Global Observatory on Health R&D

Preliminary analysis
for R&D for leishmaniasis

Prepared in collaboration with the
WHO Neglected Tropical Diseases Department

World Health Organization
Leishmaniasis today

Leishmaniasis is:
- caused by parasites transmitted by the bite of sandflies
- a complex condition, with different species of *Leishmania* parasites causing a spectrum of diseases.

These leishmaniases are a group of the world’s most neglected tropical diseases (NTDs) and are prevalent in 98 countries and 3 territories on 5 continents (1).

- An estimated 900 000 to 1.3 million new cases and 20 000 to 30 000 deaths occur annually (2).
- Over 3 million disability-adjusted life years (DALYs) are lost to the disease (3).

The three main forms of leishmaniasis disease are:
- visceral leishmaniasis (VL; also known as kala-azar. This is potentially fatal if untreated);
- cutaneous leishmaniasis (CL; this is the most common and potentially disfiguring form);
- mucocutaneous leishmaniasis

Post-kala-azar dermal leishmaniasis (PKDL) can appear 6 months to 1 or more years after apparent cure of VL.
Over 1 billion people are at risk from the different forms of leishmaniasis: over 616 million for VL and over 431 million for CL (4). While widespread across many continents and latitudes, the majority of cases are concentrated in few high-burden countries:

- In 2014, more than 90% of new VL cases reported to WHO occurred in six countries: Brazil, Ethiopia, India, Somalia, South Sudan and Sudan.

- The majority of CL cases occur in Afghanistan, Algeria, Brazil, Colombia, the Islamic Republic of Iran, Pakistan, Peru, Saudi Arabia and the Syrian Arab Republic.

- Almost 90% of mucocutaneous leishmaniasis cases occur in the Plurinational State of Bolivia, Brazil and Peru (5).

Leishmaniasis outbreaks are often a consequence of unrest and conflicts, which are associated with large population movements from non-endemic to endemic areas.

Recurrent epidemics of VL in East Africa (Ethiopia, Kenya, South Sudan and Sudan) have caused high morbidity and mortality in affected communities while major epidemics of CL have affected different parts of Afghanistan and the Syrian Arab Republic.

Leishmaniasis has strong but complex links with poverty, with the burden of disease falling disproportionately on the poorest segments of the global population.

- Poverty is associated with poor nutrition and other infectious diseases, which increase the risk that a person (once infected) will progress to the clinically manifested disease.

- Lack of healthcare access causes delays in appropriate diagnosis and treatment and accentuates leishmaniasis morbidity and mortality, particularly in women.

- Leishmaniasis diagnosis and treatment are cumbersome and expensive and can lead to a vicious cycle of disease and poverty (6).

People who are immunocompromised (e.g. because they are infected with HIV or are malnourished) have a higher risk of getting the disease and of experiencing recrudesences after treatment.
Strategic vision – reducing morbidity and mortality

The vision is to reduce the morbidity and mortality from leishmaniasis. There is no global consensus on what is feasible in the long term, which makes it difficult to provide clear targets in terms of disease control.

For VL the most important target is to reduce mortality, while for CL the target is to reduce morbidity – especially to avoid large facial skin lesions which are highly stigmatizing.

WHO promotes early case-finding and prompt treatment of leishmaniasis. The previous WHO NTD roadmap strategy (7) was to detect at least 70% of all cases of CL and treat at least 90% of all detected cases in the WHO Eastern Mediterranean Region by 2015.

In the Indian subcontinent, 100% case-detection and treatment of VL is feasible by 2020, implying that it is possible to achieve less than 1 case per 10 000 population at district and sub-district levels (7). Once achieved, this status will need to be sustained.

Current products and their limitations: why we need new products

Several drugs are available for the treatment of leishmaniasis (see Table 1), but many of the newer medications are not yet available in all endemic areas.

Current drugs used to treat leishmaniasis have many limitations related to safety, resistance, stability, high cost, low tolerability, long treatment duration and difficulty of administration. They are therefore not suitable for many healthcare delivery systems that serve poor and vulnerable populations.
Table 1. Current drugs for treatment of leishmaniasis

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosing</th>
<th>Availability</th>
<th>Comments</th>
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<tbody>
<tr>
<td>Pentavalent antimonials:</td>
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<tr>
<td>Sodium stibogluconate, (SSG)</td>
<td>30+ days, IM or IV</td>
<td>All endemic regions</td>
<td>Toxic side effects and drug resistance are common</td>
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<tr>
<td>Meglumine antimononate</td>
<td>injections or 17 days in combination with paromomycin ointment</td>
<td>Used in East Africa</td>
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<tr>
<td>Liposomal amphotericin B</td>
<td>1–5 days, IV injections</td>
<td>Approved in 1997 in the United States of America (USA) for VL</td>
<td>IV injection limits its use in peripheral settings; requires cold chain</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Used in the Indian subcontinent to replace more toxic traditional formulation of amphotericin B as single-dose first line treatment</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Used as second line treatment in East Africa</td>
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<tr>
<td>Miltefosine</td>
<td>28 days, oral</td>
<td>Approved in India in 2003 for VL</td>
<td>Only oral drug for VL; side effects limited, include diarrhoea or vomiting; cannot be given to women in child-bearing age without contraception (teratogenic); adherence to 28 day treatment is an issue; high price, limited availability</td>
</tr>
<tr>
<td>Paromomycin</td>
<td>17 days, IM injection</td>
<td>Used as first line treatment in combination with pentavalent antimonials in East Africa</td>
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Drug resistance is a concern in regions using monotherapies for treatment. Drug combinations may be a better treatment option - there is laboratory and clinical evidence that drug combinations can be very efficacious while shortening treatment duration. Drug combinations are also expected to provide mutual protection against resistance.

Better diagnostic tools are needed as current diagnostics are not sufficiently sensitive, or are invasive, and are not always available at point of care. This makes it difficult to make an early diagnosis (which also impacts on transmission potential).

There is also a need for tests for cure. Bone marrow or organ tissue samples are used currently to detect reduced parasite burden after VL treatment, which are difficult and dangerous to obtain in a low resource setting. Rapid diagnostic tests (RDTs) need to have a higher sensitivity in endemic regions, such as for East Africa, as the current tests do not reliably exclude a diagnosis of VL (8). There is currently no vaccine against the different leishmaniases.
Public health value proposition: what are the R&D priorities and how are they defined?

**Priorities**

Development of a leishmaniasis vaccine must be a priority, as immunization would be the method of choice for future control (3) – ideally one that prevents infection. A vaccine that can prevent the development of the disease (signs and symptoms) would also be beneficial. In addition, there is merit in considering the combining of therapeutic vaccines with drugs.

Regarding treatment, there is an urgent need for drugs that can be delivered easily and safely in peripheral healthcare facilities. New, effective, safe and affordable drugs, preferably oral, are needed for VL, mainly in the Americas, Europe and East Africa. (In South-East Asia one single dose liposomal amphotericin B is currently highly effective).

A simple, safe and effective oral medication or topical cream treatment that also prevents scar formation is needed for all forms of CL.

Second line treatment options are needed for all forms of leishmaniasis.

Ideally, future treatments should clear infection and not be reliant on the additional role of the immune system.

New and improved diagnostics are also needed. Point-of-care cheap, reliable and easy-to-use, non-invasive tests are necessary for the early diagnosis of VL and CL. There is also a need for a simplified test-of-cure assay (using easily obtained specimens such as peripheral blood or saliva) that can be performed in low resource settings.

In order to ensure sustained VL elimination in the Indian subcontinent, there is a need for:

- tools that provide early detection of current infection – ideally a point-of-care diagnostic that can detect active infection before it becomes symptomatic.
- tools to interrupt transmission.

If asymptomatic healthy carriers are proven to be an important source of infection, then there is a need for a safe and highly effective, short-course treatment that can be given to people with patent infection.

Novel methods of prevention are necessary as part of broader integrated vector control, with the aim of reducing or interrupting transmission of disease (9). The most effective methods to reduce human leishmaniasis is to control sandfly vectors by:

- using chemical control (e.g. indoor residual spraying; spraying of resting sites of sylvatic species; use of insecticide-impregnated materials such as bednets and curtains; wall painting or wall lining; and pyrethroid-impregnated dog collars),
- environmental management (e.g. relocation of human settlements away from sandfly habitats and physical modification of the habitats)
- personal protection.
Insecticide-treated nets (ITNs) have proven to be a sustainable alternative to the traditional vector control approach of spraying houses with insecticide. ITNs are useful in areas where both leishmaniasis and malaria are endemic and where only human-to-human transmission occurs.

The use of several approaches together in an integrated vector management approach is recommended to improve efficacy of vector control.

**Setting the agenda**

Following the World Health Assembly approved Resolution 60.13 (9) on the control of leishmaniasis in 2007, WHO took a leading role in providing technical assistance for the initiation, maintenance and expansion of leishmaniasis control programmes.


Although the experts concluded that adequate control of leishmaniasis worldwide was feasible with the medicines and diagnostic tools available, it was acknowledged that there was a crucial lack of funding, political commitment and national and international cooperation (3).

**Products in the pipeline and funding for leishmaniasis products**

Several organizations are working in collaboration with WHO to prevent control leishmaniasis as outlined below.

The Drugs for Neglected Diseases initiative (DNDi) is working on new medicines and new combination therapies with an intensive effort currently underway to register and encourage adoption of newer, safer VL medications outside of India – mainly through more extensive clinical trials of combination therapies of the drugs previously mentioned in table 1. DNDi has set the following targets, to be achieved by 2020 (10):

- a safe, effective, low-cost, and short-course combination treatment;
- a new treatment for PKDL that has a shorter course and is better tolerated than current options;
- treatment options for HIV/VL co-infected patients;
- a new first-line treatment regimen for VL in Africa and Latin America.

Meanwhile the Foundation for Innovative New Diagnostics (FIND) is focussing on the development of improved diagnostic solutions for VL, including activities working on diagnosis in eastern Africa and in immunocompromised patients and on developing a test-of-cure for both VL and PKDL (11).

Finally, the Special Programme for Research and Training in Tropical Diseases (TDR) have been supporting a multicentre trial being conducted in east Africa and on the Indian subcontinent to compare diagnostic tests.
Summary

The recent progress in defining the population at risk and global burden demonstrates that Leishmaniasis is one of the world’s most neglected diseases that impacts on the poor.

The challenges of controlling and managing the diverse health impacts induced by different *Leishmania* species cannot be underestimated.

Although adequate control is feasible by optimizing existing tools, research and development is essential to fulfil the strategic vision of significantly reducing morbidity and mortality.

By further improving access to existing therapies and developing novel combination therapies significant progress can be made to both reduce the risk for drug resistance and shorten treatment course length.

Most of the clinical trials for leishmaniasis include new combinations and new formulations of existing drugs, with efforts being directed towards expansion of registration and use of existing products. Development of oral combination therapies remains a priority, as does the development of a vaccine for prevention of leishmaniasis.

References

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