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Appraising Onchocerciasis Community Directed Treatment with Ivermectin: Problems, Progress and Prospects

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Summary

Onchocerciasis is a disease complex caused by the nematode worm belonging to the Genus *Onchocerca*. Of the 34 species known, only *Onchocerca volvulus* (Nematoda: Filarioidea) is anthropophilic, others are zoophilic. Onchocerciasis causes dermatological and ocular clinical manifestations, loss in man-hour and disability adjusted life years. The Onchocerciasis Control Programme was established in 1975 in 11 participating countries succeeded in bringing the disease under control except in Sierra Leon due to internal strife. Ivermectin (IVM) was patented for human use in 1987 and generously donated by the manufacturer, Merck Sharp and Dohme (USA) to be distributed free of charge in endemic communities as long as required. This blazed the trail for public private partnership in disease control. The long-term treatment intervention has moved from control to eradication with a worrisome situation of under dosages, therapeutic and geographic under-coverage, diverse treatment compliance rates, and possible emergence of drug resistance. These factors may hamper the attainment of the set goal to break the transmission cycle and eventually eliminate the disease. Deciding when and where to stop treatment will depend on sustained active surveillance and monitoring of control strategy. Recently, IVM was reported to have direct macrofilaricidal action against adult *O. volvulus* worms found to be in deteriorating condition. The search for a macrofilaricidal drugs as an alternative is of high priority because sustaining CDTI remains a major challenge. A dire situation of low economic return on invest is disincentive for drug and diagnostic development for filarial and helminthic diseases an unattractive portfolio to big pharmaceutical and biomedical companies.

Key Words: Elimination status, Ivermectin (Mectizan®), Macrofilaricides, Microfilaricides, Onchocerciasis transmission, Treatment impact, Endosymbiotic *Wolbachia.*

Introduction

Onchocerciasis (synonym: river blindness or 'craw-craw' or Roble's disease) is a disease complex caused by the nematode worm belonging to the Genus *Onchocerca*. Of the 34 species known, only *Onchocerca volvulus* (Nematoda: Filarioidea) is anthropophilic, others are zoophilic. The occurrence of other filarial in sympatric with onchocerciasis has been documented in the Americas and in Africa including Nigeria (Medeiros *et al*., 2009; Morales-Hojas, 2009; Ta Tang *et al*., 2010). Onchocerciasis is the fourth cause of blindness and second cause of infectious blindness after trachoma the world over (Winthrop *et al*., 2011). The adult worms produce microfilariae, which are responsible for the disease pathogenesis by activating the complement system (Meri *et al*., 2002). Onchocerciasis occurs mainly in Africa with more than 99% of the 26 million infected people living in 31 countries in sub-Saharan Africa (WHO, 2014a). Meri *et al*. (2002) found that the adult worms produce microfilariae, which are responsible for disease pathogenesis by activating the complement system. The activation stops before the formation of terminal complement complexes. The *O. volvulus* mf may evade human complement by binding factor H (fH) that promotes inactivation of C3b into iC3b. Prior to commencement of Onchocerciasis control, an estimated 125million people in 37

disease-endemic countries were at risk of infection and 96% of them are in 30 sub-Saharan Africa countries (Figure 1), one in Arabian Peninsula (Yemen) and six Latin America countries (Hodgkin *et al*., 2007) as shown in Figure 2. Onchocerciasis occurs mainly in Africa with about 99% of the 26 million infected people living in 31 countries in sub-Saharan Africa (WHO, 2014a). The Democratic Republic of Congo (DRC) accounted for highest cases of onchocerciasis with 8.3 million (Herricks *et al*., 2017). About 99% of the 18 million infected people live in Africa. As of 1995 about 800,000 were visually impaired, 270,000 were blind and 6.5 million were with severe skin conditions from onchocerciasis. By the year 2016 treatment had been given to 132,883,439 people in Africa, 162,798, Yemen and 20,998 and in Latin America countries (NGDOs, 2018). In Yemen, treatment is ongoing with an estimated 500,000 people at risk (Mahdy *et al*., 2018). In Brazil and Venezuela, there is ongoing treatment in Amazonas focus with 12,787 and in South focus with 14,079 people under treatment, respectively (NGDO, 2021). Figure 3 shows the map of onchocerciasis and (IVM) distribution in Nigeria that account for one third of global onchocerciasis estimates. At least one million are either blind or severely visually disabled and 40,000 blind cases were added each year (WHO, 1995). Nigeria accounts for about 7 million infections, and 32 states including the Federal Capital Territory are endemic excluding Akwa-Ibong, Bayelsa, Delta and Rivers states (FMoH, 2012). Some cases of onchocerciasis have been reported among migrants and residents of Lagos by Hunponu-Wosu and Somorin (1977). The worst endemic foci may be found in Taraba River valley in Northern Nigeria (Akogun *et al*., 1992). Nigeria was undoubtedly ranked first in cases of dracunculiasis (Guinea worm), onchocerciasis (river blindness) and schistosomiasis (Bilharziasis) and third for lymphatic filariasis (LF) or elephantiasis in the world (Njepuome *et al*., 2008). Interestingly, dracunculiasis has been eradicated globally and onchocerciasis has been brought under control and eliminated in some foci. There is remarkable achievement using preventive chemotherapy (PC) for LF and Schistosomiasis (SCH).

Countries of the former Onchocerciasis Control Programme (OCP) in West Africa(1974-2002).

Countries of the on-going African Programme for Onchocerciasis Control (APOC), founded in 1995

Figure 1: Onchocerciasis in Africa – endemic regions and partnership alliances. Annual ivermectin treatment is adopted in the APOC operational areas. Elimination of onchocerciasis have been reported in some foci in Mali, Nigeria, Senegal and Sudan. Source: Tropical Disease Research (2007) (TDRnews) Pre-view No. 79.

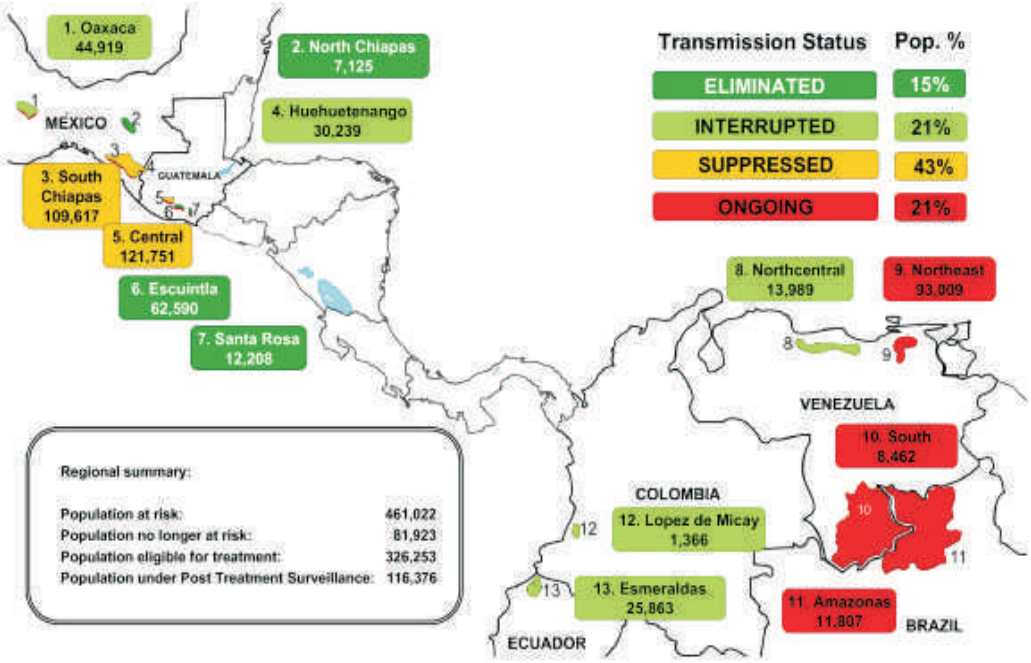

Figure 2: Geographic distribution and transmission status of the 13 onchocerciasis foci in the Americas as of December 2010. Biannual treatment is adopted in the Onchocerciasis Endemic Countries of Americas (OECA). Some foci have been declared to be free of onchocerciasis. Source: Gustavsen *et al*. (2011).

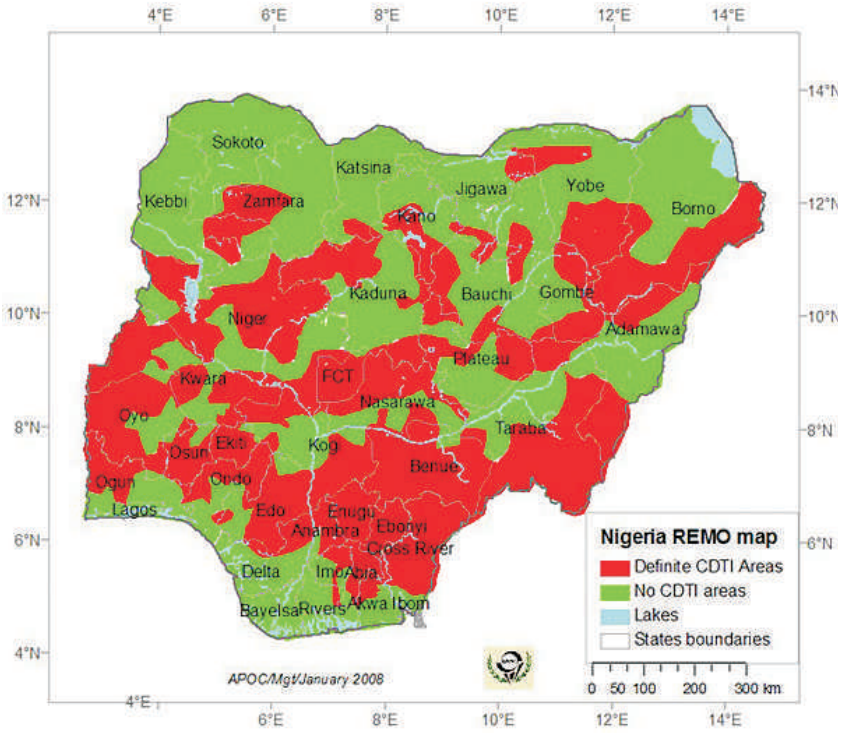

Figure 3: Rapid epidemiological mapping of onchocerciasis in Nigeria 2003. Areas (in red) are where community-directed treatment with ivermectin is needed. Almost all the states are endemic to varying degrees excluding Bayelsa, Delta and Lagos states. Notwithstanding the probable mobile cases of the disease may be found in these three states. Source: WHO/APOC. www.who.int/apoc/countries/nga/en

Clinical Outcome of Onchocerciasis

Although onchocerciasis is insidious and has zero mortality, it causes debility and morbidity associated with various burden of skin clinical manifestations and eye lesions that result in poor vision and blindness (WHO, 1995, Murdoch *et al*., 2002). The *Onchocercal* skin diseases (OSD) are severe pruritis, nodule or onchocercomata, papular and chronic onchodermatitis, dyspigmentation (hypopigmentation and hyperpigmentation), 'leopard skin', localized onchodermatitis or 'sowda', lichenified skin, thick or 'lizard skin', skin atrophy, lympho-adenopathy, hernia, hanging groin, and elephantiasis of scrotum, labia, and leg (Murdoch *et al*., 1993, Murdoch *et al*., 2002). The eye or ocular lesions comprised of anterior segment lesions, microfilariae in anterior chamber, fluffy opacity, punctuate keratitis, chronic iritis, and secondary glaucoma, early and chronic uveitis. The posterior segment lesions are choroid-retinitis, choroid-retinal atrophy, acute optic neuritis, and optic nerve atrophy (WHO, 2014a). Some psycho-social implication of OSD are social isolation, shame and low self-esteem, restlessness/sleeplessness, and marital problems (Okaka *et al*., 2003; Okoye and Onwuliri, 2007; Wogu and Okaka, 2008). The socio-economic effects of the disease are stigmatization, family or community dislocation and relocation, abandonment of fertile arable lands along riverbanks. Onchocerciasis and lymphatic filarial have become a problem of immigrants (Higazi *et al*., 2011; Jimenez *et al*., 2011). Molecular biology diagnostic methods have been shown to be more sensitive than parasitological diagnostic techniques.

Geospatial Data of Vector-Host Interaction

Blackflies form a uniform family Simulidae in the order Diptera. Entomologists have recognized and scientifically named about 1554 *Simulium* species. The blackflies comprise only 1.3% of the 119,000 species of Diptera known to Science (Crosskey, 1990). Disease apart, the blackflies are in many regions feared of all biting insects because of the relentless and intolerable nature of their attack –not only on man, but livestock, poultry, and wildlife (Crosskey, 1990). The name *Simulium* meaning 'little snub-nosed being' was created for the blackflies in 1802 by Pierre Latreille, the great father of French entomology. The fly was first associated with the transmission of onchocerciasis by Robles 1917 (Crosskey, 1990). In West and Central Africa including Nigeria, *Simulium damnosum* complex has 26 cytospecies including *S. damnosum* s. s.*, S. sirbanum* found in Sudan and *Guinea savannas*, *S. squamosum* and *S. santipauli* in forest zone, all breeds in fast flowing rivers with rapids; are the vector of onchocerciasis (Post *et al*., 2011). Blackflies are broadly classified into two groups depending on the vegetation of the ecology of their breeding sites (forest and savannah types). Many of these species are anthrophilic, while few are zoophilic. The 34 known *Onchocerca spp.* are mostly parasites of domestic and wild animals. The blackflies have the ability for long flight, which is associated with intake of carbohydrate through feeding on nectar obtained from flower. The common cytological method of differentiating between these two types is the colour of the wing turf. It is graded as pale or dark in colour with variation in between these extremes. Whether this has any influence on the types of *O. volvulus* causing different clinical manifestations remains unknown. Forest species of the parasite is associated with severe skin manifestations while the savannah type has been known to cause more blindness (Abiose *et al*., 1993). Studies applying molecular biology analytical tools have shown clear biomarkers that distinguished parasites of veterinary importance and between the two human infective strains (Meredith *et al.,* 1991; Herder *et al*., 1994; Adewale *et al*., 2005; Nuchprayoon, *et al*., 2005;Fukuda *et al*., 2008; Fukuda *et al*., 2010a; Fukuda *et al*., 2010b) using genomic finger prints in random amplified polymorphic DNA (RAPD) and restriction fragment length polymorphism (RFLP) based on PCR amplification of random DNA fragments. This may not be readily feasible because of difficulty in breeding blackfly in the laboratory.

People mostly at high risk of infection are those having one or more activities close to the breeding sites. They include miners, tourists, farmers, fishermen, hunters, and bathers. It is well established that the fly can travel long distances up to 140 kilometers to establish new breeding sites. Only an infected black fly can

transmit the disease. Most black flies close to the breeding site are parous (newly emerged young fly) and nulliparous (old fly). When a fly takes its first blood meal it becomes engorged.

Disease Transmission:
When a blackfly feeds on an infected person microfilariae are imbibed with blood meal and they undergo obligate developmental transformation from first to third larval (L1-L3) stages. In subsequent feeding on a human host, the infective L3 stage (one or more) is then transmitted to the susceptible host. Thereafter, it develops into L4 and then an adult worm in about a year within a subcutaneous nodule (onchocercomata) in most cases. The female worms measure between 33 and 50 cm by 270 to 300 μm in diameter, and there may be between 2 and 3 coiled worms in a nodule in subcutaneous connective tissues, while the male worm measure 19 to 42 μm by 130 to 210 μm (Eichner and Renz, 1990). It can move from one nodule to another to inseminate the females (Albiez *et al.*, 1988). A female adult worm *Onchocera volvulus* undergoes ovoviviparous reproduction. Unlike many other filarial species, the motile larvae called microfilariae are not released continuously, but in regular periodic cycles (Schulz-Key and Karam, 1986). About 200,000-400,000 microfilariae are produced at each cycle with an estimated daily release of 1000-3000 microfilariae per female worm *in vivo* (Engelbrecht and Schulz-Key, 1984). As they migrate out from nodules, large numbers of motile microfilariae invade the skin and eye.

Even though microfilariae are found in many tissues, the different skin and eye lesions are responsible for its serious morbidity and debilitating consequences. Yet, there is no indication of any direct parasite attrition or mechanical damage involved in the disease process. With time, the larval forms (microfilariae) and adult worm (macrofilaria) age and die (Duerr *et al*., 2004). Both dead and living worms elicit host inflammatory responses with bystander effects believed to underlie dermal and ocular changes (Ottesen, 1995; Murdoch *et al*., 1996). The presence of dying, dead and the excretory products of living microfilariae contribute to lesions of affected tissues.

Immunopathology of Onchocerciasis
The spectrum of *O. volvulus* infection varies from asymptomatic microfilaridermia often associated with immunological hypo-responsiveness to severe skin and eye diseases including onchodermatitis and blindness. Establishment of infection and disease development are dependent on the specific antigen recognition and immune response of the host. The complex immune response is triggered by numerous different filarial antigens at the same time. To elucidate the mechanism of the immune response, it is essential to explore the specific reactions to individual, native parasite antigens. From all indications, it is obvious that the varied clinical manifestations of onchocerciasis are not due to direct parasite attrition. The co-factors of immune responses implicated in causing dermal and ocular lesions have been reviewed by Eezzuduemhoi and Wilson (2006); Sinha and Schwartz (2006) and Udall (2007). From experiments with rabbits, it has been shown that eosinophils and lymphocytes attach to microfilaria in the stromal cornea. The basic underlying factor in the pathology is due to excessive degranulation of eosinophil thereby releasing protein substances that may be toxic to host tissues.

The role of immune responses in pathogenesis of onchocerciasis has been attributed to involvement of antibody dependent cytoadherence (ADC). This phenomenon very much supported the role eosinophils and lymphocytes play in microfilariae clearance and tissue damage (Cooper *et al*., 1999a). After treatment with anthelmintic, the eosinophil count falls initially because of rapid migration from peripheral blood to the skin. Cataract is associated with visual impairment as reported by Nmorsi *et al.* (2002) despite IVM's treatment.

Clinical Manifestations of Onchocerciasis
The disease is broadly classified into dermatological and ocular manifestations. Briefly, the various skin clinical changes commonly referred to as OSD have been fully described and classified by Murdoch *et al.* (2002). They include acute papular onchodermatitis which involves numerous small pruritic papules that may progress to vesicles or pustules and chronic papular

onchodermatitis indicated by larger, flat-topped papules distributed symmetrically over the buttocks, waist, and shoulders. Others are skin atrophy, lichenified skin, leopard skin resulting from patchy dyspigmentation of skin mostly around the shin, hyper-pigmentation or 'Sowda', and palpable nodule or onchocercomata containing worms. Hanging groin or inguinal lymphadenopathy, elephantiasis (involving the scrotum, labia and legs) is also observed. Important dermatological symptoms associated with the disease include severe itching and musculoskeletal pain (MSP). In addition to contributing to loss in man-hour, the disease has been reported to contribute to increasing the disability adjusted life years (DALYs). Of recent, infection in children $\leq$ 5 years showed high propensity to develop nodding syndrome or onchocerciasis-associated epilepsy (OAE) as observed in Cameroon (Pion *et al*., 2009, Chesnais *et al*., 2018, Colebunders *et al*., 2018). The OAE syndrome was first detected in East Africa and onchocerciasis was suspected to be the cause but proved very difficult to substantiate then.

The ocular lesions are categorized as anterior and posterior clinical manifestations which to a greater extent determine if the blindness, they cause is reversible or irreversible. Among the anterior lesions are microfilaria in anterior chamber (MFAC), punctate keratitis which may or may not be inflammatory, corneal opacity, cataract or opacity of the lens, iritis (Kayembe *et al*., 2003). The posterior lesion involves the sclerosing keratitis, uveitis, optic nerve disease or atrophy. Others are glaucoma or cupping of the optic nerve due to high ocular pressure more than 150 mm Hg (WHO 2014b). Similarly, the global estimated visual impairment of over 1 million people and 360,000 blind cases is projected to reduce the disability adjusted life expectancy (DALE) by 10 years (Hodgkin *et al*., 2007). This is apart from the social stigmatization of affected person with disfigurement, family dislocation and school dropout due to blindness. Okoye and Onwuliri (2007) have reported that low self-esteem, withdrawal syndrome, restlessness, and other psycho-social problems were associated with OSD.

Aerial-wide Vector and Disease Transmission Control Strategies

Two early control strategies hitherto depend on larviciding, and erstwhile use of diethylcarbamazine citrate (DEC) and Suramin chemotherapy had proved unsuitable for mass drug administration (MDA). In addition, the toxicity of DEC causes “Mazzotti reaction” while Suramin induces serious eye complications (WHO, 1995). Large-scale nodulectomy was also attempted but without success. These methods failed because of several limitations including insecticidal resistance by the vector, hazard to the environment, and cost given the vast landmass to be covered. The onchocerciasis control Programme (OCP) was established in 1974 and came to an end in 2000 with 11 participating West African countries. The programme succeeded in bringing the disease under control except in Sierra Leon due to internal strife (WHO, 1995). After patenting IVM for human use in 1987, and with the generous donation by the manufacturer, Merck Sharp and Dohme (USA) to provide the drug free of charge to endemic communities if required became the very foundation for public and private partnership in disease control. Noma *et al*. (2014) provided the rapid epidemiological mapping of the 20 countries participating in APOC where ivermectin treatment distribution did not cover and areas with *Loa loa* co-endemicity (Zoure *et al*., 2011).

Onchocerciasis Elimination Program for the Americas (OEPA) was created in 1991 (WHO, 1995). The distribution of Mectizan started in Nigeria in 1992 under the National Primary Health Care (PHC). African Programme for Onchocerciasis Control (APOC) was established in 1995 to ensure the community directed treatment with ivermectin (CDTI) using community-based distributors (CBDs) was put in place in all meso- and hyper endemic communities. There are other non-governmental development organizations (NGDOs) involved in IVM or Mectizan® distribution (Bush *et al*., 2011). Onchocerciasis is among the group of 10 neglected tropical diseases (NTDs) within the programme of the Federal Ministry of Health. The strategic goal is to progressively reduce morbidity, disability, and mortality due to NTDs

using integrated and cost-effective approaches with a view to eliminating NTDs in Nigeria (FMoH, 2012). It has a timeframe that aligned with the public and private stakeholders of London Declaration by public and private stakeholders' resolution to eradicate 10 neglected tropical diseases by 2020 (Uniting to Combat NTDs, 2012). Progress in attaining this goal was appraised in 2013 (Uniting to Combat NTDs, 2014; Turner *et al*., 2014a).

Lately, the stage of intervention has moved from control to elimination phase (APOC, 2011a). A worrisome situation is the reports from studies that have shown differences in both geographic and therapeutic coverage and diverse treatment compliance rates (Yirga *et al*., 2010; WHO, 2011a). Reports emanating from Cameroon and Ghana indicated the continued transmission and prevalence of the disease despite long term mass drug distribution (Katabarwa *et al*., 2013; Eisenbarth *et al*., 2016). Such occurrence may likely be linked to growing cases of infected children $\leq$ 5-year-old that were excluded from IVM treatment based on exclusion criteria. In a study conducted by Gebrezgabiher *et al*. (2022) in Ethiopia found that of the 366 individuals (13%) were not offered IVM; 47(12.8%), 143(39.1%), and 176(48.1%) did not receive the drug because of program implementation-related reasons, ineligibility criteria, and personal issues, respectively. Maduka *et al*. (2004) found that among women of reproductive age, 35% (599/1714) were excluded due to pregnancy or nursing babies aged <1 month. Many of them did not receive treatment within year 2000 rounds of mass treatment and many were not aware of the short duration of exclusion and as nursing mothers could have located and taken treatment thereafter. Other factors include inadequate supplies of IVM, lack of supervision and monetary incentives led to significant increases in CDD attrition (Emuka *et al*., 2008). On the contrary, they found that CDD retention was significantly enhanced when distributors were selected by their community members, supervised, supplied with adequate IVM tablets, educating community members and/or involved in other health programmes.

It could be attributed to possible poor or sub-optimal response to IVM. In addition to this, is the fear that drug resistance and a reduction in effectiveness of drugs in use could emerge as reported for IVM treatment of other helminthes (De Clercq *et al*., 1997, Albonico *et al*., 2003, Osei-Atweneboana *et al*., 2011). Adherence to CDTI was positively influenced by perceived health benefits, and negatively influenced by fear of adverse events linked with economic loss. Concern of lethal adverse events was a common reason for systematic non- adherence (Forrer *et al*., 2021). Treatment failure that may arise from the adaptation of the parasites or the hosts to IVM (Churcher *et al*., 2009) could hamper the success of the control programs. Resistance has occurred in several veterinary parasitic nematodes (Kaplan, 2004), and in human helminthic infections (Albonico *et al*., 2003). All these factors will no doubt hinder the attainment of the set goal to break the cycle of transmission, which will eventually lead to elimination and eradication of the disease. Deciding when and where to stop treatment will depend on sustained active surveillance and monitoring of control strategy.

A national programme for mass treatment of onchocerciasis with Mectizan® or IVM started in Nigeria in 1992 under the Primary Health Care (PHC) programme. It was later renamed community directed treatment of onchocerciasis with ivermectin (CDTI). Eligible residents of the endemic communities in sub-Saharan Africa receive treatment once a year (annual) while bye-annual treatment was adopted in Onchocerciasis Endemic American Countries (OEAC). With the adoption of this strategy, epidemiologic indices of the disease were expected to change. A study in parts of Cameroon by Duerr *et al.* (2010) established there was strong relationship between low infection rates in children, which increased with age in adults, is evidence that a factor may be responsible. It may be attributed to reduced level of host-blackfly contact and higher risk of exposure to infection. According to the projection of FMoH (2012) all the 32 endemic States and the FCT have reached the minimum standard of therapeutic coverage (65%). With the huge success already recorded in bringing the disease under control, it is now at the elimination stage. This fit was achieved faster in the OECA where biannual CDTI (bCDTI) is practiced,

while it took longer time to attain a similar outcome in APOC operational countries where annual CDTI (aCDTI) is in place (Turner *et al*., 2013; Turner *et al*., 2014b). One very strong limitation identified so far is the low or non-compliance to treatment that can thwart the effort to achieve elimination and eventual eradication if certain places where this problem exist persist (Katabarwa *et al*, 2011; Katabarwa *et al*., 2013). Perceptions about the SAEs are core reasons for non-compliance whose rates are very high in places where transmission have been ongoing despite long-term IVM treatments (Senyonjo *et al*., 2016, Duamor *et al*., 2017). Interventions to improve compliance in the area should focus on health education using epidemiological data to increase risk perception and dispelling misconceptions (Yirga *et al*., 2010). The map of onchocerciasis endemicity levels has proven very valuable for onchocerciasis control in the APOC countries (Zoure *et al*., 2014) particularly for planning treatment, evaluating impact, and predicting treatment end dates in relation to local endemicity levels.

Current Control of Onchocerciasis

The best preventive measure for onchocerciasis is eliminating the vectors (*Simulium spp.)* and the *Onchocerca volvulus* microfilariae from the host (Ndyomugyenyi *et al*., 2004). The feat achieved by the Onchocerciasis Control Programme (OCP) in 11 countries of West Africa prompted other donor agencies and stakeholders to initiate the control of the disease in other 19 endemic countries of sub-Saharan Africa and the elimination of the disease in the Americas. Following the discovery of its microfilaricidal activity, and its being well tolerated, IVM or Mectizan® was adjudged suitable for mass treatment (Aziz *et al.*, 1982; Boatin *et al*., 1998; Remme *et al*., 1995; 2002). After undergoing the stages of clinical trials in human, it was patented for use. This evolved a unique public private partnership that paved way for the birth of the African Programme for Onchocerciasis Control (APOC) and Onchocerciasis Elimination Programme of the Americas (OEPA) that institute annual and biannual treatment strategy (Blanks *et al*., 1998; Colatrella, 2003; Gustavsen *et al*., 2011). The suitability of IVM for mass treatment depends on its mode of action by disrupting the invertebrate neuro-transmission involving gamma-amino butyric acid, i.e. GABA channels (Campbell, 1985). In contrast to the two previous drugs in use, IVM (Stromectol, Mectizan®, Appendix II) a semi-synthetic macrocyclic lactone produced by *Streptococcus ivermetilis* was found to be free from serious side effects. Cases of severe adverse drug reaction have been documented (Twum-Danso and Meredith, 2003) and did not differ significantly with history of consumption of alcoholic beverages (Takougang *et al*., 2008). This drug was initially patented and widely used as a broad-spectrum veterinary nematicide. Merck and Co. USA generously donated drug, IVM free of charge as long as needed by disease endemic communities.

Community directed treatment with ivermectin in Nigeria

The current control by mass drug administration (MDA) with IVM or Mectizan® (Merck Sharp and Dome (MSD) was started in 1988 (Remme *et al*., 2002; Amazigo and Boatin, 2005) after it was first licensed for human use in 1987. This innovation was awarded Nobel Price for Physiology or Medicine jointly to Dr. William Campbell, MSD and Prof. Santosh-Omura of the Kitasato Institute for developing and use of IVM for onchocerciasis treatment. MDA later evolved into community directed treatment of onchocerciasis with ivermectin (CDTI) using trained community-based distributors (CBDs). The control strategy has proven effective, disease burden is falling, and elimination is planned (Emuka *et al*., 2004, WHO, 2005). There are issues of under dose, therapeutic and geographic under-coverage observed by Remme *et al*. (2007). The issue of serious concern is the non-adherence to treatment consequent to fears of lethal SAEs particularly in most areas where onchocerciasis and loasis are co-endemic (Forrer *et al*., 2021) is complicit in the ongoing transmission in areas enlisted long-time (15-25 years) for aCDTI. The search for a macrofilaricide remains a top priority because sustaining CDTI will continue to remain a major challenge. Effectiveness of this strategy depends on high geographic and demographic therapeutic coverage of endemic communities as observed by Akinboye *et al*. (2010) in small farming settlement in Oyo State, Nigeria. There are

reports of prevalence of onchocerciasis and palpable nodules in rain forest south eastern parts of Nigeria by Abanobi 2010; Iroha *et al*. (2010) and Okoro *et al*. 2014). Ivermectin treatment distribution within the study areas and treatment compliance were lacking. Report from Cameroon showed persistence of transmission in two communities with meso-endemicity despite long time aCDTI was temporally attributed to onchocerciasis infected children $\leq$ 5 yrs old following the exclusion criteria (Kamga *et al*., 2016). Study by Okeibunor *et al*. (2011) showed the drug had improved social, psychological, and economic well-being of the people. Yet, there are fears been entertained on the probable failure of aCDTI to attain the desired goal to control/eliminate onchocerciasis and possible resurgence of transmission following the winding up of APOC in 2015. To expand NTD programmes across Africa, the WHO created the Expanded Special Project for the Elimination of NTDs (ESPEN) in 2016, broadening the NTD agenda and absorbing APOC activities (Hopkins 2016, NGDO, 2018). It is more desirable now because of the inherent benefits derivable from integrated disease and/or vector management (IDM/IVM), which appeared to be more cost-effective by reducing waste and optimizing gains.

Possibility of development of drug resistance to ivermectin

So far, no proven resistance to IVM treatment has been reported except sub-optimal response (SOR) to treatment in terms of rapid repopulation of skin with mf as observed in individuals in Ghana (Awadzi *et al*., 2004; Osei-Atweneboana *et al*., 2007; Churcher *et al*., 2009; Osei-Atweneboana *et al*., 2011). There is growing apprehension of *O. volvulus* developing resistance to IVM (Awadzi *et al*., 2004a; Awadzi *et al*., 2004b; Osei-Atweneboana *et al*., 2011, Mackenzie *et al*., 2012) attributed to genetic basis associated with selection on ATP-binding cassette (ABC) transporters (e.g. P-glycoproteins), and α- tubulin (Ardelli and Prichard, 2004; Ardelli and Prichard, 2007; Bourguinat *et al*., 2008; Taylor *et al*., 2009; Nana-Djeunga, *et al*., 2012). The IVM resistance is found in some parasites of veterinary importance like *Haemonchus contortus* and *Cooperia oonchophera* by Blackhall *et al*. (2003) and Njue *et al*. (2004) identify cases of sub-optimal response. Similarly, resistance to the related drug, moxidectin has been documented and IVM-treated patients have shown decreased diversity at many genetic loci for P-glycoprotein (Ardelli *et al*., 2005; Eng and Prichard, 2005), suggesting changes in allelic patterns that may lead to resistance. Thirdly, there may be selection of O. *volvulus* more refractory to ivermectin occurring in areas with higher drug pressure due to long-term CDTI (Doyle *et al*., 2017) as observed in Cameroon and Ghana.

Macrofilaricidal action of ivermectin

It has been concluded that IVM *per se* has direct macrofilaricidal action against adult female worms (Duke, 2005). Many reports indicated the effect of IVM on the population of adult worms of *O. volvulus* were found to be in deteriorating condition as observed in Mexico, Guatemala and Ecuador (Nana-Djeunga *et al.*, 2014). This is indicative that semi-annual IVM treatment of 6 years has had a profound effect on survival and reproduction of this species (Duke *et al*., 1991; Rodríguez-Pérez*et al*., 2008a; Rodríguez-Pérez*et al*., 2008b). Results showed that both strategies had achieved elimination after 15 to 17 years of treatment (Mackenzie *et al*., 2012). At the same time, up to 5% of untreated female *Onchocerca volvulus* filariae develop potentially fatal pleomorphic neoplasms, whose incidence is increased following IVM treatment.

Expansion of community directed treatment with ivermectin (CDTI)

In 1998 Merck expanded the donation of Mectizan to include the Programme for the Elimination of Lymphatic Filariasis (PELF) in 28 countries in African and Yemen where both diseases are co-endemic (Alleman *et al*., 2005; Thylefors and Alleman, 2006; Thylefors *et al*., 2008). Nigeria is co-endemic with many neglected tropical diseases (Fig. 4). The study area is within the zone endemic for leprosy, lymphatic filariasis, malaria, onchocerciasis, and schistosomiasis (FMoH, 2012). Mectizan is indicated for the treatment of onchocerciasis caused by *Onchocerca volvulus* and for the treatment of microfilardermia caused by infection with *Wuchereria bancrofti*, the causative agent of LF in Africa. Cases of adverse

reaction (AR) to IVM treatment have been documented in areas co-endemic with *O. volvulus* and *Loa loa* as observed by Chippaux *et al*. (1996); Gardon *et al*. 1997; Boussinesq *et al*. (1998); Otubanjo *et al.* (2008) including parts of South-west Nigeria. More intense surveillance and monitoring in the first 2 days after mass distribution in ivermectin-naive populations would assist in early recognition, referral, and management of these cases (Twum-Danso and Meredith, 2003). These severe adverse events (SAE) include probable *L. loa* encephalopathy temporally related to Mectizan-treatment (PLERM) has not been reported in Nigeria. As Kipp *et al*. (2005) had observed that IVM can safely be used for mass treatment in areas where the prevalence of onchocerciasis and HIV-1 infection are high.

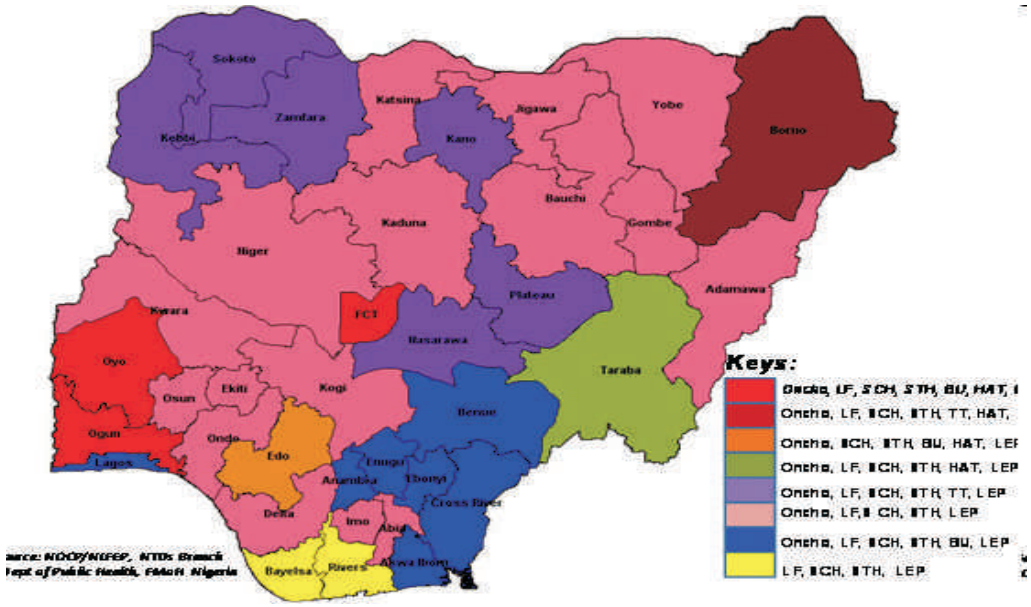

Figure 4: Neglected Tropical Diseases Co-endemicity Map of Nigeria. Nigeria is one of the countries that are co-endemic of neglected tropical diseases (NTDs). Only Bayelsa and Rivers States are non-endemic for onchocerciasis. BU= Buruli ulcer, HAT= human African trypansomiasis, LEP= leprosy, LF=lymphatic filariasis, Oncho= onchocerciasis, SCH- schistosomiasis, and STH= Soil transmitted helminthes. Source: FMoH (2012).

Impact of CDTI on onchocerciasis epidemiological status

Extensive evaluation of the CDTI control strategy carried out in selected foci in Kaduna state, Nigeria and parts of Latin American countries showed that prevalence and skin microfilariae loads were reduced to zero or thereabout (Guderian *et al*., 1997; Lindblade *et al*., 2007; Gonzalez *et. al*., 2009; WHO, 2011; **Cruz-Ortiz *et al*.,2012**). Using bi-annual CDTI (bCDTI) in the Americas transmission was interrupted in 11 out of the 13 foci or 4 out of 6 countries; Brazil, Colombia, Ecuador, Guatemala, Mexico, and Venezuela (Gustavesen *et al*., 2011). Nigeria with the largest population at risk of infection and highest rate of infection after Democratic Republic of Congo (DRC) and has recorded modest level of onchocerciasis transmission interruption in three (Kaduna, Kebbi and Gombe States) out of the 36 states including the Federal Capital Territory, Abuja. Although the public health risk of the disease may no longer be the same, availability of macrofilaricides will ensure elimination through a shorter time sustained distribution (Alley *et al*., 2001). Reduction in transmission after 5-8 years of annual IVM treatment has been reported (Collins *et al*., 1992; Borsboom *et al*., 1997; Opara and Fagbemi, 2008; APOC, 2011a). Eradication of the disease has been recorded in 3 hyper-endemic foci in Mali and Senegal after annual or six monthly IVM treatment ((Diawara *et al*., 2009, Traore *et al*., 2012) and in Abu Hamed focus in northern Sudan (Binnawi, 2013; Higazi *et al*., 2011, 2013) and in

Wadelai focus of Ugandan (Katabarwa *et al*., 2012) using aCDTI. Other areas where elimination have been attained include isolated focus in Yemen (NGDO, 2018) and some of the Onchocerciasis Endemic Countries of Americas (OECA) particularly in places like Santa Rosa focus of Guatemala (Lindblade *et al*., 2007; Cruz-Ortis *et al*., 2012), from Northern and Southern Chiapas and Oaxaca focus in Mexico (Rodriguez-Perez *et al*., 2008a; Rodriguez-Perrez *et al*., 2008b; Sauerbrey, 2008, Rodriguez-Perrez *et al*., 2013a) using twice a year IVM treatment strategy which commenced in 1994 (Fig. 5). In these foci, no more evidence of on-going transmission was found from their studies. Ndyomugyenyi *et al*. (2004); Mackenzie *et al*. (2012) had observed that twice yearly treatment alone or annual treatment with IVM coupled with vector control, infection rates continued to fall implying that interruption of transmission could be rapidly attained.

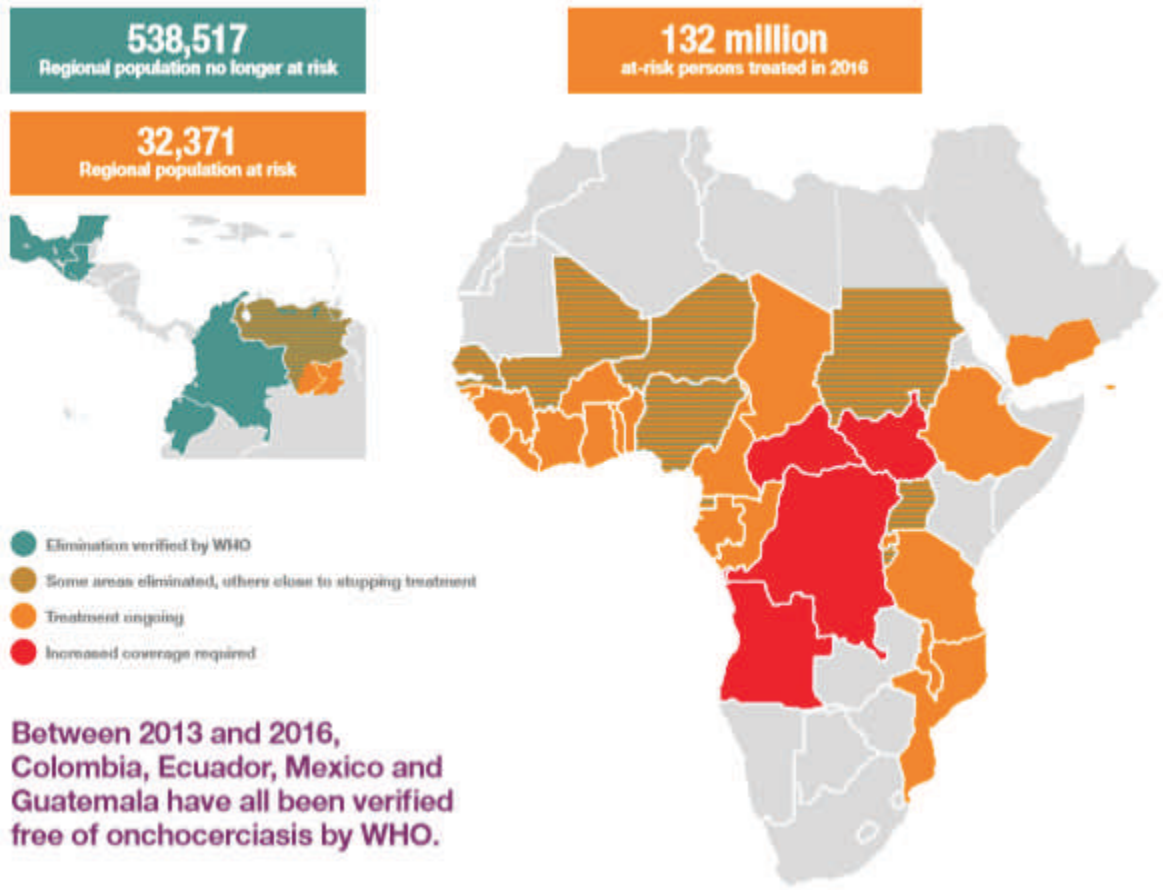

Figure 5: Onchocerciasis distribution in the Americas (left) Onchocerciasis distribution in Africa and Yemen (right). Source: NGDO group for onchocerciasis elimination.

Onchocerciasis is responsible for an estimated one million disability adjusted life years (DALYs) and disability adjusted life expectancy (DALE) reduced by 10-13 years (WHO, 1995). African Programme for Onchocerciasis Control (APOC) estimated that between 1995 and 2010, mass treatment with IVM averted 8.2 million DALYs due to onchocerciasis in APOC areas, at a nominal cost of about US$257 million. It was expected that APOC will avert another 9.2 million DALYs between 2011 and 2015, at a nominal cost of US$221 million (Coffeng *et al*., 2013). It reduces immunity and resistance to other diseases and interferes with immunization (Cooper *et al*., 1999b; Abraham et al., 2002). Onchocerciasis is responsible for man hour loss, impedes optimal land use for sustainable agricultural and rural development and limits national self-sufficiency in food production.

Effect of ivermectin treatment on adult worm

Lately, there are strong supporting observations from field surveys, the impact of IVM treatment on adult worms leading to death as highly significant increase in the number of moribund/dead female worms per nodule were observed (Plaisier *et al*., 1995; Cupp *et al*., 2004; Cupp and Cupp, 2005). Ivermectin had an embryostatic effect on *O. volvulus*, but the effect was reduced in the frequently treated cohort compared with the control population (Nana-Djeunga *et al*., 2014). Therefore, complaint of nodule remission or dissolutions or disappearance has been reported from studies carried out at Imo and Kaduna States of Nigeria by Ukaga *et al*., (2000); Emuka *et al.* (2004); Osue *et al.* (2013). Preponderance of higher number of such cases were more prevalent in OEPA areas where bi-annual treatment as against annual treatment was adopted in Sub-Saharan Africa. Comparable macrofilaricidal effect of annual and quarterly IVM treatments from field trials resulted in magnitude of 50% and 70% reduction, respectively in adult worm life-expectancy (Gardon *et al*., 2002). Walker *et al*. (2017) and Campillo *et al*. (2020) model data analysis suggestive of repeated doses and quarterly IVM treatments may result in macrofilaricidal action and reduce the incidence of new nodules been formed compared to annual treatments.

In one study, a long-term repopulation of the skin after single dose treatment was recorded by Awadzi *et al.* (2004). Three main possible challenges for onchocerciasis control have been identified: (1) how can adequate treatment coverage with IVM be established and sustained in those African settings where MDA is indicated?; (2) what are the means to determine where and when treatment can be stopped?; and (3) how does one ensure effective surveillance in areas where active control has come to an end? (Hodgkin *et al*., 2007). In some quarters, there is growing advocacy for targeted treatment. The ease of identifying target population is very critical as the cost of CDTI per dose delivered may be less than targeted therapy unless screening method is inexpensive (Poolman and Galvani, 2006). Therefore, the need for macrofilaricide against *O. volvulus* cannot be underscored. There are conflicting reports on the impact of repeated aCDTI and bCDTI on female worm fecundity was only of little effect (Bottomly *et al*., 2008, Pion *et al*., 2013). This, coupled with non-deployment of the newly patented drugs; moxidectin and doxycycline, and inability to attain geographical and population treatment coverage (optimal therapeutic coverage and treatment compliance) have brought the targeted elimination date for 2025 to serious scrutiny of it feasibility in these circumstances (Dadzie *et al*., 2018).

Criteria for cessation of ivermectin treatment

The plan for certification of the elimination of onchocerciasis developed by OEPA is made up of four phases (WHO, 2001b). Phase I includes IVM treatment for 2–4 years, which results in suppression of transmission. In phase II, suppression is maintained through treatment of the mean reproductive lifespan of the adult female (approximately 13–14 years). Anti-*O. volvulus* antibodies were not found in samples from non-endemic controls from Mexico, but 3 of 71 samples from residents in the onchocerciasis area of Oaxaca, Mexico, and who have been under IVM treatment during the last 10 years were only positive to IgG. No IgG_4 isotype was detected, and low (4.2%) anti-*O. volvulus* IgG antibody prevalence was found (Gómez-Priego *et al*., 2005). After this, (in phase III), it was expected that the adult parasite population would die by senescence and maintaining the suppression of transmission will no longer be dependent on IVM distribution. Thus, in phase III, IVM distribution will cease, and intensive surveillance will be conducted to document that transmission will not re-develop. Finally, in phase IV, the elimination of the *O. volvulus* infection will be certified. Going by the APOC initial work plan for the control, elimination and eradication of Onchocerciasis was hinged solely on ivermectin/Mectizan MDA. Though attained substantial level of impact but has been beclouded with daunting threat and challenges. This includes possible re-infection from hypo-endemic areas not covered by ongoing CDTI, those excluded based on the exclusion criteria for the use of IVM serving as reservoir for re-infection, and the waning of stakeholders' interest, supports and participation due to long-time implementation induced fatigues and apathy have all come to play

(Coffeng *et al*., 2013). Fears have been expressed that these situations may erode the gains already made over three decades ago when the current IVM treatment strategy was conceived, then conceptualized and its implementation was globally galvanized. In Uganda, the combined vector and IVM treatment approach has yielded good results facilitating early stoppage of MDA as reported by Ndyomugyenyi *et al*. (2009). Targeted fly control during the peak of the dry spell when the migration or dispersal will be limited by very low humidity and high incidence solar radiation (ISR) that restricted the tsetse flies to their breeding sites (Osue, 2017) is also applicable to blackfly control. Within the 3 years post-treatment surveillance period (WHO, 2001) requires that recrudescence is absent when no evidence of recurrent transmission has occurred based on polymerase chain reaction (PCR) testing for *O. volvulus* DNA in a substantial sample of parous vectors (blackflies). Any evidence of infection demands that serologic antibody testing (Ov1.6 ELISA) in children less than ten years of age be carried out and those positive be confirmed by PCR testing of skin snip following the procedure on Fig. 7.

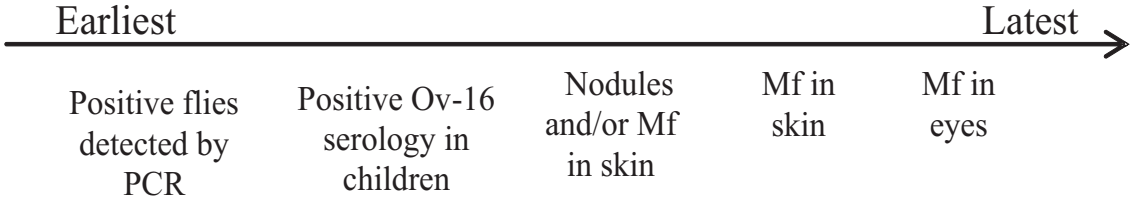

Figure 7: Sequential steps in the evolution of onchocerciasis recrudescence. Abbreviations: Mf, microfilariae; Ov-16, recombinant antigen of *O. volvulus*; PCR, polymerase chain reaction. Source: Cupp *et al*. (2012).

Research and Development for Macrofilaricides

Even though there is a control tool in place for onchocerciasis, the door for research and development into the disease has not closed. One important aspect is in drug screening for macrofilaricide. Advances made so far are the clinical trial of vibramycin (doxycycline) from Pfizer Company, Germany at 100 mg/day for 6-8 weeks eliminate endosymbiotic *Wolbachia* bacteria (Hoerauf *et al*., 2001). Also, a trial with rifampicin treatment administered for 2 to 4 weeks have shown some promise of clearing the *Wolbachia* bacteria endosymbiont of *O. volvulus* (Specht *et al*., 2008). It has been established that moxidectin sterilizes adult worms (Tagboto and Townson, 1996). Both drugs reduce microfilarial loads and decrease adult worm viability. From mathematical model it has been predicted that availability of a 100% effective macrofilaricide and 100% coverage, elimination could be achieved instantaneous (Alley *et al*., 2001; Hodgkin *et al*., 2007; Turner *et al*., 2014a). Whatever control is in place, there could be emergence of recrudescence and pocket of hypo-endemic foci that may not be enlisted for treatment. Most filarial parasites of humans and domestic animals contain a bacterial endosymbiont (*Wolbachia pipientis*) which is involved in the process of development and reproduction (Taylor *et al*., 2005). Antibiotic treatments that clear *Wolbachia* cause stunted growth, infertility, and eventual death of adult filarial worms (Hoerauf *et al*., 2001; Hoerauf *et al*., 2003a; Hoerauf *et al*., 2009) can readily serve as drug target of biochemical pathways or processes (Slatko *et al*., 2010). Also, RNA interference and gene deletion in *C. elegans* further showed that N-myristoyltransferase (NMT) is essential for nematode viability. The effects observed are likely due to disruption of the function of several downstream target proteins (Sheng *et al*., 2010; Wright *et al*., 2010; Galvin *et al*., 2014). The authors have suggested that targeting NMT could be a valid approach for the development of chemotherapeutic agents against nematode diseases including filariasis. Recently, Bhabak *et al*. 2011; Madeira *et al*. 2011; Bulman *et al*. (2015) reported that triethylphosphine gold or deacetylated auranofin, a gold-containing drug used for rheumatoid arthritis, was effective *in vitro* in killing both *Brugia* spp. and *O. ochengi* adult worms and in inhibiting the molting of L3s of *O.*

volvulus with IC_{50} values in the low micromola r to nanomolar range. According to Bulman *et al*. (2015), auranofin may be beneficial if used in areas where *Onchocerca* and *Brugia* are co-endemic with *L. loa*, to prevent severe adverse reactions to the drug-induced death of *L. loa* microfilariae.

Wolbachia* Bacterial Endosymbiont of *O. volvulus

Wolbachia is an endosymbiotic bacterium of the major human and animal filarial worms such as *Brugia malayi*, *B. pahangi*, *Wuchereria bancrofti*, *Onchocerca volvulus*, *O. ochengi*, *Ogibsoni*, *O. gutturosa*, *Dirofilaria immitis*, *D. repens*, *Litomosoides sigmodontis* (Bandi *et al*., 1998; Taylor *et al*., 1999; Taylor *et al*., 2005). *Acanthocheilonema viteae, Chandlerella quiscali*, *L. loa, O. flexuosa* and *Setaria digitata* are *Wolbachia*-free (McNulty *et al*., 2012a). Differences have been reported by Fenn *et al* (2006) on *Wolbachia*, a bacterium that belongs to the Anaplasmataceae in the Rickettsiales, comprise of a diverse group of intracellular symbionts. In other Rickettsiales, the symbiosis is usually parasitic or pathogenic, and many of these bacteria cause significant human and veterinary disease problems (Tamarozzi *et al*., 2011). *Wolbachia* increase the number and degranulation of mast cells at the site of infection, resulting in greater vascular permeability (Specht *et al*., 2011). Rickettsiales have also been identified as symbionts of arthropods and are implicated in causing reproductive manipulations in their hosts like those of *Wolbachia*.

Parasitic filarial nematodes of the Onchocercidae, including several major human pathogens, harbour intracellular *Wolbachia* (Sironi *et al*., 1995). No other nematodes are known to harbour *Wolbachia* (Bordenstein *et al*., 2003), though other nematode–bacterial symbioses are common. In the onchocercids, the *Wolbachia* can be divided into two major clades, C and D (Bandi *et al*., 1998), which, unlike the arthropod *Wolbachia* clades, show phylogenetic congruence, with their hosts (Casiraghi *et al*., 2001; 2004). Killing the bacteria with tetracycline affects nematode growth, moulting, fecundity, and lifespan (Bandi *et al*., 1999; Hoerauf *et al*., 1999; Langworthy *et al*., 2000; Smith and Rajan, 2000). In arthropods, in most cases, tetracycline treatment yields cured, healthy hosts, and related parasitic nematodes that do not harbour *Wolbachia* are unaffected by treatment (Hoerauf *et al*., 1999; Smith and Rajan, 2000; Trees *et al*., 2000; Casiraghi *et al*., 2001). There is significant reduction in *Onchocerca ochengi* nodules through absorption process in tetracycline treated cattle (Bah *et al*., 2014). On the other hand, Sinkins and Gould (2006) and McMeniman *et al.* (2009) concluded that *Wolbachia* is a potential biological control agent of vector for spreading desirable genetic modifications in insects.

Several filarial species are major human pathogens, and antibiotics with activity against *Wolbachia* offer a promising new therapeutic approach since the adult worms are relatively refractory to conventional anthelmintics but depend on *Wolbachia* for reproduction and viability. Makepeace *et al.* (2006) found that in a natural filarial parasite of cattle, *Onchocerca ochengi*, intermittent chemotherapy is adulticidal whereas the equivalent dose administered as a continuous treatment is not. The authors recorded the accelerated depletion of bacteria after antibiotic withdrawal relative to the rate of elimination in the continuous presence of the drug. Comparisons between the mitochondrial genome sequences of *Wolbachia*-dependent and independent filarial worms may reveal differences indicative of altered mitochondrial function (McNulty *et al*., 2012b). The authors found that 9 mitochondrial genomes were similar in size and AT content and encoded the same 12 protein-coding genes, 22 tRNAs and 2 rRNAs. Synteny was perfectly preserved in all species except *Chandlerella quiscali,* which had a different order for 5 tRNA genes. Protein-coding genes were expressed at the RNA level in all examined species. In phylogenetic trees based on mitochondrial protein-coding sequences, species did not cluster according to *Wolbachia* dependence.

Macrofilaricidal activities of some antibiotics

Moxidectin clinical trials and commercialization was another breakthrough in the search for filaricidal drug discovery. Just like ivermectin, moxidectin, a drug used in veterinary medicine was found to have promising macrofilaricidal activity in animal models (Langworthy *et al*.,

2000). Moxidectin is a fermentation product from *Streptomyces cyanoeogriseus* var. *noncyanogenus*. It is chemically related to the nematocides, is a milbamycin compound and like IVM, it has been used extensively in veterinary medicine. Moxidectin had proven to be more potent than IVM (Tagboto and Townson, 1996). It is feared that any resistance to IVM may be shared by moxidectin because they are closely related (Shoop, 2003; Townson *et al*., 2006). Like ivermectin, it has microfilaicidal effect and the macrofilaricide action may be cumulative reduction in embryogenesis (Mackenzie *et al*., 2011; 2014, Turner *et al*., 2014a). Already, results from the pre-clinical studies carried out showed that the compound fulfilled the criteria for a potential macrofilaricide (TDR 2007). This drug has been reported to kill adult worms after a single treatment. It has been found to produce 'slow' death of adult worms in girds and dogs, sterilization of worms in cattle.

The longer plasma half-life of 20 days compared to 2 days for IVM will allow for either less frequent treatment or higher efficacy with similar frequency of treatment. Moreover, it has been very effective in infection with animal helminthes that are resistant to IVM. The phase III clinical evaluation of Moxidectin as a macrofilaricide was conducted in three African countries. The work ranges from the development of a formulation for human use and initial studies in healthy volunteers, to clinical studies and community studies in Africa (WHO, 2009). Result from the study proved promising as in Phase II clinical trial, moxidectin reduced skin microfilarial loads to statistically significantly lower levels and for substantially longer than IVM (Awadzi *et al*., 2014). Recently, Moxidectin was approved for commercial production by the World Health Organization (FINACIAL, 2015). The Global Health Investment Fund (GHIF) investment will be used to support the manufacture of moxidectin, and the compilation of the regulatory dossier required for the registration process for use in humans. Should the drug be approved, Medicines Development for Global Health will work towards ensuring a secure supply of moxidectin for onchocerciasis and GHIF will continue to research other potential human uses of moxidectin for infectious diseases. A significant cost effectiveness between annual and biannual community directed treatment with ivermectin and moxidectin (aCDTI and aCDTM or bCDTI and bCDTM) have been undertaken. Turner *et al*. (2013) had projected aCDTM strategy can be compared to both aCDTI and bCDTI, assuming aCDTM was donated; it will culminate in cost savings estimated at 60% or more per year than aCDTI.

Doxycycline or Vibrimycine : Treatment with antibiotics to clear the bacterial endosymbionts of the filarial parasites has given rise to superior therapeutic alternative to current anthelminthic drugs (Hoerauf *et al*., 2001; Taylor *et al*., 2005; Johnson *et al*., 2007; Hoerauf, 2008). The rationale for this novel treatment targeting *Wolbachia*- a bacterial because it has been found to be essential for worm development, fertility and survival and inducer of inflammatory disease pathogenesis. The field trials carried out by Hoerauf *et al*. (2003b) showed that doxycycline at 100 mg/day when administered for 4-8 weeks demonstrated efficacy in reducing skin microfilarial loads, sterilizes adult worms, and decreases adult worm viability and most importantly death of adult worms. However, the efficiency of using doxycycline in mass treatment campaigns has been questioned (Sinha *et al.*, 2006). The length of treatment is logistically incompatible with the community-directed strategy used for filariasis control, contraindication for children >9 years and pregnancy (Taylor *et al*., 2009). The slow-kill outcome of doxycycline treatment has several advantages including elimination of the inflammatory inducing bacteria (Hoerauf *et al*., 2001; Keiser *et al*., 2002; Saint Ande *et al*., 2002) and the avoidance of the potential ARs to nematode products with rapid-kill as observed in co-infection with *Loa loa* (Turner *et al*., 2010; Wanji *et al*., 2009). Taylor *et al*. (2009) opined that the outcome of trials to establish a definition of the minimal effective regimen will provide an important advance in the treatment options for individual cases outside the control areas.

Combination Therapy:
The three standard antifilarial anthelmintics:

albendazole (ABZ), DEC, and IVM are used as the mainstay of MDA elimination programs for filariasis. Both the DEC and IVM are direct microfilaricides, ABZ inhibits mf production. ABZ/DEC combination treatment is administered to eliminate LF outside Africa where ABZ/IVM combination is used due to contraindications of DEC in onchocerciasis (Taylor *et al*., 2010). A synergy between the (ABZ) and drugs depleting the filarial endosymbiont, *Wolbachia*, a proven macrofilaricide target reduces treatment from several weeks to 7 days in preclinical models with registered drugs ready for clinical testing. ABZ had negligible effects on *Wolbachia* but synergized with minocycline or rifampicin (RIF) to deplete symbionts, block embryogenesis, and stop microfilariae production. Greater than 99% *Wolbachia* depletion was attained after 7-day combination treatment with RIF+ABZ, which also led to accelerated macrofilaricidal activity (Turner *et al*., 2017). Beneficiating IVM treatment on soil transmitted helminthes (STH) in school aged children (SAC) and pre-school aged children (PAC) have been established for *Ascaris lumbricoides, Strongyloides* and *Trichuris tricuria* but not for hookworms (*Necator americanus* and *Ancyclostoma duodenales*) (Gutman *et al*., 2010). There was no clinical evidence of pharmacokinetics interactions in uninfected (healthy) volunteers administered oral IVM (200 µg/kg body weight), oral praziquantel (PZQ) 40 mg/kg body weight and oral ABZ (400 mg) given concurrently with any uncommon or severe adverse events than when each drug is given individually (Na-Bangchang *et al*., 2006). All treatment regimens showed acceptable tolerability profiles. In a study, doses of fruit-flavoured ABZ (40mg), IVM (150µg/kg) and PZQ tablets (40mg/Kg) or Distocide®, Shin Poong, Seoul, South Korea were given at the same time (Eigege *et al*., 2008). Whereas Hopkins *et al*. (2002) found that when treatments for onchocerciasis and LF were separated by at least 1 week prior to treating schistosomiasis did not show any negative impact on the coverage of onchocerciasis programme.

Strategy for Onchocerciasis Drug Discovery Initiative

Ivermecin (patented in 1989 for human use) is not a macrofilaricide and regular administration is required to kill young worms has prompted the need to develop new drug belonging to a different compound. Nwaka and Hudson (2006) proposed that the target profile of the new drug should include the following characteristics: (i) inexpensive and (ii) its safety should be equal or better that ivermecin or combination for lymphatic filariasis. (iii) Short treatment courses ideally single oral dose, (iv) safety profile compatible with use without diagnosis and (v) safe in children and pregnant women (and stable under tropical conditions (shelf life >2 years). A prevailing dire situation in which there is lack of incentive for drug development against onchocerciasis and other filarial and helminthic diseases is due largely to the low investment return that has made research and development in this area an unattractive portfolio to big pharmaceutical companies. Hence, the pharmaceutical industry began its withdrawal from the discovery and development of new drugs for tropical diseases in the mid-1970s (Shoop, 2003). To mitigate this problem, a paradigm shift has been championed with the creation of the Helminthes Drug Initiative (HDI) in 2006 and African Novel Drugs and Diagnostics Innovation (ANDI) which came on board in 2009 to stem the tide. A protocol for drug development and drug discovery chain has been designed as described in the reviews by Nwaka and Hudson (2006) and Nwaka *et al.* (2009). The hit criteria for onchocerciasis are observation of *O. lienalis* microfilarial 100% inhibition of motility at 1.25 x 10^{-5} M and *O gutturosa* adults' 100% inhibition of motility or formazan formation at 1.25x10^{-5}M with no obvious sign of toxicity to monkey kidney feeder cell layer.

The criteria for lead activity are *O. lienalis* microfilaria: active *in vivo* (mice) when given intraperitoneally or subcutaneously in 10% dimethyl sulphoxide (DMSO) formulation at 5x100 mg per Kg as measured by statistically significant reduction in worms (>80% is highly active). It should not be overtly toxic in animals at efficacious dose. Note that values are

illustrative (Nwaka *et al.,* 2009). The three strategies for drug discoveries are label extension, which involves the extensions of existing treatments for human and animal ailments to tropical diseases (Witty, 1999). Moxidectin, an analogue of IVM, is an example of such an approach (Cotreau *et al*., 2003). Second, a piggy-back discovery entails exploring molecular targets present in parasites that allow identification of chemical starting points (Gelb *et al.,* 2003). Third, is the *de novo* discovery, which focuses on identification of new chemical entities (Nwaka and Hudson, 2006) both synthetic compounds and natural products as novel anti-parasitic drugs. According to Townson *et al.* (2006) assay for drug screening depends on adult male *O. guttural* cultured on a monkey kidney cell (LLCMK 2) feeder layer in 24-well plates with antibiotics and antibiotic combinations (6 to 10 worms per group). The macrofilaricidal CGP 6140 (Amocarzine) can be used as a positive control. Worm viability can be assessed by two methods, (i) motility levels and (ii) MTT/formazan colorimetry. The yellow compound MTT [3-(4, 5-dimethylthiazol-2-yl)-2, 5-diphenyltetrazolium bromide] is reduced by the mitochondrial enzyme succinate dehydrogenase of living tissues to produce the blue precipitate MTT formazan (Comley *et al*., 1989a; 1989b). Worm motility was scored on a scale of 0 (immotile) to 10 (maximum) every 5 days up to 40 days. On day 40, worm viability was evaluated by MTT/formazan colorimetry, and results were expressed as a mean percentage reduction compared with untreated control values. Marcellino *et al*. (2012) reported new computer-based monitoring of hit compound activities to adult worm. Halliday *et al*. (2014) developed a 'pan-filarial' small animal research model with adequate capacity and throughput, to screen existing and future pre-clinical candidate macrofilaricides.

Alternative Treatment Methods

In recent time, many options have emerged for the adoption of alternative treatment methods against onchocerciasis. Any new protocol should be sustainable, highly efficacious, cost effective, and satisfying the criteria for mass drug administration strategy has been propounded based on the superior clinical performance over aCDTI and bCDTI that were adopted in APOC and OEPA in SSA and OECA, respectively. In addition to early proposed targeted treatment other latter options included the quarterly or tri-monthly (3-monthly) four-times a year, qCDTI strategy was used in the restricted/isolated Wadei focus in Yemen targeting about 300,000 people (McKenzie *et al*., 2018, Al_Kubarti *et al*., 2022). With the recent approval given by WHO for the use of Moxidectin for treating human onchocercdsiasis aged $\geq$12 years (WHO, 2015) has elicited curiosity over the overwhelming advantage it has over IVM. Moxidectin is a milbemycin endectocide used in the treatment of nematode and ectoparasitic infections of livestock and companion animals. At 8 mg therapeutic dose, it exerts a potent microfilaricidal effect and a stronger and more prolonged suppression of microfilaridermia than annual IVM treatment due to strong embryostatic effect (temporary inhibition of microfilarial production by adult female worms), although other mechanisms cannot be ruled out (Awadzi *et al*., 2014, Milton *et al*., 2020). Both moxidectin and ivermectin are macrocyclic lactone belonging to the avermectin family but differ in the absence of a disaccharide attached to carbon 13, the presence of an olefinic side chain at carbon 25, and a methoxime moiety at carbon 23 (Verdu *et al*., 2018).

Like its counterpart, IVM share similarity in macrofilaricidal effect after long time treatment, no SAEs needing medical interventions; it is well tolerated and suited for community directed treatment. This has therefore given rise to aCDTM and bCDTM and qCDTM. It has been proposed that both drugs could be distributed jointly or separately within endemic communities to speed up the elimination and eventual eradication of the disease. Another drug that has indirect high level of macrofilaricidal activity is doxycycline, an antibiotic (Hoerauf *et al*., 2008), and is administered at 100 mg dose daily for six weeks (Tamarrozi *et al*., 2011). It has an added advantage because it can be applied in areas with onchocerciasis and loaisis co-endemicity (Wanji *et al*., 2009, Tamarrozi *et al*., 2012) against contradiction for the use of IVM in such situation. There was no serious side effect observed during the six-week treatment period. Doxycycline

provides the much-needed optional treatment in those areas with clear evidence of either poor or SOR to IVM and co-infection of onchocerciasis with loaisis are widespread within vast forest of Africa. Where ivermectin-related SAEs and deaths with loiasis are very likely, the use of the LoaScope-based Test and Not Treat strategy to identify and exclude from treatment of *L. loa* cases from the population at risk for SAEs might help increase adherence (Kamgno *et al*., 2017). The role of eosinophils in SAEs such as Mazzotti reaction after DEC and IVM/Mectizan for loaisis infected persons have been well established (Behm and Ovington, 2000, Hartl *et al*., 2020). This, however, has prompted the need for simple test to determine the status of eosinophilia amongst patients or population in helminth endemic areas. It could serve as a guide for MDA to exclude those with hyper-eosinophilia from treatment (Osue *et al*., 2023).

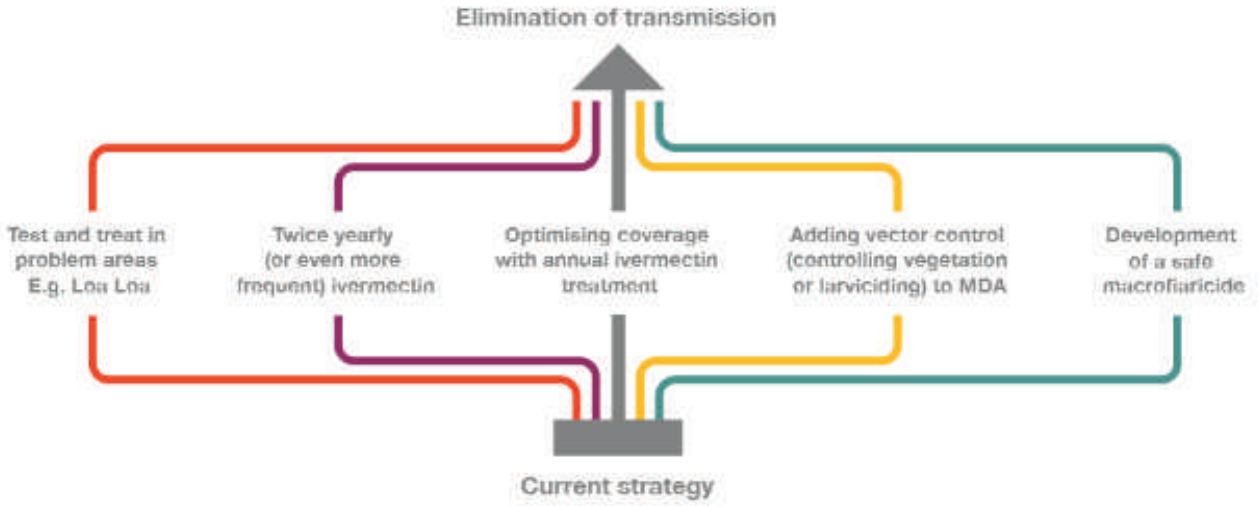

Figure 6: Onchocerciasis: Alternative treatment strategies. Source: NGDO Group for Onchocerciasis Elimination, Onchocerciasis-Advocacy Document, pdf

A priority was the creation of National Onchocerciasis Elimination Committees (NOEC) in all endemic countries, with a broad spectrum of expertise from national and international members, to assist and guide national programmes to achieve elimination of the disease (NDGO, 2018). The main roles of NOECs are to review national program progress, to assess remaining gaps and to guide and make recommendations to the national programmes on programmatic and technical approaches in the following aspects: (i) Determining and assessing the real geographical coverage; the number of treatments delivered and the number of people who successfully take the treatments or have access to them. (ii) How best to improve population estimates for drug requisitions? (iii) The optimal methods for trapping and monitoring vectoral capacity and distribution of blackfly populations in different areas. (iv) Analysing factors causing persistent foci of infection and use of alternative strategies. (v) How to plan and execute at the national level the implementation of the WHO guidelines on stopping MDA. (vi) How to build country capacity and improve access to the necessary laboratory facilities or trained personnel to carry out the tests. (vii) Decision making on alternative treatment strategies where they appear necessary to achieve elimination.

Conclusions:

There is no doubt that over the years there have been programmatic challenges, success and promises and very clear way forward for the elimination of onchocerciasis as a public health problem it was in the time past. The first active onchocerciasis control was based on aerial-wide blackfly insecticidal spraying with helicopters adapted by OCP involved huge capital outlay that could not be sustained in other endemic countries by the Donor partners. A targeted black flies control using handheld spraying equipment in conjunction with MDA has been

proven to be very effective and efficient in breaking disease transmission. The feat attained by OCP in breaking onchocerciasis transmission spore the formation of APOC, from 1995-2015 had engaged in the control of onchocerciasis in 19 other African countries using the CDTI. The difficult terrain, large foci of infections, huge population and different socio-cultural milieu, have compounded attaining the required geographic distribution and high demographic treatment compliance of 65% and 85% in hyper-endemic areas of APOC (aCDTI) and OEPA (bCDTI), respectively (Cupp *et al*., 2018). Of all the daunting challenges facing Ivermectin/Mectizan MDA programme is the inability to achieve a break in disease transmission beyond the expected targeted life span of 15-20 years of an adult female worm. This has been attributed to the low rate of population treatment coverage and high rate of non-adherence to treatment. Depending on the community pre-intervention endemic status, many socio-economic factors such as migration, emigration, exemption due to many exclusion critieria, etc. interplayed in thwarting the disease eradication goal by sustaining continued transmission despite many years of IVM MDA. It is ominous that the intervention scheme has lost steam and needed rejuvenation of the interest and attention of all stakeholders at global, continental, regional, national, and local levels to renew commitment to the intervention goal. Bearing in mind that there are more competing emerging health problems such as COVID-19, HIV AIDs, Ebola, and avian human influenza among others. Galvanizing political and administrative will, institutional collaboration, scientific cooperation, programme capacity and capability building, advocacy, sensitization, mobilization drive in endemic communities and countries remain imperative to protect the gains already attained by past programmes. The integration of onchocerciasis control into ESPEN is a welcome idea that will foster using collective initiatives to undertake cost-effective interventions of NTDs which in most cases are co-endemic within the same geographical and ecological locale and demographic distribution. Despite many advances that have been made in drug development, it is equally very important to effectively deploy existing repurposed drugs for field use adopting either MDA strategy or test and treat protocol. Furthermore, research is required to obtain best optimal utilization of existing drugs, which should not preclude the need for new drug discovery. Hence, the importance of applying alternative treatment options becomes extremely crucial to sustain the gains already made towards the eradication drive. Combined MDA and targeted control of existing black fly population by ground spraying is worth considering. It has been speculated for long that a reservoir host of *O. volvulus* exists in domestic and wild animals and those excluded from treatment needed to be diagnosed to determine their infection status for purpose of monitoring and enlisting into test and treat protocol.

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