Review

Elimination of onchocerciasis from Africa: possible?

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Human onchocerciasis, a parasitic disease found in 28 African countries, six Latin American countries and Yemen, causes blindness and severe dermatological problems. In 1987, efforts to control this infection shifted from vector approaches to include the mass distribution of ivermectin – a drug donated by Merck & Co. for disease control in Africa and for disease elimination in the Americas. Currently, almost 25 years later, with the Americas being highly successful and now approaching elimination, new evidence points towards the possibility of successful elimination in Africa. We suggest several major changes in the programmatic approach that through focused goal-directed effort could achieve global elimination of onchocerciasis by 2025.

History of river blindness control efforts

Since the donation of ivermectin for onchocerciasis (Figure 1) and the resulting community-directed treatment with ivermectin (CDTI) model for mass treatment, greater successes in disease reduction have been achieved with several tropical diseases through preventive chemotherapy (PCT) [1,2]. The pioneering mass drug administration (MDA) model using the CDTI strategy established with ivermectin distribution for onchocerciasis control is widely recognized as a successful example of public–private partnership [3], which has encouraged other pharmaceutical donations for the control of neglected tropical diseases (NTDs). To date, over 900 million treatments with ivermectin have been given as part of the onchocerciasis control program in 34 countries. The six onchocerciasis endemic countries in Latin America are close to entering the certification phase of elimination of transmission of the disease with treatment now stopped in 7 of the 13 endemic foci. The target date to stop treatment in all foci in all six endemic countries is 2012, although surveillance will still be required for a further 3 years. The remarkable success in the Americas, particularly over the past decade, has provided much encouragement for achieving similar successes in the much larger areas of transmission and disease prevalence in Africa, and also in Yemen.

Merck's Mectizan Donation Program (MDP) began almost 25 years ago to control onchocerciasis and, more specifically, initially to reduce the prevalence of blindness caused by the infection (Figure 2). The program was supported at the field level by nongovernmental development organizations (NGDOs), many of which focused on eye health. These partners were key to assisting national programs develop river blindness control programs. As the impact of ivermectin MDA was better understood, and with an improved understanding of the dermal manifestations of the disease (Figure 3) [4,5], the goals of African MDA programs actively included the control of skin disease. The creation of an organizational entity to support African countries establish sustainable onchocerciasis control programs for the distribution of Mectizan, the African Program for Onchocerciasis Control (APOC), spearheaded the expansion of efforts to the whole of Africa, and has been the central catalyst for the success in MDA to date. This is in contrast to the approach taken in Latin America where, in 1992, the Onchocerciasis Elimination Program for the Americas (OEPA) was established to eliminate new onchocercal ocular morbidity and, where possible, transmission of the disease from the 13 relatively small endemic foci in six countries by distributing ivermectin twice a year [2]. As a result of the distribution of biannual ivermectin for over 12 years or more, a number of these latter foci are now celebrating the elimination of transmission and are working towards certification of elimination by the Pan American Health Organization.

In 2002, a conference was held to assess the possibility that onchocerciasis could be eliminated in Africa and in the Americas; the conclusion was that it was possible in the latter region but that it could not be achieved in Africa given the tools available [2]. Here, we revisit this conclusion as it relates to Africa and suggest strategies to achieve similar success in Africa.

There are several fiscally related reasons to discuss the possibilities of elimination at this time. An important change in the public health and donor communities is the classification of tropical diseases into the so-called NTDs, many of which overlap geographically and are therefore eligible for integration of interventions. This move to combine programmatic activities under the banner of NTDs and integrating interventions is appealing to donors, and over the past 5 years the availability of funds for program implementation has increased. There are still several challenges that come with integrating interventions for control and elimination efforts, as discussed below, but overall this is a positive change that should help strengthen efforts to eliminate onchocerciasis and other diseases from Africa.

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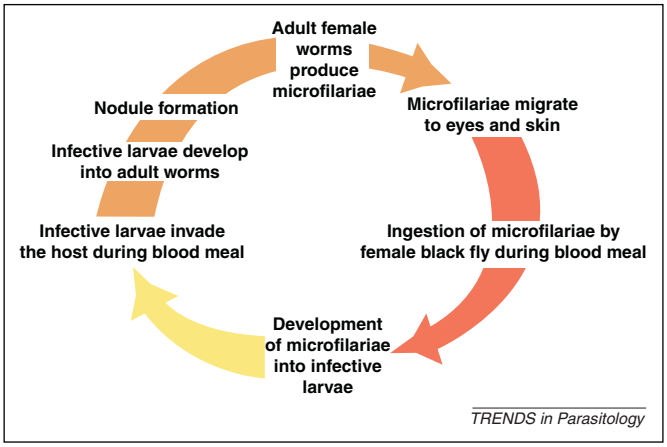

Figure 1. Lifecycle of onchocerciasis. L3 larvae infect when a blackfly takes a blood meal. Some 10–14 months later mated adult *Onchocerca volvulus* females produce microfilaria that move to the skin and ocular tissues. Parasites enter into the vector stage again during their blood-feeding activities. The typical clinical disease and tissue damage of onchocerciasis occurs when the microfilariae die and induce damaging inflammatory responses in the host.

The political momentum generated as a result of increased funding is an important element in any global disease control effort, both at the international and national levels. The success of the MDA strategies observed over 25 years of the donation of ivermectin for onchocerciasis, and 12 years of the donation of albendazole and ivermectin for lymphatic filariasis (LF) has further generated momentum making this an opportune time to investigate how African onchocerciasis can progress from a control to an elimination program.

The current situation

Africa carries some 99% of the world's population afflicted by this infection, and where the entomological and epidemiological characteristics of the disease are often somewhat varied. Vector control (Box 1) alone was used in West Africa, in the former Onchocerciasis Control Program (OCP, before it was combined with ivermectin distribution; in some of these areas, transmission has been interrupted [6]). Another site where transmission has in all likelihood ceased is the Abu Hamad focus in northern Sudan [7]. This is a site with different epidemiological characteristics than those foci in West Africa and underlines the possibility of elimination in characteristically different foci. However, the geographic and demographic heterogeneity of the African foci will probably need more focused and locally tailored strategies for the needed progress in reducing infection and transmission that would support a timely movement towards the goal of elimination.

Figure 2. A man suffering from 'river blindness' in Southern Sudan is guided by children; the iconic image of this important tropical eye disease.

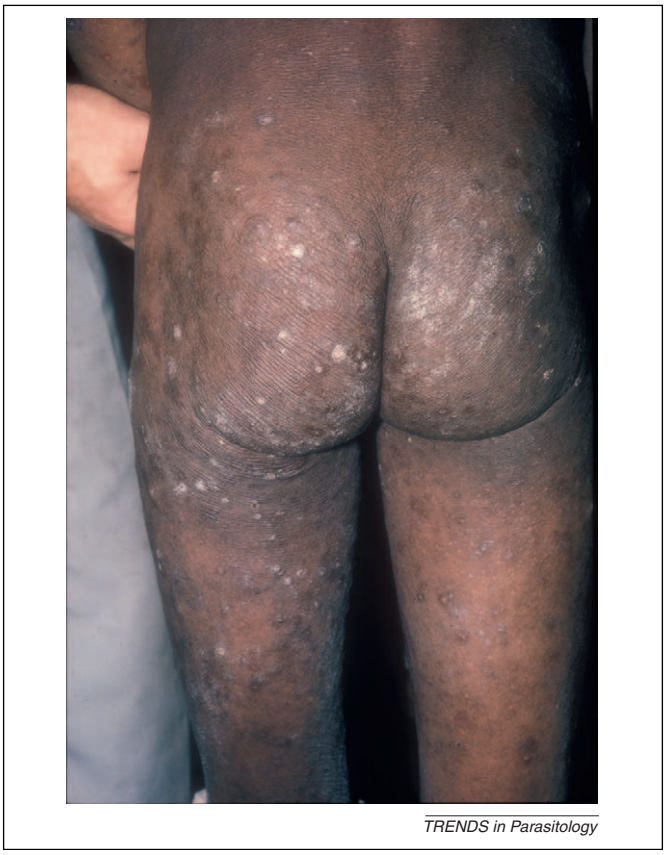

Figure 3. Severe onchodermatitis in a young Sudanese male. The indurated papular dermatitis with extensive pigmentary changes seen in the midbody region are typical of active host responses to the death of microfilariae in the skin.

Any planning for elimination of onchocerciasis in Africa should include consideration of what is happening with the LF program as it involves the distribution of ivermectin combined with albendazole for LF elimination. The LF elimination program rolled out in 2000 in Tanzania, Ghana, Togo and Nigeria with other countries joining soon after. In areas where onchocerciasis and LF are co-endemic, the use of these drugs to eliminate LF has enhanced national efforts against onchocerciasis. The integration that is now occurring through the NTD programs should assist the new goal of the onchocerciasis effort as long as the goal of elimination is accommodated within the integrated framework. It should be noted, however, that integration is somewhat of a double-edged sword that can, particularly in countries that have well-established vertical programs, be difficult at least for an initial period and can cause difficulties in management and implementation.

Although most onchocerciasis endemic areas in Africa are well understood, have a well-established drug distribution system and are moving towards, or have reached,

Box 1. Vector aspects of onchocerciasis

- *Onchocerca volvulus* is transmitted by *Simulium damnosum* complex in Africa. This blackfly vector breeds in well-aerated waters with larval stages typically being deposited on rocks and vegetation in the fast-moving waters.
- The common name of the disease, 'river blindness', is believed to have been first coined in the 1920s by the wife of the district medical officer in Wau, Southern Sudan; the ferrymen and people living near the Simulium breeding sites on the local Jur River were most badly affected with ocular disease.
- Local vector control commonly involves larvicidal treatment using agents such as Abate or *Bacillus thuringiensis*.
- The detection of *O. volvulus* in *Simulium* sp. is currently achieved by polymerase chain reaction amplification of the 0–150 genes of *Onchocerca* parasites, often using a pool screening technique [7].
- The intensity of transmission is often estimated by determining the daily biting rate (DBR), and from the number of infective larvae in these flies, the daily transmission potential (DTP), and finally the annual transmission potential (ATP) from additional entomological information [24].
- Higher biting rates are recorded for those living in rainforest endemic sites than in savannah areas, e.g. rainforest biting rates are often 20 times greater than in the savannah areas [25].

very low levels of transmission following distribution of ivermectin, there are still areas that are very challenging due to the lack of strong national programs, civil unrest or the presence of *Loa loa* infections. The latter, another filarial disease, when found in onchocerciasis endemic areas where ivermectin is being distributed, can be associated with serious adverse events (SAEs) in those individuals carrying extremely high loads of *L. loa* microfilariae.

An important legacy of the 25 years of ivermectin distribution in Africa, and the time invested training community distributors and local medical personnel, is the solid platform that has been established on which a shift from control to elimination can be built. The sustainability established by empowering the local community to take responsibility for drug distribution has increased therapeutic and geographic coverage significantly throughout Africa [8]. Indeed, this approach is now being utilized by other drug distribution programs and is an important contribution to improving health in rural communities throughout much of Africa.

It is important to note that the ancillary benefits of ivermectin for onchocerciasis encourages communities to maintain strong programs by reducing suffering caused by scabies and lice. Ivermectin is an effective treatment for ectoparasites and some intestinal parasites (notably *Ascaris* and *Strongyloides*), and the prevalence of these has been greatly reduced throughout the areas where onchocerciasis MDA programs have been well implemented [9]. The loss of these additional positive effects of ivermectin distribution after the cessation of drug distribution is an issue that should be considered by national health authorities to prevent recrudescence of these other parasites. Communities are often concerned when MDA for onchocerciasis ends and the ancillary benefits are lost (R.V. Lovato *et al.*, unpublished).

Evidence that suggests elimination is possible

As mentioned previously, in Latin America the mass distribution of ivermectin alone has worked to achieve elimination of transmission in many of the 13 foci of the region. For the past 10 years, almost all endemic foci in the Americas have been achieving 85% or greater therapeutic coverage of the eligible population at least once a year and in the majority of cases, twice a year. This high coverage is a major contributing factor to the success in the Americas.

The success in Ecuador is particularly encouraging. The isolated focus in Ecuador probably began in the 1850s when a trade ship containing slaves from Africa wrecked off the coast. The disease in Africans and Amerindians living in this remote jungle river site, when first examined in the 1980s, and unlike other endemic areas in Latin America, had similar characteristics (disease form, transmission intensity, etc.) to those seen in many onchocerciasis foci in Africa, and is thus arguably a suitable comparator. The vector in this focus, *Simulium exiguum*, is very efficient and in many ways comparable to the African vector *Simulium damnosum* spp. Despite the remote location of this focus, and the intensity of infection, elimination of transmission has been achieved, and treatment has been stopped [10], giving hope for a similar result in Africa.

It is important to note the MDA programs in Ecuador and in the other five endemic countries began as elimination programs rather than a control program; therefore, the overall treatment strategies were different from Africa. Additionally, the populations in endemic foci in the Americas are much smaller than endemic communities in Africa, and the vector in most foci is less efficient [11], which made elimination in Latin America feasible from the beginning. Despite difficult geography, remote populations, severe disease and an efficient vector, elimination is being achieved through the distribution of ivermectin.

Another positive insight into the possibility of elimination lies with the success of LF elimination efforts using PCT. Several LF foci around the world, including Africa (e.g. Zanzibar, Togo and certain districts in Tanzania), have now reached a point of stopping MDA after around 5 years of treatment; transmission in these sites has reached a level where the disease is no longer a public health problem. Admittedly, onchocerciasis differs from LF in several ways, including vector, lifespan and epidemiological characteristics; nevertheless, ivermectin, in combination with albendazole, has been effective in reducing infection and transmission levels to the point of elimination in a relatively short time.

Important evidence for parasite elimination comes from Mali and Senegal [6] where the first definitive evidence of the effectiveness of long-term ivermectin can reduce the prevalence of *Onchocerca volvulus* to levels compatible with elimination. The importance of vector control, which has a long history in the very successful World Bank initiated Onchocerciasis Control Program (known as the OCP), in elimination efforts has been demonstrated in Africa, even where fly populations are dense [12,13]. This is clear evidence that with focused and flexible strategies, and the always-essential financial support, onchocerciasis transmission can be eliminated in Africa as it has been in Latin America. These will most probably require the tailoring of specific strategies, or combinations of approaches, for each of the targeted foci.

The challenges

There are many challenges to eliminating a disease that affects rural communities in the most isolated places of Africa. The achievement of controlling, and in some areas eliminating, onchocerciasis in Africa to date are remarkable and a testament to the dedication and diligence of a constellation of partners from the community to the international level.

The question whether ivermectin is still suitable for achieving elimination of onchocerciasis without fear of resistance or recrudescence is important. Ivermectin has been effective at eliminating the disease in some areas due to the efficacy of ivermectin and the high level of coverage achieved over many years. Concern has been raised over the potential for drug resistance by *O. volvulus* to ivermectin. Although there is much academic debate on this issue, particularly regarding the Asubende focus in Ghana where resistance was first suspected [14], it must be recognized that resistance is a possibility that needs to be carefully monitored. Alternative treatment strategies, such as the use of doxycyline, which targets the symbiotic bacteria in *O. volvulus* and inhibits embryogenesis, are being developed in the event that ivermectin resistance becomes a problem in some areas [15].

A major impediment to achieving elimination is the occurrence of SAEs with the use of ivermectin in those patients who carry very high loads of *L. loa* microfilariae (>3000 mf/ml blood). Some 130 people have died following treatment with ivermectin due to a condition that involves an embolic encephalopathy. Others have survived but were left with central nervous system impairment. The area of endemic loiasis encompasses a large proportion of rainforest Africa [16] and is thus a major inhibition to the ivermectin MDA program in this area – at least in the first year of drug distribution when the *L. loa* microfilarial levels can be high. This risk has even prevented the initiation of MDA for onchocerciasis in many areas where loiasis is also endemic. Thus, this co-infection is a major inhibitor of progress towards elimination and needs to be solved if elimination is to be achieved in any realistic time frame.

Adequate financial support is always central to any national or international effort and the increased effort and activities that will be needed to achieve elimination will undoubtedly require additional funding at both the international and national levels. The latter may be difficult for some countries. The concept of 'donor fatigue' is well known and may become a significant problem for onchocerciasis control programs. A shift towards elimination may reinvigorate the donor community and improve funding opportunities. This underscores the need for active and well-designed advocacy for this new effort.

Availability of ivermectin is not likely to be a problem due to the generous commitment of Merck&Co. to donate this anthelminthic (as Mectizan®), and the strength of the supply chain. However, distribution and management of drug supplies in-country at the national level can be challenging in some situations and further problems may develop as onchocerciasis programs are integrated into other NTD programs. At the community level there is a danger of 'distributor fatigue'. MDA activities for the additional diseases that are part of the new NTD program will require more work by the distributors who typically distribute ivermectin voluntarily without compensation, or with only small incentive payments; this may be a problem that hampers progress towards elimination of onchocerciasis.

Finally, onchocerciasis elimination in Africa will always be constrained by any political instability in countries; this has happened in the Democratic Republic of the Congo, Sierra Leone and in Sudan. These unfortunate situations often cause migration of endemic populations, prevent drug distribution and destroy the infrastructure necessary for successful MDA. Despite stories of heroic distributors achieving remarkable levels of therapeutic coverage in conflict areas, instability will remain a challenge to compliance, program management and reporting.

Changes in approach

Presentation as an 'elimination' program

To achieve elimination there will need to be a focused and concerted effort with this specific goal in mind. Other disease elimination efforts have set 2020 as their goal; this may not be feasible for onchocerciasis elimination, but for the purposes of advocacy, perhaps this should be the target date used. Redirection and refocus from control to elimination will be needed at the international, national and community levels. In addition, the place of onchocerciasis elimination within the framework of the integrated efforts for NTDs will have to be carefully considered as this goal may not be fully embraced by other disease partners in this framework. It will be important to identify the onchocerciasis program as an elimination program rather than a control program as soon as possible.

Redefining target populations

In Africa, the current onchocerciasis control strategy is to target mesoendemic and hyperendemic areas. This strategy has worked to control the disease in these areas, and ocular morbidity has been significantly reduced [17]. However, a shift from control to elimination will necessitate the inclusion of the currently ignored hypoendemic areas. Ironically, a policy of omitting hypoendemic areas, unfortunately, despite being a disease control effort, neglects many of the people suffering from the severest form of dermal onchocerciasis who commonly live in areas of low transmission [18]. A shift to include hypoendemic zones for elimination will therefore provide the added benefit of providing relief to those suffering from severe disease in these low transmission areas.

Thus far, onchocerciasis has been controlled based on a broad assessment of endemic areas identified using rapid epidemiological mapping of onchocerciasis (REMO) based on a survey of targeted communities that have undergone rapid epidemiological assessment (REA), which measures onchocerciasis prevalence through the detection of subcutaneous onchocercal nodules. Nodule prevalence allows each community to be classified as hypoendemic, mesoendemic or hyperendemic so that mass treatment with ivermectin could be focused on the high-priority areas with the highest prevalence. The use of more sensitive assays to define infected residents in treated populations, especially

Box 2. Important areas for research and understanding in support of achieving elimination

1. Chemotherapy
   a. Development of a safe, field-usable macrofilaricide
   b. Management of loiasis-associated SAE
   c. Improving use of existing drugs, e.g. 2×/annum versus 1×/annum
2. Detection tests
   a. Diagnostic tests for low intensity infections, e.g. circulating antigen tests
   b. Rapid screening tests for high *Loa loa* microfilarial loads
   c. Rapid tests for detecting infected flies
   d. Detection of drug resistant parasites
3. Programmatic issues
   a. Mapping of hypoendemic areas
   b. Optimizing improving coverage
   c. Understanding local drug distribution challenges (for better coverage)
   d. Definition of criteria for ending treatment and for surveillance
4. Vector issues
   a. Understanding the association between vector dynamics and endemicity in the different geographic areas
   b. Relative contribution of vector control in reducing transmission

in those areas that are approaching elimination, will be necessary including the development of new assays (Box 2).

Currently, national programs conduct onchocerciasis control in Africa with treatment zones based on topography (river basins) and disease prevalence. To achieve elimination, a shift to identifying and treating areas based on aspects related to the ways of decreasing transmission rather than on simple geography will be needed. Increasing coverage is an essential component, which will require careful consideration of the local factors that will assist improvement and maintenance of high levels of compliance. The redefining of treatment zones to include entire endemic areas that consider vector characteristics and control, level of endemicity, migratory populations and conflict areas, etc., should be considered to enable targeted strategies. This approach would help address cross-border issues and assist vector control where feasible. Classifying endemic areas in this manner would also allow for careful prioritization of efforts and funding and would help redefine high-priority areas and identify the hypoendemic areas that have been excluded from treatment. The level of pretreatment endemicity is a major factor, together with maintenance of high drug distribution (coverage) levels, in successful reduction in parasite loads and thus successful elimination; the importance of these two factors has been identified and often emphasized by APOC. Coverage is probably the central factor in success achieved in Ecuador (R.V. Lovato *et al.*, unpublished).

Research

Success will always be enhanced by continuing to carry out research that specifically addresses the goal of elimination (Box 2). In the past, onchocerciasis was diagnosed and the burden of disease in the community was measured by counting microfilariae present in a skin snip. This is an invasive practice that causes discomfort and creates risks for HIV or other blood-borne pathogen transmission. Alternative tools are now used including an antigen-based immunological assay, a diethylcarbamazine patch test, and palpation of the head and body to detect onchocercal nodules present in the subcutaneous tissue. A simple, effective, accurate screening test for detecting the presence of *O. volvulus* parasites in an individual (rather than just exposure), such as the blood test based on antigen detection, or perhaps the multi-antigen luciferase immunoprecipitation systems (LIPS) assay, will need to be made readily available and cost-effective to achieve elimination [19,20].

A drug that does not elicit SAEs in individuals co-infected with loiasis or an alternative strategy to treat loiasis patients would be greatly beneficial to the goal of elimination. A means of identifying, and then safely treating, those individuals in the population at risk of this SAE would be an important step towards addressing this very important, program inhibiting, problem. New treatment protocols for these at-risk individuals, or for MDA in these endemic areas, is another important research goal; this may include development of new agents or the use of currently available drugs in different ways.

Although the current annual treatment strategy has interrupted transmission in some areas in Africa, it may not be the best approach in areas if elimination is to be the goal. To address the different challenges to onchocerciasis elimination, special treatment strategies will need to fit the circumstances of each targeted zone. Further research into using different drugs, different combinations of drugs and different regimens of these drugs is needed to achieve elimination. Twice-yearly treatment, such as in Latin America, or the development of a macrofilaricidal drug may assist in achieving elimination in Africa; no field-practical, universally safe macrofilaricide is currently available. Developing new drugs for onchocerciasis and the other filarial diseases is a difficult task given the lead time required for new agents and other issues that affect the development of any drug. The application of an existing anthelmintic, flubendazole, which has been used for intestinal worm treatment, but not in tissue parasites, is being tested [21] as a macrofilaricide for MDA. A variety of treatment options would allow for flexibility in strategies for onchocerciasis elimination in Africa depending on each local situation. Thus, one of the most important research issues needing to be addressed, and soon, is that of assessing the different treatment strategies that might be used in the African context or contexts.

The situation in Yemen, which is geographically separated from the African continent only by a narrow strip of the Red Sea, is a good example of where changing the ongoing protocol will greatly aid the progress to elimination from that focus. Here, some 300,000 people are exposed to the infection in the rough, mountainous terrain in the southwestern part of the country in eight mountain valleys rising from the Red Sea coast. The onchocerciasis control strategy of Yemen consists of administering ivermectin quarterly only to individuals with severe dermatitis [22]. To date, this approach has not successfully eliminated transmission, and moving the program from treating individuals to a MDA for entire communities is thought to be a

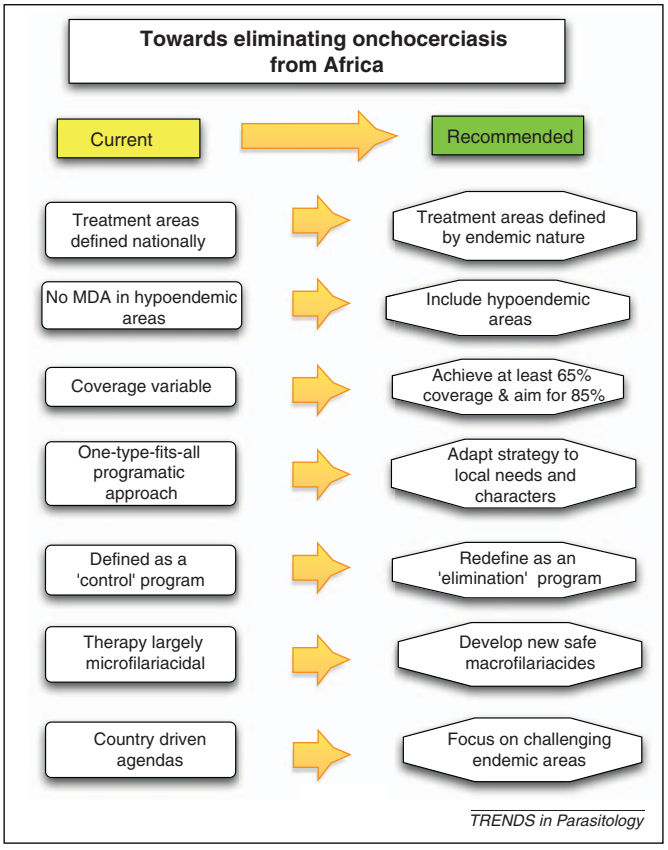

Figure 4. Suggested changes in onchocerciasis program strategy that would assist progression towards elimination.

more valid approach for achieving elimination. This new approach, combined with focused vector control, should move the relatively small focus to elimination.

There are also fundamental entomological questions that need to be addressed, e.g. what level of transmission needs to be reached to ensure that *O. volvulus* will naturally die out and recrudescence will not occur? What are the transmission dynamics in remaining hypoendemic areas? Understanding the contribution that vector control can make to elimination is very important; in specific geographic locations the addition of vector components may be crucial for tipping the scale against transmission.

Concluding remarks

Although there are several challenges to achieving onchocerciasis elimination, many are already being addressed. The different onchocerciasis endemic areas should be classified on the basis of programmatically important characteristics, such as geography, special drug distribution challenges and any vector-control possibilities, as soon as possible, and targeted for treatment. An early focus on the most difficult and challenging areas will be needed to 'shrink the map' of onchocerciasis endemicity in Africa. Advocacy will remain an important element to achieve success as it has been well established by other disease control and elimination programs that the job becomes more difficult and resources become scarce when the end is in sight. The central player in African onchocerciasis control, APOC, have themselves in recent years seriously addressed the issue of elimination and supported the concept. It should also be noted that mathematical models of onchocerciasis transmission are in agreement with the possibility of elimination in Africa, although these have often cautioned that the financial and human cost of such a goal is high [23].

The question we have posed, namely, "is it possible to eliminate onchocerciasis from Africa?", remains one that will continue to be discussed by experts (ref. anon.) but, in our opinion, over the past decade there has been a shift towards the perception that it is indeed possible. Success in Latin America, the shift to integrated NTD control and the successful elimination in some areas of Africa all provide reason to believe it is achievable and that it is time to move programmatically, and philosophically, from control to elimination. It is important to set elimination as the specific goal, rather than aiming just for control, to be successful; nevertheless, successful elimination will undoubtedly require significant shifts in strategy and a strong and intensive collaborative effort to achieve global elimination (Figure 4).

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