The 25th Meeting of the International Task Force for Disease Eradication (ITFDE) was convened at The Carter Center from 8:30 am to 5:00 pm on November 8, 2016 to discuss "Lymphatic Filariasis and Trachoma: Successes and Challenges in Stopping Mass Drug Administration." The Task Force members at the time of this meeting were Sir George Alleyne, Johns Hopkins University; Dr. Stephen Blount, The Carter Center (Chair); Dr. Dirk Engels, World Health Organization (WHO); Dr. Donald Hopkins, The Carter Center; Dr. Julie Jacobson, Bill & Melinda Gates Foundation; Dr. Hamid Jafari, Centers for Disease Control and Prevention (CDC); Dr. Adetokunbo Lucas, Harvard University; Professor David Molyneux, Liverpool School of Tropical Medicine (retired); Dr. Patrick Osewe, The World Bank; Dr. Stefan Peterson, UNICEF; Dr. David Ross, The Task Force for Global Health; Dr. Dean Sienko, The Carter Center; Dr. Nilanthi de Silva, University of Kelaniya, Sri Lanka/WHO Strategic and Technical Advisory Group (STAG); Dr. Roberto Tapia, Carlos Slim Foundation; Dr. Ricardo Thompson, National Institute of Health (Mozambique), and Dr. Dyann Wirth, Harvard School of Public Health. Twelve Task Force members (Alleyne, Blount, Hopkins, de Silva, Jacobson, Jafari, Lucas, Molyneux, Ross, Sienko, Thompson, Wirth) attended this meeting, and two were represented by an alternate (Dr. Gautam Biswas for Engels; Dr. Luwei Pearson for Peterson).

Presenters at the meeting, which was chaired by Dr. Stephen Blount, included Dr. David Addiss, The Task Force for Global Health; Dr. Paul Emerson, International Trachoma Initiative (ITI); Dr. Jonathan King, World Health Organization; Dr. Tom Lietman, Francis I Proctor Foundation/University of California at San Francisco; Dr. Scott Nash, The Carter Center, and Dr. Julie Jacobson.

The meeting was opened with a moment of silence for Dr. Harrison Spencer of the Association of Schools of Public Health, who had served as a member of the Task Force since 2001.

In its published report in 1993, the ITFDE became the first international body to recognize the potential eradicability of lymphatic filariasis and reviewed that disease again in 2002, 2008, and 2014. WHO provided a comprehensive update as of 2014 on the progress of the Global Program to Eliminate Lymphatic Filariasis (GPELF).[1] This report summarizes progress made in 2015 and

[1] World Health Organization, 2015. Global programme to eliminate lymphatic filariasis: progress report, 2014. *Wkly Epidemiol Rec*. 90(38): 489-504.

recent developments regarding the potential use of triple-drug therapy for lymphatic filariasis mass drug administration (MDA).

Mediterranean, 52% in South-East Asia, and 65% in the Western Pacific. To date, 1,250 IUs with a cumulative population of 351 million persons no longer require MDA. A total of 18 countries have halted MDA nationwide and six of these (Cambodia, Cook Islands, Maldives, Niue, Sri Lanka and Vanuatu) were acknowledged by WHO as having eliminated LF as a public health problem. Nonetheless, 2,738 IUs across 54 countries, with approximately 946 million people, are still considered to require MDA to achieve elimination targets.

GPELF currently faces numerous challenges in order to meet the goal of LF elimination by 2020. First, 29 countries have either not started MDA or have not achieved 100% geographic coverage of endemic IUs. These countries are not on target to stop MDA by 2020 under current WHO guidelines. Thus, urgent support is needed to initiate MDA in all endemic IUs in these 29 countries. Alternative MDA strategies that could reduce the number of rounds or time required to achieve elimination targets also are needed.

Clinical trials are currently underway to determine if combination triple drug therapy with ivermectin, DEC, and albendazole (IDA) is safe and superior to currently recommended two-drug regimens. These include DEC-albendazole used in areas outside of Africa and ivermectin-albendazole used in Africa, because of the potential for DEC-associated severe adverse reactions in individuals infected with *Onchocerca volvulus*; use of ivermectin with DEC is contraindicated in areas endemic for *Loa loa*. Data from a pilot study in heavily infected individuals in an MDA-naïve area of Papua New Guinea (PNG) indicate that 100% (n=12) of individuals treated with IDA were microfilaremia negative after 12 months compared to only one of 12 individuals treated with DEC plus albendazole.[4] No serious adverse events were observed. Reported adverse events were mild to moderate, resolved within 72 hours, and correlated with baseline levels of microfilaremia. Similar safety and efficacy results were observed in a larger unpublished trial in the same area. Preliminary data from Cote d'Ivoire comparing IDA with ivermectin plus albendazole suggest improved efficacy over the current regimen, but Mf clearance was lower than observed in PNG. Based on these results, modeling data indicate that IDA would decrease the number of rounds of MDA required to reach elimination thresholds. Additional, larger studies are planned to confirm the safety and efficacy profile of IDA.

Regardless of any alternative regimen, each round of MDA must achieve good coverage, which highlights the second major challenge of GPELF. In 2015, only 75% of IUs achieved effective coverage ($\geq$65% of the total population) during MDA. Where effective coverage is not achieved, more MDA rounds are required to reduce infection below elimination thresholds.[5] To maximize coverage WHO recommends to utilize distribution strategies acceptable by the communities targeted and directly observed treatment.[6] Low coverage during MDA has been identified as a likely cause of a third challenge, unsuccessful TAS outcomes.[7] Fourteen countries have

[4] Thomsen et al., 2015. Efficacy, Safety, and Pharmacokinetics of Co-administered Diethylcarbamazine, Albendazole, and Ivermectin for Treatment of Bancroftian Filariasis. *Clin Inf Dis.* DOI: 10.1093/cid/civ882.
[5] Irvine MA et al. Effectiveness of a

experienced at least 1 IU that failed TAS despite implementing MDA for several years. Interestingly, *Brugia*-endemic areas are more likely to fail TAS1 (28% failure rate) compared to *W. bancrofti* areas (3% failure rate).

Fourth, the meaning of elimination as a public health problem (as opposed to elimination of parasite transmission) is not universally understood. In a new standardized framework, WHO defines elimination as a public health problem as the achievement of measurable targets for infection and disease and when reached continued action is required to maintain the targets and advance to elimination of transmission.[8] A standardized process of validation is used for assessing claims of having achieved elimination of LF as a public health problem.[9] The current infection thresholds measured during sentinel and spot-check surveys and TAS are based on empirical evidence of elimination of parasite transmission. TAS is a robust, standardized survey methodology to determine whether infection is above or below the el

WHO strategic plan for STH control,[11] published in 2012, broadened the scope of attention to include PSAC and, importantly, operationally defined elimination of STH as a public health problem as no more than 1% of at-risk individuals having "moderate to heavy-intensity infection" based on egg counts on stool examinations. Unfortunately, this important document – and the WHO goal – have been almost completely ignored, eclipsed by the release, also in 2012, of the WHO Neglected Tropical Disease (NTD) Roadmap, which retained the 75% drug coverage target for STH but remained silent on the goal toward which such coverage was intended. Consequently, parasitologic monitoring has been infrequent and inadequate. In addition, PC for STH is delivered through a variety of public health programs or "platforms", including schools and child health days. In 2015 periodic deworming was provided to approximately 48% of at-risk PSAC and 63% of SAC.[12] Pharmaceutical donations of albendazole and mebendazole through WHO are currently limited to SAC.

In contrast, WHO's LF elimination program, which began around the same time, provides community-based PC to all eligible members. In 2015, among persons reported to WHO as having received deworming drugs, 24% of PSAC, and 33% of SAC,[12] received these treatments through the LF program. For WCBA, reliable data are not available, but treatments for STH were delivered principally through the LF program. Thus, LF elimination has contributed significantly to STH control. However, LF programs, having been successful, are beginning to scale down, and with them the crucially important community-based drug delivery platform. In the minority of countries where there has been an effective "hand-off" from the LF to the STH program, it has focused almost entirely on the school-based platform, leaving PSAC at risk and WCBA virtually without ongoing PC for STH. The lack of parasitologic monitoring together with the inherent costs and lack of sensitivity of stool examinations makes it difficult to determine the proper frequency of PC following such a transition.

Thus, the success of the LF program, which is to be celebrated, potentially creates a crisis, or at least a wake-up call, for STH control. Sustaining the gains against STH made possible by the LF program will not be possible without taking the parasitologic goal seriously, planning carefully for the "LF-to-STH handoff" and increased monitoring to guide program decisions.

Trachoma is caused by the obligate intracellular bacterium *Chlamydia trachomatis*. Trachoma is transmitted by person-to-person contact, via fomites, or via eye-seeking flies that have been in contact with the ocular discharge of an infected individual.[13] Trachoma infection afflicts predominantly young children.[14] After repeated infections, the inflammatory response can lead to scarring of the inner surface of the eyelid, which can cause entropion and trachomatous trichiasis

[11] World Health Organization, 2012. *Soil-transmitted helminthiases: Eliminating soil-transmitted helminthiases as a public health problem in children: Progress report 2001-2010 and strategic Plan 2011–2020.* Geneva: WHO. WHO/HTM/NTD/PCT/2012.4

[12] World Health Organization. Schistosomiasis and soil-transmitted helminthiases: number of people treated in 2015. *Wkly Epidemiol Rec.* Nos. 49/50, 2016, 91, 585–600.

[13] Taylor HR, Burton MH, Haddad D, West S, Wright H. Trachoma. *Lancet* 2014;141-11.

[14] Solomon AW, Holland MJ, Burton MJ, et al. Strategies for control of trachoma: observational study with quantitative PCR. *Lancet* 2003 Jul 19;362(8379):198-204.

(TT). Untreated TT can further lead to corneal opacity and blindness. Women are more likely to develop trichiasis, possibly owing to their prominent position in caregiving roles that results in increased exposure to infection from children.[15]

In 1998 the World Health Assembly passed a resolution (51.11) calling for the elimination of trachoma as a public health problem by the year 2020.[16] The elimination strategy developed by the WHO Alliance for the Global Elimination of Trachoma (GET2020) is encapsulated by the acronym "SAFE": Surgery for advanced disease; population based treatment with Antibiotics to clear *C. trachomatis* infection and reduce the infectious reservoir in the community; promotion of hygiene and sanitation through Facial cleanliness; and Environmental improvement to reduce transmission. Guidelines for the SAFE strategy call for annual community-wide MDA with azithromycin for a number of years based on the baseline district prevalence of trachomatous inflammation-follicular (TF). If the prevalence of TF among children ages 1-9 years (TF_{1-9}) is between 5 and 9.9%, at least one year of intervention including MDA is warranted before reassessment, if TF_{1-9} is between 10 and 29.9%, at least 3 years of AFE are warranted, and if TF_{1-9} is greater than 30%, at least 5 years of AFE are warranted before reassessment.[17] Elimination of trachoma as a public health problem is defined as: (i) a prevalence of TT "unknown to the health system" of less than 1 case per 1,000 total population; and (ii) a prevalence of TF_{1-9} of less than 5% in each district or community.[17]

of the disease, and data from December 2016 suggest that close to 50% of the people at risk for trachoma reside in Ethiopia, Nigeria, and Malawi.[19] Trachoma also still exists in the Eastern Mediterranean, the Western Pacific, South-East Asia, and in some focal areas in the Americas.

ITI data from 2005-2009 show the average annual shipment of Zithromax® treatments to endemic countries was 38.6 million doses to 10 countries. From 2010 to 2015, the annual treatments shipped rose to an average of 52.4 million doses a year to 15 countries, and in 2016 this number increased dramatically to over 120 million doses shipped to 24 countries. The increased shipment in 2016 was due to the completion of the GTMP, which identified the global need as 200 million persons in both previously identified and new intervention districts and communities. Between 2014 and 2015, access to trachoma elimination expanded to include six new countries and 334 new districts with a population of 45.1 million persons.

Mounting evidence suggests that some combination of programmatic activity and infrastructure improvement are reducing the burden of trachoma worldwide. In 2016, rigorous impact surveys, using the same technique and methodology as the baseline mapping, showed that 143 districts, with a population of 29.7 million persons, reached the elimination target for TF and no longer warranted MDA. At the community level, national trachoma programs and their NGO partners have had local success even in once hyper-endemic communities. In several studies in the Amhara region and the Gurage zone of the Ethiopian Southern Nations, Nationalities, and Peoples' region of Ethiopia, repeated mass antibiotic distributions dramatically reduced infection; approximately half of the study communities had no evidence of infection in children by polymerase chain reaction (PCR) after 3 to 4 years of treatment.[20,21,22,23] Recently published surveys in Nepal and the Gambia as well as unpublished surveys in several other once-endemic countries, have found essentially no evidence of ocular chlamydial infection.[24,25]

Mathematical models suggest that if an infectious disease is disappearing, the different prevalences found across regions will approach an exponential distribution. The ITI data suggest that the district-level prevalence of $TF_{1\text{-}9}$ approached this distribution in 2011; thus models suggest this once endemic disease is on the way out.

The trachoma program in Amhara began in 2000, and early survey data demonstrated an extremely high prevalence of trachoma throughout several administrative zones. Starting in 2003 the program began scaling up interventions in geographic areas as increased funding became available for trachoma, and increased antibiotics became available through the Zithromax® donation

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[20] Melese M, Alemayehu W, Lakew T, et al. Comparison of annual and biannual mass antibiotic administration for elimination of infectious trachoma. *JAMA* 2008;299(7);778-784.
[21] Gebre T, Ayele B, Zerihun M. Comparison of annual versus twice-yearly mass azithromycin treatment for hyperendemic trachoma in Ethiopia: a cluster-randomized trial. *Lancet* 2011:379(9811);143-151
[22] Biebesheimer JB, House J, Hong K, et al. Complete local elimination of infectious trachoma from severely affected communities after six biannual mass azithromycin distributions. *Ophthalmology* 2009;116:2047-2050.
[23] Gill DA, Lakew T, Alemayehu W, et al. Complete elimination is a difficult goal for trachoma programs in severely affected communities. *CID* 2008:46;564-566.
[24] Pant BP, Bhatta RC, Chaudhary JSP. Control of trachoma from Achham district, Nepal: A cross-sectional study from the Nepal national trachoma program. *PLOS NTD* 2016:10(2).
[25] Harding-Esch EM, Sillah A, Edwards T. Mass treatment with azithromycin for trachoma: When is one round enough? Results from the PRET trial in The Gambia.

program. By 2007, all districts in Amhara were pursuing the full SAFE strategy. From 2011 to 2015, after at least 5 years of MDA, district-level population-based impact surveys were completed in all districts of Amhara. Overall, unpublished data show regional TF_{1-9} declined from 39% in 2003 to 26% in 2016, a 32% reduction. The results of these surveys demonstrated variable success, with progress being shown in the northwest and the southeast of Amhara. Recently, the first surveillance surveys in the region demonstrated that a number of districts remained below the elimination threshold after 2 years without MDA.

However, despite 7-10 years of programmatic activity region-wide, progress has been slower than anticipated for many districts of Amhara, where TF_{1-9} prevalence has stabilized at a lower, yet still hyper-endemic level. Many districts in the region will require an additional three or more rounds of MDA in the coming years. Data from various sources such as randomized-trials in Ethiopia and cohort studies in other countries, as well as mathematical modeling demonstrate that the situation in other hyper-endemic areas is similar to the experiences in Amhara.[26,27,28,29] These various sources suggest that in areas which started at a high TF_{1-9} prevalence, reaching elimination in five years under the current strategy of annual community-wide MDA is impossible. Several trials testing more intensive antibiotic distributions and non-antibiotic water and hygiene measures are now underway, including two in Amhara. The limiting step to controlling trachoma worldwide may be determining whether a more intensive strategy can control the disease in the most hyper-endemic areas of Ethiopia.

Even though the global program is moving in the right direction, it will take years for trachoma to disappear at the current rate of progress in some hyper-endemic areas. Both regression and mathematical transmission models suggest that the 2020 target for elimination of trachoma as a public health problem will not be reached in some of the world's most affected areas. On one hand, programs have had remarkable success in reducing the clinical signs of trachoma several fold, and even more success in reducing PCR evidence of infection. On the other hand, the most severely affected areas such as Amhara, Ethiopia, despite regional success, have numerous districts where TF_{1-9} remains 4-fold higher than the target prevalence of less than 5%, despite being at scale with SAFE for a number of years.

There has been tremendous progress in scaling up the global trachoma program since the ITFDE last reviewed the disease.[30] The near completion of the TF_{1-9} prevalence map for all endemic districts propelled the global community to assess intervention needs, attempt to fill funding gaps, and focus immediate interventions on the countries that will require the most effort. There has been a collaborative effort to identify partners within countries to focus on all aspects of the SAFE

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[26] West SK, Munoz B, Mkocha H, et al. Number of years of annual mass treatment with azithromycin needed to control trachoma in hyper-endemic communities in Tanzania. *JID* 2011:204(15)268-273.
[27] Melese M, Chidambaram JD, Alemayehu W, et al. Feasibility of eliminating ocular chlamydia trachomatis with

contribute to the alleviation of poverty. However, both elimination programs remain underfunded.

3. Success in meeting the elimination targets for both diseases will require that funding and political will be intensified at both the global and national levels through 2020 and beyond.
4. The ITFDE noted that the MDA component of these programs is only one element in the strategies to eliminate LF and blinding trachoma as public health problems. In both programs, morbidity components need to be strengthened.
5. The ITFDE believes that the logic for careful integration of LF and trachoma programs at the local, national, and continental levels, particularly in Africa, is persuasive, with mutual benefits in programmatic terms for both programs, as well as improved operational efficiencies. The argument for integration of LF and onchocerciasis elimination programs in Africa also remains persuasive.
6. In light of the need to more carefully monitor and report on progress toward elimination, the ITFDE strongly encourages national NTD programs to submit program data to WHO in a timely manner.
7. IDA has the potential to accelerate elimination of LF outside of Africa. However, LF co-endemicity with onchocerciasis and loiasis in Africa threatens the feasibility of IDA use due to concerns about associated adverse events. Further study of safety and efficacy is warranted in those settings. LF programs must increase access to hydrocele surgery and implementation of morbidity management programs to prevent those still afflicted from being ignored and further marginalized.
8. Progress towards LF elimination is significant and although all countries may not achieve the 2020 target, with persistence and new tools the elimination goal will be achieved.
9. Similar to LF, clarity is needed on the global STH elimination objective and epidemiological end-points.
10. STH programs need to rapidly plan on how they will compensate for the cessation of important albendazole drug delivery platforms as LF MDA is withdrawn.
11. Greater emphasis is needed for providing adequate STH treatment coverage to women of child bearing age and PSAC.
12. For trachoma, the WHO-endorsed SAFE strategy currently has no WHO-endorsed indicators for the F and E components, the absence of which hinder efforts of countries to monitor and evaluate their progress. The ITFDE recommends that such indicators be developed as soon as possible.
13. For the S component of the SAFE strategy, the ITFDE recommends that national programs and their partners should prioritize immediate surgical interventions to reduce ocular morbidity while continuing other interventions.
14. For the A component of the SAFE strategy, in some foci annual community-wide MDA does not appear to be sufficient to reduce trachoma prevalence to elimination levels in highly endemic areas. And thus more research into alternative antibiotic treatment regimens to accelerate elimination of trachoma is needed.

15. The districts that have the highest TF_{1-9} prevalence should be prioritized for immediate and full scale SAFE interventions given they may take longer to reduce prevalence to elimination levels.