Informal consultation on end-game challenges for trachoma elimination

Task Force for Global Health, Decatur, United States of America
7–9 December 2021

World Health Organization

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Contents

1. Background

Trachoma is the leading infectious cause of blindness worldwide *(1)*. It is most common in poor rural communities. Repeated infection with particular strains *(2,3)* of *Chlamydia trachomatis* causes episodes of conjunctival inflammation ("active trachoma") that resolve with scar formation *(4)*. Eventually, scarring can draw the eyelashes inwards to rub on the surface of the eye ("trachomatous trichiasis"), potentially damaging the cornea and impairing vision. Since 1993, the World Health Organization (WHO) has recommended the "SAFE" strategy (surgery, antibiotics, facial cleanliness, environmental improvement) to reduce the prevalence of trachoma *(5)*. The S component is offered to individuals with advanced disease. The A, F and E components are offered to entire districts or "evaluation units" (EUs) of 100 000–250 000 people *(6)* in which the prevalence of the active trachoma sign "trachomatous inflammation—follicular" *(7)* in 1–9-year-olds ($TF_{1–9}$) is ≥ 5%.

Since 1996, trachoma has been targeted for elimination as a public health problem worldwide *(8,9)*. The active trachoma criterion for national elimination as a public health problem is a $TF_{1–9}$ < 5%, sustained for at least two years in the absence of antibiotic mass drug administration (MDA), in each formerly endemic EU *(10)*. Using A, F and E, health ministries and their partners have made considerable progress towards achieving this criterion in formerly endemic EUs worldwide. In 2002, an estimated 1517 million people lived in EUs in which EU-wide implementation of the A, F and E components of SAFE were thought to be needed for the purposes of global elimination of trachoma as a public health problem *(11)*; by June 2021, that number had fallen to 136.2 million, a 91% reduction *(12)*. Approximately 85% of the 136.2 million people living in EUs needing A, F and E in June 2021 were in WHO's African Region *(12)*.

Alongside this general progress, it is evident that in a small proportion of EUs there is difficulty sustaining $TF_{1–9}$ < 5%. Such EUs fall into two broad categories: those in which $TF_{1–9}$ remains at or above the elimination threshold (5%) despite implementation of interventions *(13–15)*; and those in which $TF_{1–9}$ < 5% is achieved at impact survey, but subsequently returns to ≥ 5% during the two-and-a-half-year period of surveillance after stopping MDA [data in press]. Using current A, F and E interventions, modelling suggests a low likelihood of successful elimination by 2030 in at least some of these EUs *(16,17)*.

How these EUs should be managed is presently unclear. Uncertainty is deepened by programmatic reliance on $TF_{1–9}$ as the WHO-recommended indicator for decision-making; this marker is known to lag behind the prevalence of conjunctival *C. trachomatis* infection as infection prevalence declines *(18–22)*, and would likely lag behind population-level infection recrudescence too.

Health ministries and their partners are keen to find solutions to this group of problems. In response, WHO convened an informal consultation on 7–9 December 2021 to discuss affected EUs of Ethiopia, Mozambique, Niger, Uganda and the United Republic of Tanzania, where the absence of a plan of action agreed between stakeholders put programmatic funding for 2022 at risk. Given the ongoing COVID-19 pandemic and the associated travel restrictions, a hybrid meeting format was adopted whereby some participated in person at the Task Force for Global Health in Decatur (GA), USA, and others virtually.

Professor Simon Brooker and Mr Fikre Seife were elected as Co-chairs of the meeting. The participants are listed in Annex 1. Invited experts completed the WHO declaration of interests form before the meeting. The declarations were assessed by the Secretariat. Declared interests are listed in Annex 3.

The agenda is reproduced in Annex 2. On day 1, working definitions were agreed and the magnitude of the problem outlined. On days 2 and 3, reviews of published evidence were presented by designated meeting participants, and consensus was reached amongst participants on special measures that could be incorporated into programmes.

2. Working definitions

In order to increase the efficiency of the conversation, estimate the potential magnitude of the problem and facilitate future research, the following working definitions were adopted:

- a **category 1 EU ("persistent TF")** is an EU with at least two impact surveys at which $TF_{1–9}$ is ≥ 5%, without ever having had a $TF_{1–9}$ < 5%; and
- a **category 2 EU ("recrudescent TF")** is an EU with at least one surveillance survey at which $TF_{1–9}$ is ≥ 5%.

Notes:

(a) In the definition of category 1, reference to data from two impact surveys implies that there has been a baseline survey in the EU, followed by implementation of A, F and E interventions both before the first impact survey and between the first and second impact surveys of this pair.

(b) In the definition of category 1, exclusion of EUs in which $TF_{1–9}$ has ever been < 5% restricts the focus to EUs that remain problematic and makes categories 1 and 2 mutually exclusive.

3. Magnitude of the problem

In December 2021, 176 EUs worldwide, or 8% of all EUs that had ever been observed to have a $TF_{1–9}$ ≥ 5%, met the criteria for category 1. The majority of category 1 EUs (145/176, 82%) were in Ethiopia (Table 1). Within category 1 EUs, those in Ethiopia were more likely than those in other countries to have a most recent[1] $TF_{1–9}$ ≥ 10% (113/145, 78%, in Ethiopia; 14/31, 45%, in all other countries combined).

Of 774 EUs worldwide that had conducted at least one surveillance survey, 123 (16%) met the criteria for category 2, of which 57 (46%) were in Ethiopia (Table 2). Of the 45 EUs with subsequent impact survey data, 35 (78%) had subsequently recorded a $TF_{1–9}$ < 5%. The 10 EUs that did not were in Ethiopia (8), Uganda (1) and the United Republic of Tanzania (1).

[1] "Most recent" is used in this context because some of the EUs in question have undergone more than one impact survey.

Table 1. Evaluation units (EUs) meeting the criteria for category 1, by country and current (most recent) prevalence of trachomatous inflammation—follicular in 1–9-year-olds ($TF_{1–9}$), compared to the number of EUs ever found to have a $TF_{1–9}$ ≥ 5% (Ever $TF_{1–9}$ ≥ 5%). The numbers in each "category 1" column are a subset of the numbers in the column immediately to its left.

Country	Ever $TF_{1–9}$ ≥ 5%	Category 1 (current $TF_{1–9}$ ≥ 5%)	Category 1 (current $TF_{1–9}$ ≥ 7%[2])	Category 1 (current $TF_{1–9}$ ≥ 10%)
Ethiopia	795	145	134	113
Kenya	33	5	3	2
Mozambique	71	6	3	0
Niger	98	9	6	5
Nigeria	127	1	1	1
South Sudan	27	1	0	0
Sudan	29	1	1	0
Uganda	57	1	1	1
United Republic of Tanzania	77	4	3	2
Zambia	45	3	3	3
Total (% of EUs ever $TF_{1–9}$ ≥ 5%)	**2144 (100%)**	**176 (8%)**	**155 (7%)**	**127 (6%)**

[2] The 7% threshold is arbitrary and based on the observation that EUs in which the $TF_{1–9}$ is < 7% tend to have zero to very low prevalence of conjunctival *C. trachomatis* infection.

Table 2. Evaluation units (EUs) meeting the criteria for category 2, by country and subsequent estimates of prevalence of trachomatous inflammation—follicular in 1–9-year-olds

Country	TSS1 ever done	Category 2	Category 2, awaiting next TIS	Category 2, next TIS < 5%	Category 2, next TIS ≥ 5%	Category 2, TSS2 < 5%	Category 2, TSS2 ≥ 5%	Category 2, TSS3 < 5%
Cameroon	22	2	2					
Chad	25	2	2					
Eritrea	11	1	1					
Ethiopia	103	57	41	8	7		1	
Guinea-Bissau	12	3		1		2		
Kenya	13	5	5					
Malawi	44	3				3		
Mali	40	6		1		4		1
Mozambique	37	6	6					
Niger	63	11	3	8				
Nigeria	69	2		2				
Solomon Islands	9	9	9					
Sudan	10	2	2					
United Republic of Tanzania	70	6	3			2	1	
Uganda	56	6	3	2	1			
Zambia	7	2	1	1				
Others	183	0						
Total	**774**	**123**	**78**	**23**	**8**	**11**	**2**	**1**

TIS: trachoma impact survey; TSS1: first trachoma surveillance survey; TSS2: second trachoma surveillance survey; TSS3: third trachoma surveillance survey.

4. Emerging groups of category 1 and 2 evaluation units

Meeting participants agreed that not all EUs meeting the criteria for category 1 or category 2 will be epidemiologically equivalent. Indeed, multiple sets of circumstances may have led to EUs qualifying for these categories. Potential contributing factors theoretically include: very high baseline *C. trachomatis* transmission intensity[1]; inadequate coverage of antibiotic MDA *(23–25)*, whether homogeneously low, low in particular parts of the EU, or low in particular demographic subsets of the EU population; MDA frequency too low to drive down *C. trachomatis* infection prevalence *(19,26,27)*; macrolide resistance in *C. trachomatis (28)*[2]; inadequate facial cleanliness or environmental improvement interventions *(29–32)*; high population turnover or population mobility *(33)*; and misclassification of TF prevalence due to measurement error.

Based on these theoretical contributing factors, category 1 and category 2 EUs were broadly and provisionally grouped as follows:

- high transmission EUs in which alternative intervention approaches may be required;
- special population EUs, such as migratory or remote populations, in which more tailored intervention approaches may be required; and
- anomalous EUs, in which stochastic fadeout may be likely.

This grouping allows systematic consideration of potential interventions. For example, where tailored intervention approaches are being designed for nomadic populations who cross EU and administrative borders, coordination between subnational or national governments could ensure that interventions are delivered comprehensively and systematically, thereby reducing the risk that any part of the affected population is left untreated.

Most but not all category 2 EUs identified to date now have a $TF_{1–9}$ < 5% (Table 2). Meeting participants proposed that where $TF_{1–9}$ at surveillance survey was not very high and surrounding EUs already have $TF_{1–9}$ < 5%, it is at least moderately likely that category 2 EUs will reach the elimination threshold without additional antibiotic MDA.

5. Special measures that could be incorporated into programming for category 1 and 2 evaluation units

Meeting participants:

Recalling that current WHO guidance for implementation of the A, F and E components of SAFE *(34)* is intended for the usual or average EU, not for EUs meeting the criteria for category 1 and 2;

Noting that evidence is scarce to suggest that category 1 EUs will consistently achieve $TF_{1–9}$ < 5% by simply continuing implementation of A, F and E in the way it has previously been delivered;

Mindful that for some but not all groups of category 1 and 2 EUs identified in section 4, the total number of EUs worldwide may be too low to prospectively test new management strategies by conducting community randomized trials;

1. *Agreed* that, for as long as the evidence base for optimal management of category 1 and 2 EUs remains weak, tailored management of each EU guided by expert opinion is likely to be appropriate;

2. *Recommended* that, where tailored management is to be adopted, all available evidence on the epidemiology of (a) trachoma, (b) conjunctival *C. trachomatis* infection and exposure to *C.*

[1] EUs with very high baseline *C. trachomatis* transmission intensity that are showing significant progress towards TF1–9 < 5% after two impact surveys may be systematically different to category 1 EUs that are making limited or no progress towards that threshold.
[2] To date there have been no reports of programmatically significant macrolide resistance in conjunctival *C. trachomatis (28)*.

trachomatis infection, and (c) access to water and sanitation, in the EU and any surrounding administrative areas, plus the history of interventions in the EU and any surrounding administrative areas, should be made available by the national programme manager to a trusted multidisciplinary team in conjunction with the request for guidance, and that if age-stratified data on *C. trachomatis* infection (using a nucleic acid amplification-based test) and/or anti-*C. trachomatis* antibodies are unavailable, consideration be given to generating such data;

3. *Welcomed* the ongoing development of geostatistical analytical approaches to more precisely estimate the prevalence of trachoma and related metrics *(35,36)*;

4. *Encouraged* consideration of grid-based *(37)* and adaptive *(38)* sampling of first-stage clusters in trachoma surveys, in conjunction with the development of geostatistical analytical approaches;

5. *Recommended* that tailored management should include

(a) efforts to ensure high-quality delivery of agreed A, F and E interventions with maximal coverage in all geographical and demographic divisions present in the EU,

(b) high-fidelity measurement of that coverage, including in demographic subgroups, and

(c) detailed documentation of process and outcomes, with rapid sharing of data among all relevant stakeholders, to maximize collective learning;

6. *Proposed* that tailored management could include

(a) adjusting the EU population size to enable the most appropriate measurement of the burden of disease or infection within, and deliver interventions to, migratory populations, particularly where such populations move across administrative borders,

(b) more rounds of MDA and extended periods of delivery of F and E interventions before re-survey,

(c) more frequent than annual delivery of MDA rounds, with the possibility of delivering additional MDA rounds only to demographic subgroups likely to have the highest prevalence of conjunctival *C. trachomatis* infection *(39–42)*,

(d) more intensive delivery of F and E interventions, with intervention design based on established health promotion and behaviour change frameworks *(30)*, and/or

(e) discontinuing MDA and continuing surveillance if there is a justifiable expectation that TF_{1-9} will regress to < 5%; and

7. *Invited* support from all stakeholders for 1–6 above.

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Annex 1. List of participants

Invited experts

Professor Amza Abdou, Ministry of Public Health, Niamey, Niger

Dr David Addiss, Task Force for Global Health, Decatur, United States of America

Professor Robin Bailey, London School of Hygiene & Tropical Medicine, London, United Kingdom

Professor Simon Brooker, Bill & Melinda Gates Foundation, Seattle, United States of America

Professor Paul Courtright, Groote Schuur Hospital, Cape Town, South Africa

Dr Paul Emerson, Task Force for Global Health, Decatur, United States of America

Dr Marília Eugénio Massangaie Guambe, Ministry of Health, Maputo, Mozambique

Dr Esmael Habtamu, London School of Hygiene & Tropical Medicine, London, United Kingdom

Dr Emma Harding-Esch, Tropical Data, London, United Kingdom

Ms PJ Hooper, Task Force for Global Health, Decatur, United States of America

Dr George Kabona, Ministry of Health, Community Development, Gender, Elderly and Children, Dodoma, United Republic of Tanzania

Dr Anna Last, London School of Hygiene & Tropical Medicine, London, United Kingdom

Professor Tom Lietman, Francis I. Proctor Foundation, San Francisco, United States of America

Mr Chad MacArthur, MacArthur/Tapert Global Health Consulting, Harpswell, United States of America

Dr Diana Martin, Centers for Disease Control and Prevention, Atlanta, United States of America

Dr Francis Mugume, Ministry of Health, Kampala, Uganda

Dr Scott Nash, The Carter Center, 53 Freedom Parkway, Atlanta, United States America

Dr Jeremiah Ngondi, RTI International, Cambridge, United Kingdom

Ms Stephanie Palmer, FHI 360, Washington, United States of America

Dr Babar Qureshi, CBM International, Oakington, United Kingdom

Ms Kristen Renneker, Task Force for Global Health, Decatur, United States of America

Ms Lisa Rotondo, RTI International, Washington, United States of America

Mr Fikre Seife, Federal Ministry of Health, Addis Ababa, Ethiopia

Professor Sheila West, Johns Hopkins School of Medicine, Baltimore, United States of America

Observers

Dr Rebecca Flueckiger, RTI, Atlanta, United States of America

Ms Julie Jenson, Pfizer Inc., New York, United States of America

Dr Charles Knirsch, Pfizer Vaccines Clinical Research, New York, United States of America

Mr Aryc Mosher, United States Agency for International Development, Washington, United States of America

Ms Emily Wainwright, United States Agency for International Development, Washington, United States of America

Secretariat

Dr Amir Bedri Kello, WHO Regional Office for Africa, Brazzaville, Congo

Dr Sunghye Kim, WHO Regional Office for the Western Pacific, Manilla, Philippines

Dr Martha Idalí Saboyá-Díaz, Pan American Health Organization, Washington, United States of America

Dr Anthony Solomon, WHO headquarters, Geneva, Switzerland

Dr Supriya Warusavithana, WHO Regional Office for the Eastern Mediterranean, Cairo, Egypt

Dr Aya Yajima, WHO Regional Office for South-East Asia, New Delhi, India

Annex 2. Agenda

Tuesday, 7 December 2021: Session 1 (What's the problem?)

Time	*Topic*	*Speakers / Facilitators*
08:00–12:00	Opening and welcome	Anthony Solomon
	Introduction of participants Purpose, outcome and outputs of meeting Summary of declarations of conflicts of interest Nomination of officers Adoption of agenda	Anthony Solomon Chair
	Administrative announcements	Amanda Bradica
	Concerns	Abdou Amza Fikre Seife Francis Mugume George Kabona Marilia Massangaie Emily Wainwright Babar Qureshi Paul Emerson Julie Jenson Anthony Solomon
	Working definitions for persistence and recrudescence of active trachoma	Amir Kello
	Magnitude of the problem: analysis of global data	Kristen Renneker
	Discussion	All

Wednesday, 8 December 2021: Session 2 (How well can we determine whether there is a problem in a given EU?)

Time	*Topic*	*Speakers / Facilitators*
08:00–12:00	How could we generate better TF estimates?	Emanuele Giorgi
	Is the empirical prevalence of TF in 1–9-year-olds determined 1–5 years after starting MDA the optimal way to assess whether MDA should continue?	
	1. Summary of discussions from previous meetings	Anthony Solomon
	2. Conjunctival *Chlamydia trachomatis* infection	Fikre Seife
	3. Serology	Diana Martin
	4. Predicting the probability of TF <5% at impact survey	Jeremiah Ngondi
	5. Predicting the probability of TF <5% at surveillance survey	Tom Lietman
	Discussion	All

Thursday 9 December 2021: Session 3 (How can we solve the problem?)

Time	*Topic*	*Speakers / Facilitators*
08:00–12:00	What to do about persistence and recrudescence?	
	1. Insights from modelling	Anna Borlase
	2. Stop and see	Kristen Renneker
	3. How good is antibiotic coverage? How can we make it better? What about nomads, refugees and internally-displaced people?	Anthony Solomon
	4. More-frequent-than-annual antibiotic MDA	Tom Lietman
	5. Facial cleanliness / environmental improvement approaches	Anna Last
	6. Bespoke management of EUs (a more flexible survey schedule and antibiotic approval process)	Anthony Solomon
	7. Implementation research	Tom Lietman / Anthony Solomon
	Discussion, including consideration of whether and how data collection, data flow, communication, decision-making and implementation will change	All

Annex 3. Declarations of interest

All invited experts completed declarations of interests for WHO experts, which were submitted to and assessed by the WHO Secretariat before the meeting. Significant interests are defined by WHO as:

- interests valued at ≥ US$ 5000 for the expert, a family member, or other associated party;
- a professional or intellectual bias; or
- circumstances that might lead to an unfair competitive advantage,

current as of the time of the meeting, or within the previous four years.

The following significant interests were declared:

Dr Paul Emerson, Ms PJ Hooper and Ms Kristen Renneker declared personal salary and programme support provided by Pfizer Inc. (the manufacturers of azithromycin) to their employer, the Task Force for Global Health.

Dr Emma Harding-Esch declared personal salary provided by the Task Force for Global Health, using funds from Pfizer Inc., to her employer, the London School of Hygiene & Tropical Medicine.

These interests were reviewed and considered not to affect the objective participation of these participants.


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