Fifteenth meeting of the Strategic and Technical Advisory Group for Neglected Tropical Diseases

7–8 February 2022
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Dedication

This report is dedicated to the memory of Dr Mwelecele Ntuli Malecela, Director, WHO Department of Control of Neglected Tropical Diseases and former member of the Strategic and Technical Advisory Group for Neglected Tropical Diseases, who passed away on 10 February 2022.

During her tenure as Director she spearheaded the development of the new NTD road map – *Ending the neglect to attain the Sustainable Development Goals: a road map for neglected tropical diseases 2021–2030* – launched in January 2021.

“Mwele”, as she was widely known, will be remembered as a courageous, inspirational figure, a dedicated leader and a committed listener who spent much of her life improving the health and well-being of the most vulnerable. An eloquent speaker, her approach was characterized by passion and dedication to people and causes. Her preference for telling the truth over seeking to please earned her widespread respect. Throughout her life, she advocated for the empowerment of women, for gender equality and for the welfare of women and girls. She also championed, inspired and encouraged youth.

Previously she served as Director in the Office of the WHO Regional Director for Africa (Brazzaville, Congo), as Director-General of the National Institute for Medical Research (United Republic of Tanzania) – the first woman to occupy this position – and as founding Director of the National Lymphatic Filariasis Elimination Programme. Lymphatic filariasis was her main area of academic interest, starting as a junior scientist focusing on the immuno-epidemiology of filarial infections.

Born on 26 March 1963 in Dar es Salaam, the daughter of former Tanzanian Prime Minister and Permanent Representative to the United Nations, John Malecela, Mwele attended Weruweru Girls Secondary School and later enrolled at the University of Dar es Salaam, where she graduated in zoology. She completed her PhD in parasitology at the London School of Hygiene & Tropical Medicine.

The recipient of many distinctions, Dr Malecela was awarded the Kyelem Prize by the Coalition for Operational Research on Neglected Tropical Diseases (2017) and an honorary Doctor of Science by the Liverpool School of Tropical Medicine (2021). She was also repeatedly included in the top 100 list of the most influential women in Africa.

Mwele's death will be felt deeply and personally by many worldwide, and her inspiration, enthusiasm and engagement will continue to guide all those who knew her.
## Abbreviations and acronyms

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
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<tbody>
<tr>
<td>CL</td>
<td>cutaneous leishmaniasis</td>
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<tr>
<td>DTAG</td>
<td>Diagnostic Technical Advisory Group for Neglected Tropical Diseases</td>
</tr>
<tr>
<td>FCDO</td>
<td>Foreign, Commonwealth and Development Office (United Kingdom of Great Britain and Northern Ireland)</td>
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<td>EU</td>
<td>European Union</td>
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<td>FDA</td>
<td>Food and Drug Administration (United States)</td>
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<tr>
<td>IVD</td>
<td>in vitro diagnostic</td>
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<td>IVDR</td>
<td>in vitro diagnostics regulation</td>
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<tr>
<td>MDA</td>
<td>mass drug administration</td>
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<td>NTD</td>
<td>neglected tropical disease</td>
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<td>PAHO</td>
<td>Pan American Health Organization</td>
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<td>PCR</td>
<td>polymerase chain reaction</td>
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<td>PEL</td>
<td>Performance Evaluation Laboratory</td>
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<td>PQ</td>
<td>prequalification</td>
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<td>QA</td>
<td>quality assurance</td>
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<td>RDT</td>
<td>rapid diagnostic test</td>
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<td>STAG</td>
<td>Strategic and Technical Advisory Group</td>
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<td>TPP</td>
<td>target product profile</td>
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<td>USAID</td>
<td>United States Agency for International Development</td>
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<td>VL</td>
<td>visceral leishmaniasis</td>
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<tr>
<td>UN</td>
<td>United Nations</td>
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<td>WHO</td>
<td>World Health Organization</td>
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The fifteenth meeting of the Strategic and Technical Advisory Group for Neglected Tropical Diseases (STAG-NTD) was held virtually on 7–8 February 2022. The agenda is attached as Annex 1 and the participants are listed in Annex 2.

Opening remarks

Dr Ren Minghui, Assistant Director-General, Universal Health Coverage/Communicable and Noncommunicable Diseases, World Health Organization (WHO), opened the meeting, welcomed the participants and wished them a productive meeting.

COVID-19 is continuing to impact the work of the Organization and its Member States, putting additional pressure on health systems as they try to implement the new NTD road map for 2021–2030. Since the previous (fourteenth) meeting (22–June 2021), a new platform has been launched and World Neglected Tropical Diseases Day was commemorated on 30 January 2022. A lot more remains to be done, however. Diagnostics and leishmaniasis are on the agenda for the present meeting, but stronger health systems will be critical to achieving the NTD goals.

Purpose of the meeting and expected outcomes; administrative matters; appointment of rapporteurs

Professor David Mabey, chairperson of STAG-NTD, said that the purpose of the meeting was to review the impressive progress made by the Diagnostic Technical Advisory Group for Neglected Tropical Diseases (DTAG) and the status of programmes on visceral leishmaniasis (VL) in Africa and South America.

Professor Lucille Blumberg, Centre for Emerging, Zoonotic and Parasitic Diseases, South Africa, and Dr Albis Francesco Gabrielli, Strategic Information and Analytics, WHO Department of Control of Neglected Tropical Diseases (WHO/NTD), were appointed rapporteurs.
Session

Diagnostics for neglected tropical diseases
Situation analysis and critical issues

1. Introduction and overview

Dr Daniel Argaw Dagne, Unit Head, Prevention, Treatment and Care, WHO/NTD, introduced the session.

Based on the assessment that there was an urgent need to develop accurate, reliable and cost–effective diagnostics, 60 specific diagnostic tests were identified as programme needs across the 20 NTDs. This was a huge task to undertake with limited resources, so a prioritization process was devised by DTAG. One of the criteria was to determine whether programme decision-making was hampered by the lack of diagnostics, and whether this threatened the achievements of targets.

Of the 19 diagnostic target product profiles (TPPs) developed through a public consultation process, nine have been published (see Table).

<table>
<thead>
<tr>
<th>Disease</th>
<th>Subject</th>
<th>Web link to publication</th>
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<tbody>
<tr>
<td>HAT</td>
<td>Diagnostic TPP for a gambiense human African trypanosomiasis test to identify individuals to receive widened treatment</td>
<td><a href="https://apps.who.int/iris/handle/10665/352579">https://apps.who.int/iris/handle/10665/352579</a></td>
</tr>
<tr>
<td>HAT</td>
<td>Diagnostic TPP for a test for rhodesiense human African trypanosomiasis diagnosis usable in peripheral health facilities</td>
<td><a href="https://apps.who.int/iris/handle/10665/344165">https://apps.who.int/iris/handle/10665/344165</a></td>
</tr>
<tr>
<td>LF</td>
<td>Diagnostic TPP for lymphatic filariasis to support decisions for stopping triple-therapy mass drug administration</td>
<td><a href="https://apps.who.int/iris/handle/10665/340080">https://apps.who.int/iris/handle/10665/340080</a></td>
</tr>
<tr>
<td>LF</td>
<td>Diagnostic TPP for surveillance of lymphatic filariasis</td>
<td><a href="https://apps.who.int/iris/handle/10665/340081">https://apps.who.int/iris/handle/10665/340081</a></td>
</tr>
<tr>
<td>ONCHO</td>
<td>Diagnostic TPP for mapping onchocerciasis</td>
<td><a href="https://apps.who.int/iris/handle/10665/341719">https://apps.who.int/iris/handle/10665/341719</a></td>
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<tr>
<td>ONCHO</td>
<td>Diagnostic TPP for stopping mass drug administration for onchocerciasis</td>
<td><a href="https://apps.who.int/iris/handle/10665/341719">https://apps.who.int/iris/handle/10665/341719</a></td>
</tr>
<tr>
<td>SCH</td>
<td>Diagnostic TPP for monitoring and evaluation</td>
<td><a href="https://apps.who.int/iris/handle/10665/344813">https://apps.who.int/iris/handle/10665/344813</a></td>
</tr>
<tr>
<td>SCH</td>
<td>Diagnostic TPP for transmission interruption and subsequent surveillance</td>
<td><a href="https://apps.who.int/iris/handle/10665/344813">https://apps.who.int/iris/handle/10665/344813</a></td>
</tr>
<tr>
<td>STH</td>
<td>Diagnostic TPP for monitoring and evaluation of soil-transmitted helminthiases control programmes</td>
<td><a href="https://apps.who.int/iris/handle/10665/342539">https://apps.who.int/iris/handle/10665/342539</a></td>
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</table>

Access, quality of diagnostics and local capacity are issues affecting many national programmes. The new European Union (EU) in vitro diagnostics regulation (IVDR) requirement, due to come into force in May 2022, will bring additional challenges. Given the limited market for NTD diagnostics, the new regulation could discourage manufacturers from continuing to develop new diagnostics. WHO is developing a transparent, streamlined process for risk assessment to facilitate approval for NTD diagnostics and enable countries and partners to procure quality-assured products. The Organization is also addressing the standardization of validation and evaluation of diagnostic tests.
Some of the NTD diagnostics have been included in the second and third editions of the Second WHO model list of essential in vitro diagnostics (1), thus providing evidence-based guidance for endemic countries to adapt to their needs, as well as to inform procurers of diagnostics and advise the private sector in medical technology on diagnostic priorities.

2. Update on DTAG and TPP development

Dr Patrick Lammie, Director, Neglected Tropical Diseases Support Center, presented the update.

On the importance of diagnostics for the success of NTD programmes and to the limitations of available tests, he commented that 19th century technology (e.g. microscopy) should not be used to guide 21st century programmes. The DTAG was established in 2019 to review the needs for NTD diagnostics and facilitate the development of new diagnostic tools. Work is carried out by disease-specific and cross-cutting subgroups of DTAG. Common issues addressed by the cross-cutting groups include surveillance, manufacturing and regulatory pathways, clinical diagnosis, imaging and microscopy, advocacy and resource mobilization. The parent DTAG has held four meetings to date.

During the first year and a half of its work the DTAG has focussed on developing TPPs to guide test development where tools to inform decisions on interventions for individuals or programmes are inadequate. The TPPs comprehensively evaluate the needs and technical requirements for required tests.

TPPs published on the WHO website (see Table) and in peer-reviewed journals include those for:

- **human African trypanosomiasis** (one to identify individuals with suspected gambiense infection to receive treatment and one for rhodesiense sleeping sickness useable in peripheral health facilities);
- **lymphatic filariasis** (one for stopping triple-therapy mass drug administration and one for surveillance);
- **onchocerciasis** (one for mapping and one for stopping mass drug administration);
- **schistosomiasis** (one for monitoring and evaluation and one for transmission interruption and subsequent surveillance); and
- **soil-transmitted helminthiases** (for monitoring and evaluation).

Other TPPs, mainly for skin diseases, are in the final stages of review:

- **Buruli ulcer** (for diagnosis at primary health care level);
- **leishmaniasis** (for a point-of-care rapid test for dermal leishmaniasis);
- **leprosy** (one to guide post-exposure prophylaxis and one to guide multidrug therapy);
- **mycetoma** (one to differentiate between eumycetoma and actinomycetoma and one to determine when treatment can be stopped);
- **scabies** (one for starting and one for stopping mass drug administration); and
- **yaws** (one for case detection and one for azithromycin resistance).

Having completed much of the work around TPPs the DTAG will now focus on other priority agenda items including the development of gold standards for validating tests. Currently, validation is often based on microscopy or other 19th century techniques. New tests are more sensitive than classical tests, creating a challenge for evaluating test performance.

On advocacy, WHO is working with DTAG to design and implement a plan for attracting new resources and partners to support the agenda for NTD diagnostics. The TPPs clarify to the donor community which tools are
needed to enable partners to engage in discussion about how to meet those needs. The advocacy and resource mobilization group is conducting a landscape analysis to better understand the status of donor support and of current or planned investments in order to improve coordination among donors.

Several donors have launched new requests for proposals to support test development, namely the Global Health Innovative Technology Fund, the United States Agency for International Development and the Bill & Melinda Gates Foundation. An important consideration in developing new tests is the availability of well-characterized samples to support standardized testing and evaluation, which require the development of a biobank. DTAG is working with the Foundation for Innovative New Diagnostics to define the needs for (and costs of) NTD biobanks to support test development.

Other advocacy efforts include taking on extra diseases that were not initially prioritized. In 2022, it is hoped to form new subgroups to develop tools for surveillance, including for trachoma, and to address critical issues related to developing and maintaining laboratory capacity to support NTD programmes, with focus on coordination of capacity across countries and standardization of laboratory quality. External quality assurance (QA) is an important issue that will be addressed by a new subgroup on laboratory capacity.

Regulatory aspects are critical steps in the development pathway for new diagnostic tests. However, there is lack of clarity among the NTD community about how this will work, and WHO must play a leading role in this effort. The WHO prequalification (PQ) team is working with the manufacturing and regulatory pathway subgroup of DTAG to define regulatory pathways for NTD diagnostics (see below).

Other disease-specific issues include the development of additional TPPs for:

- **dracunculiasis** eradication, to design a new tool for surveillance, especially in animal populations;
- **strongyloidiasis**, to be included in the expanded focus of the subgroup on soil-transmitted helminthiases;
- **female genital schistosomiasis**, to tackle the incredible burden of this condition; and
- **onchocerciasis and skin diseases**, to ensure that reagents are of high quality for use in molecular assays (as an alternative to home-grown tests).

### 3. Validation and evaluation of new or existing NTD diagnostics, and need for a standardized validation protocol (for programme/policy recommendation)

Dr Patrick Lammie presented the item.

New products coming into the pipeline will require laboratory and field evaluation. Field validation of new tools planned for early 2022 includes Ov16, LF antigen and LoaScope.

*What role should DTAG play in the oversight of laboratory and field evaluations?*

The evaluation process should be standardized. Rigorous laboratory evaluation is needed for any test during its development; this should include an independent evaluation conducted in an unbiased way by independent scientists. Afterwards the test should be evaluated in the field to check whether it is robust enough for such
use and whether it meets the specific requirements for the programmatic use case, its acceptability to the end user and its ease of use. So far, this evaluation has been handled haphazardly and needs to be standardized. A standardizing process will enable access to tests of high quality, allow test developers to understand the standards they have to meet and any processes they have to go through, and generate data that can be considered by WHO for a final recommendation.

4. Prequalification of NTD diagnostics

Dr Susie Braniff, Scientist, WHO In Vitro Diagnostics Assessment, described the work of the PQ team at WHO.

The aim of the PQ team is to promote and facilitate access to safe, appropriate in vitro diagnostics (IVDs). Work is focussed on priority diseases and use of IVDs in resource-limited settings. IVDs are identified by stakeholders, and the types of technologies for each disease are defined in consultation with WHO programmes and alignment with WHO testing guidelines. The PQ status of each diagnostic is used to guide the procurement of IVDs by interested parties including United Nations agencies.

A risk-based approach is taken to assess the diagnostics, and an internationally accepted classification system is applied. This process guides the level of stringency and scope. The four classes of risk (A to D) are based on individual and public health risks; class D is the highest risk.

The PQ assessment process for individual IVDs has three components: a review of the dossier, a performance evaluation, and a manufacturing site inspection. A review of the labelling instructions comes with the package.

The dossier is reviewed by a subject matter expert who validates the data. Considerations include: Are the manufacturer’s claims of quality, safety and performance supported? Are the data of good quality? Are the validation studies appropriate and well designed? Is there evidence of completeness (throughout the life-cycle of the product from its initial design to release onto the market), accuracy and consistency? Are standard operating procedures available? What quality control steps are included? How does the manufacturer monitor the product? Has the manufacturer considered use of the test in resource-limited settings? Does the test perform under a range of conditions?

The performance evaluation is a laboratory-based assessment that independently verifies the analytical, clinical and operational performance of the IVD. It is conducted by designated laboratories worldwide (a WHO Collaborating Centre and/or a Performance Evaluation Laboratory [PEL]) using a standard PQ protocol. The manufacturer evaluates the IVD to check that the claims for it are sound and replicable. The evaluation serves also to better understand how the product performs.

For the manufacturing site inspection, evidence of a fully implemented quality management system is sought at all sites involved in the manufacture of the product. Three assessment components are considered in the evaluation: Does it meet ISO 13485 design and manufacture needs and ISO 14971 risk management needs? Is the product robust and does it meet the constraints of the intended use setting? Is the product in routine manufacturing and does the manufacturer have sufficient capacity to maintain quality if demand for the product is high?

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1 Classification originally created by the Global Harmonization Task Force, but now maintained by the International Medical Device Regulators Forum.
The PQ decision is based on these three assessment components. A public report is then prepared and posted on the WHO website, after which the product becomes eligible for procurement by WHO and other United Nations agencies.

To add a new disease to the PQ pipeline, various steps must be taken. Currently there are no NTDs within the scope of PQ. Technical specifications should therefore be developed and tailored to the specific pathogen and assay and address the needs of lower middle-income countries and likely users as well as minimum performance requirements. Next the dossier is reviewed, after which a laboratory performance protocol is designed, a specimen panel is constructed and PELs are identified. Once these technical specifications are finalized, the PQ pipeline can be opened for that disease. The timeframe for developing PQ technical specifications, evaluation protocols and designating PELs is usually 9–12 months.

Owing to the pandemic, COVID-19 tests have been prioritized, causing delays in the pipeline. However, in expanding the scope of PQ dossiers, progress is being made and it is hoped to open the pipeline for three new tests. Before the pandemic, the expansion plan was, for 2021, tuberculosis, yellow fever, dengue fever, gonorrhoea and *Chlamydia* infections; for 2022, measles, rubella, leishmaniasis and schistosomiasis; and for 2023, infection with *Mycoplasma genitalium* and onchocerciasis. New timelines are now needed.

The aim of PQ is thus to promote and facilitate access, not to erect barriers but rather to ensure that products are of assured quality and available at low cost. Technical specifications are tailored to a specific pathogen and assay.

In answer to a query, the meeting learnt that WHO coordinates the assessments but that the assessments themselves are conducted by independent PELs which work to international standards. The assessment does not involve a field evaluation, but the manufacturer is expected to have conducted one, which is then assessed during evaluation of the dossier.

Professor Steve Lindsay, University of Durham, expressed concern about how quality is ensured downstream and how the sensitivity of the product is checked for any changes. He noted that WHO\(^1\) follows up on complaints and seeks customer experience; expects a yearly report from countries that bought the product; follows up on queries and complaints to assess how the manufacturer is handling them; and ensures that labelling instructions are clear about how a customer can contact the manufacturer. Nevertheless, an independent evaluation might be better to check for any changes in sensitivity.

### 5. Impact of IVDR on NTD diagnostics, and its mitigation

Ms Robyn Meurant, Principal consultant, ACT-IVD, spoke about the regulations for IVDs. The tests used for NTDs range from microscopy to those requiring approval from the United States Food and Drug Administration (FDA), and everything in between.

Which tests fall under the scope of regulation is a complex landscape to navigate. If results are to be given to an individual from whom the sample has been taken, they are to be regulated; if not given to an individual,\(^1\) the WHO PQ Inspections Team also conducts re-inspection of manufacturing sites every 3–5 years or more frequently if issues with a product have been reported.
they might be included in a different category. If the result of a test has a clinical impact on a patient, it is to be regulated, but this might not apply to all tests. If a test is to be used for surveillance for instance, and where the individual might never receive the result, it is considered as a specific type of medical devices category that differs from other medical devices because the harm is indirect, and harm happens if a patient receives an incorrect result. A diagnostic test based on microscopy might be regulated or not, depending on whether it is considered as general laboratory equipment or is for clinical use.

A product might be regulated depending on the claims that come with it. Polymerase chain reaction (PCR) tests might be for research use only, but might also be a regulated product, depending on the claims that come with the test. The components of an antibody probe might be regulated or not, usually depending on the jurisdiction in which the test is to be performed and whether it falls on the side of device regulation or not. In many places there are no regulations. The new EU regulation includes laboratory-developed tests, which will be included under the regulation if the laboratory is to ensure that the result goes to the right patient.

Why is the new EU IVDR regulation such a major concern? Up until now, fairly loose rules have defined regulation in Europe, and many products have found their way onto the market as being self-declared without any pre-market regulatory approval assessment before receiving the CE mark. About 80% or 85% of products with a CE mark currently on the market have never been assessed before market by the accepted regulatory authority or, in the case of Europe, by so-called “notified bodies”. SARS and COVID-19 products, for example, do not require pre-market approval; the manufacturer simply indicates that the requirements have been met.

Europe has been designing the new regulatory scheme for the past 10 years, and it will begin to come into effect on 26 May 2022. However, as neither the 26 Member States nor the European Commission are fully ready for the new regulation, it will be implemented in stages over the next 5–6 years. Whereas previously 85% of products were self-declared as meeting the requirements, in future 85% will need to have been assessed before market by a notified body. The classes range from class A to D depending on risk (as for PQ), with D being the highest risk. COVID-19 is class D so will require pre-market approval in future. Manufacturers will no longer be able to market their products based on the CE mark.

As a result, this will have an impact on a lot of manufacturers who will no longer be able to CE mark their products. This will be problematic for NTDs because the diagnostics have a clinical purpose. Currently many products enter the market in Africa and in many countries based on the presence of a CE mark.

**Regulatory approach**

Regulations should specify that a device on the market is safe and performs as intended. Some solutions may arise through a pre-market assessment conducted by another regulatory body in the country in which the product is to be introduced, where there will be mechanisms to recognize another type of pre-market approval.

The goal of regulation is to ensure safety, quality and performance. While not every product for NTDs needs to be regulated, it will need to be assessed for quality, whether intended for clinical diagnosis or for surveillance. The PQ approach (above), with the various assessments and evaluations, is an excellent approach especially for the highest risk products, and will involve many more activities. Unfortunately, few regulatory schemes have strong post-market requirements in place, so programmes will need to insist on other mechanisms being available to monitor the post-market scene. Controls should be proportionate to the risk, and regulatory oversight should

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1 A CE mark is a symbol applied to a product to indicate that it conforms with relevant EU directives regarding health and safety or environmental protection.
increase in line with the potential to cause harm. A low-risk product could be put in the lower risk category, as for those used for surveillance, but, if the result has a clinical output, it must be included in the higher risk category.

Many manufacturers are using the new EU regulation as a way to rid themselves of tests that are of low value and low volume, as are many of those for NTDs, thus introducing a further complexity.

**QA actions**

To ensure that QA activities are proportionate to the risk of a product, some considerations should apply. Is the product sustainable? Are QA activities already in place? Can regulatory approval be leveraged?

Manufacturing must take place under a suitable quality system. Standard ISO 13485 is expected for medical devices and diagnostics that are regulated if they have a clinical outcome. If the product is for surveillance only, it might instead meet another quality system requirement such as ISO 9001.

External QA schemes are one of the most powerful and efficient ways for monitoring ongoing performance. Experts in performance evaluation, regulation, medical device auditing and proficiency testing are needed here, but it is important also to have local network participation and involve national regulatory staff in any assessment activities.

Many countries are without any regulation, so programmes must be designed that are appropriate to the risk and use procedures that follow good regulatory practice, are balanced, evidence-based, transparent and well documented.

**Next steps**

It is proposed that WHO leads the development of a generic protocol or template for risk profiling of a device, based on case management versus surveillance, intensified disease management versus preventive chemotherapy, screening versus diagnosis, device versus method, etc. Then it is recommended that programmes undertake risk analysis and grade the risk. For low-risk products, an independent evaluation might be sufficient, but for higher risk products, monitoring and a PQ programme would be needed.

Responding to a question about post-marketing surveillance, the speaker informed the meeting that manufacturers are obligated under ISO 13485 to do this, as also under the new EU IVDR regulation. An increasing number of jurisdictions will be looking to monitor proactively, whereas up until now much has been the responsibility of the manufacturer. The simplest place to start would be some simple QA activities such as introducing external QA schemes to test laboratory proficiency; other activities might include testing a batch of product after its arrival in a country. WHO post-market surveillance guidance includes a number of suggestions.

Another question concerned whether there was a time frame for a company to be assessed for QA. The speaker was not certain that FDA imposed obligations on the manufacturer, but generally relied on a reactive process.
Discussion

On production issues

It is frustrating when a manufacturer decides suddenly that it is not cost effective to continue producing a diagnostic and halts production, but at what stage are production issues considered in the process? WHO is trying to work with manufacturers on this issue and is trying also to lower the price, if possible through donations, but, if this is not possible, to encourage the manufacturer to continue production on a differential price basis. For emergency diagnostics, different arrangements are being made, and WHO is working also with companies in transferring technology. In these ways it is hoped to continue production at minimum cost.

On developing TPPs

Aspects to consider when developing a TPP include the need for evaluation of a product in different geographical areas with diversity of organisms; how to decide on acceptable sensitivity and specificity of a test, whether for surveillance or diagnosis, given the difference in prevalence and stage of programme (control or elimination); and how to include a specimen type that is easy to access and of good quality (for respiratory diseases or blood samples this is generally not difficult; however, for a field test for rabies, obtaining a brain specimen is more challenging).

It is important for STAG to recognize that DTAG is not developing TPPs in a vacuum. Rather, DTAG works closely with the working group on monitoring and evaluation. Each TPP is tied to a use case, with requirements set by the context in which the test will be used. Geographical variation could present a challenge for antigen and antibody tests, so it is important to ensure that all the approval pathways are built in.

Regarding the diagnostic procedure under development for female genital schistosomiasis, a question arose about how those who have already started creating awareness about the disease in health facilities and communities should proceed in the meantime? The existing diagnostic approach recommended by experts could be used; that is, visual inspection of lesions in the female genital tract with speculum/enhanced camera or a colposcope. There is interest in using artificial intelligence to assist with diagnosis; this is where DTAG would become involved.

On the feedback received from the online public consultation on the two leprosy tests under development, the participants were reminded that TPPs are being developed for two use cases: (i) a diagnostic test to detect *Mycobacterium leprae* and *Mycobacterium lepromatosis* infection; and (ii) a test to confirm the diagnosis of leprosy in individuals with clinical signs and symptoms. The draft TPPs were posted on the WHO website for 28 days for public consultation, and comments have been collected but not yet reviewed. The Global Leprosy Programme will coordinate and submit the feedback to the DTAG subgroup for review. There is revived interest in support for advocacy and technical work; and the TPPs will be published in scientific journals.

Referring to WHO’s work with the Foundation for Innovative New Diagnostics on biobanks, and the mention of a “virtual biobank” (assumed to be a database with information on samples in different physical biobanks and accessible from different websites), there was a question about how these initiatives are related.
USAID has provided funding to the Filariasis Reference Reagent Repository for samples of blood, urine and skin originating from ongoing moxidectin trials. This project serves as a model for future investments in supporting the development of new diagnostic tools by ensuring availability of samples via a virtual biobank.

**On regulatory pathways**

Since PQ of IVD requires funding (as PQ does for medicines), would a diagnostic already authorized by a stringent regulatory authority be eligible for a no-cost “PQ lite” for PQ listing (as for medicines), to avoid costs to the manufacturer of diagnostics for a “not for profit disease”? How does this work with the FDA being the stringent regulatory authority, as it is known that FDA approval for medicines is “hard to translate” to PQ? In this case, to reduce costs to the applicant, far less information is asked for; there is also an option to waive costs, and a set a fee for full assessment.

Regulatory pathways were discussed based on the risk characteristics of products. The process is stringent for classes C and D, but for diagnostics in lower risk classes A or B – for example onchocerciasis, schistosomiasis and yaws – it was proposed to establish an independent assessment mechanism guided by the recommendations of the PQ team.

There was discussion about how the process could be accelerated, how donors could engage with the manufacturers, and how small manufacturers could be incentivized. A quality system and performance monitoring should be done by regulators for all diseases. If a product has several uses, the manufacturer could be asked to make an intended use application. How could the proposed criteria be aligned with programme goals, disease burden and stage of the respective global programme in the context of higher profile issues? An expedited process is needed for “smaller footprint” diseases in order to roll out the NTD road map. WHO should prioritize and accelerate action and garner political support. Unless the process is simple and rapid, donors will not invest, and small- to medium-sized manufacturers will not become involved.

**On donor perspectives**

From a donor perspective, has any thought been given to modelling the cost-effectiveness of diagnostics for selected NTDs? It is a question of “showing value”. Many NTD diagnostics have no high commercial value, so such an analysis might be needed. Without a justification, how could donors be persuaded to invest in this area? A donor needs justification for how diagnostics will facilitate improvement, and for investing, perhaps for instance by lowering the need for costly medicines. It was suggested that the NTD Modelling Consortium might be interested in undertaking work to make the economic case.

Reflecting on the scenario of the pandemic, a donor needed to know the impact of COVID-19 on the incidence and burden of NTDs. Would there be increased surveillance for new cases? If a new epidemiological site were to be identified, for example for leprosy, and if the number of new cases were to increase rapidly, would there be a sufficient supply of medicines?
On timelines and generic protocols

WHO is working to develop and expedite new timelines for each diagnostic; the process is due to be completed in 2022. In the interim, any new diagnostic for risk assessment could be worked on by the designated group. A simple post-marketing procedure could be used for lower risk products in the interim.

The NTD community is fragmented, and efforts to develop and evaluate new tests are not coordinated. Disease-specific communities could establish a set of expectations about what an evaluation process should look like. For laboratory performance, how many specimens should be examined? How should specificity be defined and tested? If a test survived a rigorous laboratory-based evaluation, then it would need to be tested in the field against the use case. Different research groups have a role in developing generic protocols and in establishing a level playing field with the diagnostics development community from which everyone could work towards the same set of expectations. Whether a dossier was going through a more elaborate PQ process for case management or whether it would go through something a little less robust around an expert review panel, the information would be consistent across all diseases.

Availability of a gold standard for each disease must be addressed. DTAG will work with WHO to develop terms of reference that recognize the diversity of the diseases and disease groups. A “one-size-fits-all” approach will not be appropriate. Rather, the disease-specific groups should consider what to do about reference standards, and which statistical methodology will be needed to establish a pseudo gold standard or clear reference standard. It is hoped that, by the end of the year, DTAG will have a White Paper to share.

Guidance for manufacturers on what information they were going to be assessed against would limit the time required. A lesson learnt from PQ was the amount of time it took (often 18 months). Even if a manufacturer has a good product and has been doing everything correctly, without a proper paper trail they will need to generate documented evidence for assessment. PQ is not however appropriate for all diagnostics and is not beneficial for lower risk products, so this type of guidance will be valuable to a manufacturer. This information should be made available in the technical specifications – the sooner a manufacturer has some understanding of what is needed, it will shrink the time required.

On the possibility of cross-cutting disease testing platforms

There was discussion about cross-cutting disease testing platforms and the possibility of devising a test for several NTDs simultaneously in order to save costs. Skin diseases are the most suitable group in this respect. Otherwise integrated surveillance is of interest but it would be challenging to identify the right frame. The skin diseases group have discussed dividing into imaging techniques and clinical microscopy subgroups and developing a multiplex. Discussions are ongoing. This type of platform would be very useful, especially for surveillance and evaluation; if a laboratory network on quality were to be established, the networking experience of the malaria group and the Stop TB groups would be invaluable.
Conclusions and recommendations to the Director-General

On diagnostic and NTDs, the STAG-NTD:

1. **Thanks** the Secretariat and meeting participants for their contributions to the discussions on development, oversight and regulation of IVDs for NTDs;

2. **Commends** the quantity and quality of work undertaken by the DTAG;

3. **Encourages** planned work by DTAG on the state of the art of evaluating IVDs in the absence of a gold standard test;

4. **Highlights** the need for IVDs that are robust, affordable and appropriately sensitive and specific for their intended purpose and settings for future use, which are characterized, inter alia, by marked resource limitations and extremes of temperature.

5. **Recommends** that:

   a. WHO establishes an Expert Review Group, to report to the STAG Working Group on Access to Health Products, to assess the risk, quality, safety and performance of diagnostics for possible NTD programme use; the assessment process should be as cost-, time- and effort-efficient as possible while appropriately safeguarding individuals and communities affected by NTDs;

   b. the IVD assessment process be conducted independently of test developers and require data generated both in the laboratory and in the field in different geographical contexts, with the geographical diversity and extent of separation being dictated by the epidemiology of the disease or infection in question as well as the intended purpose of the IVD (e.g. individual patient diagnosis, treatment response, surveillance);

   c. when selecting IVDs, the potential cost-savings for NTD programmes be taken into account (e.g. whether treating only confirmed cases vs syndromic/empiric treatment);

   d. WHO requests the NTD Modelling Consortium to help explore the economic case for increased investment in IVD development for NTDs;

   e. as soon as feasible, and without waiting for the Expert Review Group to be established, WHO commences work to develop external quality assurance systems for NTD diagnostics, in line with existing WHO guidance and recommended processes, and establishes external proficiency testing for field diagnostics, as in the Buruli ulcer diagnosis model;

   f. with support from WHO, DTAG establishes a Laboratory Capacity and Networking Subgroup, which should include in its scope of work consideration of how best to ensure that adequate specimen biobanks are made available for routine quality assurance/quality control processes; and

   g. work on cross-cutting “platforms”, such as for soil-transmitted helminthiases and skin diseases, is considered where appropriate.
Session II

Visceral leishmaniasis in Africa and the Americas
Situation analysis and critical issues

1. Global overview and financial resources

Background, global overview

Dr Saurabh Jain, Scientist, WHO leishmaniasis programme, presented the report.

According to information available from Member States in 2020, VL is endemic in about 80 countries, CL is endemic in a greater number of countries and 71 countries are endemic for both conditions. WHO collects a minimum set of indicators: six indicators (three each for VL and CL) are published in the Global Health Observatory and 30 indicators for high-burden VL and CL countries are detailed in country profiles.

Resolution 60.13, adopted by the Sixtieth World Health Assembly in 2007, highlights the importance of controlling leishmaniasis and guides WHO’s work. In 2020, about 13 000 VL cases were reported to WHO. The true underlying annual global incidence, however, is estimated at 50 000–100 000 cases in three hotspots: the Indian subcontinent, East Africa and Brazil. The highest disease burden is currently in East Africa, with > 90% of new cases in seven countries: Brazil, Ethiopia, India, Kenya, Sudan, South Sudan and Somalia.

Regional distribution of VL, and distribution by age and gender

There has been a marked shift in annual VL trends across the six WHO regions in recent years. Around 2010, the South-East Asia Region accounted for the maximum number of VL cases reported to WHO. Other regions contributed about 5 000–10 000 cases annually, except in the European and in the Western Pacific regions where only China is endemic. In 2020, however, the South-East Asia Region reported the lowest number of cases from its peak in 2010.

Information on two indicators (age and gender) collected by WHO from high-burden countries contributing > 95% of new cases globally has increased significantly during the past 7 years. Most cases of VL are in children and young adults; the ages of > 80% of patients are now known (up from 50%). Generally in high-burden countries the male to female ratio of cases is 2:1, indicating improvement in surveillance systems in Member States.

Expanding endemicity and eco-epidemiology in three hotspots

The endemicity of VL is expanding. Cases are now being reported for the first time from ever more areas once considered non-endemic, previously reported or doubtful, and from new countries (e.g. Cameroon, Sri Lanka and Uruguay). This increase could result from improvements in reporting. During the past 7–8 years, for example, the number of districts known to be endemic for VL in Nepal has increased from 12 to 23; in Bangladesh, more than 30 subdistricts have reported new cases.

The eco-epidemiology of VL is so complex that it manifests differently in different geographies. Consequently, the response to the disease must be adapted to the local context. Eco-epidemiological factors associated with
its presentation include geography, parasite species, vector behaviour and reservoir and their specific response to interventions. In South-East Asia incidence and case-fatality rates are declining and the disease is mostly eliminated as a public health problem. Conversely, in East Africa and the Americas there is no evidence of a decline in incidence, tools are insufficient and case-fatality rates are increasing.

**Reasons for the success of VL elimination in the WHO South-East Asia Region**

Key factors in the successful elimination of VL in the South-East Asia Region included the availability of well-performing diagnostic tests; highly effective single-dose treatment (liposomal amphotericin B) that was readily accessible through a donation programme; good vector control programmes; and stable governance.

The situation in East Africa differs: diagnostic tests do not perform well; only a combination regimen – involving a painful injection – is available for treatment as the first-line regimen, which requires a treatment course over a minimum of 17 days; no first-line drug donation programme exists; there is no proven effective vector control; and, even though political commitment exists, it has not yet had an impact on disease incidence.

Effective vector control methods (indoor residual spraying) and domestic funding were the hallmarks of success in South-East Asia, where support from multiple donors complemented other efforts. The signing of a Memorandum of Understanding in 2005 for an elimination initiative in three countries (Bangladesh, India and Nepal) was an important political tool that helped to secure and sustain funding. The result of this commitment was palpable. From a high of 50,000 cases in 2005, VL incidence declined by > 90% and elimination of VL as a public health problem was achieved in 98% of implementation units in 2020; most of them have sustained this accomplishment for at least 3 consecutive years.

Consequently, whereas 15 years ago the South-East Asia Region contributed 70% of VL cases globally, it now contributes only 18%.

**Diagnostic challenges in East Africa**

The overall performance of rK39 for VL diagnosis in terms of sensitivity, specificity, user friendliness, affordability and requirements for infrastructure is lower in East Africa than on the Indian subcontinent.

In a Cochrane review (2) of rapid diagnostic tests (RDTs) for VL in clinically suspected patients, the rK39 had shown the likelihood ratio of a positive test to be very high and confirmed VL disease; the same was not true when the test was negative because of the low sensitivity and negative predictive value. In these patients therefore WHO suggested another test (e.g. direct parasitology or direct agglutination test). Drawbacks to these latter tests included that the results were not immediately available, nor were facilities readily available in the field but only at district hospitals; the sensitivity of parasitological diagnosis varied and there was risk of haemorrhage following splenic aspirate.

Several commercial brands of RDTs are available based on different recombinant antigens, but not all brands perform similarly. Of the companies that agreed to participate in a study of RDTs in East Africa, the company that produced the best performing RDT has already announced that it will be discontinuing production. Of the
other RDTs claimed to have high sensitivity and specificity, this proved to be the case only in the laboratory; in prospective studies of rK28 RDTs undertaken in blood and serum samples, only low and very low specificity of the tests was found. As such, there is no useful RDT available, at least for East Africa.

WHO recommends using the rK39 RDT at primary health care level and using diagnostic tools at other levels depending on their availability.

**Financial resources**

Collaboration with the global leishmaniasis programme and Gilead Sciences started in 2012 for donated liposomal amphotericin B (AmBisome), but, even in 1992, there was agreement on preferential pricing for this medicine. The donation has greatly improved access to treatment, and it is hoped it will be extended for the next 5 years. Financial contributions from Gilead Sciences which started in 2016 have also been a major support, but it is uncertain whether they will continue. Financial contributions from the United Kingdom Foreign, Commonwealth and Development Office (FCDO) during 2012–2018 enabled WHO to expand implementation worldwide, but this is now discontinued. Crown Agents supported the procurement of medicines and tests on a needs basis for a short while. Sanofi provided minor support mainly for cutaneous leishmaniasis (CL) control activities. However, the Bill & Melinda Gates Foundation has generously supported WHO Country Office activities in India.

As a result of this support, WHO has reached almost 300 million at-risk population with medicines and other support. In India for example, reporting of surveillance indicators has improved significantly, by more than 90% during 2014–2020.

Funding to support Member States is now uncertain. WHO has been active in providing normative guidance and standards; updating national programme policies and strategies (manuals and guidelines); coordinating advocacy; results-based planning and scaling up activities; maintaining emergency stocks; providing cold chain support; improving case detection, outbreak response and access to treatment, referral services, surveillance and evaluation; and generating capacity-building and expertise. WHO may now be forced to curtail these activities, depending on funding.

Market failures affect all leishmaniasis health products. Challenges include the availability of essential medicines and diagnostic tests mostly originating from single manufacturers; minimum ordering quantities; companies not registering medicines due to lack of a profitable market; relatively expensive medicines with potentially toxic effects; and absence of a donation programme other than for AmBisome and for diagnostic tests.

**New global target**

The new global target set in the new 2021–2030 road map, as endorsed by the Seventy-third World Health Assembly in November 2020, is to eliminate leishmaniasis as a public health problem by reducing the case-fatality rate to < 1%. This is expected to stimulate early diagnosis and treatment and for national programmes to follow up and discharge hospitalized patients, many of whom succumb to comorbidities thereafter. The first road map for 2012–2020 retained the previous regional elimination target of < 1 case/10 000 population in the South-East Asia Region. The target for CL is to detect and report 85% of all cases and treat 95% of them.
2. Visceral leishmaniasis in the Americas

Mandates

Ms Ana Nilce Elkhoury, WHO/Pan American Health Organization (PAHO) Regional Leishmaniasis Program, presented the report.

Work with countries in the Americas takes place under two mandates:
- the new road map (2021–2030), with its target to eliminate VL as a public health problem (defined as < 1% of VL lethality as a primary disease), which may be achievable in countries where *Leishmania donovani* is the circulating species, as on the African and Asian continents, especially where transmission is anthroponotic; and
- the PAHO Disease Elimination Initiative in the Americas, with its two specific goals for VL to detect < 1 case/10 000 inhabitants and reduce VL lethality by 50% compared with the 2019 baseline (7.72%).

Epidemiological status

VL is a zoonotic disease in the Region of the Americas, the main determinants of which relate to environmental, social and economic factors. The responsible wild reservoirs are canids and marsupials, and dogs in the domestic environment. Vectors are present throughout the year.

VL is endemic in 13 countries of the Region where the circulating parasite is *Leishmania infantum*. The main vector present in all countries is *Lutzomyia longipalpis*; however, *Lutzomyia evansi* is a vector in countries of Central America, the Bolivarian Republic of Venezuela and Colombia. *Lutzomyia cruzi* occurs in specific areas of Brazil and the Plurinational State of Bolivia. Secondary vector species are present in Argentina and Brazil.

For the past 5 years the mean incidence has been 3 cases per 100 000 inhabitants and an average of 3149 cases, with 97% concentrated in Brazil. In 2020, there were 1988 reported cases.

Transmission is rural in Central America (Costa Rica, El Salvador, Guatemala, Mexico, Nicaragua). The prevailing transmission is rural in the northernmost countries of South America (Colombia and Venezuela [Bolivarian Republic of]), with rural and periurban transmission in specific areas and with dogs as the reservoir in urban areas. In the southernmost countries (Argentina, Brazil, Bolivia [Plurinational State of], Paraguay and Uruguay), transmission is mainly urban.

Case numbers were somewhat stable for 20 years until 2018 when a significant reduction was observed; this is unlikely to be related to the COVID-19 pandemic. Despite this reduction, VL has expanded geographically to the North Central Region of Brazil, to Southern Venezuela (Bolivarian Republic of), to southwestern Colombia and, more recently, to northern Argentina, the Plurinational State of Bolivia and Uruguay.

Most cases of VL are in men (68.3%) and children aged under 5 years (25%). Of the cases registered in the Regional Leishmaniasis Information System in the Americas (SisLeish), 88% were laboratory-confirmed; the cure rate is 64%.
In 2020, 12% of patients were coinfected with HIV, representing an increase from 2018 (7%) due to HIV testing in patients with VL. The VL case fatality rate (8.1%) was three times higher than the overall global lethality (2.7%). Mortality in children aged under 5 was 6%, and in those over 50 years was almost 16% due to comorbidities and coinfection with HIV.

A retrospective cohort study investigated factors such as age, HIV, area, ethnicity and education that influenced the time of onset of symptoms and death (3). Of 1589 individuals who died due to VL reported in Brazil during 2007–2014, 8.6% were coinfected with HIV. The time to onset of symptoms and to notification of death differed in the two age groups studied: in children aged under 5 years it was 17 days and 6 days respectively and in patients aged over 5 years it was 28 days and 10 days respectively. While the results indicated a reduction in the time to diagnosis, the patients were seemingly arriving at a more advanced stage of the disease, evolving rapidly to death. The survival time for HIV-coinfected patients was greater than for those who were non-infected with HIV; coinfected patients were referred to and treated in reference services by specialized case management staff.

There are two main populations of *L. infantum* in the Americas whose presumed origin is from two populations arriving from Europe, possibly through infected dogs, and are established in two different areas. A phylogenetic study of isolates from dogs in the Americas and from dogs in Europe and Africa showed genetic modification to have occurred in the isolate arriving from Europe. In vitro, this modified population showed resistance to miltefosine. A phase II study in Brazil showed that 50% of patients treated with miltefosine relapsed; in this population the isolate also seemed to be more virulent. The different populations of *L. infantum* are likely directly affecting the epidemiology and clinical evolution of VL and could be contributing to its higher lethality.

**Diagnosis**

Parasitological tests are executed through bone marrow puncture (the gold standard). PCR is available in specialized services and rapid testing is available closer to endemic areas but needs to be more decentralized. The test currently available for purchase by countries through the PAHO Strategic Fund is the Kala-azar Detect rapid immunochromatographic strip assay for the qualitative detection of antibodies to VL, but it has to be performed through serum samples, making it difficult to operationalize.

In Brazil, four tests for rapid diagnosis of VL using the rK39 protein are registered with the national regulatory agency. Initial studies showed specificity of more than 90%, but none of the tests was independently validated.

**Treatment**

An updated guideline for the treatment of VL is due to be published in 2022. A virtual course on treatment and diagnosis of leishmaniasis will also be launched. The virtual course includes modules on CL, mucosal leishmaniasis and VL. For patients with non-immunocompromised VL, liposomal amphotericin B is strongly recommended; pentavalent antimonials or other formulations of amphotericin B are conditionally recommended, but there is strong recommendation against the use of miltefosine. For immunocompromised patients, liposomal amphotericin B is strongly recommended, or, when it is not available, amphotericin B in any of its lipid complexes; there is a recommendation against the use of pentavalent antimonials.
**Epidemiological surveillance**

SisLeish is available online for the 13 endemic countries in the Region. Countries can input their data and notify alerts, outbreaks, cases of human infection, infections in dogs and vectors. A manual of procedures (4) and annual epidemiological reports (5) are available. Training sessions (in loco and virtual) in basic epidemiology (data collection, management, analysis) and on geographical information systems have taken place. Other technical cooperation and financial support is being provided to strengthen epidemiological surveillance for endemic countries.

**Surveillance and health care: human cases**

PAHO hosts courses on case management and treatment of human cases, and a virtual distance learning site is available online; an atlas has also been published (6). PAHO also provides the necessary medicines (meglumine antimoniate and liposomal amphotericin B, with stock for special cases); technical cooperation and financial support; and capacity-building in diagnosis, clinical management and treatment of patients. For the past 2 years training has been carried out virtually on Kala-Cal software to support professionals in calculating the severity of VL in patients and to identify those with a probability of evolving to death.

**Surveillance and control: vectors**

Progress in surveillance and vector control includes investigating, surveying and monitoring of phlebotomines according to epidemiological status; workshops, training and technical advice on entomological surveillance and vector control; and courses on identification and taxonomy of phlebotomines. FioCruz (Oswaldo Cruz Institute) is responsible for training and provides support for quality control of all species of phlebotomines identified by countries.

**Surveillance and control: reservoirs**

PAHO provides support for surveillance of domestic reservoirs and for focus studies for VL, with training of professionals in clinical suspicion of VL and on taking samples for serological, parasitological and PCR diagnosis. Brazil is specifically supported to define methods for local risk stratification in planning surveillance and control activities, which include implementing deltamethrin-impregnated collars in dogs to control domestic reservoirs and sandflies in urban areas.

**Challenges**

Challenges include: resuming field activities after the COVID-19 pandemic; reducing the VL case-fatality rate; ensuring the availability of a rapid test at primary health care level; ensuring the production and implementation of liposomal amphotericin B as first-line treatment; reducing contact between vectors and humans and domestic reservoirs; and ensuring financial resources to maintain technical cooperation and staff.
Financial resources

Globally during 2011–2021 WHO financially supported the Regional Leishmaniasis Program with 80% of the resources needed; PAHO contributed 20%. In 2022, financial resources are strictly limited and there are no specific WHO resources.

Discussion

On financial resources, funding and stakeholders

Dr Jain clarified that he had spoken only of financial resources available globally. At country level the Bill & Melinda Gates Foundation has provided substantial support for programme implementation in India for many years, which has now been extended for one or more years to the national programmes in Nepal and Bangladesh following the sudden withdrawal of FCDO funding in 2021.

Contributions for programme funding for VL in East Africa are being provided by The END Fund\(^1\) for 2 years for programmatic work to ensure that treatment is not interrupted.

Following the launch of the new road map, WHO/NTD and the Special Programme for Research and Training in Tropical Diseases have undertaken a stakeholder analysis of donors, partners and Member States in South-East Asia and East Africa. What lessons might be applicable in other settings such as East Africa? The manuscript is not yet finalized, but an important outcome is that all stakeholders have asked for a similar initiative in the East African setting.

On the availability of medicines and diagnostics

What are the future challenges regarding the availability of medicines and diagnostics for VL – and will manufacturers from endemic countries be engaged? Endemic countries are already engaged, but it is hoped that more companies will come forward to support production. Anti-VL medicines produced in India include: generic sodium stibogluconate, which has been manufactured by a local company for nearly five decades and provides a “good model for a humanitarian approach from a profit-making company”; generic paromomycin; generic miltefosine (under development); and a first formulation of generic liposomal amphotericin B.

Countries endemic for VL are encouraged to identify funds in their national health systems for accessing essential medicines and diagnostic tests. Support from partners is, of course, welcome.

What actions are being taken to fill the gap once Bio-Rad ceases production of the rK39 test? According to information from Bio-Rad, the last batch due to be produced (in May 2022) will expire in June–July 2023, after which a new company will continue to produce the same test under a technology transfer agreement. In 12–18 months therefore a new test will have been validated in the field, and the IT-leish brand name will continue to exist. It is therefore hoped that no vacuum will be left after July 2023.

\(^1\) A philanthropic investment platform.
On the effectiveness of medicines

Is there much treatment failure to AmBisome? The number of non-responders in the South-East Asia Region for treatment of VL cases is negligible and the medicine has the highest therapeutic index among all the antileishmanials.

In the Region of the Americas, liposomal amphotericin B and meglumine antimoniate are recommended for treatment of VL. The response is faster with amphotericin B than with antimoniate, and, while it is hoped to implement liposomal amphotericin B as a first-line treatment in the Region, this represents a huge challenge for procurement. Can the treatment be improved?

Technology transfer to a laboratory on the American continent is under way.

In East Africa the first-line treatment is sodium stibogluconate plus paromomycin for a minimum of 17 days. This combination has been used for the past 8 decades; shortened regimens, oral formulations and cheaper medicines that can be administered safely are now needed.

In the area of drug discovery, DNDi (the Drugs for Neglected Diseases initiative) is collaborating with Novartis.

There was discussion also about treatment for CL, especially following an outbreak of CL in a province of Pakistan where 4000 cases were recently reported. Azole-based medicines are not recommended because there is insufficient evidence for their efficacy. Some cases of CL are self-healing; for other cases there is good experience with use of cryo- and thermal therapies. For intralesional treatment, meglumine antimoniate is preferred; however, it is not cheap, and securing a donation or the medicine at very low cost is challenging.

On improving diagnostics

Will the sensitivity and specificity of the rK39 test be sufficient for use as a post-elimination test to monitor interruption of transmission? This tool will not be sufficient. The limitations of existing tools suggest there is a long way to go before interruption of transmission can be proposed in the South-East Asia Region. Antigen-based tests are needed to determine elimination of transmission. The DTAG subgroup on VL is developing a TPP for early detection of antigen; a prototype test should be available in the next 2 years, after which interruption of transmission may be achievable. The problem, however, is in East Africa where the sensitivity and specificity of RDTs are much lower than on the Indian subcontinent and in Latin American countries. Other tools, for vector control and for reservoir control, are important in Latin America (where transmission is zoonotic) and in East Africa (where transmission may have a zoonotic component) and must be enhanced.

The specificity and sensitivity of diagnostics must also be improved. Regional differences in test performance warrant evaluation of tests in different epidemiological settings. Greater manufacturing capacity and diversification of that capacity are needed to avoid dependence on a single manufacturer.

In areas where VL transmission has a zoonotic component, would a One Health approach be appropriate? Two RDTs for animals are available in the Americas: Kala-azar Detect® and a Dual Path Platform (DPP®) rapid test. BioManguinhos has a rapid test for dogs, but it is currently available only in Brazil, so diagnosis must be laboratory-confirmed with enzyme-linked immunosorbent assay.
A number of possible manufacturers have been approached. Mologic is at an advanced stage of discussion with Bio-Rad on technology transfer, which is expected to happen within the next year or so. A Korean company (SD Biosensor) produces a canine leish diagnostic test and has accepted a request to develop a prototype, currently under laboratory evaluation in a WHO Collaborating Centre. A new TPP VL subgroup has been established under DTAG.

**On vector control**

Could vector control methods be used to help reduce transmission of VL in East Africa? (see 7–9).

There are no proven effective vector control interventions in East Africa due to lack of well-designed controlled studies. Two distinct transmission patterns are observed: (i) in the north, where *Phlebotomus orientalis* occurs mainly in acacia trees, VL affects migratory seasonal labourers who sleep under these trees or in temporary huts in nearby fields; and (ii) in areas where *P. martini* is present in termite mounds and transmission is both peridomestic and sylvatic. Insecticide-treated nets are of immense benefit as a personal protective measure, but community protection depends on several factors including regular use of nets. Studies on outdoor residual spraying have demonstrated the efficacy of the intervention, as discussed by the Vector Control Advisory Group, which recommended at its eighth meeting in 2018 to conduct community cluster-randomized trials with support from donors (10). Two emerging issues are: (i) the effectiveness of insecticide-treated nets for leishmaniasis control in areas coendemic for leishmaniasis or malaria; and (ii) the scalability and effectiveness of outdoor residual spraying in extensive areas.

Concern was expressed about the expansion of vectors in Latin America, where integration will be an essential strategy going forward. The co-prevalence of HIV and VL, for example, was shown only after all HIV patients began to be tested for VL. New tests and methods will be strong elements in promoting integration, both in the field and in the clinic.

**On engaging the community**

What research has been done regarding community understanding of VL? Could communities become more engaged to better understand the situation? FCDO KalaCORE programmes have supported programmes on both the Asian and the African continents and have undertaken studies on social understanding and barriers to accessing treatment. Local researchers in endemic countries have provided information on social aspects and dynamics. For example, in a highly endemic region for VL in India (in a tribal dominated community), hot iron rods are placed at the left side of the lower abdomen to cure VL. However, there is insufficient sustainable funding from health ministries, particularly in Africa, to advance work; domestic financing has been the main driver for success.

Is it acceptable to the community to treat dog collars with insecticide? Is any documentation available on these aspects (11)? *L. longipalpis* has totally adapted to urban and periurban environments, and work has been done with community support. Use of impregnated collars began in 2021 in response to the low effectiveness of chemical control for vectors. This has been validated in Brazil with active participation of the population. While owners must be careful with their pets, it is feasible to use the collars, and the method is acceptable to the population. Treatment of dogs, especially in Argentina, Brazil and Paraguay, is authorized and supported by practitioners only when carried out with medicines not used in humans; protocols are being created.
On the epidemiology of *L. infantum* in the Americas

How long ago did *L. infantum* make its way from Europe to the Americas? Microsatellite studies indicate that *L. infantum* arrived in the Americas about 500 years ago, but this information has not yet been consolidated.

Could microsatellite mapping be used to monitor the origin of spread of new infections across the Americas? Yes, other studies are being carried out. However, in surveillance, spread has been monitored. The first cases of spread of VL occurred on the border between Argentina and Uruguay in the municipalities of Concórdia (Argentina) and Salto (Uruguay), and on the Argentine border with São Borja in the State of Rio Grande do Sul (Brazil), and from northern Argentina to southern Bolivia. Today, a VL Alert system is in place at international borders to support monitoring and actions in these areas.

Have cases of HIV–VL coinfection been detected only in Brazil? A few cases have been detected in Argentina and Colombia, but nothing compared with the impact seen in Paraguay and Brazil.

Conclusions and recommendations to the Director-General

On VL in Africa and the Americas, the STAG-NTD:

1. **Thanks** the Secretariat and meeting participants for their contributions to the discussions on VL in Africa and the Americas.

2. **Commends** the progress of the VL elimination initiative in the South-East Asia Region and of WHO's support to endemic countries globally, and notes the challenges to control in other geographies of East Africa and the Americas.

3. **Commends** WHO, Member States and stakeholders’ cross-border efforts to address the control and elimination of visceral leishmaniasis, and **urges** continued coordination between governments to ensure seamless provision of care to affected persons, diligent surveillance and implementation of vector control where applicable according to WHO recommendations.

4. **Commends** WHO’s work with manufacturers, donors, academics, health ministries and other stakeholders, to replace and improve VL RDTs following proper IVD evaluation criteria.

5. **Notes** that improved rapid tests are urgently needed for East Africa and the Americas, and **urges** WHO and donors to support evaluations in accordance with the criteria established by DTAG.

6. **Urges** WHO to explore funding opportunities for evaluation of VL RDTs through donor proposals.

7. **Recommends** that:
   
   a. WHO requests all appropriate stakeholders to take steps to expand the manufacturing capacity and diversity of the manufacturing base for IVDs, including within countries endemic for visceral leishmaniasis; DTAG to request the subgroup on visceral leishmaniasis to draft an evaluation protocol for visceral leishmaniasis–IVD;
b. WHO urges donors to continue and increase their funding for the global leishmaniasis programme, particularly to support procurement of medicines and diagnostic tests;

c. WHO leads advocacy efforts to attract new donors to the programme;

d. WHO works with health ministries and appropriate experts to facilitate early investigation of endemicity particularly in populations in which elimination as a public health problem is the programmatic target;

e. WHO engages partners with appropriate expertise to initiate a search for antileishmanial treatments and treatment regimens that are less toxic, easier to administer and have a shorter treatment course, in order to make them more appropriate for resource-limited and remote settings; and

f. WHO, in collaboration with Member States and other stakeholders, develops a bi-regional proposal for elimination of visceral leishmaniasis in East Africa.

Wrap-up and closure

In concluding the meeting, Professor Lucille Blumberg, designated by Professor Mabey as co-chair for this meeting, commended WHO’s work with manufacturers, donors, academics, health ministries and other stakeholders to replace and improve RDTs, and recognized that improved tests are needed for East Africa and the Americas. She requested stakeholders to take note of capacity for diagnostics, especially in endemic countries, urged donors to increase funding, and requested WHO to lead advocacy efforts and to work closely with health ministries and countries with programmatic targets.

In his closing remarks, Professor David Mabey mentioned: expediting the approval process; the importance of specimens to evaluate new diagnostics; advocacy; and regulatory barriers.

The next (sixteenth) meeting of the STAG will be held later in 2022 (dates to be confirmed).

Finally, Dr Gautam Biswas, Acting Director, WHO/NTD, thanked everybody for their interesting and candid discussions and active participation. He added that WHO remains committed to engaging with stakeholders and to advancing work to make diagnostics affordable, useable and of assured quality. Political will and financing are important messages to take away from the meeting, as is the supply of medicines and diagnostics. Despite the ongoing COVID-19 pandemic, work must continue. Annual NTD reports will reflect progress and challenges. Finally, he hoped that the next meeting would be in person and thanked everyone again.

After the customary exchange of courtesies, the meeting was closed at 16:15.
References


## Annex 1. Agenda

### Day 1: Monday 7 February 2022

<table>
<thead>
<tr>
<th>Time</th>
<th>Topic</th>
<th>Presenter</th>
<th>Pre-read</th>
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<tbody>
<tr>
<td>13:00–13:10</td>
<td>Opening remarks</td>
<td>Ren Minghui, ADG/UCN</td>
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<tr>
<td>13:10–13:20</td>
<td>Purpose of the meeting and expected outcomes; administrative matters; appointment of rapporteurs</td>
<td>Chair</td>
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**Session I – Diagnostics for NTDs**

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<th>Time</th>
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<tr>
<td>13:30–14:15</td>
<td>Situation analysis and critical issues:</td>
<td>Daniel A. Dagne, Pat Lammie, Susie Braniff,</td>
<td>DTAG reports 1, 2, 3 and draft of 4 TPP dashboard</td>
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<tr>
<td></td>
<td>1. Introduction and overview</td>
<td>Pat Lammie</td>
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<td></td>
<td>2. Update on DTAG and TPP development</td>
<td>Susie Braniff</td>
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<td></td>
<td>3. Validation and evaluation of new or existing NTD diagnostics, and need for a standardized validation protocol (for programme/policy recommendation)</td>
<td>Robyn Meurant</td>
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<td></td>
<td>4. Prequalification of NTD diagnostics</td>
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<td>5. Impact of IVDR on NTD diagnostics, and its mitigation</td>
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<th>Time</th>
<th>Discussion and recommendations</th>
<th>Chair</th>
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### Day 2: Tuesday 8 February 2022

**Session II – Visceral leishmaniasis in Africa and the Americas**

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<th>Time</th>
<th>Topic</th>
<th>Presenter</th>
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<tbody>
<tr>
<td>13:00–13:45</td>
<td>Situation analysis and critical issues:</td>
<td>WHO/NTD</td>
<td>Four-page summary from 2021–2030 NTD road map</td>
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<tr>
<td></td>
<td>1. Global overview &amp; financial resources</td>
<td>Saurabh Jain/ Ana Nilce Elkhoury</td>
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<td></td>
<td>2. Rapid diagnostic tests</td>
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<td>3. Emerging endemicity</td>
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<th>Time</th>
<th>Discussion and recommendations</th>
<th>Chair</th>
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| Time       | Wrap-up and closure                                                   | Chair and Acting Director, WHO/NTD            |                |
Annex 2. List of participants

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