Elimination of Kala-Azar from the Southeast Asia Region

Sujit K. Bhattacharya^{1*} and Aditya Prasad Dash²

¹General Medicine, Glocal Hospital, Krishnanagar, West Bengal, India; ²Central University of Tamil Nadu, Tiruvarur, India

Abstract. Visceral leishmaniasis (VL), popularly known as kala-azar, is essentially a disease of poverty. Kala-azar is caused by a parasite, *Leishmania donovani*. Recent review indicates that worldwide 98 countries are endemic for kala-azar. Approximately 0.2–0.4 million new VL cases occur each year worldwide. More than 90% of global VL cases occur in Bangladesh, Brazil, Ethiopia, India, South Sudan, and Sudan. This trend is slowly changing due to the progress in kala-azar elimination in southeast Asia, where Bangladesh has reported an average of some 600 new cases in 2014–2015. With the advancement in our knowledge about the disease and development of tools to diagnose and treat VL, it was considered that elimination of kala-azar was possible from India, Nepal, and Bangladesh. The three countries signed a memorandum of understanding in 2005 for collaboration. Miltefosine is the first ever oral drug developed to treat VL, which was later replaced by lipid amphotericin B. The main components of the strategy are early diagnosis using rK39 strip test and complete treatment utilizing miltefosine for 28 days. Dichlorodiphenyltrichloroethane or pyrethroids were deployed for vector control. There was much to be desired for better performance of the vector control activity. Pharmacovigilance and monitoring of drug resistance were the weakest part of the program. In the post-elimination phase, surveillance reinforced by active case finding will of a crucial factor for sustainability of the elimination. A strong political will is required to ensure elimination of kala-azar from the Indian subcontinent and its sustainability in the post-elimination phase.

INTRODUCTION

Visceral leishmaniasis (VL), popularly known as kala-azar, is essentially a disease of poverty and affects the underprivileged communities in many developing countries. Kala-azar is caused by a parasite called *Leishmania donovani* and transmitted from one person to another by the bite of infected female sand fly known as *Phlebotomus argentipes*. Recent review indicates that worldwide 98 countries are endemic for kala-azar. It is estimated that approximately 0.2–0.4 million of new VL cases occur each year worldwide. Over 90% of new cases occur in six countries: Bangladesh, Brazil, Ethiopia, India, South Sudan, and Sudan. In the Indian subcontinent, 90% of VL cases occur in India, particularly in the northern part of Indian state of Bihar; Bangladesh and Nepal contribute to the rest of the disease burden in the Indian subcontinent. Attempts were made in India to control the disease in the past, but due to lack of resources, the activities were discontinued. As a collateral benefit of dichlorodiphenyltrichloroethane (DDT) spraying for malaria control, kala-azar also disappeared. When these activities are discontinued, the disease reappeared. With the advancement in our knowledge about the epidemiology (agent, parasite, host, environment, reservoir) of the disease and development of user-friendly field-tested strip test (rK39)¹, effective and safe oral drug (miltefosine)^{2–10} and vector¹¹ control by DDT/pyrethroids, it was considered that elimination of kala-azar is possible from India, Nepal, and Bangladesh.¹²

MEMORANDUM OF UNDERSTANDING

India, Nepal, and Bangladesh in 2005 signed a memorandum of understanding as an instrument of their commitment to cooperate and collaborate with each other in

efforts to eliminate the disease from their respective countries. It was also essential since about 40% of all kala-azar cases were located in the cross-border areas of the three countries. The target of elimination was < 1 case per 10,000 populations at the district/upazila/subdistrict level in the disease-endemic areas of the three countries and it was hoped that elimination can be achieved by 2010. The target date was extended to 2014 and now to 2020. World Health Organization (WHO), Geneva, WHO Tropical Disease Research (TDR), and WHO Regional Office for south-east Asia extended valuable technical support to the program and facilitated program-oriented research. A host of national and international institutions and agencies extended strong, useful, and focused research support or training to the program.

DEVELOPMENT OF MILTEFOSINE

Miltefosine,^{2–10} the first ever oral drug was developed against kala-azar in India in collaboration with Indian Scientists and Zentaris, the pharmaceutical company located in Germany (currently Gilead). Clinical trials showed that the drug is safe (except gastrointestinal side effects like vomiting and diarrhea) and effective (~95%). Phase 4¹³ trial revealed that the drug could be dispensed to outpatients and compliance was acceptable for the program. In view of these findings from well-controlled studies, miltefosine was recommended as the first-line drug for the kala-azar elimination program. Meanwhile, data were generated that compliance may be low since the drug has to be administered for 28 days. It was also contemplated that since the drug is given as monotherapy, resistance to the drug will develop soon. Subsequently, it was recommended by the WHO Regional Technical Advisory Group for kala-azar elimination program that miltefosine should be phased out and replaced by lipid amphotericin B.¹⁴ This drug is very safe, highly effective with cent percent compliance. Clinical trials also demonstrated that combinations of lipid amphotericin B with either miltefosine or paromomycin¹⁵

*Address correspondence to Sujit K. Bhattacharya, General Medicine, Glocal Hospital, Krishnanagar 741102, West Bengal, India. E-mail: sujitkbhattacharya@yahoo.com

were highly effective and appearance of drug resistance may be avoided or at least delayed. It is worthwhile to mention that clinical trials of miltefosine, paromomycin, amphotericin B (an antifungal agent), and lipid amphotericin B were all carried out in India, particularly in the highly kala-azar-endemic state of Bihar. Some clinicians prefer to use several courses of amphotericin B with a gap of 2 weeks between the two courses of the drug. It is nephrotoxic. The other second line of drugs includes paromomycin and stibogluconate, where the parasites are sensitive to the drug. Paromomycin is particularly useful in females of childbearing age who cannot be relied to adhere properly to contraceptive recommended by the physician. U. N. Brahmachari developed urea stibamine for the treatment of kala-azar. The drug was lost for use after he died because the composition of the drug was not known.

PROGRESS OF THE ELIMINATION PROGRAM

The main components of the strategy were early diagnosis using rK39 and complete treatment using miltefosine for 28 days. DDT and pyrethroids were deployed for vector control. India, Bangladesh, and Nepal continued to have transmission of the disease. Recently, a new focus of kala-azar was found in Bhutan. Similarly, Thailand has also reported few cases in recent years. About 147 million people living in the region are at risk. It has been estimated that 100,000 cases of kala-azar occur per year with 15,000 deaths in the region. India contributes to more than 80% of total burden. The three countries have made significant progress toward achieving the target of kala-azar elimination program. The number of cases has decreased by 59% and case fatality by 61%. Nepal has eliminated kala-azar at district level and could sustain the status for the last 2 years. On the other hand, Bangladesh could reach the elimination target in 90% of endemic upazilas. In more than two-thirds of endemic blocks, India has achieved the target. Table 1 shows the year-wise (2010–2015) distribution of kala-azar cases and deaths in India and, in particular, Bihar. It is evident from the figures that India has made substantial progress but not yet reached the target, particularly in its most endemic state of Bihar. The post-kala-azar dermal leishmaniasis (PKDL) cases and asymptomatic infections are considered to play an important role in this context. The search for PKDL cases and the containment of asymptomatic infections are major challenges. The strategies for containment of asymptomatic infections are not yet developed. Underreporting of cases is well known.

TABLE 1

Year-wise (2010–2015) distribution of kala-azar cases and deaths in India and, in particular, Bihar

Year	Number of cases		Number of deaths	
	India	Bihar	India	Bihar
2010	29,000	23,084	105	95
2011	33,187	25,222	80	76
2012	20,600	16,036	29	27
2013	13,869	10,730	11	17
2014	9,241	7,615	11	10
2015	8,243	6,280	5	5

Adapted from National Vector Borne Disease Control Data.

ISSUES RELATED TO THE IMPLEMENTATION OF THE PROGRAM

Pharmacovigilance and monitoring of drug resistance were the weakest part of the program in all the three countries. TDR-sponsored research in the three countries revealed that active search for case finding was superior to passive search, but the former was costlier. As the program will reach elimination goal, active search will have to be mandatory to mop up the remaining cases. It has also been found that around an index case, there are several individuals who are infected but have no symptoms (asymptomatic)¹⁶ and a proportion of these individuals will develop full-blown disease (kala-azar). Thus in the post-elimination phase, surveillance reinforced by active case finding will be a crucial factor for sustainability of the elimination. Among others, DDT spraying is the main stay of vector control in India. There is a dearth of trained man power for vector control. Although spray equipment are old, new equipment have been purchased. Supervision of spray-related activities and payment of their wages should have been better coordinated.

Since most of the kala-azar-affected children are malnourished, nutritional rehabilitation should be given due importance. Housing is another aspect requiring improvement. Government of India allocated funds for this purpose. A sizable number of cases of kala-azar attend the clinics of quacks, private practitioners, and other nongovernment hospitals. These data were generated by studying the health-seeking behavior of patients with kala-azar. There is therefore underreporting of cases. Actual number of cases is certainly more than reported cases. The Indian program started giving incentives to attract more patients to Government health facilities. This strategy was useful in attracting many more patients with kala-azar to government health facilities. It has been mentioned earlier that about 40% of kala-azar cases reside across the international borders of the three countries. Sharing of information between the countries is crucial to the success of the program. Cross-border collaboration needs to be strengthened.

Research and training supported by TDR and other agencies contributed a lot toward the program implementation. Research findings were mostly incorporated in the program. Laboratories for monitoring drug resistance require strengthening or upgradation. There is a need for more focused research on PKDL and training of scientists. Twelve weeks of miltefosine treatment of PKDL cases has been developed and recommended for the program. PKDL is considered to be a reservoir of infection. Many of them do not come to the health facility for treatment because of innocuous nature of the lesions, particularly macular lesions, and stigmatization. Active case search for PKDL is important.

CONCLUSION

Once elimination is achieved, sustainability of the achievement will depend on availability of funds, political will, focused research, and strong surveillance. Active case finding, pharmacovigilance, and monitoring of drug resistance will be required. PKDL case finding and treatment will play an essential role during the elimination and post-elimination phases. The natural history of asymptomatic infection should be elucidated as they seem to play a critical role in the

post-elimination phase. A simple study, involving the contacts kala-azar patients of earlier epidemics, to see what proportion of these contacts developed frank disease over a time period, will resolve the issue.

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Authors' addresses: Sujit K. Bhattacharya, General Medicine, Glocal Hospital, Krishnanagar, West Bengal, India, E-mail: sujitkbhattacharya@yahoo.com. Aditya Prasad Dash, Central University of Tamil Nadu, Tiruvarur, Tamil Nadu, India, E-mail: apdash@gmail.com.

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