Onchocerciasis: diagnostic target product profile to support preventive chemotherapy

Epidemiology

Onchocerciasis, also known as river blindness, affects an estimated 21 million people, with 99% of cases reported in 31 sub-Saharan countries (WHO, 2020a). The disease is caused by the filarial worm *Onchocerca volvulus*, which is transmitted by *Simulium* flies. Adult worms live in nodules, some of which are subcutaneous. Conversely, the embryos (microfilariae) can migrate through the skin, causing debilitating pruritus and skin disease, and to the eyes, leading to progressive and permanent blindness. Onchocerciasis is also hypothesized to lead to neurological disorders including epilepsy (Chesnais, 2020), nodding syndrome (Geelhand de Merxem, 2020) and stunted growth.

Public health response

Currently, at least 217.5 million people live in areas known to be endemic for onchocerciasis (WHO, 2019). Morbidity is controlled by annual mass drug administration (MDA) of ivermectin, with 157 million treatments delivered in 2018 (WHO, 2019). Ivermectin temporarily blocks transmission of infection by clearing microfilariae but does not kill the adult worms, which have a reproductive lifespan of about 10 years, requiring MDA to be continued for over a decade.

In 2010, based on progress towards the elimination of transmission of onchocerciasis in the Region of the Americas as well as in a few foci in sub-Saharan Africa, global targets were revised from the control of morbidity to elimination (interruption of transmission) (WHO, 2010). In 2020, following several rounds of public consultation, WHO published the draft road map for neglected tropical disease 2021–2030 (WHO, 2020b), which the Seventy-third World Health Assembly is expected to endorse. The road map identifies as a critical action the mapping of suspected onchocerciasis-endemic areas, with launch of MDA wherever indicated. It further identifies as critical the development of improved diagnostics to facilitate mapping and decision-making (WHO, 2020b; Fig. 12). The principal disease-specific target for onchocerciasis is to increase the number of countries verified as having interrupted transmission from four (12%)[1] in 2020 to 12 (31%) in 2030 (WHO, 2020b; Table).

This shift requires treatment to be expanded to include hypo-endemic settings which were previously excluded from MDA. Hypo-endemic areas are defined as having a palpable subcutaneous nodule prevalence < 20%, corresponding to a microfilariae prevalence of approximately < 35% (Zouré, 2014). Some of these hypo-endemic areas have been mapped, while others have not, and the maps are not necessarily current, leading to an uncertainty in the total number of people who must be reached. It is estimated that in 2011, 98 million people lived in areas in which the prevalence of palpable subcutaneous nodules was 0–4.9%, 77 million in areas of 5–20% nodule prevalence and 62 million in areas of > 20% nodule prevalence (Zouré, 2014).

[1] Colombia, Ecuador, Guatemala and Mexico.

Available diagnostic tools and their limitations

The main diagnostics for onchocerciasis fall into the following categories.

1. Analysis of skin biopsies, also known as skin snips, by microscopy or molecular techniques is considered to be definitive but is relatively insensitive, has low throughput and can be painful for the patient if appropriate equipment and techniques are not ensured. Populations are reluctant to participate in skin snipping, especially when onchocerciasis is not viewed by the locals as a problem and/or when children are involved.

2. Nodule palpation has been a main driver of the African Program for Onchocerciasis Control, being used for the rapid epidemiological assessment or rapid evaluation and monitoring of onchocerciasis. A prevalence of approximately 5% of people having palpable nodules of other etiologies makes this technique acceptable for meso- and hyper-endemic areas but insufficiently specific for hypo-endemic areas.

3. The DEC patch is a diethylcarbamazine-containing transdermal patch that kills microfilariae in the skin, triggering a reactive urticaria (the Mazzotti reaction) that can be visualized. The fact that it requires 2 days in the field[1] to monitor skin reactions is a limitation, and there are specificity issues in areas co-endemic with *L. loa* (Ozoh, 2007). "Ready-to-use" DEC patches (Awadzi, 2015) made under good manufacturing practice conditions by a manufacturer specialized in transdermal-delivery systems are available to health ministries requesting them from WHO (TDR contact: Dr A.C. Kuesel). Large-scale evaluation of the DEC patch has to date only occurred in populations that were skin snip negative (Diawara, 2009) and needs to be conducted in populations with different levels of skin microfilariae density to assess its performance and safety.

4. Ov16 serology is part of the current WHO criteria for stopping MDA, alongside entomological investigations (WHO, 2016). Identification of hypo-endemic areas is also under consideration. The third meeting of the WHO Onchocerciasis Technical Advisory Subgroup (Geneva, 26–28 February 2019) summarized the results of the evaluation of different Ov16 assays in a variety of programmatic contexts and identified differences in performance with different types of specimen and concerns of accuracy (WHO, 2020c). The enzyme-linked immunosorbent assay (ELISA) always requires dried-blood spots; a rapid diagnostic test performs better with dried-blood spots than with whole blood. One issue is the lack of standardization across different versions of these serological tests.

5. Entomological identification of ongoing transmission consists of detecting infective or infected *Simulium* flies by polymerase chain reaction (PCR). It requires trained personnel for laboratory work and field teams knowledgeable about methodologies for finding and capturing flies.

[1] One day for setting the patch, the next day for readout.

Diagnostic Technical Advisory Group

The WHO Department of Control of Neglected Tropical Diseases manages a diverse portfolio of 20 diseases and disease groups, each with its own unique epidemiological, diagnostic and control challenges. In 2019, WHO's Strategic and Technical Advisory Group for Neglected Tropical Diseases, the Organization's principal advisory group on neglected tropical diseases (NTDs), recommended the establishment of a Diagnostic Technical Advisory Group to help ensure a consistent approach to identifying and prioritizing diagnostic needs and to inform WHO strategies and guidance on the subject. The first meeting of the Group (Geneva, 30–31 October 2019) discussed priorities for the year ahead as well as how to manage the complexity of supporting the diagnostics agenda across the entirety of the WHO portfolio of NTDs. It was clear that all NTDs had diagnostic needs which would have to be addressed in due course. One of the recommendations was to create a sub-committee dedicated to onchocerciasis, with an initial mandate to define the target product profiles of new diagnostics necessary to reach the 2030 goals.

Need for novel target product profiles

With more than 150 million doses of ivermectin distributed each year, the fight against onchocerciasis is a major international public health programme. Means to identify all populations in need of treatment are still required, and new diagnostics are needed to support all programmatic activities, especially in areas of low prevalence or low intensity of infection. The 2020 road map recognizes the critical need "to develop improved diagnostics to facilitate mapping and decisions to eliminate transmission" of onchocerciasis (WHO, 2020b; Fig. 12).

Mapping. A sensitive, specific assay is required to map onchocerciasis in hypo-endemic areas and to overcome the limitations of the existing tools. The WHO Onchocerciasis Technical Advisory Subgroup recommended establishing a biological threshold of 2% antibody prevalence in adults for decisions to start treatment (WHO, 2020c). To have confidence of estimates around this threshold, sensitive and specific tests are critical. Field-based operational research to generate empirical data to validate or refine starting and stopping thresholds is under way.

Monitoring and evaluation. In areas of higher endemicity, progress is evaluated with skin snips (microscopy or PCR) or using serology. Serology is performed in children as sentinel groups. It is recognized that generally children are less exposed to infection than adults (e.g. working outdoors), but for serology, adults cannot be used as a sentinel group because of the long-lasting nature of the Ov16 response. In areas of low endemicity, serology may not be sufficiently sensitive for characterizing communities, but monitoring of infected or infective vectors may be appropriate. Target product profiles for human and vector-based diagnostics are needed to advance monitoring and evaluation agendas. Unlike mapping, which is done only once, monitoring must be continued for at least a decade, and therefore the new tools need to be especially affordable.

Stopping MDA. In 2016, WHO published guidelines for stopping MDA and verifying elimination of human onchocerciasis (WHO, 2016). The guidelines require that both entomology and serology

be used to demonstrate the interruption of transmission of *O. volvulus* for the purpose of stopping MDA.

- **Entomology** ("strong recommendation, high certainty of evidence"): O-150 PCR (Poolscreen) testing in black flies should be used to demonstrate interruption of transmission of *O. volvulus*, with an upper bound of the 95% confidence interval of a prevalence of vectors carrying infective larvae of 0.05%. Research priorities for entomological evaluations include standardizing the PCR diagnostic test itself and the protocols for fly catching.
- **Ov16 serology** ("strong recommendation, low certainty of evidence"): Ov16 ELISA[1,2] should meet a threshold of 0.1% positivity in children aged 10 years or younger (upper bound 95% confidence interval). Evidence to support this threshold and age group is low, and research is ongoing to identify the most informative age groups and define associated thresholds in different epidemiological settings (Coffeng, 2019). Research priorities identified in the WHO guidelines also include investigating the sero-reversion of Ov16 responses and validating the Ov16 rapid diagnostic test.

Stopping should ideally be a one-time event, and one may justifiably use more resources or more expensive tests for the sake of supporting appropriate decision-making on MDA cessation.

Post-treatment surveillance. These tests are conducted 12 months after the last round of MDA and at the time in which parasite transmission, if still occurring, would be at its peak. After a period of post-treatment surveillance of 3–5 years, and on the advice of the national oversight committee, interruption of transmission is confirmed, by entomological (O-150 PCR Poolscreen) test and, if necessary, by additional serological (Ov16) testing. It is only when such surveillance is completed for all transmission foci within a country that, upon submission of a dossier by the Ministry of Health, WHO can grant elimination status.

Post-elimination surveillance. Next, a national programme establishes a post-elimination surveillance system to detect possible renewal of parasite transmission (recrudescence or reintroduction) both in previously endemic and in non-endemic areas as well as in areas where imported cases might be expected to occur. Such post-elimination surveillance can be centred on entomological assessments by the demonstration of the absence of infective-stage larvae of *O. volvulus* in the vector population as determined by O-150 PCR using *O. volvulus*-specific DNA probes. Such assessments should be conducted at regular intervals until elimination is verified in all countries in the relevant WHO region, or at least until any risk of recrudescence or reintroduction can substantially be excluded.

With many countries still being far from interruption of transmission, diagnostics specifically designed for post-elimination surveillance are regarded as a lower priority *at this time*. However, there will eventually be a need for a tool that can detect either transmission or human infection at very low prevalence levels, or with low intensity of infections, and identify individuals carrying

[1] This guideline related to a single ELISA with a sensitivity of < 50%.
[2] With follow-up with skin biopsies on Ov16-positive participants.

fecund adult female parasites so that they may be individually treated. It is likely that in a post-elimination surveillance setting, few resources will be available and that transmission or entomology may be too expensive and technically demanding to be routinely performed. It would therefore be desirable to have a diagnostic that can be easily integrated with other surveillance programmes.

Conclusion

One of the challenges posed by the current diagnostics is the difficulty of comparing epidemiological data obtained with different techniques, i.e. skin biopsies, versus rapid evaluation and monitoring of onchocerciasis, versus serology. Rather than having different diagnostics for mapping, monitoring and stopping decisions, it would be more effective to have a single platform that could support all these functions, while providing longitudinal data.

All activities described in the WHO 2016 guideline are to be applied to onchocerciasis "transmission foci" or "transmission zones", but currently there are no WHO-recommended protocols to delineate such foci.

Addressing onchocerciasis in areas endemic for *L. loa*, where ivermectin can lead to severe adverse events, remains a major problem (Vinkeles Melchers, 2020). Unless new treatments are identified that are suitable for use within MDA campaigns and not microfilaricidal, diagnostics for *L. loa* infection are needed to exclude those at risk of severe and serious adverse reactions to microfilaricides. This holds particular importance for areas in which onchocerciasis is hypo-endemic and *L. loa* is co-endemic, which will need to be included in interventions for elimination of onchocerciasis, where the risks associated with distribution of ivermectin may outweigh the benefits.

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