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Strategies for Suppression and Elimination of Onchocerciasis in Endemic Countries: A Review of the Literature

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Authors' contributions

This work was carried out in collaboration between both authors. Author MOE designed the study and wrote the first draft of the manuscript. Author IAO managed the literature searches. Both authors read and approved the final manuscript.

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ABSTRACT

Onchocerciasis is one of the neglected tropical diseases with great public health importance in the Americas and in many African countries. River blindness, can lead to severe dermatologic and ophthalmologic complications that may terminate in blindness and other associated social stigmatizations. Preventive chemotherapy with the use of annual mass drug administration with ivermectin (Mectizan®) has been the only sustainable management and control measure of the disease in Africa, though with limited efficacy. Based on those limitations, there is doubt that suppression and elimination of the disease targeted to take place in 2020 and 2025 respectively may be actualized. The aim of the review is to update knowledge on existing strategies relevant to achieving suppression and probable elimination of onchocerciasis in endemic countries and to highlight identified obstacles militating against such strategies. Review of past and recently published relevant literature on the topic was carried out using electronic databases such as Google scholar. For feasible suppression and elimination in the stipulated years, some strategies may have to be carried out. The suggested strategies include incorporation of insecticides with chemotherapy,

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adoption of semi-annually or quarterly ivermectin in-take compliance, inclusion of every member of endemic communities in treatment, avoidance of interruption in drug distribution, correction of misconception of onchocerciasis and use of gold standard diagnostic techniques. With adherence to the suggested strategies of control, the story of onchocerciasis as a public health problem would become a history and the disease could be elimination in all transmission foci.

Keywords: Onchocerciasis; elimination; suppression; Africa; strategies; ivermectin.

1. INTRODUCTION

Onchocerciasis is a parasitic disease caused by a parasitic helminth identified as Onchocerca volvulus and transmitted by insect vectors of the genera Simulium. It is one of the neglected tropical diseases (NTDs) which are endemic among people from under-developed, resource-constrained and poverty-stricken countries of the world. The NTDs are the sources of suffering and deaths because of their disfiguring and debilitating roles [1]. The NTDs have been eliminated as a public health problemin developed countries, and are left in the developing nations where they trap populations in cycles of poverty and disease [1].

Here it is interesting to ponder conceptually about the difference between the terms eradication and elimination, where eradication as used in this review means permanent reduction to zero level of incidence of onchocerciasis as a result of deliberate interventions with no more natural risk of re-introduction and no more intervention required while elimination is reduction to zero of the incidence of infection caused by a specific agent in a defined geographical area as a result of deliberate efforts with continued measures to prevent re-establishment of transmission [2].

Several species of Simulium have been identified as vectors of onchocerciasis worldwide. In some countries, they are species that form a complex of species, bringing more complexity to the entomological monitoring, where some of these species are known to inhabit specific endemic areas.

Onchocerciasis is a devastating and debilitating parasitic infection that is characterized by dermatologic, ophthalmologic, lymphatic and in some cases, systemic signs and symptoms [3]. It has been reported that onchocerciasis can cause epilepsy [4]. Severe itching, skin pigmentation (Leopard skin), disfiguration, visual impairment and in severe conditions, permanent blindness are the hallmarks of a typical river blindness disease. In the rainforest southern part of Nigeria, the infected individuals develop dermatologic conditions that range from itching, rashes, onchodermatitis (including acute papular, chronic papular and lichenified), to onchocercomas. The dermatological complications may be psychologically and socially embarrassing, with its associated stigma.

The aim of the review is to update knowledge on already existing strategies relevant to achieving elimination of onchocerciasis in endemic countries and to highlight identified obstacles militating against such.

2. MATERIALS AND METHODS

This mini narrative review was carried out using electronic databases such as Google scholar. Comprehensive search and review of literature that addresses onchocerciasis issues that are related and relevant to the theme of the present article was carried out. Articles that are published in peer reviewed and indexed journals were consulted on the course of writing the present review. For clarity and better understanding, the article was structured into sections as introduction, methods, economic consequences, endemicity of onchocerciasis, efforts to control the diseases, preparedness of countries to control the disease and conclusion.

2.1 Economic Consequences of Onchocerciasis

The negative effects of the disease on economic growth are that it causes people to abandon blackfly invaded fertile arable lands for blackfly-free zones as they avoid the bites of the vectors, and that expensive medical care is involved, especially as it concerns the eye when the condition progresses to blindness. Onchocerciasis has immensely contributed to vicious cycle of poverty and persistent food insecurity in endemic countries. Unemployment, low income, loss of man hours and the economic burden of continuous need to buy protective

clothing so as to cover the disfigured part of the body have been reported as some of the economic consequences of the disease [5] It is prevalent in 36 African countries. Globally, 120 million people are at risk of being infected while 18 million who are already infected have dermal microfilariae, with more than 6.5 million suffering severe dermatitis and 270,000 already battling with blindness [6].

2.2 Endemicity of Onchocerciasis

Onchocerciasis has been reported to be endemic in some part of the world, including Africa, the Americas [7] and Yemen in Asia [8]. Over 99% of infected people live in Africa while the remaining victims are resident in the Americas and Yemen [6]. It has been reported that the endemic range of O. volvulus extends across Africa from Senegal on the West through the centre of the continent to Ethiopia in the east [9]. The disease is prevalent in all states of Nigeria, with differing intensity and severity of endemicity and pathogenicity [10].

2.3 Efforts to Control Onchocerciasis

The public health importance of onchocerciasis as a neglected tropical disease in the affected African countries attracted the attention of World Health Organization and non-governmental organizations**.** Following the generated attention and awareness, efforts towards the control of the disease were initiated by the introduction of the Onchocerciasis Control Programme (OCP) in West Africa in 1974. This control programme targeted the disease with the application of aerial insecticides, directed against the larvae of the vectors of the disease. Although the vector control method was effective where it was employed, the method was eventually discontinued for lack of cost effectiveness [11] and environmental unfriendliness. The withdrawal of the control method left other affected parts of Africa battling with the disease. Introduction of preventive chemotherapy, whose utmost aim was to avert the morbidity that accompanies the infection [12] and subsequently the disease, was a new line of thought for control of the disease. In 1987, Merck Company promised to be donating ivermectin (Mectizan®) to as many that needed it and to as long as it is needed [13]. This promise was fulfilled by distributing the drugs in 1978. In 1992, Onchocerciasis Elimination Programme for the Americas (OEPA) was launched. In 1995, African Programme for Onchocerciasis Control (APOC) was launched with the aim of controlling the disease by establishing community-directed treatment with ivermerctin (CDTI). The programme was a preventive chemotherapy, saddled with the responsibility of putting under control, onchocerciasis in endemic African countries, with the intention to wind up at the end of 2015 [12] though eventually extended further in pursuit of elimination rather than just control. Then, mass drug supply of ivermectin came into full force. Endemic communities appointed their people who were trained in the distribution of ivermectin. This programme, called Community Directed Treatment with Ivermectin (CDTI), was established with the objective of achieving both geographical coverage in the distribution and treatment coverage of the regimen, and the drugs were administered once per year. In 2013, Mectizan Donation Programme (MDP) approved 167,984,016 Mectizan treatments for Africa, Latin America and Yemen, for control and elimination of onchocerciasis [14]. A total of 1,322,829,539 cumulative treatments have been reportedly approved for control and elimination of the disease from inception of the MDP to 2013 [15]. Towards the end of 2013, approximately 100.7 million people in 132,919 African communities were receiving ivermectin (Mectizan®) [16]. A scale up of administration of the drug increased the number of people utilizing ivermectin to an estimation of 112.5 million in 2014 [17]. Approximately 185.6 million people and 12 million people globally require onchocerciasis chemotherapy and are infected respectively [17].

2.4 Preparedness of Countries for Elimination of Onchocerciasis

In 2014, Cameroon, Cote d' Ivoire, Ethiopia, Ghana and Nigeria were grouped together as African countries that were targeted to discontinue treatment for onchocerciasis in 2020 [18], a gradual process to elimination of the disease, which was expected to be followed by a-five-year post treatment surveillance (PTS) before verification for eradication could be approved by the WHO in 2025; following 0% prevalence obtained by applying both entomological and parasitological surveillance methods. PTS means looking for active cases of onchocerciasis in endemic areas where mass drugs administration has stopped. The process normally last between a period of 3-5 years. After this period, entomological surveys are carried out to look for cases of recrudescence. If no transmission has reoccurred, elimination is ascertained [15]. Columbia, Ecuador, Mexico,

and Guatemala were verified and declared free of onchocerciasis in 2013, 2014, 2015, and 2016, respectively [9]. The accomplishment of elimination in the above cited countries was attributed to the effort of Onchocerciasis Elimination Programme for the Americas (OEPA), a programme that was in progress in the Americas as APOC was in Africa. OEPA embarked on biannual mass drug administration (MDA) of ivermectin to the endemic communities. This strategy was different from that of APOC who employed the use of single treatment per annum in affected areas.

Suppression and elimination of river blindness in some endemic African countries have been scheduled for 2020 and 2025 respectively. The target might be achieved but not as easy as planned, as it is laden with many obstacles and problems. Some potential strategies have been proposed to overcome the identified obstacles. The strategies are discussed as presented below.

2.4.1 Incorporation of insecticides with chemotherapy

In an attempt to achieve the elimination and control of onchocerciasis following the established roadmap, the use of ivermectin alone as a control measure should be critically examined, reviewed and possibly modified to incorporate other control measures [19]. The use of ivermectin has been confronted with problems of non-compliance of clients in treatment, emergence of drug resistance, and poor response to the treatment [20]. It has been reported that despite ongoing MDA with ivermectin in onchocerciasis endemic communities, there have been scanty reports on the efficacy of treatment, attributed to the fact that the disease differs in its distribution, endemicity and chemotherapeutic coverage [21]. In view of the drawbacks of Mectizan, incorporation of environmental-friendly insecticides, an improvement on what was used during the OCP era is strongly advocated as an adjuvant control measure. Though it has been argued that the use of insecticides is not cost effective, it will facilitate elimination of the disease and shorten the period of elimination and indirectly save the capital and human resources required for long term plan for elimination, using Mectizan as the only control option. Combination of use of insecticides with chemotherapy with more emphasis on target of the vectors (use of insecticides), would be more efficacious approach towards suppression and possible elimination of the disease.

2.4.2 Adoption of semi-annual or quarterly ivermectin treatment

The achievement of river blindness elimination with annual community directed treatment with ivermectin could be possible but might be prolonged. Adoption of biannual treatments or even quarterly treatments of endemic communities should be a better strategy to the elimination and consequent eradication of onchocerciasis in Africa. Quarterly treatment of onchocerciasis with ivermectin has been reported to be capable of reducing the number of female worms, acute itching and skin lesions, parasite transmission, and changing the duration of control programme [22]. The 6-monthly intervention strategy has proved successful in the Americas where onchocerciasis elimination has been achieved [9]. Recurrent treatment with ivermectin at semi-annual intervals has been reported to be effective against the macrofilaricides with resultant loss of fecundity and increased mortality [9].

Documented reports indicated that 15 years and 17 years of single annual treatments with Mectizan in Cameroon could not interrupt transmission irrespective of chemotherapeutic coverage [23]. In addition to transmission interruption, reduction of predicted years of treatment can be achieved with semi-annual mass drug administration [24], provided that good treatment and geographical coverage are achieved. Early and regular treatments have been reported to reduce the burden, alleviate the suffering and reduce the degree, severity and outcomes of morbidity in infected individuals, with assurance of greater productivity and quality of life for individuals in poor settings [9]. The need for semi-annual treatments with ivermectin arises from the fact that studies from disease modeling have suggested that it might not be possible to achieve onchocerciasis elimination even with 50 years annual ivermectin treatments [25] though compliance and levels of parasite transmission were determinants. However, the bi-annual treatment has some financial and personnel implications as it has been reported that bi-annual treatment with ivermectin was 60% costlier than annual treatment [26]. Moreover, more volunteers would be trained in the MDA and such individuals might not be easily recruited in the affected foci.

2.4.3 Incorporation of safe and efficacious macrofilaricidal drugs

It has been established that ivermectin seems to have only limited effect on the adult worms (macrofilariae) but does not kill them. The drug only suppresses the release of microfilariae for a few months post treatment [9]. The suppression in the production of microfilariae has been probably attributed to paralysis of the reproductive tract of the worm by the drugs [27]. The parasite's inability to release microfilariae for a few months [9] following treatment with ivermectin is usually reversed within few months and production resumes, long before the next drug administration commences (usually 12 months after). The time interval between when the worms have started producing microfilariae and the period for the next treatment could be responsible for maintaining transmission of the disease in many endemic foci. This situation has spurred many scientists into seeking alternative drugs that might be efficacious in killing the macrofilariae. Doxycycline in extended dosage has been found to be macrofilaricidal but its safety of utility for routine field use is yet to be determined [28]. Many other chemotherapeutic agents are still in trial phases as candidate Onchocerca volvulus macrofilaricidals. Moxidectin has been reported to be more efficacious in lowering skin microfilaria loads than ivermectin and has been taken to be a better candidate for reducing parasite transmission between treatment rounds [29]. In addition, annual treatment with Moxidectin has been reported to achieve similar reduction in programme duration (proposed thresholds for stopping treatment) with biannual treatment with ivermectin but at a lower cost, thereby presenting Moxidectin as a superior chemotherapy for onchocerciasis especially when biannual treatments are not achievable because of resource limitations [30].

In the absence of any other safe drug that can kill the adult worms, increasing the annual frequency of ivermectin distribution and treatment to either twice or quarterly should be necessary in the fight against the disease. With increased frequency of administration of the regimen and efficient monitoring within a year, there could be massive clearance of the microfilariae and highly- reduced, or even no time for accumulated release of microfilariae by the surviving adult worms. This is a similar strategy employed in the Americas where the disease has been eliminated.

2.4.4 Introduction of O. volvulus more sensitive drugs

There have been reported apparent developments of resistance to ivermectin by *Onchocerca volvulus*. The unproven likely widespread emergence of drug resistance in O. volvulus introduces doubt in the use of ivermectin alone.

A phenotype with sub-optimal response (SOR) to ivermectin has been reported in Ghana [31]. The SOR, however, could be attributed more to female macrofilariae resuming early reproductive activity [32] rapidly than expected, following Mectizan treatment than to drug resistance by the parasites, although this could be a manifestation of empirically unconfirmed ivermectin resistance [33].

In response to the suspected resistance to ivermectin, a great need for an efficacious chemotherapy therefore arises. Such a drug should be devoid of the shortcomings of doxycycline, a formerly apparently promising drug that has lost the qualities of a candidate for routine mass administration. Moxidectin has been reported to be a more efficacious drug [34].

2.4.5 Encouraging and improving consistency in compliance to intake of ivermectin

Consistent in-take of ivermectin according to its administration schedule is a realistic approach to successful elimination of onchocerciasis in endemic communities. In APOC countries, it is estimated that at least 65% of the total population of people living in an endemic area need to take ivermectin annually in order to control the disease whereas 80% compliance is needed for elimination of onchocerciasis as a public health problem. Dissak-Delon et al. [35] in Cameroon have reported inconsistent compliance in ivermectin in-take. In one of the studies [36], only 18.0% of the entire studied population took the medication ≥ 7 times out of the 10-12 rounds of distributed ivermectin.

Adherence to treatment was so inadequate as to have maintained onchocerciasis transmission at prevalence as high as 47.0% after more than 10years of commencement of Mectizan mass drug administration. Any skipped period of drug treatment has great negative multiplier effect in efforts to eliminate and possibly eradicate riverblindness as such an attitude could encourage the survival of reproduced

microfilariae and enhance parasite transmission potential. In such a scenario, the parasite prevalence may reverse to a level greater than or equal to what it was at the beginning of the control programme.

Support from family members, perceived performance of the community drug distributors, short period of Mectizan administration and perception of disease risk, could influence drug in-take compliance [36]. Added to these efforts, they should also be a good technical and scientific management.

2.4.6 Inclusion of every member of an endemic community in treatment

APOC does not include certain group of people such as children less than 5 years, pregnant women, lactating mothers and chronically ill people in treatment, for some inexplicable health-related reasons. No significant congenital malformation or developmental abnormality among infants of pregnant women unknowingly treated with ivermectin in Liberia was observed [36]. The observation is similar to reports of other findings [37]. Non-significant levels of ivermectin were detected in breast milk produced 6 ½ hours post administration of the drug to lactating mothers [38]. The implication and interpretation of the findings is that lactating women are supposed to be part of the treatment group during mass drug administration (MDA) with ivermectin.

Ivermectin MDA has not been implemented in localities where loaisis is co-endemic with onchocerciasis, for avoidance of associated risks of severe adverse events (SAEs) that could arise from rapid death of microfilariae [39]. MDA can be observed in such settings if loaisis test and not treat strategy [40] are practiced. Test and treat (TNT) principle involves testing everybody in localities where onchocerciasis co-exist with loaisis. Individuals in such communities who are infected with Loa loa are left untreated. People excluded from treatment are not being excluded from the bites of blackfly vectors of onchocerciasis, and this maintains transmission.

2.4.7 Avoidance of interruption in drug distribution

Lack of both treatment and geographical coverage in ivermectin distribution are factors militating against elimination of river blindness in Africa. Offei and Anto [41] in Ghana, reported significant loss of household coverage by the CDTI to an extent of 56.2% of the eligible people. Residents who were absent during the distribution and administration exercise and eligible people whose names were not in the drug register were denied access to the drugs [41].

Interruption of MDA of ivermectin can arise from many factors including outbreak of communicable fatal diseases, conflicts and wars. Outbreak of Ebola virus disease interrupted the progress of ivermectin MDA in Liberia [42]. Poor motivation of the village health team volunteers, including non-payment of allowances and no training workshops demoralize and kill their spirit of volunteerism and make them not put in their maximum efforts in MDA. Poor community sensitization and lack of information have also been included as problems faced by the community drug distributors. Poor drug distribution, poor community sensitization and poor incentives have been suggested to be likely responsible for poor distribution and utilization of ivermectin [43].

2.4.8 Correction of misconception of river blindness

Despite created awareness of onchocerciasis, misconception of the disease remains a problem. Some cultural groups have not understood it's a etiology, pathogenesis and preventions. Some associate the disease with wraths of local gods and aging process, whereas others associate appearance of nodules with enhancement in libido during sexual intercourse. Okoye et al. [43] stated that high onchocerciasis transmission in Nigeria has been attributed to many factors, including misconception of the disease by some cultural groups.

Therefore, it is necessary to raise awareness and information about Onchocerciasis among afflicted communities, always using social technology as a base tool, also bearing in mind the continuing education of health professionals, including those who conduct Onchocerciasis elimination and control programs.

2.4.9 Use of gold standard diagnostic techniques

Timely, accurate, and precise diagnosis can be useful contributory efforts to eliminate onchocerciasis in endemic settings in Africa. Use of less sensitive approaches like skin snipping and nodule palpations, practiced in

many resource-constrained countries affects onchocerciasis elimination efforts.

Ivermectin has been reported to decrease the sensitivity of microscopy in detecting microfilariae with skin snips, supporting the need for alternative diagnostic approaches [44]. Decreased sensitivity can lead to misdiagnosis in the sense that at certain levels of low parasite density, skin snip taken after administration of ivermectin may not be able to indicate the presence of the parasite.

Alternative diagnosis include indirect detection of microfilariae with diethylcarbamazine (DEC) patch test, detection of antibodies to Onchocerca antigens, and detection of O. volvulus DNA in skin snips by PCR [44]. Use of quantitative polymerase chain reaction (qPCR) has detected higher prevalence of onchocerciasis infections, when compared with results obtained with conventional skin snip microscopy and palpation [44].

Poolscreen carried on head of the black fly vectors to detect infection with infective stage (L3) larvae accompanied with OV-16 serology test [39] on children less than 10 years of age are required current diagnostic techniques.

Use of results with poor sensitivity and specificity could be very misleading in diagnosis of onchocerciasis especially with regard to mapping out communities where (MDA) should be discontinued. Micro mapping methods could be employed to indicate SAEs in onchocerciasis-loaisis endemic foci [45].

3. CONCLUSION AND RECOMMENDATION

Combining insecticides with chemotherapy, annual or quarterly treatment with ivermectin, use of safe and efficacious microfilaria drugs, replacement of ivermectin with moxidectin, improvement in compliance with ivermectin intake, inclusion of all members of endemic communities where loaisis does not co-exist with onchocerciasis in treatment, effective drug distribution, correcting misconception and use of gold standard diagnostic techniques have been suggested in other to achieve suppression and elimination of onchocerciasis in 2025.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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