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Evaluating diagnostics: VL

This supplement on evaluating diagnostics for visceral leishmaniasis (VL) is the third in a series of user-friendly operational guides explaining how to conduct evaluations of diagnostic tests for infectious diseases that are of public health importance in the developing world. Here, Robert Ridley, Director of TDR, introduces the supplement.

This supplement follows the first two in the series, which looked at the evaluation of diagnostics for malaria and sexually transmitted infections (STIs), respectively. There are, however, some key differences between developing, evaluating and manufacturing diagnostics for visceral leishmaniasis (VL) compared with malaria and STIs. Although malaria and STIs are relatively neglected, there is sufficient market incentive to ensure that several commercial rapid diagnostic tests have been developed and are available for evaluation. Some agencies are also making significant funds available for innovative diagnostics research for these diseases. This is not the case for VL.

Few diagnostic tests are available for VL case management. The 500,000 annual cases of VL, which is caused by the bite of a sandfly residing, for example, on the mud walls of houses, do not constitute a viable commercial market. The gold standard remains microscopic evaluation after invasive procedures such as splenic aspiration — a risky procedure with a mortality rate of 1 per 1,000. The drive for improved, easy to use diagnostics has therefore remained an under-resourced public health responsibility.

There is some optimism that the value of VL diagnostics is now being recognized. One of the drivers for this is the decision by the governments of India, Nepal and Bangladesh to eliminate the disease as a public health problem from the Indian sub-continent by 2015. The availability of new drugs, such as the oral drug miltefosine and, more recently, the inexpensive injectable drug paromomycin, combined with a significant price reduction in the highly efficacious injectable drug, liposomal amphotericin B, is a major cause for such optimism. However, if elimination is the goal, then the development of diagnostics to inform correct treatment and monitor the epidemiological situation is also crucial. The implications of the goal of elimination on the Indian sub-continent are being assessed in the other part of the world where VL is a major problem, namely the Horn of Africa, where the issue in some places is further complicated by HIV co-infection and social breakdown.

Apart from the lack of investment by public sector agencies and lack of commercial incentive, three major challenges in this field deserve highlighting. First, there is

the scientific challenge to identify and develop diagnostic methodologies and techniques that can readily guide treatment. This is further complicated by the multiple *Leishmania* species that can cause VL and the multiple disease manifestations. Second, there is the challenge — addressed by this supplement — of ensuring effective and harmonized evaluation of diagnostic tests. Third, there is the need to develop regulatory controls that ensure appropriate evaluation of diagnostic tests before they come on the market and ensure sustained quality of manufacture and production, against defined standards, after they have been given marketing authorization.

The need for all three challenges to be addressed coherently is illustrated by one of the success stories of VL diagnostics, the rK39 test, which detects anti-leishmanial antibodies and thus can detect whether a person has been infected. It is, however, not a good prognostic indicator of disease progression and further innovation is therefore still required. The specificity and sensitivity of rK39 have been validated in the Indian sub-continent and this test is being integrated into national elimination programmes, but rK39 has lower sensitivity in African populations and needs improvement. Thus, regional variations must be fully taken into account when defining policy. Finally, since rK39 was approved for use in the VL control programme in India, several generic versions have appeared on the market. This presents a challenge; without stringent controls on products in the private and public sector, it will be difficult to know which tests meet the standard of the original product.

It should be recognized that inappropriate diagnosis, owing to a poor quality diagnostic tool or process, can lead to death just as easily as a poor quality drug. To make progress in this area will require collaborative engagement and dialogue between researchers in the public and private sectors, and between manufacturers and regulatory agencies. It also requires strong public sector guidance and evidence-driven policy. TDR, a research programme, is working with WHO colleagues with responsibilities for control and regulatory policy, and with national authorities, research agencies and investigators, to promote this dialogue and help ensure quality-assured diagnostics are available and accessible to those in need.

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