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COMMENTARY

Development of *Leishmania* vaccines in the era of visceral leishmaniasis elimination

Christian R. Engwerda[a,*] and Greg Matlashewski[b]

[a]*QIMR Berghofer, Brisbane, Australia;* [b]*Department of Microbiology and Immunology, McGill University, Montreal, Canada*

*Corresponding author: E-mail: Christian.Engwerda@qimr.edu.au

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A visceral leishmaniasis (VL) elimination target set for the Indian subcontinent in 2005 is being met in many endemic areas without a vaccine. This begs a question: is a VL vaccine needed if elimination targets can be met with current control programs? Here, we argue that a vaccine will be critical if the success of recent VL control efforts are to be sustained. However, not only do we require a safe and effective vaccine, but we also need to know how this should be used for maximum impact. In particular, identifying appropriate target populations to vaccinate will be crucial.

Visceral leishmaniasis (VL) is a potentially fatal disease caused by *Leishmania donovani* in the Indian subcontinent and East Africa, and *L. infantum* (*chagasi*) around the Mediterranean and in Central and South America. Nearly one-half of all VL cases occur in India and surrounding areas, and an elimination target of one VL case in 10 000 by 2015 in all endemic areas of the Indian subcontinent was set at a World Health Assembly in 2005.[1] Although unlikely that this target will be met in all areas, considerable progress has been made towards achieving this goal, particularly in Bangladesh and Nepal. Significant improvements in vector control, diagnosis, drug treatment and access to appropriate primary health care have all contributed to reducing numbers of VL cases. It is anticipated that current strategies will continue until elimination goals are achieved. But, what happens then?

One danger is that despite reduced incidence of disease, there is still sufficient parasite burden remaining in previous endemic areas to allow continued and regular transmission by the sand fly vector. This is possible because cured VL patients retain persisting parasites and the majority of people infected with *L. donovani* remain asymptomatic.[2] Under these circumstances, a sustained VL monitoring and treatment program will need to continue over an extended period. If not, VL cases will increase again, potentially causing new epidemics. This may be compounded by changing circumstances in VL endemic areas, such as increased levels of HIV and helminth or other concomitant infections that suppress immunity. In addition, changing political circumstances can also impact upon this situation. For example, civil unrest in Southern Sudan has caused the displacement of stressed and malnourished people into areas of greater exposure to sand fly vectors, with an alarming increase in the number of VL cases.[3] Therefore, it is imperative that not only are VL monitoring and treatment programs maintained and improved, but that parasite reservoirs in populations are identified and minimised to reduce the risk of transmission. Vector control and management programs should continue to be a critical part of this strategy, but a safe and effective vaccine could make a significant impact on the re-emergence of VL cases once elimination goals have been achieved.

The development of an effective vaccine to protect against VL is a realistic goal. Previous programs of leishmanization, a process involving the deliberate infection of people with parasite species that cause cutaneous lesions on unexposed areas of the body to establish an infection that is controlled, have been effective in establishing long-term immunity.[4] In addition, as mentioned earlier, only a fraction of infected individuals develop clinical VL, indicating that many infected individuals naturally develop immunity against disease. Furthermore, most VL patients that have undergone successful drug treatment will be protected from disease for the rest of their life.[5] Hence, development of protective immunity is achievable. The increased risk of developing VL in patients with HIV supports data from experimental models showing a critical role for cell-mediated immunity in protection against VL. However, immunity is most effectively achieved and maintained by the presence of persisting parasites,[6] therefore an effective vaccine may need only strengthen immunity against development of disease rather than provide sterile protection. The apparent requirement for concomitant immunity (i.e., persisting parasites to maintain effective anti-parasitic $CD4^+$ T cells) presents significant challenges for vaccine design.

An improved understanding about parasite transmission will be needed to appropriately target any future vaccination programs. In the Indian subcontinent, most evidence points towards exclusive anthroponotic transmission. However, this situation is different for VL caused by *L. infantum*, where dogs, in particular, act as a major parasite reservoir. In east Africa, some rodent species can harbour *L. donovani*, although the contribution of

these reservoirs to human transmission is not clear. Thus, in situations where zoonotic transmission can occur, parasite burdens in domestic and wild hosts will need to be considered in control programs, and while vaccination may be a potential strategy for dealing with this in domestic animals, such as dogs, this is unlikely to be feasible for wildlife.

Post-kala-azar dermal leishmaniasis (PKDL) is a complication of VL resulting in chronic macular, papular or nodular rash, usually occurring in months to years after drug treatment. However, PKDL can sometimes develop at the same time as VL or in patients with no history of disease.[7] The nodular forms of PKDL are thought to play a role in anthroponotic transmission, and as such, targeting PKDL via a therapeutic vaccine may be one way to reduce transmission and better manage a disease which is more difficult to treat than VL. However, we need to have a clear understanding about which infected humans are likely to promote transmission by sand flies. One statistical model predicts that transmission of *L. donovani* in the Indian subcontinent is predominantly maintained by asymptomatic infected individuals.[8] Since these asymptomatic individuals are not reached through treatment, it will be necessary to have an effective vaccine to sustainably reduce transmission of parasites. Xenodiagnostic studies will be important for establishing the potential contributions of asymptomatic individuals, patients with VL and individuals with PKDL in transmission of parasites. This information will allow a vaccine to be appropriately targeted for maximum benefit.

Diagnosis of asymptomatic infection is currently problematic with relatively poor correlation between current methods.[9] This is an area that needs to be improved so that asymptomatic individuals can be identified and the evolution of infection and/or transmission closely monitored. For example, some asymptomatic individuals may have very low levels of parasites, while others may have high levels of parasites and progress to disease. New methods, such as detection of parasite small RNA or protein in blood or parasite metabolites in breath or body fluid samples, may hold the key to improvements in this area, and potentially help identify a target group for vaccination to strengthen immunity against disease.

In summary, in an era when VL elimination is a realistic goal, we must be mindful of the consequences of reducing monitoring and treatment programs when VL case numbers become very small, but parasite reservoirs remain. Better methods of parasite detection are needed to accurately assess parasite burdens and identify asymptomatic individuals, and we must establish which individuals help transmit parasites in settings of anthroponotic transmission. Vaccination, regardless whether it be implemented via a sub-unit, DNA, genetically modified or live attenuated vaccine, will be critical if the results from VL elimination programs are to be sustained over time.

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References

1 WHO. Regional strategic framework for elimination of Kala-azar from South East Asian Region (2005–2015). New Delhi: World Health Organization; 2005.

2 Sacks D, Lal S, Shrivastava S et al. An analysis of T cell responsiveness in Indian kala-azar. J Immunol 1987;138:908–13.

3 Abubakar A, Ruiz-Postigo JA, Pita J et al. Visceral leishmaniasis outbreak in South Sudan 2009–2012: epidemiological assessment and impact of a multisectoral response. PLoS Negl Trop Dis 2014;8:e2720.

4 Handman E. Leishmaniasis: Current status of vaccine development. Clin Microbiol Reviews 2001;14:229–43.

5 Khalil EA, Ayed NB, Musa AM et al. Dichotomy of protective cellular immune responses to human visceral leishmaniasis. Clin Exper Immunol 2005;140:349–53.

6 Sacks DL. Vaccines against tropical parasitic diseases: a persisting answer to a persisting problem. Nature Immunol 2014;15:403–5.

7 Boelaert M, Sundar S. Leishmaniasis. In: Farrer J, Hotez PJ, Junghanss T et al. (editors). Manson's Tropical Diseases. 23rd ed. Amsterdam: Elsevier; 2014, p. 631–51.

8 Stauch A, Sarkar RR, Picado A et al. Visceral leishmaniasis in the Indian subcontinent: modelling epidemiology and control. PLoS Negl Trop Dis 2011;5:e1405.

9 Hasker E, Kansal S, Malaviya P et al. Latent infection with *Leishmania donovani* in highly endemic villages in Bihar, India. PLoS Negl Trop Dis 2013;7:e2053.