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Innovation for neglected diseases in South Asia

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INNOVATION FOR NEGLECTED DISEASES IN SOUTH ASIA

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Innovation is vital for elimination of neglected diseases in South Asia

Despite some success in reducing the substantial mortality many challenges remain, say **Suman Rijal and colleagues**

The sustainable development goals set a target to end epidemics of neglected tropical diseases by the year 2030. The task can seem daunting. Equally, having a clear objective can steer global action towards this important health problem that disproportionately affects poor people. The World Health Organization prioritises neglected tropical diseases for control or elimination. Over a billion people worldwide are affected by these diseases, which are seen more commonly in tropical regions.

South Asia has substantial morbidity and mortality associated with infectious diseases, including numerous neglected tropical diseases, and bacterial infections such as neonatal sepsis and enteric fever are of growing concern. Until recently, the Indian subcontinent accounted for 60% of the global burden of visceral leishmaniasis.[1] Over 40% of the global population requiring mass drug administration for lymphatic filariasis elimination is in Bangladesh, India, and Nepal.[2] The number of people affected by snakebites is also highest in India and Bangaldesh.[3]

This special collection of *The BMJ* highlights notable successes of public health programmes in neglected diseases in South Asia and identifies areas where research and supportive policy is needed to advance plans for control or elimination. A unifying theme of this collection is innovation in diagnostics, treatment, and prevention of neglected diseases to create solutions that are effective, relevant, locally feasible, and sustainable.

The collection draws on examples of elimination programmes for lymphatic filariasis, visceral leishmaniasis, and snakebite in South Asia. Authors from across South Asia and the world worked together in teams to map the progress in specific disease areas, identify remaining challenges in elimination efforts, and propose solutions to meet this gap. The challenges and strategies on the path to elimination are likely to be similar for other neglected diseases. The articles on typhoid and neonatal sepsis highlight the growing problem of antimicrobial resistance in South Asia, which has greatly limited the available treatment options and leads to treatment failure and higher mortality.

Importance of collaboration

A few key lessons stand out. Firstly, partnerships and regional collaborations are vital to sustain momentum and foster transfer of knowledge and technology. Driven by a strategic regional collaboration under the kala-azar elimination programme, Nepal and Bangladesh have eliminated visceral leishmaniasis as a public health problem and India has considerably reduced the disease burden.[4] A regional framework such as this can offer a mechanism to address challenges in other disease control programmes. For example, the antivenom used to treat snakebites across South Asia is sourced from India. However, shortages are common, resulting in much higher mortality from snakebites in South Asia than in other areas. Local studies also show the need for antivenoms effective against a wider range of locally prevalent venomous snakes.[5] Scientists, policy makers, and health professionals must come together to tackle these issues, which cross borders.

A singular focus on disease elimination tends to yield wider action and have a greater impact, as seen with visceral leishmaniasis and lymphatic filariasis. Sri Lanka and the Maldives have successfully eliminated lymphatic filariasis through a combined approach of mass drug administration and robust disease surveillance under the Global Program for Elimination of Lymphatic Filariasis (GPELF).[6] Over 60% of the population in endemic areas of South Asia received prophylactic chemotherapy as part of this programme. Political will and continued community ownership will be crucial to successfully eliminate lymphatic filariasis from South Asia.

Need for new treatments

The strategies have had to evolve to sustain the momentum towards elimination, particularly in larger countries like India. An outlook of fostering continual innovation is critical to meet the changing demands of disease elimination programmes. For example, research conducted by the Drugs for Neglected Diseases initiative in India has shown that post-kala-azar dermal leishmaniasis, a skin condition that occurs in 3-5% of treated patients with visceral leishmaniasis, may be an important reservoir for transmission, as are patients coinfected with HIV. Current treatment regimens are not optimal for these patients, making sustainable progress towards elimination difficult. New and improved treatments are needed, and for the first time, there is a rich portfolio of oral drug candidates for visceral leishmaniasis, which may result in a new therapy within the next decade.[4]

Similarly, the menace of growing antimicrobial resistance to most firstline drugs for typhoid has given impetus to vaccine discovery. A conjugate typhoid vaccine developed in India has been approved by WHO and is now recommended for routine immunisation of children in endemic countries.[7]

Better systems

A major challenge in disease control efforts in South Asia is the lack of robust surveillance data. In the absence of an understanding of true disease burden across geographies and changing trends in resistance patterns, it is difficult to design and deliver effective solutions. This is particularly seen with snakebite envenoming, which is a serious public health concern affecting mainly rural and poor populations. It has, however, been neglected until recently because under-reporting and absence of notification and surveillance mechanisms have resulted in a lack of data on its burden.[5] WHO's recognition of snakebites as a neglected disease by the WHO last year should help drive greater government engagement and regional cooperation to pool together scientific, technological, and financial resources and foster basic research, surveillance, antivenom development, and advocacy.

Disease elimination initiatives tend to function largely as focused vertical programmes, but the need for strengthening health systems in South Asia cannot be overlooked. Deficiencies in availability of drugs, trained staff, critical care support, and transport must be overcome to tackle the high mortality from snakebites, neonatal sepsis, and other diseases in South Asia. A robust primary care network will be important in the post-elimination stages of diseases such as lymphatic filariasis to support surveillance, morbidity management, and disability prevention in those affected. Furthermore, in some areas, population testing and treating may become more cost effective than continuing to scale up mass drug administration.[6]

Antimicrobial stewardship is urgently required across all levels of health facilities, and the paper on neonatal sepsis in this collection offers a simplified model for implementation.[8] Improved treatment options and standard treatment guidelines are needed to help clinicians and improve outcomes for patients. As part of the Global Antibiotic Research and Development Partnership programme, India is one of 11 countries participating in studies on neonatal sepsis and current antibiotic prescribing practices with the objective of developing improved antibiotic regimens for newborns. The Indian Council of Medical Research is collecting data on antimicrobial resistance from collaborating centres in hospitals across the country part of an Antimicrobial Resistance Surveillance Research Network. The data generated through this network will be useful to monitor trends in resistance and devise treatment guidelines. Similar surveillance mechanisms are needed across the region, alongside studies correlating prescription practices with drug resistance patterns in the community and investigating underlying mechanisms of resistance.

South Asia has a unique role in combating these diseases globally as well as regionally, given the high disease burden and regional expertise in end-to-end solutions, from drug discovery and clinical studies through to regulation, manufacture, and distribution. Such "bench to bedside" leadership could grow rapidly with supportive policy for research and development in neglected diseases.[9] We are launching this collection at a meeting in New Delhi in January 2019, where stakeholders engaged in neglected diseases control, research, and advocacy in South Asia will come together to celebrate the successes so far and plan for further collaborative action. We call on the diverse communities in the readership of *The BMJ* to reflect on the issues brought forth in this collection and push for greater action on neglected diseases in their respective fields.

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Elimination of lymphatic filariasis in South East Asia

Expanding treatment options alongside ensuring high coverage of mass drug administration can accelerate progress in elimination of lymphatic filarisis, say **Sabine Specht and colleagues**

Lymphatic filariasis is a tropical disease that affects about 70 million people worldwide.[1] It is caused by infection with the parasitic nematodes *Wuchereria bancrofti*, *Brugia malayi*, or *Brugia timori* and is transmitted through mosquitoes. Chronic infection causes lymphatic dysfunction, resulting in progressive, irreversible swelling of the limbs and genitals (box 1). Filarial induced lymphoedema is the second leading cause of disability in the world, accounting for about two million disability adjusted life years lost.[1] The associated social stigma often causes mental health problems and poverty because of loss of employment.[1]

The third sustainable development goal calls for elimination of neglected tropical diseases, including filariasis, by 2020. Sixty three per cent of the population at risk of lymphatic filariasis and 50% of the people infected worldwide live in South East Asia. India alone harbours 40% of the world's burden of disease.[2] The region has made considerable progress towards elimination, yet several challenges remain. We present an overview of the global efforts to eliminate filariasis and progress made in South East Asia, and discuss key priorities.

Global elimination efforts

The World Health Organization launched the global programme to eliminate lymphatic filariasis in 2000. This programme comprises two key strategies: mass drug administration to prevent infection, and management of morbidity and prevention of disability.

Mass drug administration

Mass drug administration entails annual distribution of diethylcarbamazine in combination with albendazole for a minimum of five years in an endemic area.[3] These drugs are mainly microfilaricidal. The goal is to achieve a coverage of more than 65% of the population. It is based on the premise that repeated mass drug administration will reduce the microfilaria density in the community and thus halt transmission and new infections. Up to 2015, the programme has provided more than 6.7 billion treatments to over 850 million people at least once in 66 countries. Mass administration is estimated to have cured or prevented up to 96 million new cases of lymphatic filariasis and averted more than $100bn of lifetime economic loss.[4] Since 2000, the number of cases of filarial induced hydrocele has declined by about 49% to 19.4 million, and the number of cases of filarial induced lymphoedema by 23% to 16.7 million.[4]

Managing chronic disease

Long term care is important to prevent and treat chronic manifestations of filariasis. Treatment for lymphoedema includes good hygiene (regular washing with soap and water; skin and nail care), use of topical antibiotics or antifungal agents, exercise, and appropriate footwear. Providing a basic package of care to manage morbidity has been shown to reduce the frequency of acute attacks of adenolymphangitis that drive the progression of lymphoedema.[5,6]

Microfilaricidal drugs have little benefit in infected individuals with lymphoedema and hydrocele.[7] A recent trial involving 105 children with filariasis in India showed a possible benefit in reversing lymph dilation early in the course of disease,[8] and a few observational reports have also noted a benefit.[9,10] Further evidence is needed on their role in preventing the development of lymphoedema and associated disfigurement.

Monitoring impact

The number of people requiring mass drug administration fell from 1.41 billion in 2011 to 856 million in 2016.[1] It is expected that mass administration will no longer be required when the prevalence of infection has been reduced to low levels, such as microfilariae in <1% of the population or antigenaemia in <2% of the population.[11]

After five effective rounds of mass drug administration, a school based transmission assessment survey is conducted. Antigen levels are recorded in 6-7 year old children in the endemic area using a filariasis test strip. If the levels meet cut-off criteria suggesting transmission has been arrested, mass drug administration can be stopped and surveillance used

KEY MESSAGES

- Mass administration of microfilaricidal drugs has reduced new infections of filariasis
- Current challenges include management of patients with chronic manifestations, such as lymphoedema and hydrocele, and the uneven prevalence, with persisting transmission hotspots
- New drugs and regimens that kill adult worms (eg, triple therapy) and alleviate lymphoedema can help accelerate elimination efforts

Box 1: Course of lymphatic filariasis

- Adult filarial parasites reside in the lymphatic vessels of an infected person for up to eight years and produce thousands of first stage larvae (microfilaria)
- Mosquitoes of the genera *Aedes*, *Anopheles*, *Culex*, and *Mansonia* ingest microfilaria during blood meals from humans and these develop into an infective larval stage
- Larvae enter humans through the wound made by a mosquito, where they migrate and settle in the lymphatics to mature into adult worms and complete the cycle
- Lymphatic dysfunction in response to the parasites provokes severe morbidity, including progressive, irreversible swelling of the limbs (elephantiasis) and genitals (hydrocele) with acute adenolymphangitis or acute secondary bacterial infection
- Infection often occurs early in childhood in endemic areas, but clinical signs appear much later. Once triggered, symptoms may progress even after the parasites have died, being sustained by opportunistic bacterial and fungal infections

instead. Transmission surveys are repeated after one and two years. If these are successful, the region can be validated for certification of elimination. If transmission is still ongoing on assessment, mass drug administration has to be continued.

Progress in South East Asia

South East Asian countries are at different stages of implementation of the global elimination programme (table 1). In 2016, the region achieved mass drug coverage of 60.7% of the population in endemic areas.[1] Sri Lanka, Thailand, and Maldives have achieved the criteria for elimination of lymphatic filariasis. Bangladesh has stopped mass drug administration and is presently under surveillance.[1]

A guiding example in the region is Sri Lanka's Anti Filariasis Campaign, in which three rounds of diethylcarbamazine were followed by five annual rounds of diethylcarbamazine in combination with albendazole distributed in all eight endemic districts between 2002 and 2006. Two post-drug administration surveillance assessments were conducted in 2011-13[12] and repeated in areas with continued transmission in 2016. All but three areas showed strongly reduced disease transmission, and it is expected that the incidence will fall to zero without further mass drug administration.[13]

Remaining challenges

Some countries that have completed five annual rounds of mass drug administration are now struggling with suboptimal results on the transmission assessment survey. Elimination efforts have proved challenging in larger countries such as India, with 256 districts involved. Full implementation has not been achieved, and continued transmission is noted in surveys. As such, elimination may not be feasible by 2020 using currently available tools.[14]

Efforts to maintain high mass drug administration coverage must continue. Factors that can interfere with maintaining sufficiently high coverage include insufficient political will, inadequate health infrastructure, logistical issues, systematic non-compliance, and the risk of drug resistance. Recrudescence of infection owing to migration of infected people into areas with interrupted transmission presents a major challenge to elimination efforts.

Next steps

Surveillance

The Sri Lanka experience shows the importance of robust surveillance after mass drug administration to identifiy remaining transmission hot spots. The spatial distribution of lymphatic filariasis where one community may be non-endemic but a neighbouring village has a 30% prevalence makes it particularly difficult to obtain representative data, and success rates may be overinterpreted. In the past, prevalence of lymphatic filariasis was longitudinaly captured in large geographical areas to reduce surveillance costs. Smaller units compensate for spatial prevalence and are more sensitive for detecting persistence or resurgence of lymphatic filariasis.

Using a point-of-care antibody test in combination with xenomonitoring (the detection of parasites in mosquitoes) has been shown to be more sensitive than the antigen testing currently used for detecting low level transmission.[12 13] Such focused elimination strategies are costly, however, and must be weighed against the costs of upscaling or re-starting mass drug administration if transmission persists.[15] A tipping point may be reached, at least in some areas, where test and treat (that is, treatment only of those diagnosed as infected) is likely to become more cost effective, even if it requires 5-10 day treatment instead of a single dose yearly for 5-10 years.

Morbidity management

Morbidity management is even more challenging and must be continued in endemic communities even after mass drug administration has stopped, because affected patients remain in these communities. An accurate assessment of filarial cases has proved difficult. Severe lymphoedema is under-reported in Africa,[16] while reporting from South East Asia has increased over the past few years.[1]

Health systems should be strengthened to deliver a minimum package of care to all affected individuals, with a goal of achieving complete geographical coverage. WHO has developed a toolkit for managing morbidity and preventing disability for endemic countries that must be integrated into primary healthcare alongside continuing mass drug administration. Training will further support patients to continue care and to improve their quality of life.

New treatment and control options

Expanding the toolbox to prevent and treat filarial infections will help progress towards elimination. Beneficial effects of bednets have been reported from areas with Anopheles transmission and persistent lymphatic filariasis in Papua New Guinea, where infection is transmitted by indoor biting mosquitoes. The use of impregnated bednets as well as treatment has been suggested for remaining lymphatic filariasis hot spots.[17 18]

New drugs enabling reversal of lymphoedema would be highly beneficial. This has also become imperative in view of sustainable development goal 3.8, which targets individual wellbeing and thus calls for individual cure and not merely epidemiological "control as a public health problem."

Since the adult worm confers pathology in lymphatic filariasis, the ultimate goal for a new drug is to kill or sterilise adult worms. A pilot study in 24 patients showed a possible sterilising effect with the addition of ivermectin to the existing treatment regimen (diethylcarbamazine with albendazole). A single dose triple drug therapy (ivermectin in combination with diethylcarbamazine and albendazole) achieved almost total clearance of microfilaraemia at 36 hours. This effect was sustained in all patients at one year (12 patients) and half the patients at two

Table 1 | Implementation of mass drug administration for lymphatic filariasis in South East Asia, 2016[1]

Country	Mass drug administration	Total population requiring treatment	Reported No of people treated	National coverage (%)
Indonesia	Started, not scaled up to all endemic districts	61 617 614	43 783 064	71.1
India	Scaled to all endemic districts	337 024 378	187 492 171	60.7
Myanmar	Scaled to all endemic districts	36 023 429	31 867 477	88.5
Nepal	Scaled to all endemic districts	13 434 920	8 980 509	66.8
East Timor	Scaled to all endemic districts	1 167 242	778 346	66.7
Bangladesh	Stopped, under surveillance	—	—	—
Thailand	Eliminated	—	—	—
Maldives	Elimination validated	—	—	—
Sri Lanka	Elimination validated	—	—	—

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years, compared with the usual two drug regimen, where 11 of 12 patients tested positive for microfilaria at one year.[19] The triple drug therapy could accelerate interruption of transmission by reducing the number of annual rounds of mass drug administration required to achieve the elimination target. Two to three rounds of treatment with ivermectin in combination with diethylcarbamazine and albendazole may be sufficient to reduce community microfilaraemia to below the threshold level, rather than five to six rounds of dual therapy.[20 21] This would be particularly useful to accelerate progress in countries left behind through delays in mapping or initiation of mass drug administration. In 2017, WHO provisionally approved the use of triple drug therapy to interrupt transmission of lymphatic filariasis infection, and guidelines have been released for its use in Asia, where onchocerciasis and loiasis are not endemic.[22] India is currently preparing to start the triple drug therapy as part of an accelerated national programme.

Two trials from Africa have shown a positive effect of a six week course of doxycycline in reducing lymphoedema severity in the early stages in patients with filariasis[23 24] beyond that seen with improved hygiene alone. This improvement was independent of current filarial infection.[24] Currently, five multicentre placebo controlled trials are being conducted (three in Africa and two in Asia) and will provide evidence to determine whether doxycycline can be included as an adjunct therapy for morbidity management. Understanding its effect on the adult worm and microfilaria will help inform its use in reducing transmission as well.

To expand the toolbox for anti-filarial drugs, the Drugs for Neglected Diseases initiative, together with its partners from academia and industry, is developing new anti-wolbachial and direct acting drugs. Two of these, emodepside and ABBV-4083, are orginal or modified veterinary drugs and are now in phase I development for use in humans; several others are in the drug pipeline. While these drugs will be developed primarily for use against onchocerciasis, for which apart from doxycycline no safe macrofilaricide exists, their indication may extend to include lymphatic filariasis as well.

However, it has also become clear that higher efficacy drugs do not compensate for low coverage. Decision makers must assess the feasibility of, and rationale for, investing in new strategies for elimination of lymphatic filariasis, taking into consideration the costs of the programme to ensure wide coverage. Successful elimination of lymphatic filariasis will depend on more than monetary investment. Going forward, political will and continued public engagement and community ownership will be critical.[25]

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Eliminating visceral leishmaniasis in South Asia: the road ahead

Suman Rijal and colleagues highlight lessons from a regional collaboration to eliminate visceral leishmaniasis and identify priorities for the post-elimination plan

Devastating epidemics of visceral leishmaniasis, also known as kala-azar, have been recorded on the Indian subcontinent since the early 19th century,[1] most commonly affecting poor people.[2] The three most affected countries in South Asia are India, Bangladesh, and Nepal. Sporadic cases have been reported in Bhutan and Sri Lanka. Box 1 describes key features of kala-azar in South Asia. Efforts to control the disease have had limited impact.[3] Until recently, these countries accounted for more than 50% of the global disease burden.[4] Sustained elimination efforts have led to a steady decline in recent years. However, some transmission continues and outbreaks in non-immune populations remain likely. As the number of kala-azar cases becomes negligible, newer tools and strategies will be required for diagnosis, treatment, and vector control.

Regional collaboration to eliminate kala-azar

In 2005, the governments of three endemic countries in South Asia—Bangladesh, India, and Nepal—jointly established a regional alliance to eliminate kala-azar, supported by the World Health Organization.[5 6] The kala-azar elimination programme is the only regional collaboration globally to tackle this disease. It set a target to decrease the incidence of kala-azar to a level at which it was no longer a public health problem by 2015. That deadline has now been extended to 2020.[7] The development of the oral drug miltefosine[8] and a rapid diagnostic test based on the rK39 antigen[9] have had a critical role in early diagnosis and providing effective treatment to reduce the disease burden. Additionally, the programme has focused on vector control and improved surveillance to reduce transmission and improve case detection. Figure 1 depicts the strategy with the key outcomes in this initiative to achieve the target of less than one per 10 000 population.

The number of kala-azar cases in these countries has declined steadily from over 77 000 reported cases in 1992 to fewer than 7000 cases in 2016 (fig 2). In 2016, 242 new cases were reported in Nepal, 255 in Bangladesh, and 6249 in India.[10] Nepal achieved the elimination threshold in 2013,[11] and Bangladesh in 2016.[12] In India, some more effort will be required, as 8% of endemic units were still above the threshold at the end of 2017.

The impact of the kala-azar elimination programme has not been systematically evaluated, but it is likely that sustained focus and collaborative efforts through the programme have contributed to the declining incidence. Moreover, the level of reporting has improved, providing a more accurate estimate of the disease burden. Possibly, the free treatment offered by public health services under the programme has led to better notification of the disease. In India, for example, underreporting declined to a factor of 1.2 in 2015 from a factor of three to eight observed in 2003 and 2005.[13-16]

Further challenges

Caution is needed as a resurgence of kala-azar is possible. The programme did not target "elimination of the pathogen" and thus some transmission continues. Figure 2 shows that the number of cases in India seems to follow roughly 15 year cycles. This makes it difficult to assess the effect of interventions to control the disease, as the downward trend may be the result of the "natural" fluctuation of the disease.[17] Communities that had some herd immunity in the past may gradually be becoming fully susceptible.[18] The rising trend in post-kala-azar dermal leishmaniasis[19] together with the emergence of coinfection with HIV is concerning.[20] Patients with these conditions may serve as reservoirs of infection, perpetuating transmission even when the elimination targets are reached.[20 21] Treatments for both conditions are far from ideal.[19 20]

Priorities to sustain elimination

In the post-elimination phase, surveillance needs to be maintained while detection and control strategies will need to be modified.

Improved diagnostic tools

The current rapid diagnostic test detects antibodies against rK39 antigen. To confirm

KEY MESSAGES

- The kala-azar elimination programme has made substantial progress in reducing incidence in India, Bangladesh, and Nepal
- With increasing incidence of post-kala-azar dermal leishmaniasis and HIV-*Leishmania* coinfection low grade transmission continues and there is a risk of outbreaks
- Investing in the development of new drugs and diagnostics as well as innovative vector control and surveillance strategies is crucial to sustain the progress in elimination

Box 1: Course of visceral leishmaniasis

- Visceral leishmaniasis or kala-azar is caused by *Leishmania donovani* parasites and transmitted by the sand fly, *Phlebotomus argentipes*. Humans are considered the only reservoirs of infection
- After an incubation period of 2-6 months, patients develop a syndrome characterised by fever, splenomegaly, wasting, and anaemia. It is fatal if left untreated
- Demonstration of parasites in a smear or culture of aspirate from spleen, bone marrow, or lymph node is required to confirm the diagnosis. Alternatively, serological evidence in a patient with recent onset of febrile splenomegaly in endemic areas will suffice
- Treatment regimens vary by region. In Asia, a single dose infusion of liposomal amphotericin B is the first treatment, with several combination regimens as alternatives
- Around 5-10% of patients develop post-kala-azar dermal leishmaniasis 6 months or more after the disease has apparently been cured. They are a potential source of infection

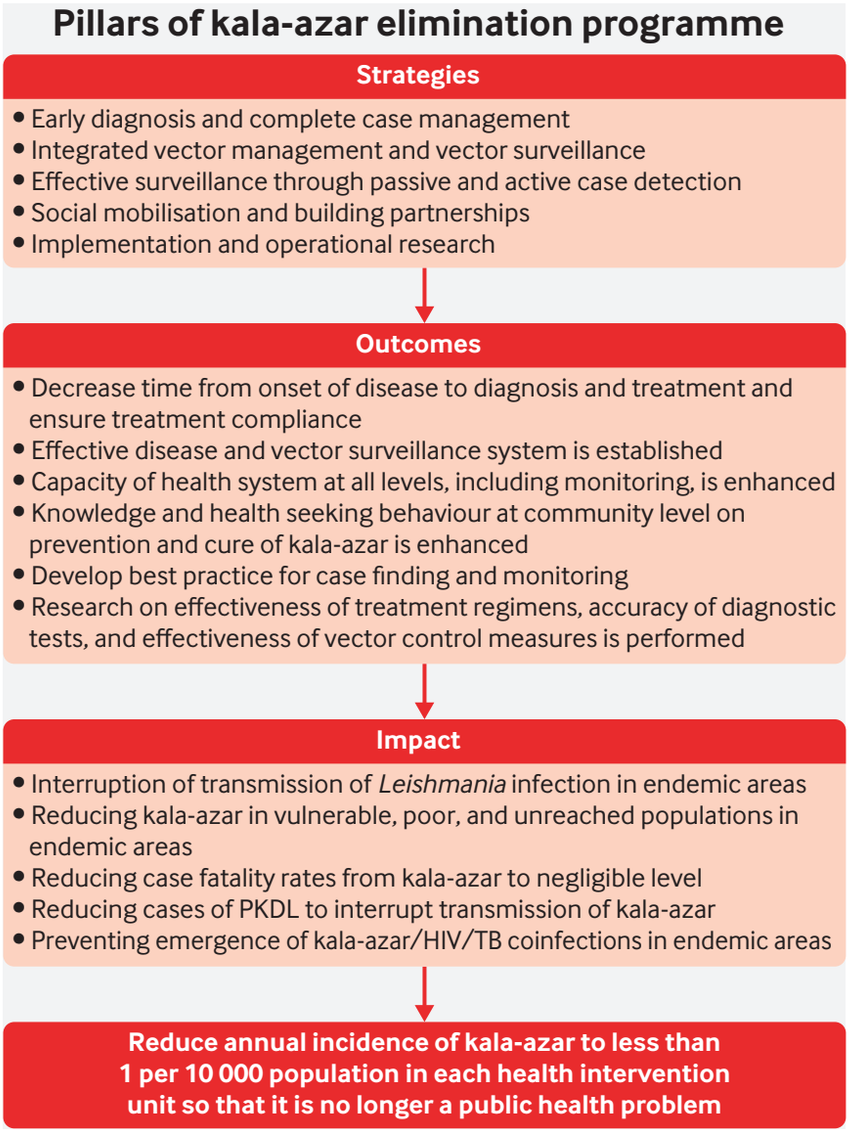

Fig 1 | Strategy for the kala-azar elimination programme in India, Nepal, and Bangladesh (adapted from WHO regional strategic framework for elimination of kala-azar[42]). PKDL=post-kala-azar dermal leishmaniasis

diagnosis and start treatment a positive result must be interpreted in conjunction with clinical features—that is, fever for two weeks and a palpable spleen. On its own, the test is not specific for the acute stage of the disease, and is also positive in latent carriers and in cured patients. The combination with a clinical case definition induces a delay of two weeks before the patient is diagnosed. Decreasing the time between onset of symptoms and diagnosis might help reduce transmission.[22]

The kala-azar elimination programme has benefited greatly from this diagnostic test for detection of cases. However, the test may become inadequate in the post-elimination phase as its positive predictive value may decrease rapidly when near elimination is achieved. Many patients with a false positive result risk being given treatment for kala-azar while the actual cause of their persistent fever (brucellosis, rickettsiosis, tuberculosis, etc) is not dealt with. A more specific test will be required, preferably based on antigen detection.[23 24] Table 1 lists some diagnostics test under development that might overcome the limitations of the current test and be more appropriate in the post-elimination era.

Newer drugs

The current drug regimens, while allowing progress towards eliminating kala-azar, will probably be inadequate for the post-elimination phase.[25] Based on WHO recommendations, the kala-azar elimination programme replaced miltefosine with a single dose infusion of liposomal amphotericin B (AmBisome) as first line treatment in 2013. AmBisome has shown greater efficacy and improved compliance, but it requires a strict cold chain. AmBisome has been used successfully in the attack phase of the programme in India. However, the entire programme (ie, primary kala-azar, relapses, post-kala-azar dermal leishmaniasis, and HIV-kala-azar cases) is now reliant on a single medicine produced by a single manufacturer. Relapses have been observed with this treatment.[25]

Paromomycin-miltefosine combination therapy is recommended as an alternative where a cold chain cannot be ensured. This regimen includes 10 days of injections with paromomycin. Miltefosine is potentially teratogenic, which limits its use in women. Current trials in India and Bangladesh (CTRI/2017/04/008421, CTRI/2015/05/005807) aim to evaluate the efficacy of different regimens of the AmBisome-miltefosine combination to reduce treatment duration, relapses, and toxicity in patients with post-kala-azar dermal leishmaniasis and HIV coinfection.

Most of these trials are using repurposed drugs developed for other indications and not according to a target product profile reflecting the requirements of a sustainable

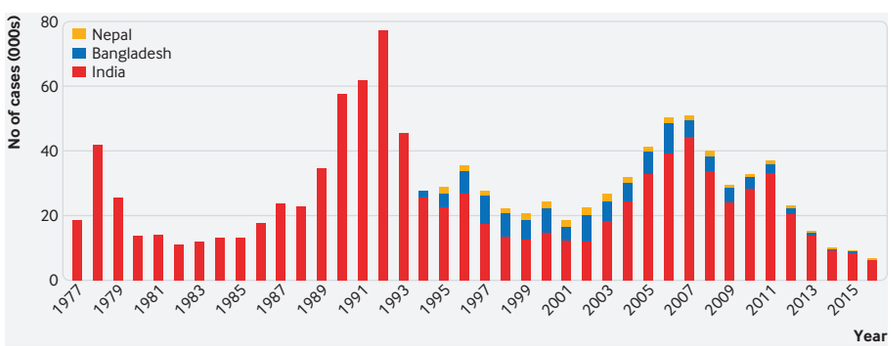

Fig 2 | Number of kala-azar cases reported by Nepal, Bangladesh, and India, 1977-2016 (WHO/Global Health Repository and country data[10])

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Table 1 | Diagnostic tests for kala-azar and post-kala-azar dermal leishmaniasis in development

Test	Description
Antibody detection rapid diagnostic test (RDT)	
Lateral flow immunochromatographic RDT: leishmaniasis IgG1 RDT[43] (Coris Bioconcept, Belgium)	Rapid diagnostic test to detect anti-*Leishmania* IgG1 as a potential biomarker of post-chemotherapeutic relapse. Raised levels of specific IgG1 were associated with treatment failure and relapse, whereas no or low IgG1 levels were detected in patients whose visceral leishmaniasis had been cured. Further evaluation is needed to determine its usefulness in the field (AfriKADIA consortium expected to yield results in 2020)
Antigen detection	
Urine—ELISA[44]: *Leishmania* antigen detection ELISA (InBios International, Seattle, USA) *Leishmania* antigen ELISA (visceral leishmaniasis ELISA) (Kalon Biologicals, UK)	Non-invasive test to detect urinary *Leishmania* antigens during the acute stage and monitor their clearance when a cure is achieved. Evaluated in Asia and Africa with good sensitivity (>90%) and specificity. Further refinement of the test is needed using more samples from endemic regions to define their usefulness in monitoring treatment. Could replace the invasive splenic aspirations and serve as a standardised tool to measure the effectiveness of emerging treatment regimens
Urine—agglutination: KAtex latex agglutination test[45] (Kalon Biologicals, UK)	Urinary *Leishmania* antigen detection agglutination test. Evaluated in Asia, Africa, Europe, and Latin America. Low sensitivity, though specificity good. Potential for evaluating a cure
Nucleic acid amplification tests	
Blood—loop-mediated isothermal amplification (LAMP)[46]: Loopamp *Leishmania* detection kit (Eiken Chemical, Japan)	Loopamp is the first LAMP test available as a kit which has been validated for kala-azar and commercially available. It is rapid, simple, and highly specific. Diagnosis of kala-azar using peripheral blood in Asia and Africa showed high sensitivity (>90%) and excellent specificity, with >90% sensitivity and specificity in diagnosis of post-kala-azar dermal leishmaniasis. Needs further validation as a test for cure
Recombinase polymerase amplification (RPA) assay[47]: *Leishmania donovani* RPA assay	Field based test for diagnosis in areas with low resources. Feasibility was shown to be good. Further validation needed at more sites

elimination programme. Ideally, a new drug should be able to be taken orally and combine high efficacy with an excellent safety profile for deployment in remote areas with poor health infrastructures. Half of all patients are children, so drug development should take this into account. An optimal drug combination would have a short (<10 days) treatment duration, different mechanisms of action to offer protection from resistance, a good safety profile, and no interaction with other drugs commonly used in these areas, such as antimalarials.

Several pharmaceutical research groups have invested heavily in discovering a drug targeting *Leishmania* parasites. Six new chemically diverse drugs, targeting five different molecular mechanisms, are in the late stages of development (table 2). All of these are oral drugs and reduce the parasite load by >95% in animal models of kala-azar when given for up to 10 days.[25] Given the typical attrition rates in the drug discovery process, one or two compounds could be registered by 2025, providing a completely different treatment for the post-elimination phase. Strategies must be developed to ensure compliance with these new treatments, similar to the directly observed treatment short course used for tuberculosis, to prevent emergence of resistance. Monitoring the safety and effectiveness of these treatments and emergence of drug resistance will be required.

Vector control measures to reduce transmission

Measures to control vectors have primarily been indoor residual spraying of insecticides in endemic villages reporting kala-azar cases in the preceding three years. A toolkit for monitoring and evaluation of entomological interventions was developed within the kala-azar elimination programme.[27] Pyrethroid spraying has been shown to be effective in reducing sand flies in carefully controlled experiments.[28] However, field studies suggest that the level of vectors has not declined significantly in villages treated by indoor residual spraying.[29] Spraying also requires a lot of equipment, is expensive, and is often not easily acceptable to communities, making it unsustainable in the long term.

In view of these drawbacks, researchers looked for alternatives that were cost effective, had a longer period of efficacy, and were easy to use and sustain. Trials in Bangladesh, India, and Nepal have shown reduction of sand fly density using reimpregnated commercial bed nets and longlasting insecticide treated bed nets.[30 31] However, they have not been shown to confer protection against visceral leishmaniasis in a cluster randomised trial in India and Nepal.[32] A comparative study in endemic villages in Bangladesh showed a greater decrease in the incidence of visceral leishmaniasis in one area where people slept under bed nets impregnated with a slow release insecticide, KO Tab, compared with the control area.[33] Durable wall lining has also shown promise in controlling sand fly density, although the initial cost is high.[34] Other tools being evaluated include wall paint containing three insecticides, including a larvicide, and an insecticide repellent combination for canine leishmaniasis.[35]

We must complete our knowledge of vector bionomics and behaviour to allow for better designed and more effective tools for vector control.[36]

Table 2 | Preclinical and clinical drug candidates in the late stages of development for visceral leishmaniasis (adapted from Mowbray[26])

Drug	Class	Mode of action
DNDi-0690	Nitroimidazole	Bioactivation by parasitic nitroreductase NTR2
DNDi-6148	Oxaborole	Unknown but active against *Leishmania* strains
XE408	Proteasome inhibitor	Inhibition of parasitic proteasome
GSK3494245/1305143	Proteasome inhibitor	Inhibition of parasitic proteasome
GSK-3186899/DDD853651	Pyrazolopyrimidine	Inhibition of *Leishmania* CRK12 kinase
DNDi-5561	Aminopyrazole	Unknown

Case detection and epidemiological surveillance

Epidemiological surveillance of kala-azar has improved considerably under the kala-azar elimination programme, and under-reporting is now minimal. As the incidence of the disease declines, awareness and knowledge of the disease will probably fall in both patients and clinicians. Active screening for case detection will stop. To be effective and sustainable in the post-elimination era, systems for case detection, notification, and surveillance will need to be redesigned.

People affected by kala-azar continue to present at a late stage to primary health centres, and diagnosis is often delayed.[22 37 38] Furthermore, these primary health centres are poorly resourced, making it difficult to provide good quality

care. Kala-azar control programmes are largely organised vertically and are often disconnected from the reality in the field. At primary healthcare level, physicians, nurses, and other medical professionals deal with patients presenting with a wide spectrum of complaints.[39] An integrated approach is required for the surveillance and management of fever at primary care level in kala-azar endemic settings to ensure that no cases are missed. A syndrome based approach to clinical management of fever must be adopted. This would include kala-azar as a differential diagnosis and allow systematic testing with a rapid diagnostic test for kala-azar and other conditions in patients with fever for more than two weeks.[40] Cooperation with the private health sector will be crucial to ensure that all patients are reached.

New tools and strategies are required for epidemiological surveillance in the post-elimination phase. These include tools for detection of kala-azar and post-kala-azar dermal leishmaniasis when their incidence is very low, an adequate response strategy to an outbreak, and proxy markers for sand fly infectivity.[11] Population based serosurveillance is a powerful tool to examine trends in infection rates and gauge the effect of the kala-azar elimination programme. Established health and demographic surveillance systems[41] in the region can contribute by monitoring trends in kala-azar incidence and seroprevalence over a longer time.

Maintaining success

Continued vigilance will be required to sustain the gains achieved through kala-azar elimination efforts. The programme will need to evolve and realign strategies to meet the requirements of this post-elimination phase. This will necessitate proportionate investments in research and development of new tools, training of health workers, and logistics and infrastructure to improve the quality of primary care. Commitment to eliminating the scourge of kala-azar from this region and globally must continue.

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The timing is right to end snakebite deaths in South Asia

Regional collaboration is crucial to end preventable deaths and disability from snakebites in South Asia, say **Ravikar Ralph and colleagues**

Five million snakebites occur globally each year, causing between 81 000 and 138 000 deaths and nearly 400 000 amputations and other permanent disabilities.[1] South Asia has the highest incidence of venomous snakebites in the world.[2] Within the region, Bangladesh, India, Nepal, Pakistan, and Sri Lanka together constitute nearly 70% of global snakebite mortality.[3]

The World Health Organization recognised snakebite as a neglected tropical disease in 2017, giving it high priority for large scale action and research.[4] A resolution passed in the World Health Assembly in May 2018 urged member states to step up efforts to tackle snakebite.[5 6] It is important that regional mitigation efforts in South Asia reflect these objectives. In this paper, we explore the determinants of poor clinical outcomes with snakebite in South Asia and propose priority actions for governments to achieve the vision of zero deaths from snakebite.

Disease burden

The region is a biodiversity hotspot for venomous snake species. The sociodemographic and occupational profile of the population contributes to increased risk of snake-human encounters. Snakebites are largely an agrarian occupational hazard in South Asia. Box 1 describes the medically important snake species in South Asia and demographic profile of groups commonly affected.

Lack of systematic preventive measures at community and national levels contributes to the high incidence of snakebite. Figure 1 shows snakebite incidence and associated mortality in South Asian countries. These estimates are drawn from extrapolations of hospital records and community surveys, and likely underestimate the problem.[7 8] Long term complications occur in around 15% of survivors and include musculoskeletal deformities, amputations, visual impairment, chronic kidney disease, and neurological deficits.[9]

High mortality from snakebites

After a venomous snakebite, the management priorities include[21] first aid to retard the progression of envenoming, rapid transport to a health facility, and antivenom therapy with optimal supportive care.

Deficiencies in these components, as outlined in figure 2, greatly increase vulnerability to death and adverse outcomes.[4]

Delayed and inappropriate treatment

Delayed treatment can be fatal, especially beyond six hours after the bite.[22-25] In many parts of South Asia, only half of patients reach a health centre within six hours of a bite, with the bite-to-treatment delay being as long as 12 to15 days in some cases.[13 26 27] As a result, 70-80% of fatalities happen before patients reach the health facility.[11 22] Nearly 97% of snakebite deaths in India occur in rural areas.[11] Sparse distribution of health facilities in rural areas results in patients having to travel long distances for treatment.[8 28 29] Lack of affordable means of transport, particularly in remote inaccessible regions, compounds the problem.[8]

Communities are rarely aware of simple first aid measures. With poor access to health facilities, they often resort to traditional faith healers, who indulge in practices such as chanting, incisions,

KEY MESSAGES

- South Asia has the highest burden of snakebite envenoming in the world and contributes to 70% of global snakebite mortality
- Inadequate first aid, delayed treatment access, and suboptimal treatment contribute to poor outcomes
- The global focus on snakebite as a neglected tropical disease provides an opportune time for South Asian countries to strengthen regional cooperation and investment in research on epidemiology, treatment, and prevention

Box 1: Snakebite: the scenario in South Asia

Venomous snake species

- Of 300 different snake species in South Asia, an estimated 70 are venomous[13]
- The "big four" include the common krait (*Bungarus caeruleus*), binocellate cobra (*Naja naja*), Russell's viper (*Daboia russelii*), and saw scaled viper (*Echis carinatus*). These are distributed across the subcontinent and are largely responsible for deaths and long term complications from snakebite.[14 15] Around 90% of snakebite deaths in India are from one of these
- Locally prevalent venomous species also contribute to the disease burden[13-18]
  - In Bangladesh, the monocellate cobra (*N kaouthia*) and Wall's krait (*B walli*) account for a majority of cobra and krait bites respectively
  - Green pit viper bites are more frequent than those by the Russell's viper in Bangladesh and Nepal. No verified reports of saw scaled vipers exist in these countries
  - Hump nosed pit vipers (*Hypnale sp*) are the commonest cause of snakebite envenoming in Sri Lanka and are now recognised as highly venomous snakes alongside the big four

Populations affected

- With more than 70% of the largely rural South Asian population still dependent on agriculture, hunting, fishing, and forestry for its livelihood, an intersection of these snake biotopes with human dwellings and occupational activities is inevitable[19]
- Over half of all snakebites occur in 30-50 year old farmers and in 60-80% of cases involve ankles and feet.[13] Dependence on non-mechanised, low cost farming techniques and barefoot farming practices place farmers at an increased risk of bites on the extremities.[8]
- Snakebites are more common among the poor.[8 20] Poor housing conditions and inadequate lighting provide easy access to snakes into living spaces and they are not easily spotted.[18]Open houses, sleeping on the floor, and open defecation are other factors increasing the risk of snake encounters[8]

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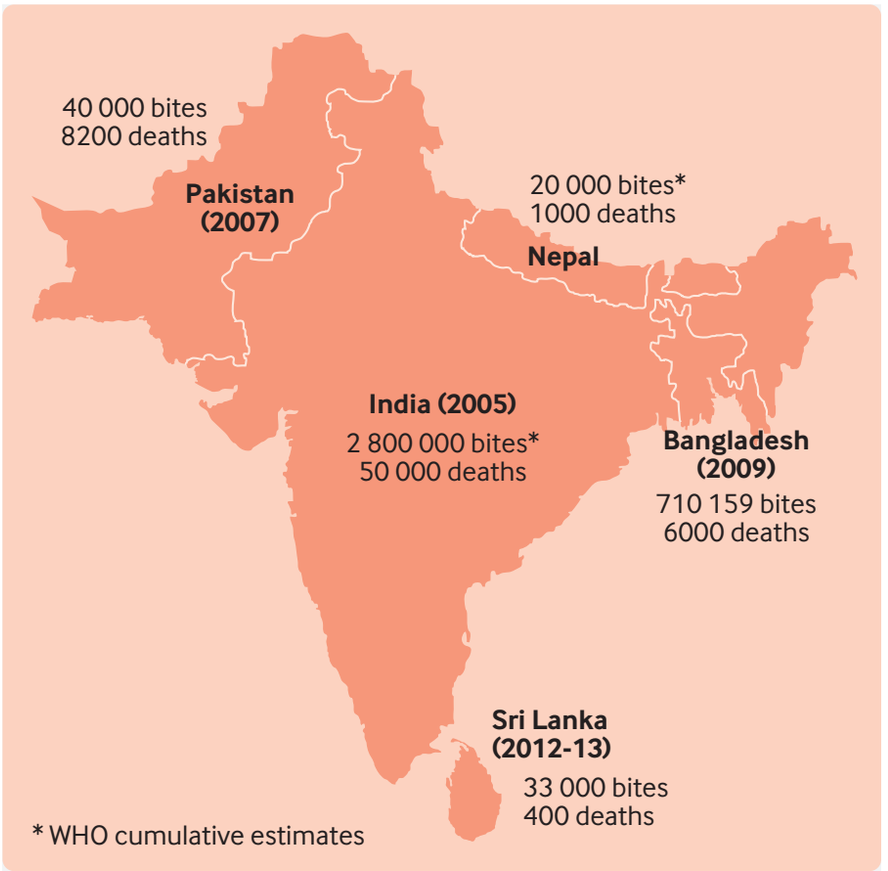

Fig 1 | Distribution of venomous snakebites and related deaths in different South Asian nations.[1 10-13] Numbers in brackets indicate year of measurement

attempts to suck venom from the bite site, tying tourniquets, or local application of herbs, cow dung, or snakestones.[10 13 30] These measures can delay treatment[20 31] and result in increased mortality.[13 25]

Suboptimal care

Rural health facilities in many parts of South Asia lack the infrastructure and manpower to provide timely and effective treatment.[5 29 32] Supportive care such as mechanical ventilation, dialysis, and blood transfusion is critical in the management of patients with complications such as respiratory paralysis, acute kidney injury, and coagulopathy induced haemorrhage. Antivenom therapy alone is insufficient in their care.[13 21] Most rural health centres and hospitals lack critical care facilities and thereby refer patients elsewhere, resulting in treatment delays.[33]

Insufficient knowledge and experience among healthcare providers is also responsible for inadequate treatment. Studies among doctors in primary care and health workers in Bangladesh, India, and Pakistan show gaps in ability to recognise systemic envenoming and

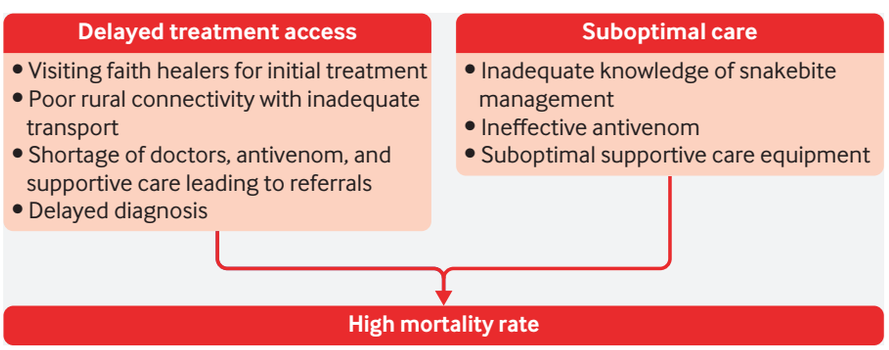

Fig 2 | Determinants of poor snakebite related outcomes in South Asia

administer antivenom.[5 30 34 35] This may be because snakebite management is not given enough focus in the medical curriculum.[36] Health workers in remote settings are also reluctant to treat snakebite because of apprehension about managing antivenom associated adverse reactions.[32] This apprehension is not entirely misplaced since up to 80% of those treated develop one or more antivenom associated adverse effects such as anaphylaxis, pyrogenic reactions, or serum sickness.[13 37]

Most South Asian countries have well formulated snakebite treatment protocols for low resource settings with a tiered referral approach. Yet these are poorly implemented with limited penetration in primary health centres. These protocols are not standardised and numerous conflicting versions exist with differing indications for antivenom administration and dosing.[38]

Antivenom production and potency

Underproduction and maldistribution of antivenom is a pressing challenge in the region.[25 32 39] Most South Asian countries import antivenom from Indian manufacturers—with the exception of Pakistan, which, in addition to importing Indian antivenom, also produces indigenous antivenom for domestic consumption.[39 40] Current production falls short of the requirements of the entire region.[25 41 42] Several manufacturers and suppliers of Indian antivenom have recently ceased operations citing reasons of price control, poor animal husbandry practices, and venom shortage.[39 43 44 45] Stringent regulations on snake handling and venom procurement have hindered the establishment of new venom collection centres in India.[43]

Indian antivenom is produced exclusively against the big four venoms, and it is ineffective against other regionally prevalent species.[46] Consequently, bites by these species are associated with poorer clinical outcomes despite the administration of large antivenom doses.[46] Recent studies also reveal significant intra-species variations in the venoms of the big four based on location.[47-51] Since all major Indian antivenom manufacturers source snake venom from the Irrula cooperative in south India, the available products vary in their neutralisation efficacy and clinical effectiveness against the big four venoms from other parts of South Asia.[14 43 47 50] A double blind clinical trial comparing Pakistani and Indian antivenoms in 70 snakebite victims in Pakistan with deranged clotting tests and local swelling revealed quicker restoration of coagulopathy at lower doses with the Pakistani antivenom,

suggesting greater specificity against indigenous snake species.[52]

Indian antivenom is manufactured in two forms—liquid and lyophilised. While lyophilised antivenoms can be stored at room temperature, liquid antivenoms should ideally be transported and stored at 2-8°C, necessitating functional cold chain and cold storage facilities.[53 54] The lack of an effective cold chain and unreliable refrigeration facilities in rural areas render it ineffective.[3 55] Non-standard manufacturing practices also result in variable antivenom effectiveness.[55 56] Stringent measures to contain or withdraw substandard batches are lacking. The government run Central Drugs Laboratory in India screens antivenoms for potency.[57] These tests cover limited brands, however, and currently batches from only four of the six main antivenom manufacturers are screened.[58]

Why do these problems persist?

Over the years, snakebite mitigation has not had enough attention in the public health agenda of the region. Lack of good quality epidemiological data on snakebites and their impact and affliction of mainly poor and vulnerable populations have contributed to this. Figure 3 summarises these challenges.

Lack of research and innovation

With the exception of Sri Lanka, South Asia has a severe dearth of quality data on snakebite epidemiology, largely because of the skewed reliance by national agencies on hospital based studies.[13] In a region where a considerable proportion of patients may die before reaching a hospital or preferentially attend traditional healers, snakebites simply pass unreported and hospital based studies tend to underestimate the problem.[59] There are few studies on chronic disability burden and socioeconomic impact of snakebites.[60]

There is limited evidence to guide treatment protocols. Most studies on snake distribution, ecology, envenoming profiles, and intra-species venom variation do not encompass all medically important species and are limited in geographical extent.[10 11 12 22] Studies on preclinical efficacy, pharmacokinetics, clinical effectiveness, and safety of current antivenoms are lacking.[37 39 56 61] The optimal dose of antivenom is still debated and regional clinical trials offer conflicting evidence. A systematic review of 10 open label randomised controlled trials in the Indian subcontinent on optimal antivenom dose concluded that there is very low quality evidence to guide practice and further research is needed.[62]

Political and financial barriers

Because of the paucity of data on snakebite epidemiology, socioeconomic impact, and disability burden, most South Asian governments have failed to prioritise snakebite as a matter of national importance needing concerted action and allocation of health resources. Snakebite mitigation strategies are practically non-existent in South Asia and national prevention awareness programmes are largely overlooked.[13]

Snakebite envenoming is also not recognised as a public health problem at the level of the South Asian Association for Regional Co-operation (SAARC). It does not feature in the organisation's list of priority diseases—which includes leprosy and rabies among others—which benefit from numerous initiatives aimed at setting up integrated networks and nodal centres for regional training, research, disease eradication, and information dissemination.[63] This lack of national and regional prioritisation has resulted in the matter being overlooked in the global health agenda, until its recognition as a neglected tropical disease by WHO in 2017.

The way forward

A substantive global target for neglected tropical diseases exists in the form of the Sustainable Development Goal 3.3 to "end the epidemics" of these diseases by 2030.[4] The recent inclusion of snakebite as a neglected tropical disease should mean greater funding for research and mitigation strategies. We present below key priorities for South Asian countries. Establishing national snake envenoming mitigation programmes in each country can help in effective and centralised execution of these efforts.

Strengthen regional cooperation

A regional collaborative centre for snakebite research and advocacy and nodal training centres for envenoming management must be established along the lines of the SAARC tuberculosis and HIV/AIDS centre.[64] This would serve as a platform to bring together research and policy experts working on snakebite mitigation from across disciplines. The centre would help collate and monitor data on snakebite incidence in the region; facilitate collaborative research and technology transfers between nations;

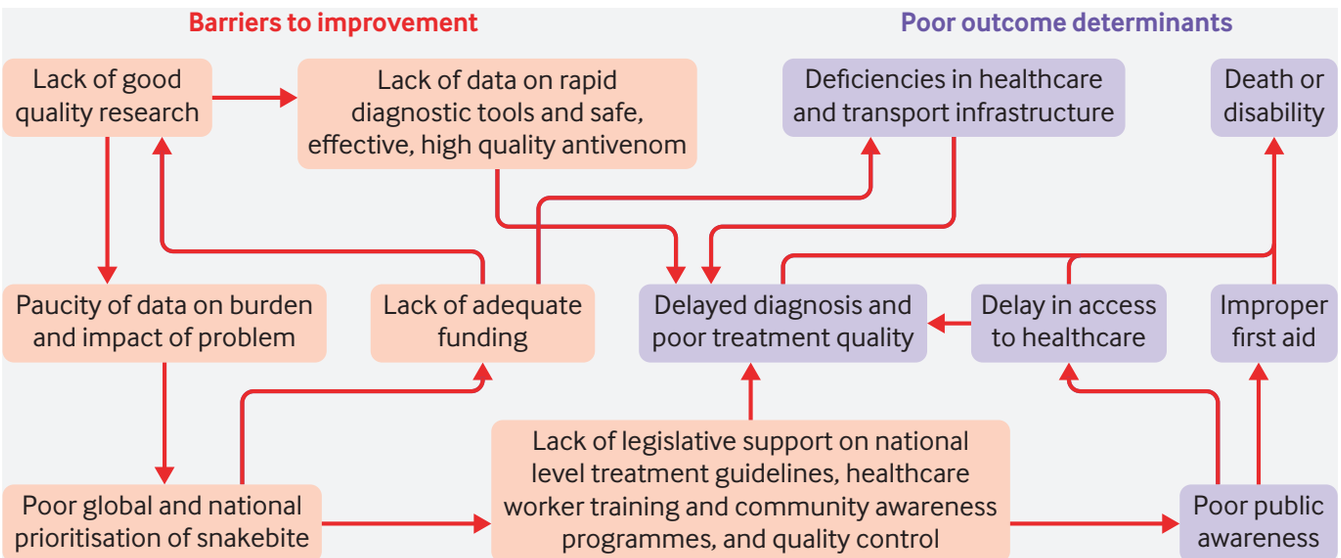

Fig 3 | The intricate web of poor outcome determinants interacting with barriers to improvement

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and support national snakebite mitigation efforts through policy guidance and technical support.

Improve reporting

Setting up sentinel reporting systems in different parts of each country can help improve the availability of epidemiological information on snakebites. The Big 4 Mapping Project (http://snakebiteinitiative.in/snake) under the Global Snakebite Initiative provides an interesting approach to understanding the distribution of snake species across India, with volunteers providing real time information on snake sightings.[65] Designating snakebite as a notifiable disease would further improve reporting from health facilities. To achieve standardisation, health workers should be encouraged to use the specific international classification of diseases code T63.0 (toxic effect of contact with snake venom) in certification of death in snakebite victims.[21] In unclear cases of snakebite death, immunological assays can be used to establish the cause.[66]

Increase awareness of preventive measures

The distinctive epidemiology combined with knowledge of snake habitats and periods of activity is important in planning preventive measures. Sleeping under a mosquito net and on a bed above ground level have been protective against krait and cobra bites, in both anecdotal reports and community based observational studies in India, Nepal, and Sri Lanka.[67 68 69] Protective footwear was distributed among paddy farmers in Myanmar 20 years ago, but its impact in reducing snakebite is unclear.[70]

Lack of awareness and high illiteracy among communities are linked to poor implementation of preventive measures such as keeping domestic areas free of rubbish, rubble, and firewood; controlling rodent populations; constructing snake proof houses; and using protective footwear.[13 26 71] Snakebite prevention and first aid training programmes targeted towards at-risk populations are essential to reduce snakebites and improve initial response.

Dissuading those bitten by snakes from visiting faith healers can be a challenge since the latter are an integral part of the fabric of many South Asian societies. A non-governmental organisation in eastern India has been trying to engage with faith healers through workshops to promptly refer snakebite victims to health centres.[32]

Strengthen rural health services

Ensuring efficient ambulance transport and facilities for dialysis, mechanical ventilation, blood transfusion, and intensive care in rural areas will be vital to prevent deaths from snakebites. A few regional initiatives have attempted to tackle these matters. In Nepal, a network of motorcycle volunteers was organised to transport snakebite victims promptly, on otherwise unpassable trails, to health centres. This simple intervention, along with community education, considerably reduced incidence and fatality from snakebites.[72] In India, free ambulance services initiated as public-private partnerships have sought to provide rapid access to care.[73] The full impact of this initiative is hindered, however, by a shortage of services in rural areas, suboptimal response times or non-attendance of calls, inadequately trained paramedics, and the absence of in-transit antidote therapy and standardised resuscitation protocols.[73 74]

Healthcare providers, particularly those practising in high burden rural areas, must be trained in using standard treatment guidelines for snakebite management. Hands-on training in airway management and treatment of anaphylaxis must also be included. Nationwide training of health workers and paramedics has been initiated in Nepal, but the impact of this programme is yet to be assessed. Integrating snakebite management in the medical curriculum and organising workshops using locally adaptable training modules based on WHO guidelines will help. Compliance with guidelines must be ensured and an audit of deaths and adverse events must be regularly conducted at the district level.

Enhance production, potency, and safety of antivenom

Measures to revive antivenom manufacturing units that have ceased production, increase snake venom availability, and improve animal husbandry practices will be critical to step up production in the region. Legislative amendments to ease restrictive Indian laws on snake capture and venom extraction need to be considered. Subsidised antivenom should be made available in sufficient quantities in both government and private health facilities and monitored for storage under appropriate conditions. Venom collection must be expanded to multination regional venom cooperatives. Establishing serpentariums for captive husbandry and adherence to WHO recommended standards during venom collection and antivenom manufacture would improve the quality and safety of antivenom. Regulatory bodies for quality control of Indian antivenoms should screen batches from all manufacturers and formulate basic minimum standards for potency and quality based on WHO guidelines.[75]

There is a need to support development of newer antivenoms against locally prevalent snake species. A collaborative initiative between Costa Rica, Sri Lanka, and the US to develop newer antivenoms specific to Sri Lanka's major snake species is an example in this direction.[76 77] A project initiated in 2018 in Bangladesh aims to establish a geographically representative snake venom production, research, and preclinical testing facility in Chittagong.

Box 2: Recommendations for future research

- Large, representative, community based epidemiological studies to estimate the true burden of snakebite morbidity and mortality, and socioeconomic impact
- Large, well designed clinical trials to establish safety, efficacy, and optimal dose of antivenoms
- Developing and testing preclinical efficacy of new antivenoms involving all medically important snake species across South Asia. These could include different regional antivenoms with specificity against local snake species in addition to the big four, or consist of two separate expanded polyspecific antivenoms against major South Asian viperid and elapid species, respectively
- Studies on envenoming syndromes to establish species-syndrome correlation and aid early identification of snake species. This could help clinicians anticipate complications and initiate appropriate treatment7879
- Diagnostic tools to identify snake species that screen for species specific venom proteins or amplify and sequence bite site snake DNA. Technical support from countries like Australia, where commercial point-of-care venom detection kits are marketed for indigenous species, could be sought to develop improved kits for South Asian snake species.[79] DNA aptamers have recently been used in venom based identification of South East Asian krait species[80]
- Clinical evaluation of pharmacological interventions to retard venom transit from bite site to circulation by slowing lymphatic flow and thereby preventing systemic toxicity in animals. These could be a promising adjunct for snakebite first aid measures[81]

Research and innovation

The global focus on snakebite provides an opportunity to boost research in this neglected area. Box 2 lists areas for further research. This would help generate critical evidence to inform policy making and more effective, economical, and feasible preventive and treatment measures.

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Multidrug resistant enteric fever in South Asia: unmet medical needs and opportunities

Investments in newer diagnostics and antimicrobial treatments are critical to improve management of enteric fever in South Asia, say **Christopher Parry and colleagues**

Enteric fever (typhoid) is the commonest bacterial bloodstream infection in South Asia.[1] It is caused by *Salmonella enterica* serovars Typhi and Paratyphi A. Despite progress in controlling enteric fever in several parts of the world, it remains an important public health burden in South Asia. The incidence is estimated to be over 100 per 100 000 population. Around seven million people are affected each year in South Asia with about 75 000 deaths.[2] However, these figures are likely to be an underestimate because of limitations in population based surveillance systems and reliable diagnostic methods.[2-4]

We discuss the challenges in managing enteric fever in South Asia in the context of growing antimicrobial resistance and highlight the need for sustained focus on improvements in diagnosis and treatment as part of an integrated control strategy.

Growing antimicrobial resistance

Since the first reports of chloramphenicol resistance in *S* Typhi in the 1970s, resistance to each new antimicrobial treatment has emerged relentlessly.[5] Multidrug resistance—that is, resistance to chloramphenicol, amoxicillin, and co-trimoxazole—is found in many areas of South Asia and was associated with numerous outbreaks in the late 1980s and early 1990s.

Fluoroquinolones then emerged as the treatment of choice.[6 7] Widespread use of second generation fluoroquinolones (ciprofloxacin and ofloxacin-levofloxacin) has now led to decreased susceptibility of organisms[5] across the Indian subcontinent.[6 8] Complete fluoroquinolone resistance, including resistance to the later generation fluoroquinolone gatifloxacin, emerged sometime after 2010 and has been associated with treatment failures and prolonged fever.[5 8-10] The doses of fluoroquinolone used in early treatment studies, although giving a clinical cure, may have been insufficient to prevent the emergence of first step mutants.

In recent data from Pakistan published as part of the surveillance for enteric fever in Asia project (SEAP), over half of all *S* Typhi isolates were multidrug resistant. Fluoroquinolone resistance was noted in nearly 90% of *S* Typhi and *S* Paratyphi isolates.[11] A longitudinal study of typhoid fever trends at three large hospitals in India showed a fall in resistance rates for ampicillin, chloramphenicol, and co-trimoxazole between 2000 and 2014, as resistance to more widely used antibiotics has risen.[12] Near universal resistance to ciprofloxacin has been observed in recent isolates from India.[12 13]

Azithromycin remains an effective oral option. However, given its wide use in a variety of clinical presentations, including suspected typhoid fever and respiratory infections, there is concern about potential emergence of resistant strains.[5 14] Third generation cephalosporins such as ceftriaxone and cefixime are increasingly used, with very low resistance reported to these drugs until recently.[12] Since 2016, outbreaks of extensively drug resistant *S* Typhi strains that are resistant to ceftriaxone and cefixime have been reported in parts of Pakistan.[15] This severely limits the antimicrobial treatment options, and salvage therapy with intravenous carbapenems may be needed.[15] These drugs are expensive and often inaccessible in low resource settings.

Inadequate diagnostic tools

Typhoid presents with undifferentiated fever in the initial stages and is often confused with other common causes of acute fever in tropical regions such as malaria, dengue, chikungunya, Zika, rickettsial infection, leptospirosis, and brucellosis.[5 16] The overlap of clinical features with other conditions makes clinical diagnosis difficult. Patients presenting with undifferentiated fever are often started on empirical treatment, once malaria has been excluded, without diagnostic confirmation. As such, diagnosis may be missed or delayed, resulting in inappropriate treatment.

Untreated, typhoid causes a prolonged and debilitating febrile illness that can last for several weeks.[5] The mortality from untreated typhoid has been estimated at 10% or more.[17] Patients can develop life threatening complications such as intestinal perforation, gastrointestinal bleeding, and, less commonly, encephalopathy and shock. There is also a risk of relapse and chronic faecal carriage. With appropriate antimicrobial treatment, symptoms typically resolve within a week and risk of mortality is below 1%.[18 19]

Inadequate diagnostic tests complicate the management of typhoid fever.[20] Isolation of *S* Typhi on blood culture is required for a definitive diagnosis. Blood culture is also the only diagnostic method that permits monitoring for drug resistance. However, its sensitivity is suboptimal, ranging between 40% and 80%. A systematic review and meta-analysis of 40 studies found a relation between specimen volume and blood culture sensitivity, with increase in sensitivity from 51% (2 mL specimen) to 65% (10 mL specimen). Subgroup analysis showed significant heterogeneity by patient age. Previous antimicrobial use and specimen collection beyond the first week of symptoms reduced the sensitivity by nearly 30%.[21] Clinicians' use of blood culture also varies considerably. In a prospective study from Nepal, of 4309 patients with acute fever, over half received a provisional clinical diagnosis of enteric fever, but only 4% of these patients had culture confirmed *S* Typhi infection.[22] Blood culture requires reliable laboratory facilities and is often not feasible in low resource settings.

KEY MESSAGES

- Relentless emergence of antimicrobial resistance has led to treatment failures and limited treatment choices for typhoid fever in South Asia
- A new conjugate vaccine approved in 2018 offers an important tool to control typhoid in South Asia
- Investments in research and development of rapid diagnostic tests and new treatments must be prioritised.

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In the absence of reliable and quick diagnostic tests, the Widal test is widely used by clinicians in South Asia to diagnose typhoid.[23] It is a serological test that relies on a fourfold or greater rise in antibody titre against the H and O antigens of *S* Typhi between the acute and convalescent stages of disease to confirm diagnosis and is intended as a tool to increase the index of suspicion for typhoid. Difficulties remain with the test's performance and with interpretation of results, particularly when it is used as a standalone test in the acute stage. Cross reactivity with other infectious agents[24] may result in false positive results and lead to overdiagnosis of typhoid fever. A striking example of this was noted in post-earthquake Nepal, where a cross reaction of the test with rickettsia (scrub typhus) infection resulted in misdiagnosis and delay in initiating appropriate treatment. Ceftriaxone was prescribed for typhoid rather than doxycycline, which is the drug of choice for scrub typhus.[25]

Control measures fall short

Enteric fever is transmitted through food and water contaminated with human waste. It can be eliminated with interventions such as access to potable water, safe sanitation, and hygienic food production practices. With improvements in water quality and sanitation, countries in North America and Europe succeeded in eliminating typhoid as a public health problem.

South Asia has made considerable progress in improving access to sanitation facilities over the past 25 years.[26] The proportion of people with access to improved sanitation increased from 25% in 1990 to 48% in 2015 and the proportion of people who practise open defecation fell from 65% to 34%. Three countries—Maldives, Pakistan, and Sri Lanka—have met the millennium development goals' sanitation target, with over 60% of the population having access to toilets. Bangladesh, Bhutan, and Nepal have made good progress as well. India accounts for over 60% (596 million) of the global population who practise open defecation. The Indian government launched the Swacch Bharat Mission in 2014 with the goal of reaching universal sanitation coverage by 2019 although this may be difficult to achieve. The programme has intensified efforts to raise awareness on the need for improved sanitation and safe water, construct household toilets, and systematically monitor the creation of villages and districts that have no open defecation.

Access to uncontaminated water in South Asia has increased from 73% to 93% since 1990. However, over 134 million people still do not have access to safe drinking water. Between 68% and 84% of water sources in South Asia are estimated to be contaminated with bacteria and/or chemicals.[26 27]

Rapid unplanned urbanisation in South Asia has compounded the challenge of ensuring safe drinking water supply and access to toilets. Urban-rural disparities in access to improved water and sanitation facilities are pronounced, with rural households more commonly practising open defecation.[28] Disparities in sanitation coverage are also observed between rich and poor households as well as by sex, education level, and caste.[29]

A small subset of patients with typhoid become chronic carriers, with faecal shedding of bacteria for several weeks after symptoms have resolved. These patients are a potential source of infection to others in the community. Despite clear links between typhoid and consumption of street foods in South Asia, there is no systematic screening for chronic carriers among food handlers. Few studies have evaluated the effectiveness of antimicrobial regimens in restricting faecal shedding.

New developments in prevention, diagnosis, and treatment

Alongside sustained efforts to improve sanitation and water safety, vaccination promises to aid typhoid control in South Asia in the coming years. Improving case management of typhoid fever requires development of alternative antimicrobial treatments and new diagnostics. *Salmonella* spp, particularly those that are resistant to fluoroquinolones, are among the high priority pathogens identified by WHO as requiring urgent research and new antimicrobials.[30]

Regional collaboration will be critical to sustain focus on typhoid elimination, boost research and development of new interventions, improve surveillance systems, and foster transfer of knowledge between nations.

Vaccines

Vaccination can have an important role in reducing the disease burden and stalling the emergence of resistant strains. Until recently, two typhoid vaccines have been available: an oral vaccine (Ty21a vaccine) supplied in enteric coated capsules taken once daily for three days, and the injectable Vi polysaccharide vaccine (ViCPS vaccine) given intramuscularly in a single dose. The protective efficacy wanes over time, and revaccination is recommended every three years.[31 32] Neither vaccine is recommended in children younger than 2 years, making it difficult to incorporate them into routine vaccination programmes in endemic settings, and so vaccines have been largely used in travellers to low and middle income countries.

In January 2018, WHO prequalified a conjugated Vi polysaccharide vaccine Typbar-TCV, indicating it meets the required standards of safety, efficacy, and quality to be rolled out in routine childhood immunisation programs in endemic countries.[33] The vaccine, which was developed by the Indian drug company Bharat Biotech, has longer and higher levels of immunogenicity than the ViCPS vaccine and is safe to use in infants older than 6 months. In October 2017, the Strategic Advisory Group of Experts (SAGE) on immunisation recommended routine use of the vaccine in typhoid endemic countries as a single dose in children aged 6- 23 months, and for catch-up vaccination in children aged 2-15 years.[31 34]

The vaccine has been registered in India and Nepal, but implementation of routine vaccination across South Asia will take time dependent on further approvals, availability, and funding. Post-licensing monitoring of effectiveness, persistence of protection, and safety will also be important.[35] The typhoid conjugate vaccine does not protect against *S* Paratyphi A, which is responsible for up to a fifth of cases of enteric fever. Developing a combination vaccine that provides complete protection against salmonella infections must be prioritised.

Diagnostics

Reliable, rapid diagnostics that do not require sophisticated laboratory infrastructure are needed to improve antibiotic stewardship and generate critical data on the burden of disease.

A Cochrane review in 2017 (37 studies, 5080 participants) evaluated the diagnostic accuracy of available point-of-care rapid diagnostic tests for enteric fever.[36] Most studies evaluated three tests and their variants: TUBEX (14 studies); Typhidot (22 studies); and the KIT Test-It Typhoid (nine studies). These are all antibody tests on blood to detect *S* Typhi infection. None of the included studies evaluated a test for *S* Paratyphi A infection. Most of the studies were in South Asia: India (10 studies), Bangladesh (five), Pakistan (four). The quality of the studies was generally low, with two thirds including patients who would not typically be tested for this

disease. The review concluded that the current tests are not sufficiently accurate to replace blood culture as a diagnostic test for enteric fever.

Newer diagnostic approaches such as serodiagnostic antigens, nucleic acid amplification tests, proteomics, metabolomics, and host response gene patterns are being explored[20] but are still a considerable way from being used in routine practice. Any new tests will also need to be shown to be cost effective before they are implemented in South Asia.

Effective case management

No recent national or regional guidelines exist for treatment of enteric fever, and evidence based diagnostic pathways and empirical treatment regimens suited to South Asia are urgently needed to support clinicians.

Antimicrobial resistance patterns are highly dynamic and need to be considered carefully. Clinicians must be aware of local resistance patterns and modify treatment based on antibiotic susceptibility results in confirmed cases of enteric fever. Short fever clearance times and low relapse rates have been reported with oral azithromycin, and it may be an effective treatment.[7] Lack of resistance against third generation cephalosporins, principally parenteral ceftriaxone and oral cefixime, in *S* Typhi and *S* Paratyphi A make these a reliable choice for suspected typhoid, particularly in regions with known resistance. For extensively drug resistant strains, potential antimicrobials include piperacillin-tazobactam, ceftazidime-avibactam, carbapenems (such as meropenem, imipenem, or ertapenem), tigecycline, fosfomycin, and colistin. These are given parenterally, but there is limited experience and evidence on their use in enteric fever.

Antimicrobial combinations are an option when the diagnosis is unclear or when polymicrobial infection is likely. For example, in areas where both typhoid and *Rickettsia* spp or *Orientia tsutsugamushi* infections are common causes of acute febrile illness, a combination of ceftriaxone and doxycycline may be appropriate as initial empirical therapy in adults, especially if confirmatory diagnostic testing is not available or while results are awaited.[37] Similarly, combination treatment may be required in typhoid associated intestinal perforation to treat *S* Typhi and other intestinal organisms causing peritonitis.

Preventing the emergence of resistance has been an important justification for the use of combination therapies in tuberculosis, HIV, and malaria. In principle, when antibiotic monotherapy is used, the drug susceptible fraction of the population is killed, while the resistant subpopulation replicates and becomes dominant. The use of two or more antimicrobials makes this less likely unless there is background resistance to both antimicrobials. For example, *S* Typhi and *S* Paratyphi A isolates acquire decreased susceptibility to fluoroquinolones by point mutations. Fluoroquinolone doses that are effective against the wild type isolates but fail to supress the first step mutants can select for the mutant strains. Combining a fluoroquinolone with a drug targeting a different pathway may prevent first step mutants from replacing the wild type.

Drug combinations, however, are costlier and have an increased risk of adverse events. Combining the right drugs in the appropriate doses will be critical.[38] An inappropriate combination may inadvertently select for new resistance profiles. Fixed dose combinations of relevant antimicrobials are available in India, but there has been relatively little research on the pharmacokinetic and pharmacodynamic parameters that predict the successful treatment of typhoid and few clinical trials of potential combinations.[39]

The priorities for future research include development of new treatments; in vitro assessments of old and new drugs and drug combinations against a relevant panel of isolates, including extensively drug resistant typhoid; and clinical trials of salvage regimens for multidrug resistant enteric fever, antimicrobial combinations for suspected and confirmed enteric fever, and antimicrobial regimens to prevent chronic carriage. New treatments and diagnostics, together with better vaccines and sanitation, will be essential for elimination of typhoid in South Asia.

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Neonatal sepsis in South Asia: huge burden and spiralling antimicrobial resistance

M Jeeva Sankar and colleagues call for urgent action to improve quality of care at birth and implement antimicrobial stewardship in health facilities in South Asia to reduce neonatal deaths from sepsis

Neonatal sepsis, a systemic infection in the first 28 days of life, encompasses bloodstream infections, meningitis, and pneumonia. It is the third most common cause of deaths among neonates, accounting for 225 000 deaths globally every year.[1]

South Asia and sub-Saharan Africa have the highest burden of neonatal sepsis in the world. Of the total sepsis related neonatal deaths in 2013, 38.9% occurred in South Asia.[1 2] Poverty, low coverage of effective interventions, including facility births, and gross inequities in delivery of healthcare[3] contribute to this situation. We review the available literature (box 1) to draw attention to the burden of neonatal sepsis, the pathogen profile, and the extent of antimicrobial resistance in South Asia, and propose priority actions for policymakers and health professionals in the region.

Paucity of high quality data

We found no data on neonatal sepsis from Afghanistan, Bhutan, Maldives, and little from Sri Lanka. While the neonatal health indicators of three of these four countries are reasonably good,[3] the paucity of data from war torn Afghanistan is a cause for concern.

More importantly, the data from the four countries with the highest burden of neonatal sepsis (India, Pakistan, Nepal, and Bangladesh) are of poor quality. With the exception of studies such as the Young Infant Study[4] ANISA,[5] and the multisite study from the Delhi Neonatal Infections Study[7] collaboration, most studies are retrospective, lack rigorous methods and standard definitions, and have used passive surveillance to identify cases. There is therefore an inherent risk of underestimating the burden of sepsis in the region.

High incidence of sepsis

The pooled incidence of culture positive sepsis in hospital based reports from South Asia is 15.8 per 1000 live births (95% CI 12.7 to 18.8, n=15 reports). This is about twofold to fourfold higher than that reported in high income countries such as England and the United States.[8 9] The incidence does not seem to have declined in the last decade.[10] About a third of neonates with culture positive sepsis died as a result (median case fatality rate 34.4%). Table 1 presents incidence and case fatality rates by country.

Sepsis is categorised into early onset sepsis (onset within 72 hours of birth) and late onset sepsis (beyond 72 hours). Early onset sepsis is thought to be caused by pathogens vertically transmitted from mothers while late onset sepsis is attributed to pathogens acquired horizontally from the environment or care givers, or both. About 62% of the infections in South Asia occur in the first 72 hours of life, roughly translating into an incidence of 9.8 per 1000 live births. This is 10-fold higher than the incidence of early onset sepsis reported in a large nationwide study in the United States.[9]

Neonatal sepsis is classified as culture positive or culture negative, depending on

KEY MESSAGES

- The incidence of neonatal sepsis in South Asia is 4 to 10 times higher than that in developed countries
- Unlike high income countries with a predominance of group B streptococci, Gram negative organisms predominate, possibly indicating horizontal transmission of infections from the environment and healthcare providers
- About 50-88% of common isolates from the health facilities are resistant to first line antibiotics—ampicillin and gentamicin
- Simple, evidence based interventions can help, such as better asepsis, hand hygiene, and exclusive breastfeeding and establishing antimicrobial stewardship programmes

Box 1: Sources and methods

We searched PubMed and Web of Science for literature published between January 2000 and August 2018 using the search terms: (newborn OR neonate) AND (sepsis OR infection OR antibiotic OR antimicrobial). The results were filtered for South Asian countries. Bibliographies of full text articles and published systematic reviews were also searched to identify additional articles.

We identified 2699 and 220 articles from PubMed and Web of Science, respectively, and 19 additional articles from reference lists of identified articles. After removing duplicates, we screened 2768 articles and reviewed 223 full text articles. Finally, 109 studies were included: 69 from India, 16 from Pakistan, 7 from Bangladesh, 14 from Nepal, 1 from Sri Lanka, and 2 multi-country studies (Young Infant Study[4] and Aetiology of Neonatal Infections in South Asia (ANISA)[5]) covering Bangladesh, India, and Pakistan). Because the datasets belonging to different time periods and/or different patient populations in a given study were considered unique, we had a total of 123 datasets from 109 studies.

Two authors (SS and SC) extracted information from the relevant studies. Most studies were hospital based, single centre studies that reported data on neonates with suspected sepsis or laboratory based studies reporting bacteriological profile and antimicrobial resistance of cultures received from neonatal intensive care units. We identified only eight relevant community based studies. Random effects meta-analysis was done to pool the results, if applicable, using the "metan" command in Stata 15.1 (StataCorp, College Station, TX). Pooling of rates was done separately for the hospital based and community based studies. See appendix on bmj.com for details of the methods and studies included.

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Table 1 | Incidence, case fatality rates, and infecting organism for neonatal sepsis in hospital based studies

	India	Pakistan	Bangladesh	Nepal	Sri Lanka	Total
No of studies (No of isolates)	64 (18 761)	16 (3557)	6 (584)	14 (1325)	1 (9)	101* (24 244)
Incidence (95% CI) of culture positive sepsis, per 1000 live births; No of studies	16 (12.8 to 19.2); n=14	NA	NA	11.6 (18.4 to 14.7); n=1	13.6/1000 patient days; n=1	15.7 (12.7 to 18.8); n=15
Case fatality rate (95% CI); No of studies	34.4 (33 to 35.7); n=14	30.9 (25.7 to 36.2); n=2	19.1 (11.7 to 26.5); n=2	64.7 (54.3 to 75); n=1	NA	34.4(33.1 to 35.6); n=19
% Infecting organism (95% CI); No of studies						
Klebsiella spp†	53.6 (50.7 to 56.5); n=21	NA	NA	33 (3.0 to 63.0); n=1	60	53.3 (50.4-56.2); n=22
Escherichia coli†	42.2 (38.5 to 46); n=16	NA	NA	50 (1.0 to 98.0); n=1	NA	42.2 (38.6 to 46.2); n=17
Meticillin resistant *Staphylococcus aureus*	43.2 (39.9 to 46.5); n=17	61 (49.1-72.8); n=1	NA	26 (12.8 to 39.3); n=3	NA	46.5 (41.9 to 51.1) n=21

Data represent pooled proportions (95% CI), unless stated otherwise. NA= not available
*Community based studies (n=8) are not included in table.
†Extended spectrum β lactamase.

isolation of pathogen(s) from blood or other sterile fluids. Based on the available data, this review focuses on the burden of culture positive sepsis, which forms only part of the total number of sepsis cases. Because of the difficulty in obtaining an adequate volume of blood in preterm neonates and the low levels of bacteraemia, blood cultures tend to be sterile in many neonates. The culture positive versus culture negative sepsis ratio ranges from 1:6 to 1:16 in high income countries.[11] The ratio is likely to be more skewed towards culture negative sepsis in South Asia, given the poor microbiological laboratory support in most units. The burden of total neonatal sepsis is therefore likely to be much higher.

The proportion of neonates with culture positive sepsis in community based studies was lower—12.3 per 1000 live births (95% CI 8.4 to 16.2). However, this was influenced by the ANISA study[5] which used a statistical model incorporating the results of molecular assays to estimate the incidence of bacterial sepsis. If only conventional blood culture positive results are included, the pooled risk of sepsis was much lower—5.5 per 1000 live births (95% CI 2.4 to 8.6).

Unique pathogen profile

The pathogen profile in South Asia is different from that found in high income countries. There is a predominance of Gram negative pathogens (>60%) and a low prevalence of group B streptococci in South Asia, compared with a high incidence of group B streptococci in high income countries.[7 10]

Among isolates from hospital settings (n=24 273), Gram negative organisms (63%) were the most common, with *Klebsiella* spp (23%), *Escherichia coli* (14%), and *Acinetobacter* spp (8%) being the top three. The most common Gram positive organisms were *Staphylococcus aureus* (20%) and *Coagulase negative Staphylococci* (9%). Gram negative organisms were associated with higher case fatality (pooled proportion 26.7%; 95% CI 0 to 41%) than Gram positive organisms (11.9%; 95% CI 10.5 to 13.3%). Among the 703 isolates from community settings, *Klebsiella spp* (25%), *E coli* (15%), and *S aureus* (12%) were the most common.

The predominance of Gram negative pathogens in South Asia suggests that the transition from Gram negative pathogens to Gram positive organisms such as group B streptococci that happened five to six decades ago in developed countries[10]—largely because of improved aseptic routines, including hand hygiene in neonatal intensive care units—is yet to take place in South Asia.

There was a striking similarity between the pathogen profile of early onset and late onset sepsis (see supplementary fig 2 on bmj.com). This challenges the assumption of attributing early onset sepsis to vertical transmission from the mothers. Although it is possible that the pregnant women in South Asia are colonised with pathogens normally found in the hospitals (such as *Klebsiella*), it is more probable that the source of infection in early onset sepsis is the unhygienic practices in the labour rooms and neonatal intensive care units. Identifying the source and transmission pathways of common pathogens of early

Table 2 | Pathogen specific antimicrobial resistance in isolates from babies with neonatal sepsis in South Asia

Pathogen (total No of isolates)	% of isolates resistant (95% CI); No of isolates					
	Ampicillin	Gentamicin	Cefotaxime	Ceftazidime	Meropenem/ meticillin	Multidrug
Hospital settings						
Klebsiella spp (n=4312)	86.8 (85.8 to 87.3); 2806	75.3 (74 to 76.7); 2954	72.5 (71.3 to 73.7); 4126	74.5 (73 to 75.9); 2455	10.4 (9.4 to 11.5); 2540	70.7 (66.1 to 75.3)
E coli (n=2798)	88.2 (87 to 89.5); 2196	67.9 (66 to 69.8); 2254	66.9 (65.3 to 68.6); 2745	69.4 (67.4 to 71.4); 1773	8.1 (6.8 to 9.4); 1551	54.0 (48.1 to 59.9)
Acinetobacter spp (n=1347)	86.2 (83.8 to 88.5); 633	68.1 (65.1 to 71); 792	80.3 (78.2 to 82.4); 1121	73.6 (70.8 to 76.3); 718	64.8 (62.2 to 67.4); 828	78.7 (73.9 to 83.4)
S aureus (n=2437)	69 (67.3 to 70.6); 2266	54.5 (52.4 to 56.6); 1773	51.2 (49 to 53.3);1753	NA	46.5 (41.9 to 51.1); 310	NA
Community settings						
Klebsiella spp (n=116)	87.9 (82.3 to 93.5)	22.8 (15 to 30.1)	25.7 (18 to 33.5)	28.5 (19.8 to 37.1)	0 (0 to 2)	—
E coli (n=37)	72.4 (58 to 86)	18.7 (6 to 31)	50.3 (35 to 65.7)	37 (13.3 to 60.6)	0 (0 to 2)	—
S aureus (n=77)	74.6 (66.6 to 82.6)	3 (0-9)	9 (2 to 16)	NA	10 (0 to 20.5)	—

Data represent pooled proportion (95% CI); n=number of isolates tested, unless stated otherwise.
NA=not applicable.

Box 2: Research priorities for neonatal sepsis in South Asia

- Establish a subnational/national surveillance database to evaluate and monitor the burden of neonatal sepsis, sepsis related mortality, and antimicrobial resistance
- Implementation research—quality improvement initiatives—to scale up the coverage of known interventions
- Identify the source of infection and transmission pathways of common pathogens
- Evaluate the impact of introducing antimicrobial stewardship programmes at different levels of health facilities
- Develop and validate point-of-care diagnostic method(s) for rapid and accurate diagnosis of sepsis

onset sepsis is essential to determine the appropriate steps to prevent infection that will help to reduce the high burden of mortality associated with early onset sepsis in the region.

Spiralling antimicrobial resistance

Antimicrobial resistance has worsened in the last decade, rendering most antibiotics obsolete. Resistance to even "reserve" antibiotics has increased—50-70% of the common Gram negative isolates are now multidrug resistant. Table 2 presents antimicrobial resistance patterns found in common pathogens in hospital and community settings in South Asia.

The common pathogens from hospital based studies uniformly exhibit a high degree of resistance to first line drugs recommended by the World Health Organization—namely, ampicillin, gentamicin, and third generation cephalosporins such as cefotaxime (table 2).[6] However, most were susceptible to WHO classified "watch group"[6] antibiotics, such as meropenem (see suppl table 1 on bmj.com). About half (pooled proportion 46.5%; 95% CI 41.9 to 51.1) of *S aureus* isolates were meticillin resistant, but most remained susceptible to watch group antibiotics such as vancomycin. The varied pathogens with high resistance patterns preclude the use of intrapartum antibiotic prophylaxis to prevent vertically transmitted infection. In contrast, the antimicrobial resistance profile in the community based studies was not so high: although resistance to ampicillin was high, resistance to gentamicin and third generation cephalosporins was low.

If the apparent dichotomy in antimicrobial resistance between the hospital based and community based studies is real, health facilities in the region should review their antibiotic policy to prevent misuse of antibiotics. The high antimicrobial resistance brings into focus the overuse of antibiotics in neonates with culture negative sepsis. The ANISA study showed that many neonates with negative blood cultures had viral infections.[5] The low case fatality in neonates with culture negative sepsis (only one fifth of that of culture positive sepsis) in the multisite study from Delhi[7] also suggests that many of these neonates either had viral infections or did not have sepsis at all. More reliable and accurate point-of-care diagnostic method(s) are needed to rule out sepsis, thereby preventing indiscriminate use of antibiotics in neonatal intensive care units.

The low antimicrobial resistance in the community allows healthcare providers in primary and even secondary level facilities to use first line antibiotics in neonates with sepsis. Steps to prevent misuse of antibiotics in other sectors such as agriculture and restriction of over-the-counter antibiotics[15 16] would ensure that the antimicrobial resistance rates remain low in community settings.

Team

- Neonatologist
- Senior nursing officer
- Microbiologist
- Statistician/public health expert

Strategies

- Scale up infection control practices
- Improve microbiology lab capacity (automated cultures)
- Standard operating procedures:
  - Obtain blood culture before first dose of antibiotics
  - When to screen and when to treat for sepsis
- Unit protocol:
  - Antibiotic policy based on culture reports of last 6-12 months
  - Stop or de-escalate to narrow spectrum antibiotics based on culture report
- Prior authorisation from antimicrobial stewardship programme team for "reserve" antibiotics

Audit and feedback

- Measure: proportion
  - In whom cultures obtained before start of antibiotics
  - Receiving "reserve" antibiotics
  - Receiving right drug, right dose, and right duration
  - Not receiving antibiotics in sick newborn care unit
- Measure: days of therapy (DOT) of common antibiotics
- Prospective audit and feedback to staff

Fig 1 | Proposed model of antimicrobial stewardship programme for health facilities in South Asia. Adapted from Ramasethu 2017; Patel 2012; Cantey 2014

Next steps

Surveillance and research

We need reliable data to track progress on neonatal sepsis in the region to enable benchmarking and cross-learning and inform policy making. A regional surveillance database—possibly under the umbrella of the South Asian Association for Regional Cooperation—could provide such a mechanism, alongside surveillance databases within each country. This could begin with passive surveillance using uniform definitions and be followed up by active surveillance. Box 2 lists the major research priorities in the region.

Quality of care and antimicrobial stewardship in hospitals

Most health facilities in the region continue to be the "hot beds" of infection transmission in sick and vulnerable neonates.[10] Lack of essential equipment and supplies including soap, sinks, running water, and

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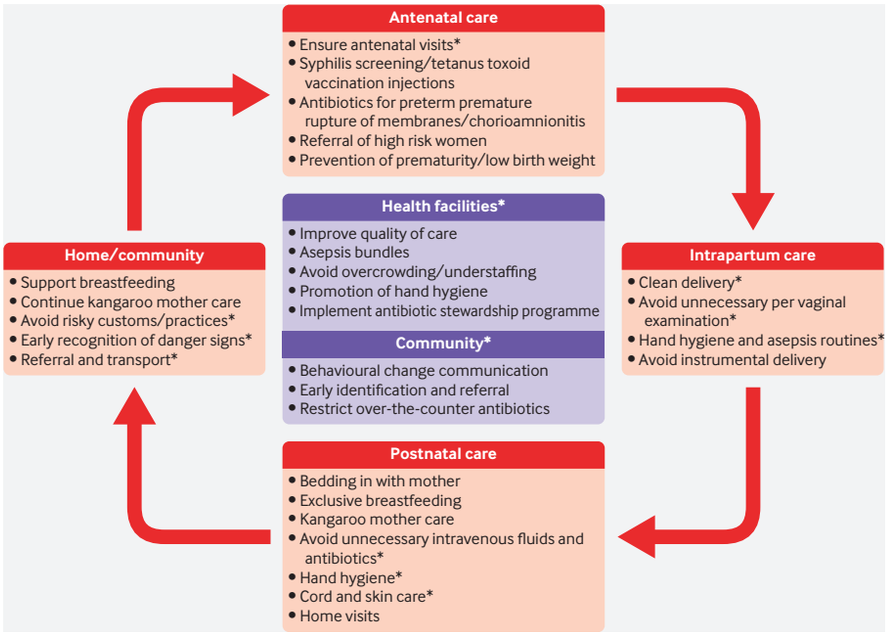

Fig 2 | Key interventions to reduce the burden of sepsis and antimicrobial resistance in South Asia. *Indicates interventions that are more relevant to the region

disposables; overcrowding and understaffing; and suboptimal disinfection practices increase the risk of horizontal transmission of infections from the labour rooms or neonatal intensive care unit.[10] The two-fold greater risk of sepsis in hospital based studies compared with community based studies suggests that horizontal transmission—that is, healthcare associated infections—plays a major part in the high incidence of neonatal sepsis in the region. Selective referral of high risk neonates to hospitals may also account for this. With increasing rates of facility births, the burden of neonatal sepsis is bound to increase unless radical measures to improve the quality of care are implemented.

Antimicrobial stewardship programmes must be implemented to rationalise antibiotic use. Policy makers and other stakeholders should develop guidelines and toolkits to facilitate implementation of these programmes across health facilities at different levels of the health system. Steps should be simplified and continuous monitoring and auditing done to inform healthcare providers of the progress made. Figure 1 depicts a simplified model of antimicrobial stewardship programmes for use in health facilities in the region.[12-14]

Scale up effective interventions

The Every Newborn series on quality of care at birth identified that scaling up of evidence based interventions could reduce infection related neonatal deaths by 84% globally.[17] This is likely to have a major impact in South Asian countries[3] because the existing coverage of these interventions in almost all countries is low, except in Maldives and Sri Lanka. For example, the proportion of pregnant women receiving at least four antenatal visits in Afghanistan (18%), Bangladesh (31%), India (51%), Nepal (69%), and Pakistan (37%) is low. The proportion of births attended by skilled health workers is 51%, 42%, 81%, 58%, and 55%, respectively.[18] The median coverage of clean birth practices is 33.9%,[3] and of the first postnatal check-up in the first two days of birth is 31% in all countries except Maldives and Sri Lanka.[18]Figure 2 lists key interventions that could reduce the high burden of sepsis, sepsis related mortality, and antimicrobial resistance.

Concerted efforts at national and regional levels to identify health system related issues resulting in high incidence of sepsis and antimicrobial resistance, to improve the coverage of known interventions, and to implement context specific solutions that are simple and effective, along with a strong political will, will go a long way to reduce the burden of sepsis related mortality and morbidity in the region.

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Appendix: Details of methods and included studies

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Can India lead the way in neglected diseases innovation?

Nirmal Kumar Ganguly and colleagues call for a comprehensive policy for neglected diseases research in India to foster innovation in drugs, diagnostics, and vaccines, critical for evolving needs of elimination programmes

India is one of the top global funders of research and development (R&D) into neglected diseases. With a promising scientific base built on the foundation of an expanding science and technology workforce,[1] the country is well placed to make a substantial contribution to innovation in neglected tropical diseases. A third of new drugs (six out of 18) and two thirds of new vaccines (six of 10) for neglected diseases registered since 2000 have had Indian involvement. Nearly 12% of drug, diagnostic, and vaccine candidates for neglected diseases in the R&D pipeline are from India.[1] The world's first leprosy vaccine was developed in India and is expected to accelerate eradication efforts.[2]

India has successfully eliminated certain infectious diseases—such as guinea worm, trachoma, and yaws—in recent years.[3-5] Yet, neglected diseases such as leishmaniasis, filariasis, leprosy, snakebite, and soil transmitted helminthic infections still pose a challenge. There persist challenges in the implementation of new technologies and major research gaps. The current model of innovation is driven by market forces and is failing to deliver a steady stream of products that reach patients through adoption into treatment programmes.[6 7] Neglected diseases predominantly affect poor and marginalised populations and do not constitute a market that is attractive enough to stimulate private sector investment. As such, the Indian government must step in with appropriate policies and investments to support innovation. In this article, we review existing policies and mechanisms, and propose actions to create an enabling environment for neglected diseases research in India.

Current policy scenario

A comprehensive policy to foster research and innovation in drug discovery, diagnostics, and vaccine development in neglected tropical diseases is lacking. Box 1 lists relevant policy statements in India in recent years. While political intent and will are expressed in a few, clear operational plans and funding mechanisms are not specified. Consequently, follow-up action is patchy or absent.

No institutional mechanism exists at a national level to identify gaps in neglected diseases research, set priorities, liaise with research institutions, or monitor research output. There is often no coordination between the various funding and research bodies to prioritise the research agenda and minimise duplication.

Not enough funding for product development

India is the fourth largest government funder of neglected diseases research, and the largest among middle income countries. Yet, funding falls far short of requirements.[14] Few public agencies disburse R&D grants for neglected diseases in India.[15] An analysis of contribution to neglected diseases research globally reveals this shortfall in public funding. The average funding by the Indian Council of Medical Research (ICMR) from 2008 to 2015 was about $26m (£21m; €23m) per year, while the National Institutes of Health in the US contributed over £1.3bn per year.[16] Indian pharmaceutical companies have filed few patents for new drugs and innovations compared with those in the US or China, which are investing heavily in innovation.[17] A recent trend with involvement of start-ups in diagnostic innovation[18] offers promise.

Slow adoption of novel and innovative technologies

The absence of market intermediaries for commercialisation of products for neglected diseases often results in innovations remaining in laboratories. Few government programmes have supported translational research to facilitate adoption of new drugs and technologies in the real world for treatment and control of neglected diseases. The ICMR has attempted to invite companies to commercialise new technologies such as diagnostic assays, reagents, devices, and vaccines for infectious diseases under a public-private partnership model. It is not clear how well

Box 1: Recent policies on neglected diseases research in India

- The National Health Policy (2017) sets an ambition to stimulate innovation to meet health needs and ensure that new drugs are affordable for those who need them most,[8] but it does not specifically tackle neglected diseases
- The National Policy on Treatment of Rare Diseases (2018) includes infectious tropical diseases and identifies a need to support research on treatments for rare diseases. It has not yet prioritised diseases and areas for research funding or how innovation would be supported[9]
- The Science, Technology, and Innovation Policy (2013) does not mention research on neglected diseases[10]
- The Draft National Pharmaceutical Policy (2017) states that one of its objectives is to create an enabling environment to develop and produce innovator drugs, but the policy does not mention drugs for neglected tropical diseases
- The National Biotechnology Development Plan (2015-2020) seeks to encourage the preclinical and clinical development of vaccines against rotavirus, cholera, typhoid, rabies (human (DNA) based), malaria, dengue, tuberculosis, and Japanese encephalitis[11]
- The National Intellectual Property Rights Policy (2016) states that it will encourage publicly funded R&D institutes and industry to develop affordable drugs for neglected diseases but does not spell out how it will do so. There has been no activity reported in this area[12]
- The Open Source Drug Discovery programme was set up by the Council of Scientific and Industrial Research for new inventions for the prevention, diagnosis, and treatment of common diseases in India. This programme is no longer being funded.[13] It could have served as a platform to discover new drug targets and drugs for infectious and non-communicable diseases

this strategy has worked for neglected diseases technologies.[19 20] The Biotechnology Industry Research Assistance Council funds translational research and has taken up the development of snakebite antivenom, but this is still in early stages.

It is our observation that national programmes for neglected diseases in India tend to delay adoption of Indian innovations. Quite often products developed in India have been accepted outside the country before their adoption at home. For example, the oral rehydration suspension was jointly developed by scientists working in India and Bangladesh[21] to treat cholera, however it has not been uniformly adopted in these countries.[22 23] An oral cholera vaccine that was tested and manufactured in India and has been approved by the World Health Organisation is not yet included as part of the national programme, thereby limiting access.[24 25] Meanwhile, the vaccine was used in Bangladesh during the Rohingya refugee crisis to prevent cholera outbreaks.[26 27]

Box 2 provides an example of innovations in management of visceral leishmaniasis in India and the need for continually evolving strategies. There is no roadmap for carrying out trials for new drugs and incorporating new innovations as part of the national visceral leishmaniasis elimination programme in India. As such, several innovations have not yet been commercialised.

Regulatory bottlenecks

Schedule Y of the Drugs and Cosmetics Rules in India does not permit phase I clinical trials of drugs or vaccines that have been developed outside India.[40] This can act as a disincentive to invest in neglected diseases prevailing in, or exclusive to, India. A favourable provision for neglected diseases is built in, however, which states that toxicological and clinical data requirements may be abbreviated, deferred, or omitted for drugs indicated in diseases of special relevance to India. This provision has not yet been deployed.

An expedited regulatory approval process can facilitate rapid adoption of proved drugs and technologies. The Orphan Drug Act in the US and the Orphan Drugs Regulation in Europe provide examples of creating an enabling policy environment that has stimulated development of new drugs for rare diseases.[41] The priority review voucher (PRV) programme in the US helped promote R&D for new drugs targeting neglected tropical diseases by supporting expedited regulatory review and thereby potentially allowing drugs to reach the market early.[42 43]

Appropriate safeguards must be built in while developing preferential regulatory approval pathways.[44] There have been challenges in enabling access to these drugs in the long run. For example, miltefosine, which is used to treat visceral leishmaniasis, was registered by the Food and Drug Administration as an orphan drug in 2014 under the PRV programme and received accelerated regulatory clearance. Yet this has had no impact on improving access.[45] Furthermore, serious side effects and treatment failures were noted after the drug was introduced on a large scale.[46]

Way forward

It is time for India to establish a comprehensive policy on neglected diseases that paves the way for greater funding and mechanisms to support research and innovation. Box 3 lists the essential elements. A unified programme on neglected diseases encompassing research and elimination measures is likely to have a greater impact in prioritising the matter in the health agenda and streamlining efforts towards disease elimination. Creating an enabling environment for research and innovation will be crucial if India is to achieve the target set in sustainable development goal 3.3 to end epidemics of neglected tropical diseases by 2030.

Box 2: Innovation in visceral leishmaniasis elimination in India

Drugs

- Increasing treatment failures using miltefosine prompted the development of a new treatment regimen for visceral leishmaniasis. New drug trials were conducted through a partnership between government research institutes in India and the Drugs for Neglected Diseases initiative, and led to development of a new treatment—liposomal amphotericin B (AmBisome). A single intravenous infusion of liposomal amphotericin B was found to be effective in treating visceral leishmaniasis[28] and is now recommended as first line treatment in the national programme in India.[29] This drug was subsequently tested and introduced in Bangladesh and Nepal
- Cases of resistance to miltefosine and liposomal amphotericin B have been reported. New drug regimens need to be developed periodically to overcome resistance

Diagnostics

- Indian labs have played a significant role in the development of rK39 and rKE16, which have demonstrated high sensitivity and specificity, good reproducibility, and, most importantly, are heat stable for tropical countries like India. However, the sensitivity is more variable in sample panels from east Africa and South America.[30] A diagnostic probe has been developed in Kolkata but is yet to be commercialised[31]

Vaccine development

- Vaccines against visceral leishmaniasis are in different stages of development[32-34] Financial support provided by the Japanese Global Health Innovative Technology Fund has played a vital role[35]
- A patented innovation from India shows that HbR-DNA from the leishmania parasite coding for HbR protein or fragments thereof is a marker for diagnosis of leishmaniasis. It is immunogenic in humans and could be a vaccine candidate[36]

Vector control

- Research into vector ecology, mathematical modelling of disease transmission, and interventions such as nets treated with insect repellent is essential to control disease transmission. The National Vector Borne Disease Control Programme implements the integrated vector management programme for eradication of neglected diseases and supports research in this area[37]
- Indoor residual spraying of insect repellent is carried out in endemic districts as part of leishmania control measures. Innovative devices—such as a hand compression pump that is easier to operate, more effective, and less costly than the stirrup pump used in the programme—are being studied
- Development of disruptive technologies for vector control using nature's own mechanisms is the new norm. The bacterium *Wolbachia* exploits the host's innate immunity to establish a symbiotic relationship with the dengue vector mosquito *Aedes aegypti*[38] and is being tested for dengue prevention. Using a similar approach, *Wolbachia* is being tested in the control of filarial nematodes[39]

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Box 3: Essential elements of a comprehensive neglected disease policy

Funding
- Earmark a proportion of public funds for neglected diseases research and innovation[47]
- Funding for translational research to support product development.
- The stress on developing internal resources for laboratories has made institutions and scientists shift their research onto diseases with potential market value. Guaranteed public funding would correct this imbalance

Regulation
- Develop mechanisms to facilitate priority regulatory pathways for innovations in neglected diseases
- Capacity building and strengthening of regulators, including institutional ethics committees, in handling regulatory process for neglected diseases
- Facilitate early adoption of innovations proved effective into national disease treatment programmes. This would incentivise innovation and provide assurance to industry that the products developed will have a market

Research environment
- A National Observatory on Biomedical R&D to prioritise, coordinate, and monitor research output, including on neglected diseases, is needed. Such an institutional mechanism would enable efficient allocation of resources and allow policy makers, funders, researchers, and patient groups to identify areas of public investment and existing gaps, and suggest improvements
- Creating common repositories of biological samples and other materials accessible to researchers, industry, and regulators would facilitate innovation. The absence of a pan-India surveillance data repository on pathogenic strains of neglected diseases poses a hindrance to innovation for vaccines
- Defining specificity and sensitivity standards for diagnosis of neglected diseases would facilitate diagnostic innovation and help regulatory authorities evaluate these
- Alternative approaches to R&D based on the principles of open innovation and product development partnerships must be explored.
- A comprehensive national surveillance database for neglected diseases is essential to monitor trends across the country. This could be achieved by strengthening the existing integrated disease surveillance programme. The use of molecular diagnostics at point of care coupled with information technology is the future for robust surveillance. Global positioning systems and mobile technology to track migratory populations are being employed in disease surveillance in Sri Lanka and in the Mekong delta region of SEARO countries, and need to be tested in India[48]
- The evolving areas of genomics, transcriptomics and proteomics research can provide a better understanding of the modes of infection and treatment options. More drug and vaccine targets can be identified, and it would provide impetus to biotechnological research and industry.

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