guidelines on the prevention of mother-to-child transmission of HIV, recommending a shift from Plan A (prophylaxis for mothers and infants) to Plan B (ART for women while pregnant or breastfeeding) to Plan B+ (lifelong ART for pregnant women).

National programs cannot fully implement many of the effective interventions because of budget constraints (16, 17, 35, 36, 45 – 47). Countries require strategies that will achieve the targets for ending the epidemics on limited resources, prioritizing behavioral and medical interventions and packaging their components. Upfront and ongoing consultations can improve conceptualization and data collection, analysis, and dissemination. Also needed are innovative methods, documentation of best practices, and identification of synergistic policies. Tools linking costs to health outcomes include cost-minimization analysis, cost-consequences analysis, cost-effectiveness analysis, cost-utility analysis, and cost-benefit analysis.

Some of the interventions listed in Table 3 are considered successful; others are labeled as failures. Most national programs have reported success with the following interventions: blood and tissue safety programs, institutional infection control, and Voluntary Counseling and Testing (VCT) services for HIV in institutions and communities e.g. Indian coverage has 70% of estimated HIV infected persons who are tested for HIV. The Sentinel Surveillance of select antenatal and STI groups, and care, support and ART combination that are applauded as best practices are in India and South Africa. However, these programs have a glaring weakness: the HIV viral load test has low coverage, just 8%–10%, for monitoring a million patients on ART. This is a major concern in the area of Care, Support & Treatment (CST) intervention.

Early detection of pediatric HIV infection, breast milk substitution strategies, and synergy of HIV with TB management and control have also been successful, especially in India and Sri Lanka. The social marketing of condoms is considered a best practice in Thailand, where the national government in 1991 embarked on an ambitious goal of 100% condom usage in brothels. After 10 years of rigorous promotion of male and female condoms, good preventive outcomes were observed. The campaign was then handed over to nongovernmental organizations; it averted the generalized phase of HIV/AIDS epidemic in Thailand (47). Sustainable models of condom use have yet to evolve at the global level, however. Although the Indonesian syringe-needle exchange program for intravenous drug users is a best practice, sustaining sexual behavior change is challenging. The Indian program has demonstrated a successful nutrition supplementation to Persons-living-with-HIV (PLHIV) while they are on ART and TB treatments.

Other interventions reported from SEAR countries have been less successful. Programs to prevent mother-to-child transmission in India, Nepal, Bangladesh, Sri Lanka, and Indonesia have low coverage, less than 35% of antenatal women in India (16, 17, 46), and suffer from low capacity and poor training. Pre-exposure prophylaxis is a nonstarter in India and most other SEAR countries because of the lack of pilot studies (14). Inadequate advocacy, weak community systems, and poorly implemented operational and biomedical research in most SEAR countries, including India, are causes of failure (7).

The major challenges for health systems development are rigid centralization of the healthcare system; resistance to integration of services for HIV/AIDS prevention, care, and support; failure to link reproductive and sexual health with HIV/AIDS and STI prevention and care; and the lack of coordination of HIV/AIDS services with the social development and education sectors in particular. Alliances and partnerships in healthcare delivery in the Health Systems Strengthening (HSS) program, especially procurement and supply chains and compatible district data management systems, are needed.

Limited targeting, low coverage (20%–40%), and ineffective prevention are major barriers to controlling the HIV/AIDS and STI epidemics. Other problems include low access to quality care and treatment; limited scope for linking with public healthcare systems; limited multisectoral involvement; weak surveillance and monitoring and evaluation systems; limited transparency and weak accountability; and limited political consideration of the healthcare systems in which HIV/AIDS services are delivered. The high level of gender inequity in healthcare systems is a major barrier to efficient disease control. Healthcare systems lack a framework for enabling involvement of communities and nongovernmental and community-based organizations; denial, stigma, and discrimination are common; and national budgets cannot sustain HIV/AIDS and STI programs, which are generally donor driven.

Research agenda

Global investment in research and development (R&D) for HIV/AIDS prevention has remained stagnant, at around US\$1.25 billion, for nearly a decade, according to a report from the HIV Vaccines and Microbicide Resource Tracking Working Group (48).

Strategic HIV and STI research should address the following areas: virus replication and gene expression, HIV assembly, virus-cell interaction, viral pathogenesis, epidemiology and disease transmission, and the complex interactions of the virus with the host. HIV and STI product development is encouraged in antiretroviral treatment (Figure 6), ARV resistance, adherence, new drug discovery, HIV/AIDS vaccines, animal models, and community acceptance of HIV vaccines. Several studies using Tier 2 or Semian HIV that generates high titers of neutralizing antibodies to envelop trimers in macaque monkeys are encouraging. It is likely that preventive vaccines could be available for human trials in the next decade. If successful, they will be the game changer for the HIV epidemic, possibly by 2030 (49). Furthermore, interventions are needed to interrupt mechanisms and interactions with disease progression, social and public health interventions, and prevention and control of viral genital infections.

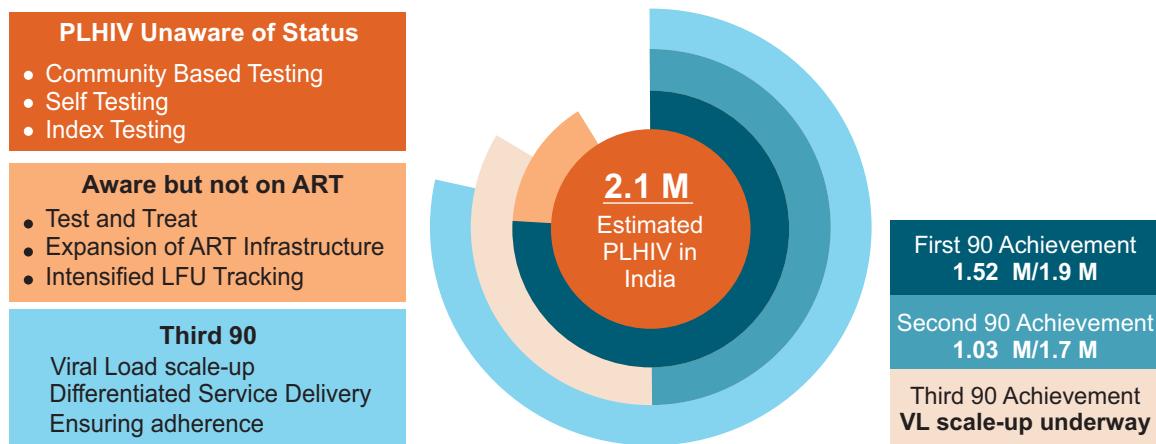


Figure 6. UNAIDS strategies to achieve universal access to quality treatment (2).

ART = antiretroviral therapy; LFU = Lost-to-follow up; PLHIV = Persons-living-with-HIV; VL = Viral Load test

The health sector strategy promotes a long-term, sustainable HIV response through strengthening healthcare and community systems, addressing the social determinants of health that both drive the epidemic and hinder the response, protecting and promoting human rights, and promoting gender equity as essential elements of the health sector response. For example, strategic priorities based on evidence from surveillance, program monitoring, and feedback from the concerned populations should accelerate prevention in at-risk populations to reduce infections. This suggests a differential approach and a better package of services more relevant to specific populations and local settings.

R&D funding for HIV/AIDS prevention is focused on the following areas: vaccines for prevention, microbicides with and without spermicidal action, pre-exposure prophylaxis, ART to reduce HIV transmission and prevent infections, mother-to-child transmission, voluntary medical male circumcision, and acceptability of and access to female condoms. R&D can also focus on HIV cures, therapeutic vaccines, herpes (HSV-2) vaccines, and multipurpose prevention technology research. Four new areas of research are the rollout of preventive interventions, better access to HIV prevention products, the pace of interventional research, and advocacy to bring in new philanthropic funders for HIV prevention.

The proposed R&D strategies in India's national strategic plan on epidemiologic and operational research are scaling up targeted interventions to increase coverage beyond 60%, designing appropriate response mechanisms to address at-risk populations, outreach through social networks, community-based screening for HIV and STIs, and integrating sexual and reproductive healthcare and other national disease control programs (8). Community ownership and engagement need to be stepped up, and cost-analysis and cost-effectiveness studies should be conducted.

Roadmap to 2040

The authors of this chapter have developed a roadmap for the Indian HIV/AIDS and STI epidemics using national and global indicators. Table 4 presents the synthesis of an extensive exercise conducted by a team of consultants—specialists, epidemiologists, economists, and scientists—who developed targets for the roadmap to 2040.

Table 4. India's HIV/AIDS and STI Indicators for monitoring targets to 2040*

Indicator	2010 Baseline	2020 UNAIDS targets	2030 SDG targets	2040 targets	Data source
1. Number of people living with HIV/AIDS in India (millions)	—	2.13	2.35	2.29	HIV estimates/ modeling
2. Number and percentage of new HIV infections (incidence)	—	80% decline <21,000	0	0	HIV estimates/ modeling
3. Annual HIV-related deaths (annual mortality rate in India is 7.3/1000 pop.; 31% deaths occur in 15–60 age group; annual mortality rate in ART naïve HIV+ adults is 4.5%*)	—	3,960 on ART plus 2,340 ART-naïve= 6,300	4,526 on ART plus 14,400 ART naïve= 19,926	5,182 on ART and zero deaths in ART-naïve =5,182	HIV estimates/ modeling
4. Adults with new GUD (millions)	0.12	TBD	TBD	TBD	Rough estimates for India -- (3, 10)
5. Male adults with new urethral discharges (millions)	1.61	TBD	TBD	TBD	Rough estimates for India -- (3, 10)
6. Estimated adults* with genital herpes in India (m), based on global prevalence rate of 10.8% in adult population (millions)	105.5	TBD	TBD	TBD	Rough estimates for India -- (3, 10)
7. Estimated adults* with human papillomavirus in India (m), based on global prevalence rate of 7.6% in adult population (millions)	74.3	TBD	TBD	TBD	Rough estimates for India -- (3, 10)
8. Percentage of sustainable HIV services financed through domestic budget	60%	80%	100%	100%	Program data
9. Percentage of condom use among key populations and sterile needles or syringes among PWID	—	80%	90%	95%	IBBS or HSS Plus
10. Number and percentage of PLHIVs diagnosed with HIV (millions)	—	1.75 (82%)	2.14 (95%)	2.24 (98%)	Program data
11. Diagnosed PLHIVs currently on ART (millions)	—	1.53 (87%)	2.03(95%)	2.20(98%)	Program data
12. PLHIVs retained and surviving on ART (12 months) (millions)	—	1.19 (78%)	1.93(95%)	2.10 (95%)	Program data
13. PLHIVs undergone VL test (millions)	—	0.13 (11%)	1.6 (80%)	2.20 (100%)	Program data

Table 4. India's HIV/AIDS and STI Indicators for monitoring targets to 2040*
(Contd.)

Indicator	2010 Baseline	2020 UNAIDS targets	2030 SDG targets	2040 targets	Data source
14. PLHIVs and on ART who are virologically suppressed (millions)	—	0.11 (85%)	1.52 (95%)	1.87 (85%)	Program data
15. Number and percentage of pregnant women tested for HIV (millions)	—	28.5 (90%)	25.69(95%)	NIL-MTCT eliminated in 2030	Program data

ART = antiretroviral therapy; GUD = Genital Ulcer Disease; NIL-MTCT = Zero mother-to-child-transmission; PLHIV = Persons-living-with-HIV; PWID = Person-who-injects-drugs; TBD = To-be-determined; VL = Viral Load test.
*India's 2018 population was 1.357 billion, with 977 million adults (72%) who were 15 years or older.

Tasks for ministries of health

Strong, undeterred, national political commitment to manage and control HIV/AIDS and STI epidemics. This has improved considerably in India and other SEAR countries since 2003 with the advent of antiretroviral treatment and establishment of UNAIDS-sponsored national fora of parliamentarians to fight HIV/AIDS.

Commitment for innovation and R&D to finding a cure. This area remains neglected because of inadequate resources.

Integration of components of national strategic plans with other disease control programs to establish synergies and cost-effectiveness. Integration of components of national control programs is often resisted because of turf battles, resource control, and lack of efficient integrated models for program managers to learn from.

Effective, efficient implementation of quality HIV and STI interventions at three levels: patient, provider, and healthcare system. At the patient level, targeted education and support are required to enhance acceptability of interventions in the community. At the care provider level, counseling and follow-up should engage a broad mix of care providers, and providers for patient management should receive adequate training. At the systems level, optimal delivery modalities, cost-effective models, resource allocation, integrated information and monitoring and evaluation systems, and affordable access to healthcare are the issues most in need of new options.

Tasks for WHO and international development partners

Technical support as requested by member countries.

Creation of a platform for sharing experience across countries and regions, with links to appropriate partners, and implementing new guidelines.

Support for countries in accessing tools and resources, collaborating with partners, monitoring progress, facilitating development of guidelines, and conducting periodic impact evaluation studies to identify cost-effective interventions.

Challenges and pitfalls

The effectiveness of behavioral interventions is likely to change as new generations become sexually active at

younger ages and experiment with drug use and casual sex. The need for community-level sexual health services for adolescent and young adults is urgent. These populations want access to scientifically accurate health information through new media. Furthermore, HIV practitioners will need to balance behavioral interventions for the diverse sexual needs, habits, and practices of new generations with biomedical interventions and transparent societal norms. A new component—mental health and empowered counseling in human sexuality—should be added to the care and support services of HIV/AIDS and STI patients, and sexual behavioral issues in most cases should be decriminalized.

Future preventive and therapeutic HIV vaccines may not remain effective as HIV subtypes continue to mutate. However, strategic investment in vaccine intervention can be a gamechanger in the otherwise progressive epidemic of HIV/AIDS. The ongoing evolution of resistance to antiretroviral medicines and a slower emergence of newer ARV molecules deserve national surveillance in SEAR countries because they have the potential to reverse all gains made so far with the HIV/AIDS epidemic.

Moreover, sustaining resource allocations at national and state levels until 2040 will be challenging. Ministries should consider innovative approaches to healthcare financing, such as public-private partnerships with Corporate Social Responsibility (CSR) and private sector support.

Equally challenging are lost R&D opportunities to identify and implement newer interventions. There is a need to cost these lost opportunities.

To accelerate control of HIV/AIDS and STI and avoid pitfalls, national programs should conduct a strategic assessment of prevention needs at regular intervals; identify what works and what doesn't work to fine-tune investments; develop or periodically revise national targets, roadmaps, and operational plans; strengthen national leadership (e.g., the Indian Parliamentary Forum against HIV/AIDS) and make institutional changes to enhance the gains; introduce policies and legal changes to create an enabling environment for the national program; develop strategic guidance, formulate cost-effective intervention packages, and identify service delivery platforms; develop comprehensive plans for capacity building and technical assistance; establish or strengthen social contracting mechanisms for civil society implementers and expand community-based programs; assess available resources and develop a strategy to reduce the financing gap; establish or strengthen HIV programs' monitoring and evaluation systems; and strengthen accountability in systems, including among all stakeholders.

Conclusion

Since 1986, when HIV/AIDS was first reported in India, related deaths have fallen significantly. High-risk behavior—casual sex, unsafe sex, drug use—remains common among young people, however (6–8). Inadequate sex education in schools and the lack of knowledge about HIV among young people lead to a “not me” belief. Substance use is a cofactor for increased transmissibility of HIV/AIDS and STI. Prevention campaigns with catchy slogans can help create awareness in young adults, such as “Believe in treatment but focus on prevention,” “If you want to avoid infection then don’t forget protection,” and “Life and death depends on your selection, choose masturbation over unprotected penetration.”

For HIV preventive interventions, “the size of intervention does not fit all communities and regions of the world,” according to UNAIDS To create effective HIV risk-reduction interventions, the following two questions must be answered: What specific pattern of HIV risk behavior can be observed within the given population? And what factors facilitate and maintain these patterns over time? The cultural, social, psychological, and economic factors that contribute to the development and maintenance of HIV-related risk behaviors need to be documented, examined, and addressed through broad development plans, poverty reduction strategies, adolescent and maternal healthcare, gender equality and empowerment of women and adolescent girls, health literacy, and strong community participation. Figure 7 shows the UNAIDS’s paradigm to ‘Fast-tracked Approach’ to ending HIV/AIDS epidemic by 2030 and it can be a game changer if implemented correctly.

Classify states and districts on level of HIV epidemic and public health setup

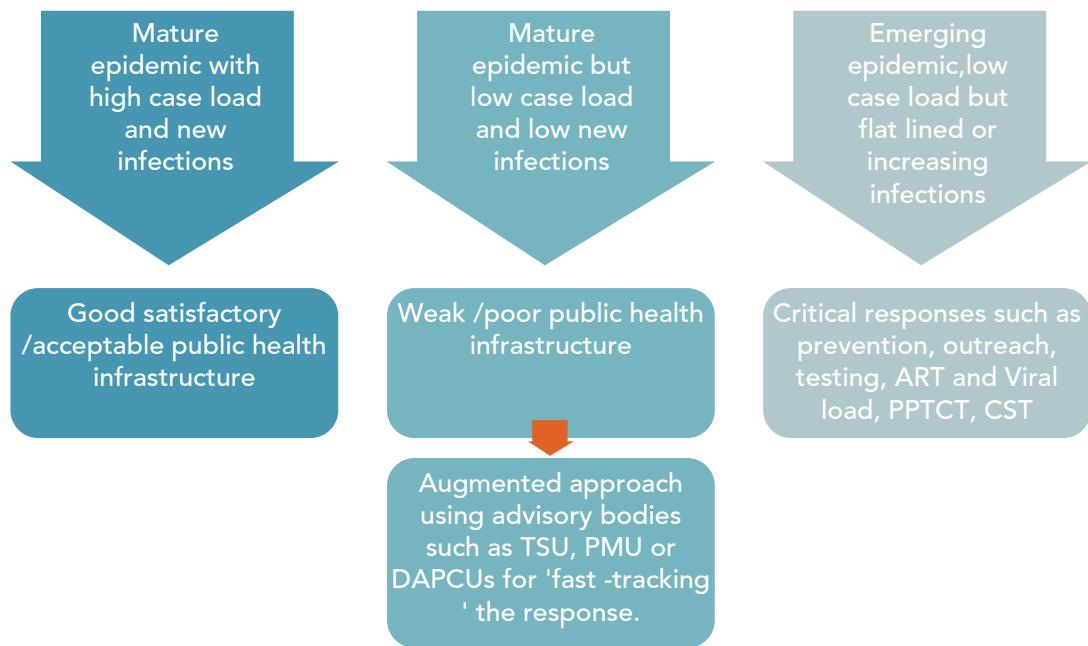


Figure 7: The 'Fast-tracked Approach' to accelerate prevention and control of HIV/AIDS in a state/district is to classify it in one of the following three paradigms: listed in blue, pink, or green verticals. Source: UNAIDS

ART: Anti-Retroviral Treatment; CST: care,support & treatment; DAPCU: District AIDS Prevention & Control Unit; PPTCT: Prevention-of-parent-to-child-transmission; PMU: Project Management Unit; TSU: Technical Support Unit.

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