Evilinating 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, most commonly affecting poor people. 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. Until recently, these countries accounted for more than 50% of the global disease burden. 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. 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. The development of the oral drug miltefosine and a rapid diagnostic test based on the rK39 antigen 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. Nepal achieved the elimination threshold in 2013, and Bangladesh in 2016. 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.

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. Communities that had some herd immunity in the past may gradually be becoming fully susceptible. The rising trend in post-kala-azar dermal leishmaniasis together with the emergence of coinfection with HIV is concerning. Patients with these conditions may serve as reservoirs of infection, perpetuating transmission even when the elimination targets are reached. Treatments for both conditions are far from ideal.

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
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.\(^2^2\)

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
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.\(^2^2\)

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

Newer drugs
The current drug regimens, while allowing progress towards eliminating kala-azar, will probably be inadequate for the post-elimination phase.\(^2^5\)

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.\(^2^5\)

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-kala-azar cases is now reliant on a single medicine produced by a single manufacturer. Relapses have been observed with this treatment.\(^2^5\)

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

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.\(^2^3\)\(^2^4\)

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.\(^2^5\)

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.\(^2^5\)

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
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 new treatment for the post-elimination era, systems for case detection, epidemiological surveillance, 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

### 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

---

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

| Test Description | Test Description |
|------------------|------------------|
| Lateral flow immunochromatographic RDT: leishmaniasis IgG1 RDT43 (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—ELISA45: *Leishmania* antigen detection ELISA (In Bios International, Seattle, USA) | 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 test45 (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 assay for *Leishmania* detection (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 |
| Reombinase polymerase amplification (RPA) assay47: 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 |
OPEN ACCESS

This article is one of series commissioned by The BMJ in collaboration with the Drugs for Neglected Diseases initiative (DNDi). The BMJ retained full editorial control over external peer review, editing, and publication. Open access fees are funded by the DNDi, Geneva.

Suman Rijal, director
Shyam Sundar, professor
Dinesh Mondal, senior scientist
Pradeep Das, director
Jorge Alvar, senior adviser
Marleen Boelaert, professor

1 Drugs for Neglected Diseases Initiative, New Delhi, India
2 Benaras Hindu University, Varanasi, India
3 International Centre for Diarrhoeal Disease Research, Dhaka, Bangladesh
4 Rajendra Memorial Research Institute of Medical Sciences, Patna, India
5 Drugs for Neglected Diseases Initiative, Geneva, Switzerland
6 Institute of Tropical Medicine, Antwerp, Belgium

Correspondence to: S Rijal snijal@dndi.org

This is an Open Access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/.

1 Peters W, Prasad LSN. Kala-azar in India—its importance as an issue in public health. In: Proceedings of the Indo-JK Workshop on Leishmaniasis. New Delhi, India: Indian Council of Medical Research, 1993.
2 Boelaert M, Meheus F, Sanchez A, et al. The poorest of the poor: a poverty appraisal of households affected by visceral leishmaniasis in Bihar, India. Trop Med Int Health 2009;14:639-44. doi:10.1111/j.1365-3156.2009.01647.x
3 Bora D. Epidemiology of visceral leishmaniasis in India. Natl Med J India 1999;12:62-8.
4 Alvar J, Vélez ID, Bern C, et al. WHO Leishmaniasis Control Team. Leishmaniasis worldwide and global estimates of its incidence. PLoS One 2012;7:e35671. doi:10.1371/journal.pone.0035671
5 World Health Organization Regional Office for South-East Asia. Regional strategic framework for elimination of kala-azar from the South-East Asia region (2005-2015). 2005. http://apps.searo.who.int/pds/docs/BO211.pdf
6 Hirve S, Kroeger A, Matheshawksi G, et al. Towards elimination of visceral leishmaniasis in the Indian subcontinent-translating research to practice to public health. PLoS Negl Trop Dis 2017;11:e0005889. doi:10.1371/journal.pntd.0005889
7 WHO. Accelerating work to overcome the global impact of neglected tropical diseases - a roadmap for implementation. 2012. https://www.who.int/neglected_diseases/NTD_RoadMap_2012_Fullversion.pdf?ua=1
8 Sundar S, Jha TK, Thakur CP, et al. Oral miltefosine for Indian visceral leishmaniasis. N Engl J Med 2002;347:1739-46. doi:10.1056/NEJMoa021556
9 Boelaert M, Verdonck K, Menten J, et al. Rapid tests for the diagnosis of visceral leishmaniasis in patients with suspected disease. Cochrane Database Syst Rev 2014;6:CD009135. doi:10.1002/14651858.CD009135.pub2
10 WHO. Global Health Observatory Data Repository (last updated 15 Sep 2017). http://apps.who.int/gho/data/node.main/NTDLEISHMVNUM?lang=en

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.

Contributors and sources: SR and MB developed the structure of the paper. All the authors contributed to the initial draft. SR and MB combined the contributions. All the authors worked on and approved the final version. SR is guarantor.

Competing interests: We have read and understood BMJ policy on declaration of interest and have no relevant interests to declare.

Provenance and peer review: Commissioned; externally peer reviewed.
and perspectives. Microbiol Rev 2018;31:e00048-18. doi: 10.1128/CMR.00048-18

20 Mowbray CE. Antileishmanial drug discovery: past, present and future perspectives. In: Rivas L, Gil C, eds. Drug discovery for leishmaniasis. Royal Society of Chemistry, 2018:24-36.

21 Special Programme for Research and Training in Tropical Diseases (WHO/TDR). Monitoring and evaluation toolkit for indoor residual spraying: kala-azar elimination in Bangladesh, India and Nepal. 2010. https://www.who.int/trd/publications/trd-research-publications/irs_toolkit/en/

22 Coleman M, Foster GM, Deb R, et al. DDT-based indoor residual spraying suboptimal for visceral leishmaniasis elimination in India. Proc Natl Acad Sci USA 2015;112:8573-8. doi: 10.1073/pnas.1507782112

23 Poché DM, Garlapati RB, Mukherjee S, et al. Bionomics of Phlebotomus argentipes in villages in Bihar, India with insights into efficacy of IRS-based control measures. PLoS Negl Trop Dis 2018;12:e0006168. doi: 10.1371/journal.pntd.0006168

24 Picado A, Das ML, Kumar V, et al. Effect of village-wide use of long-lasting insecticidal nets on visceral leishmaniasis vectors in India and Nepal: a cluster randomized trial. PLoS Negl Trop Dis 2010;4:e587. doi: 10.1371/journal.pntd.0000587

25 Chowdhury N, Fania S, Huda MM, et al. Control of Phlebotomus argentipes (Diptera: Psychodidae) sand fly in Bangladesh: a cluster randomized controlled trial. PLoS Negl Trop Dis 2017;11:e0005890. doi: 10.1371/journal.pntd.0005890

26 Picado A, Singh SP, Rijal S, et al. Longlasting insecticidal nets for prevention of Leishmania donovani infection in India and Nepal: paired cluster randomised trial. BMJ 2010;341:c6760. doi: 10.1136/bmj.c6760

27 Mondal D, Huda MM, Karmoker MK, et al. Reducing visceral leishmaniasis by insecticide impregnation of bed-nets. Bangladesh. Emerg Infect Dis 2013;19:1131-4. doi: 10.3201/eid1907.120932

28 Huda MM, Kumar V, Das ML, et al. Entomological efficacy of durable wall lining with reduced wall surface coverage for strengthening visceral leishmaniasis vector control in Bangladesh, India and Nepal. BMC Infect Dis 2016;16:539. doi: 10.1186/s12879-016-1881-8

29 Dumont P, Fankhauser B, Bouhsira E, et al. Repellent and insecticidal efficacy of a new combination of fipronil and permethrin against the main vector of canine leishmaniosis in Europe (Phlebotomus perniciosus). Parasit Vectors 2015;8:49. doi: 10.1186/s13071-015-0683-y

30 Cameron MM, Acosta-Serrano A, Bern C, et al. Understanding the transmission dynamics of Leishmania donovani to provide robust evidence for interventions to eliminate visceral leishmaniasis in Bihar, India. Parasite Vectors 2016;9:25. doi: 10.1186/s13071-016-1309-8

31 Hirve S, Boelaert M, Matlashewski G, et al. Transmission dynamics of visceral leishmaniasis in the Indian subcontinent—a systematic literature review. PLoS Negl Trop Dis 2016;10:e0004896. doi: 10.1371/journal.pntd.0004896

32 Hasker E, Singh SP, Malaviya R, et al. Management of visceral leishmaniasis in rural primary health care services in Bihar, India. Trop Med Int Health 2010;15(Suppl 2):55-62. doi: 10.1111/j.1365-3156.2010.02562.x

33 Singh OP, Hasker E, Boelaert M, Sundar S. Elimination of visceral leishmaniasis on the Indian subcontinent. Lancet Infect Dis 2016;16.e304-9. doi: 10.1016/S1473-3099(16)30140-2

34 Hercik C, Cosmas L, Mogeni OD, et al. A combined syndromic approach to examine viral, bacterial, and parasitic agents among febrile patients: a pilot study in Kilombero, Tanzania. Am J Trop Med Hyg 2018;98:625-32. doi: 10.4269/ajtmh.17-0421

35 Dumont P, Fankhauser B, Bouhsira E, et al. Repellent and insecticidal efficacy of a new combination of fipronil and permethrin against the main vector of canine leishmaniosis in Europe (Phlebotomus perniciosus). Parasit Vectors 2015;8:49. doi: 10.1186/s13071-015-0683-y

36 Cameron MM, Acosta-Serrano A, Bern C, et al. Understanding the transmission dynamics of Leishmania donovani to provide robust evidence for interventions to eliminate visceral leishmaniasis in Bihar, India. Parasite Vectors 2016;9:25. doi: 10.1186/s13071-016-1309-8

37 Cameron MM, Acosta-Serrano A, Bern C, et al. Understanding the transmission dynamics of Leishmania donovani to provide robust evidence for interventions to eliminate visceral leishmaniasis in Bihar, India. Parasite Vectors 2016;9:25. doi: 10.1186/s13071-016-1309-8

38 Hasker E, Singh SP, Malaviya R, et al. Management of visceral leishmaniasis in rural primary health care services in Bihar, India. Trop Med Int Health 2010;15(Suppl 2):55-62. doi: 10.1111/j.1365-3156.2010.02562.x

39 Singh OP, Hasker E, Boelaert M, Sundar S. Elimination of visceral leishmaniasis on the Indian subcontinent. Lancet Infect Dis 2016;16.e304-9. doi: 10.1016/S1473-3099(16)30140-2

40 Hercik C, Cosmas L, Mogeni OD, et al. A combined syndromic approach to examine viral, bacterial, and parasitic agents among febrile patients: a pilot study in Kilombero, Tanzania. Am J Trop Med Hyg 2018;98:625-32. doi: 10.4269/ajtmh.17-0421

41 Malaviya P, Picado A, Hasker E. Health & demographic surveillance system profile: the Muzaffarpur-TRMC Health and Demographic Surveillance System. Int J Epidemiol 2014;43:1450-7. doi: 10.1093/ije/dyu178

42 WHO. Regional strategic framework for elimination of kala-azar from the South-East Asia Region (2011-2015). http://www.who.int/trs/ handle/10665/205826

43 Bhattacharyya T, Ayanede A, Falconar AK, et al. IgG1 as a potential biomarker of post-chemotherapeutic relapse in visceral leishmaniasis, and adaptation to a rapid diagnostic test. PLoS Negl Trop Dis 2014;8:e3273. doi: 10.1371/journal.pntd.0003273

44 Vallur AC, Tutterrow WJ, Mohanath R, et al. Development and comparative evaluation of two antigen detection tests for visceral leishmaniasis. BMC Infect Dis 2015;15:384. doi: 10.1186/s12879-015-1125-3

45 Boelaert M, El-Safi S, Hailu A, et al. Diagnostic tests for kala-azar: a multi-centre study of the freeze-dried DAT, K39 strip test and KATex in East Africa and the Indian subcontinent. Trop Med Int Health 2008;102:32-40. doi: 10.1111/j.1365-3156.2007.00386.x

46 Adams ER, Schoone G, Versteege I, et al. Development and evaluation of a novel loop-mediated isothermal amplification assay for diagnosis of cutaneous and visceral leishmaniasis. J Clin Microbiol 2018;56:e00386-18. doi: 10.1128/JCM.00386-18

47 Mondal D, Ghosh P, Khan MA, et al. Mobile suitcase laboratory for rapid detection of Leishmania donovani using recombinase polymerase amplification assay. Parasit Vectors 2016;9:281. doi: 10.1186/s13071-015-1881-8

Cite this as: BMJ 2019;364:k5224
http://dx.doi.org/10.1136/bmj.k5224