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## Elimination of lymphatic filariasis in west African urban areas: Is implementation of mass drug administration necessary?

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### **Personal View**

# Elimination of lymphatic filariasis in west African urban areas: is implementation of mass drug administration necessary?



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Lymphatic filariasis in Africa is caused by the parasite Wuchereria bancrofti and remains a major cause of morbidity and disability in 74 countries globally. A key strategy of the Global Programme for the Elimination of Lymphatic Filariasis, which has a target elimination date of 2020, is the treatment of entire endemic communities through mass drug administration of albendazole in combination with either ivermectin or diethylcarbamazine. Although the strategy of mass drug administration in combination with other interventions, such as vector control, has led to elimination of the infection and its transmission in many rural communities, urban areas in west Africa present specific challenges to achieving the 2020 targets. In this Personal View, we examine these challenges and the relevance of mass drug administration in urban areas, exploring the rationale for a reassessment of policy in these settings. The community-based mass treatment approach is best suited to rural areas, is challenging and costly in urban areas, and cannot easily achieve the 65% consistent coverage required for elimination of transmission. In our view, the implementation of mass drug administration might not be essential to interrupt transmission of lymphatic filariasis in urban areas in west Africa. Evidence shows that transmission levels are low and that effective mass drug distribution is difficult to implement, with assessments suggesting that specific control measures against filariasis in such dynamic settings is not an effective use of limited resources. Instead, we recommend that individuals who have clinical disease or who test positive for W bancrofti infection in surveillance activities should be offered antifilarial drugs through a passive surveillance approach, as well as morbidity management for their needs. We also recommend that more precise studies are done, so that mass drug administration in urban areas is considered if sustainable transmission is found to be ongoing. Otherwise, the limited resources should be directed towards other elements of the lymphatic filariasis programme.

#### Introduction

Lymphatic filariasis is a public health problem in 74 countries and is associated with substantial morbidity and disability.<sup>1,2</sup> Lymphatic filariasis causes lymphoedema (elephantiasis), hydrocoele, renal pathology manifesting as chyluria, and acute dermatolymphangioadenitis causing regular fevers. This disease is unique because the parasite, Wuchereria bancrofti, is transmitted by five different genera of mosquitoes including *Culex* spp, Aedes spp, Anopheles spp, Mansonia spp, and Ochlerotatus spp.<sup>3,4</sup> Lymphatic filariasis is, after malaria, the most common vector-transmitted parasitic infection.5 The Global Programme to Eliminate Lymphatic Filariasis was launched in 2000,<sup>1</sup> with the aim to eliminate the disease as a public health problem by 2020, and has since scaled up implementation of mass drug administration of anthelmintics with albendazole in combination with either ivermectin or diethylcarbamazine. In 2017, WHO approved a combination of these three drugs for lymphatic filariasis for use in areas where onchocerciasis and loiasis are not endemic, which excludes west Africa.<sup>2,6</sup> Mass drug administration is a method of disease control in which treatment is distributed to the entire eligible population of an area, irrespective of the individual infection status. Those not eligible are children younger than 5 years (or who are less than 90 cm in height), pregnant women, and the severely sick. Mass drug administration has been delivered in Africa largely through community-based or directed approaches. These have been able to sustain high levels of coverage that are consistent with achieving cessation of transmission after five to seven rounds of annual treatment, although some areas did not achieve cessation, often as a result of the initial high prevalence of the disease.

By 2015, the programme had provided more than 6.7 billion cumulative treatments,<sup>2,7</sup> and as a consequence endemicity of lymphatic filariasis has reduced from an estimated 120 million infections in 83 countries in 2000 to an estimated 36.5 million global cases of disease in 2016. 18 countries are moving into a surveillance phase and several other countries have been verified as free of transmission.<sup>2</sup> The numbers of hydrocoele cases have also declined from 25 million in 2000 to 19.4 million in 2013, and lymphoedema cases from 40 million to 16.7 million.<sup>1</sup> In this Personal View, we aim to explore the current challenges to eliminating lymphatic filariasis in west African countries and the relevance of implementing mass drug administration in urban areas.

#### Mass drug administration in Africa

In 2016, coverage of the total population requiring mass drug administration was 57.9%, with 495.6 million individuals treated in 40 reporting countries, through increased coverage in several countries including Cameroon, Ethiopia, Nigeria, Zambia, and Democratic Republic of the Congo.<sup>2</sup> National mass drug administration programmes targeted 669.4 million people for treatment and achieved coverage of 74% of targeted individuals. In 2016, an estimated 28.2 million preschool-aged children (aged 2–4 years) and 135.1 million school-aged children

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#### Key messages

- Lymphatic filariasis is a public health problem in 74 countries and is associated with substantial morbidity and disability.
- Populations of urban areas in West Africa are increasing, as are the areas occupied by urban environments throughout this region as a result of conflict, pressure on rural land and water resources, and expectation of employment. High levels of rural to urban population movement have resulted in detection of prevalent cases of filariasis by antigen detection methods, but the origin of these infections is likely to be rural areas.
- Undertaking mass drug distribution in such settings is challenging and costly and cannot easily achieve the 65% consistent coverage required to achieve elimination of transmission.
- Transmission of lymphatic filariasis caused by Wuchereria bancrofti in several large cities in West Africa has been shown to be limited. Evidence suggests that transmission levels are low and effective mass drug distribution is difficult to implement, with assessments suggesting that embarking on specific control measures against filariasis in such dynamic settings is not an effective use of limited resources.
- Low vector biting rates combined with the use of vector control methods such as long-lasting insecticidal nets and mosquito repellents, in addition to environmental engineering and improved housing structures, could further limit the transmission of any residual infection in urban settings.
- Any individuals who test positive for W bancrofti infection in surveillance activities should be offered antifilarial drugs through a passive surveillance approach and patients with clinically overt hydrocoele and lymphoedema should be given necessary surgery and limb care, respectively.

 Implementation research is required to verify whether transmission is taking place in urban areas by detection of infectivity levels of mosquitoes or by assessing the presence of exposure antibodies in selected cohorts of the population.

- An assessment of the infectivity level of *W* bancrofti in mosquitoes should be done by selecting mosquito collection points close to productive *Anopheles* spp breeding sites and identified cases of lymphatic filariasis.
- Special attention should be focused on identifiable migrant groups located in urban and periurban slums.
- National programmes should review policy on mass drug administration in urban areas; this should involve decisions based on assessments of transmission risks in potentially high-risk areas.
- Such assessments might be costly, but will be cheaper than embarking on 5–7 year mass drug administration programmes.
- If mass drug administration does not take place as part of filariasis programmes in urban areas, the ancillary benefits of deworming on soil-transmitted helminths would be lost, impacting on the prevalence and intensity of these helminths; national programmes for neglected tropical diseases should assess these implications for soil-transmitted helminth strategies.
- Liaison and coordination between national neglected tropical diseases programmes, WHO, donors, and non-governmental development organisations will be necessary to develop appropriate policies.

(aged 5–14 years) were treated during mass drug administration programmes for lymphatic filariasis.<sup>2</sup>

Therapeutic coverage (ie, proportion of people treated), however, has been reported to be 83%. Additionally, mass drug administration in combination with high coverage and adherence and the use of bednets possibly contributed to accelerating elimination efforts in Togo and Malawi.8.9 Prevalence of circulating filarial antigen was 0% in Lomé, Togo and 7% in Lilongwe, Malawi.2 Prevalence of lymphatic filariasis varied between 1% and 36% in Togo and between 1% and 79% in Malawi when programmes commenced. Togo was verified as having satisfied WHO criteria for achieving elimination goals. Malawi has stopped mass drug administration, moved to the surveillance phase, and continues to make progress in disability management of patients with lymphoedema, through provision of limb care services, and hydrocoele, through provision of surgery.1 However, addressing the clinical needs of patients, an important objective of the programme, has lagged behind efforts to upscale mass drug administration in urban areas.

Vector control by use of impregnated long-lasting bednets or indoor residual spraying can greatly affect transmission of W bancrofti.10 The Gambia has passed a transmission assessment survey (ie, prevalence of infection was reduced to a level where recrudescence is unlikely to occur) as a result of the historic use of bednets without recourse to mass drug administration.11 However, because transmission assessment surveys are not sensitive enough to detect low-level persistence of lymphatic filariasis, transmission might not have been interrupted. Recombinant methodologies (eg, Wb123), immunoassays,<sup>12</sup> and molecular xenodiagnosis methods13 based on detection of DNA from the third stage larvae (L3) of the parasite in mosquitoes are appropriate tools to address such challenges. The Gambia was one of the most heavily infected countries, with prevalence of more than 50% reported in the 1950s, determined by night blood surveys for detection of microfilaria.<sup>11</sup> A decline in reported prevalence in people older than 15 years had occurred by 1975-76 but remained between 3% and 27%, whereas examination of stored serum samples taken between 1997 and 2000 using immunochromatographic tests to detect circulating W bancrofti antigen revealed a further decline in prevalence. These steady declines can be

attributed to the national bed net programme, which achieved high coverage for more than two decades."

### Challenges to mass drug administration in urban areas

A recent report has discussed the particular problems and challenges of control of neglected tropical diseases in urban settings.14 The efforts deployed to date by endemic countries and a multiplicity of partners to eliminate lymphatic filariasis as a public health problem can be hampered because large cities in most endemic countries in west Africa are not vet effectively covered by mass drug administration. Additionally, results from mapping of the prevalence on the basis of the presence of antigen-positive individuals showed that most of these cities had a prevalence of less than 1%-eg, Monrovia, Freetown, and Conakry.<sup>15,16</sup> However, in view of the findings from these studies in west Africa15-17 and the predominance of *Culex* spp in such settings, a mosquito known to be a less susceptible vector in west Africa,18-21 we propose that the status of most west African cities be re-evaluated in terms of what is described as endemicity. The situation in west Africa contrasts with that in east Africa, Asia, and Haiti, where Culex quinquefasciatus is known to be an efficient vector of W bancrofti.22

Net migration into urban areas of Africa is associated with expanding populations in search of employment, pressure on the finite rural land resources, reduced productivity from eroded or less productive land, and conflict and instability. This migration is also associated with increased access to transport networks and improved communications availability. The population of African cities is forecast to increase by 350 million people by 2030, with 50% of the population living in urban areas.<sup>23</sup> Although there is some movement to rural areas, most migration is rural to urban. Migration of individuals infected with filariasis from cities to rural areas might have a role in maintaining some rural foci of transmission locally; however, the number of infected individuals is not likely to be substantial. Additionally, there are limited data supporting the notion that urban-rural migrants will have higher rates of infection in west Africa, suggesting that transmission in west African cities is likely to be limited.

Lymphatic filariasis among populations living in urban settings is recognised as a key challenge to ongoing global efforts to eliminate the disease as a public health problem;<sup>24</sup> however, the implementation of mass drug administration for lymphatic filariasis needs to be re-evaluated in many of the large conurbations in west Africa. This is because there are numerous doubts about how best to define target areas for implementation of the strategy. First, there is a constant inward migration from rural areas to cities in west Africa and infected individuals are likely to have acquired infections in rural areas. Second, apparent foci of high prevalence are likely to be caused by the establishment of groups from rural areas forming social and cultural communities within specific areas of cities. Third, *Culex* spp mosquitoes are inefficient vectors of W bancrofti in west Africa.<sup>18-21</sup> It is important to note, too, that community-based mass treatment approaches with community-directed drug distributors, previously dev-eloped for onchocerciasis, were developed for rural areas and not for urban settings.<sup>25</sup> This situation, together with administrative challenges (eg, high population density and population heterogeneity) and the demand for incentives by drug distributors, contributes to reduce effectiveness of mass drug administration in urban settings because of reduced access and lowered adherence.<sup>26</sup> This result was exemplified in the Greater Accra Region in Ghana, which had an antigen prevalence of 8% and baseline night blood microfilaria levels of 0.2% in 2004.27 Mass drug administration in Accra district started in 2006 and had a fluctuating therapeutic coverage of 49.4%, 11.1%, 37.6%, 60.2%, and 57.8%, in 2006, 2007, 2008, 2009, and 2012, respectively, and a therapeutic coverage higher than 65% (the minimum level deemed to be adequate to interrupt transmission) in 2010, 2011, and 2013. Despite therapeutic coverage in Accra being lower than the required 65% in 2006-09 and 2012, these areas passed a transmission assessment survey done in 2015, with antigen prevalence found to be less than 1% in children aged 5-10 years, suggesting that transmission was interrupted.<sup>28</sup> Because a verification survey that aimed to confirm programme coverage (as recommended by WHO) was never implemented, data for mass drug administration coverage reported by the Ghana neglected tropical diseases programme might be hindered by issues of accuracy,<sup>29</sup> and as such coverage data might be even lower than reported. Similarly, in Malindi, Kenya, during 4 consecutive years from 2002, programme data showed that treatment coverage was far below the recommended 80% of the eligible population (48%, 46%, 46.5%, and 30%, respectively).<sup>30</sup> These observations therefore raise questions about the value of mass drug administration in urban areas in general.

Conversely, in Ouagadougou, Burkina Faso, prevalence surveys in periurban areas showed microfilaria levels of 0% in four sentinel sites and 4% in a single site. Following eight to ten rounds of mass drug administration with reported coverage consistently higher than 70% since 2005, results of transmission assessment surveys done in districts where microfilaria prevalence was less than 1% confirmed that prevalences had fallen below the operational cut-off thresholds for stopping mass drug administration.<sup>31</sup> However, transmission assessment surveys alone might not be sufficient to confirm interruption of transmission of lymphatic filariasis; a recent study has shown that circulating filarial antigen rates in schoolchildren (age groups used for transmission assessment surveys) are lower than those recorded in adults, suggesting that sensitivity of these surveys should be improved.32

By contrast with Ghana and Burkina Faso, where urban mass drug administration was implemented for several years, results of a mapping survey in Kano, northern Nigeria, in 2010, showed prevalence of circulating filarial antigen assessed by immunochromatographic test to vary between 2% and 12% in some local government areas.33 Before implementation of mass drug administration, results of baseline sentinel site surveys in 2015 showed prevalence rates of 0% (assessed by immunochromatographic test),33 although low levels of W bancrofti DNA were detected in mosquitoes, implying the parasite was present in some individuals. However, the presence of parasite DNA in mosquitoes does not show that transmission is taking place, because detection of DNA does not necessarily indicate the existence of infective larvae; W bancrofti DNA can be detected in mosquitoes, or indeed in any haematophagous arthropod, simply as a result of feeding on an infected individual. Such a signal does not provide any evidence of vectorial capacity or infectivity. Preventive measures such as the nationwide distribution of bednets used against mosquito bites might have contributed to these results.

#### The entomological argument

In west Africa, Anopheles spp, particularly Anopheles gambiae and Anopheles funestus, are considered to be the major vectors of W bancrofti, while C quinquefasciatus seems to have a much reduced vectorial capacity compared with the same species in east Africa.18-21 This variation could be attributed to genetic diversity of the parasites in different geographical locations or to the refractoriness of the west African Culex species to W bancrofti. Because many studies have shown that Culex spp is the most abundant mosquito in urban settings,<sup>15,16,34,35</sup> we believe that urban transmission of W bancrofti is unlikely to be a factor that will impede progress towards elimination of lymphatic filariasis in west Africa. A mapping survey showed that in urban areas of Abidjan, Côte d'Ivoire, and Conakry, Guinea, fewer than 1% of tested individuals had detectable levels of circulating filarial antigen, suggesting that mass drug administration is not required in these urban areas.<sup>16,31</sup> In Conakry, Guinea,16 Bolgatanga, Ghana,17 and Freetown, Sierra xenomonitoring studies Leone.15 (entomological technique for detecting the presence of parasites in mosquitoes) have recorded a low prevalence of W bancrofti DNA in mosquitoes. The data presented in these studies show that the observed prevalence of parasite DNA in mosquitoes in some locations was higher than the cutoff points suggested to be required to interrupt transmission (0.25%, 0.5%, and 1% for Culex spp areas32,36,37 and 0.65% for Anopheles spp areas<sup>38</sup>). However, the wide confidence intervals surrounding the results from these studies also reflect a lack of precision of the prevalence estimates, indicating that larger sample sizes are needed to determine significant prevalence levels of W bancrofti DNA and how these levels should be interpreted.39

The low vector biting rates seen as a result of the limited number of productive mosquito breeding sites, and the use of insecticide spray and mosquito coils, fans, and air conditioners in households in urban areas make sustained transmission of lymphatic filariasis unlikely, because the vector-to-human ratio will be lower in urban areas than in rural areas. One study estimated that more than 15000 bites by infective *C* quinquefasciatus mosquitoes are required to produce one case of W bancrofti infection in an Asian urban setting.<sup>40</sup> Other studies of *Culex* spp, *Anopheles* spp, and Aedes spp vectors in different parts of the world have produced estimates ranging from 2700 to more than 100000 infective bites per new human case.<sup>41</sup> Biting rates as low as 44 infective bites per person per year were estimated to occur in Freetown, Sierra Leone;15 therefore, transmission of W bancrofti by mosquitoes in urban areas is unlikely to be sustained in the face of improved vector control interventions and malaria control strategies.

The arguments regarding the implementation of mass drug administration in urban areas cannot be complete without reference to transmission thresholds and vector-parasite density-dependent processes. The densitydependent processes that influence larval infection dynamics differ between mosquito species in different geographical locations.<sup>42-45</sup> The elimination strategy based on mass drug administration is itself based on the knowledge that vector species exhibit the phenomena of facilitation, limitation, or proportionality.<sup>42–45</sup> In facilitation, the transmission of W bancrofti by anopheline vectors can microfilariae, designated as Webber's Critical Point.42 By contrast, limitation results in stable transmission of W bancrofti by culicines even at low levels of microfilariae.44.48 Proportionality is non-regulated transmission by vectors, with a constant percentage (linear relation) of microfilariae ingested by the vector during a blood meal developing into the infective stage. Limitation and facilitation in vectors cause deviations from this linear relation.48 As a result, anopheline-transmitted filariasis might be easier to eliminate than culicine-transmitted filariasis, given the same infection levels and control interventions.<sup>49</sup> However, we believe that the complex vector-parasite interactions required to sustain transmission of lymphatic filariasis cannot be sustained in west African cities in view of other density-dependent processes occurring in the parasite lifecycle,50,51 such as acquired immunity that regulates infection in the human population.<sup>52</sup> Modelling studies have shown the importance of reducing vector biting rate as well as the parasite reproduction rate. A reduction in the culicine vector biting rate to less than ten bites a month (ie, 120 per year) and the anopheline vector biting rate to less than 200 a month (ie, 2400 per year) would be sufficient to break transmission.<sup>49</sup> On the basis of these estimates, the vector biting rates recorded in west African cities15,53,54 are not sufficient to favour transmission of W bancrofti. Additionally, there is a lack of genetic susceptibility of Culex spp in west Africa, as previously described.

While countries are progressing towards elimination of lymphatic filariasis, it is important for programmes to undertake xenomonitoring studies to assess the presence of *W bancrofti* L3 infectivity within mosquito populations as the definitive measure of absence of transmission in urban areas. We consider this to be the only effective parameter, supplemented by immunological assessments, which will enable programmes to decide whether mass drug administration is required in these increasingly populous urban areas in west Africa. These studies should be implemented before mass drug administration is considered because of the long-term resource consequences for national programmes and donors.

Urban areas themselves might be prohibitive to continued transmission of lymphatic filariasis. During the past three decades, populations of the major cities in west Africa increased from less than 1 million to close to 2.7 million in Ouagadougou and Conakry, and to more than 4 million in Abidjan and Accra,55 and Lagos is now estimated to have a population of 21 million.<sup>56</sup> Civil war in Côte d'Ivoire and insecurity in northern Nigeria have contributed substantially to the increase in the numbers of people migrating from rural areas to cities such as Abidjan and Kano. In Côte d'Ivoire, civil unrest, starting in 2002, led to the migration of some 1.7 million displaced people from western, northern, and central regions to Abidjan<sup>57</sup> while 3.3 million people were displaced from Borno, Yobe, and Adamawa states to Kano because of Boko Haram attacks in the past 5 years.<sup>58</sup> The development of urban areas, coupled with environmental engineering, could result in a reduction in vector breeding sites.59 Enhanced construction methods, such as building of mosquito-proof houses with screens and ceilings, have the potential to reduce indoor densities of mosquitoes.60 However, rural to urban migration might also result in an increase in urban and periurban slums, and the creation of polluted water bodies because of the absence of provision for appropriate water and sanitation facilities, creating conditions for increased *Culex* spp breeding sites. Such sites should be monitored because they could result in the creation of local urban transmission foci, requiring implementation of mass drug administration at small scale. However, we consider this risk to be low in view of the limited vectorial capacity of *Culex* spp to transmit W bancrofti in west Africa.

#### Reappraisal of policy for urban areas in west Africa

In view of the observations and experiences outlined in this Personal View, we believe that the policy of mass drug administration for lymphatic filariasis in urban areas in west Africa needs to be reappraised. Although vector control measures, particularly bednets and use of other domestic preventive measures against mosquito bites, might have a role in reducing the prevalence of *W bancrofti*, the significance of finding positive antigen prevalence, which might merit mass drug administration in a rural setting, fails to recognise the demographic and social factors that could have influenced the findings of a similar level of prevalence in an urban environment. We suggest that xenomonitoring must focus on the presence of infective *W* bancrofti larvae rather than the existence of *W* bancrofti DNA in mosquito sample pools, the epidemiological significance of which is uncertain.

National programmes should review policy on mass drug administration in urban areas; this should involve decisions on assessing infectivity rate of lymphatic filariasis transmission in potentially high-risk areas. Such assessments might be costly, but will be cheaper than embarking on 5–7 years of mass drug administration programmes.

#### Conclusion

In conclusion, we recommend that more precise studies are undertaken to define whether transmission is ongoing in urban areas before implementation of mass drug administration. Such studies should be based on sentinel site or spot check surveys by xenomonitoring to detect infective larvae in mosquitoes, the true measure of the existence of a susceptible vector and continuing transmission. In parallel, studies should include immunological approaches such as Wb123 assays12 to detect exposure antibodies as an acceptable surrogate of active transmission, as well as the use of antigen detection methods such as the immunochromatographic card test<sup>61</sup> or the Filariasis Test Strip<sup>62</sup> in specific and well characterised age groups. Such studies could confirm if mass drug administration is required, provided the appropriate cutoff points could be agreed. There is a degree of urgency to define the true epidemiological situation in these urban centres in view of continued population expansion and the need to develop a consistent policy between countries. However, individuals with lymphoedema and hydrocoele also need to be identified. Such patients should be asked in-depth questions to establish the origin of the likely acquisition of their infection as well as to provide the necessary opportunities for access to patient care services and, if necessary, hydrocoele surgery. Any individuals found to be positive for W bancrofti in surveillance activities should be offered antifilarial drugs through a passive surveillance approach.

The implementation of mass drug administration in the large cities of west Africa might not be essential to interrupt transmission of lymphatic filariasis, saving huge costs for programmes, avoiding many millions of treatments, and perhaps allowing the disability management and disability inclusion elements of the lymphatic filariasis programme to be implemented at the expense of mass drug administration. A further priority is to assess whether vector control other than that associated with malaria control can be implemented, because the challenge of controlling *Culex* spp—due to its larval habitats in polluted water bodies such as cesspits and waste water containments—is not considered practicable despite the proven efficacy of polystyrene beads at small scale.<sup>63</sup> The numbers of Culex spp larval habitats in urban settings would preclude a sustained operation because of the logistics and costs. A similar conclusion was reached when the use of the larvicide Lysinibacillus sphaericus (previously known as Bacillus sphaericus) was assessed for Culex spp control in west Africa.<sup>64</sup> The success of the lymphatic filariasis programme in rural environments will mean that the focus of national activities might shift to address the potential problems of lymphatic filariasis in urban environments, which will become an increased focus of elimination efforts over the coming years. Liaison and coordination between national neglected tropical diseases programmes, WHO, donors, and nongovernmental development organisations will be necessary to develop appropriate policies.

#### Contributors

BGK and DHM developed the concept of the Personal View. DKdD and BGK wrote the first draft. N-KB, RB, MA, and EE provided country-specific information. EE and SB contributed to the development of the content. DHM provided policy directions, critical review, and editing. All authors agreed to the final draft of the manuscript.

#### **Declaration of interests**

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