Diagnostic target product profiles for trachoma surveillance

World Health Organization

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1. Introduction

Trachoma is the leading infectious cause of blindness worldwide. In April 2023, it was a public health problem in approximately 40 countries, with an estimated 116 million people at risk and 1.5 million people affected by the late blinding stage of the disease *(1)*. About 84% of those at risk of trachoma are in the World Health Organization (WHO)'s African Region; about 52% of those at risk of trachoma live in Ethiopia.

2. Epidemiology

Trachoma is caused by ocular infection with the bacterium *Chlamydia trachomatis*, which results in inflammation of the conjunctiva. This is known as "active trachoma", which can be characterised by the presence of the signs trachomatous inflammation—follicular (TF) and/or trachomatous inflammation—intense (TI). *C. trachomatis* infection is mainly found in children. After many episodes of reinfection, the upper conjunctiva can become scarred, causing the eyelashes to turn inwards, scratching the eyeball. This is known as trachomatous trichiasis (TT) and is rarely found in children. If left unmanaged, TT can lead to irreversible corneal damage and blindness *(2)*.

Transmission of *C. trachomatis* is thought to occur from person to person through contact with nasal and/or ocular discharge, through shared fomites and, indirectly, via eye-seeking flies (in particular, *Musca sorbens*) *(3)*.

3. Public health response

Trachoma is targeted for elimination as a public health problem by 2030 *(4)*, which is defined as: a prevalence of TT unknown to the health system of < 0.2% in adults aged ≥ 15 years in each formerly endemic district; a prevalence of TF of < 5% in children aged 1–9 years in each formerly endemic district; and evidence that the health system can identify and manage incident TT cases *(5)*.

The WHO-endorsed strategy for trachoma elimination is known as SAFE: Surgery for TT, Antibiotics to clear infection, and Facial cleanliness and Environmental improvement to limit transmission *(6)*. Surgery is offered at an individual level to those with TT, whereas the "AFE" components are implemented at the evaluation unit (EU) level (the unit for healthcare management, generally with a population 100 000–250 000 people *(7)*). Antibiotics are distributed through mass drug administration (MDA) in whole EUs that have a TF prevalence ≥ 5%. Health promotion and improvements to water, sanitation and hygiene (WASH) access aim to achieve the "F" and "E" components.

As of June 2023, 17 countries have been validated by WHO as having eliminated trachoma as a public health problem. From 2002 to 2022, there was a 92% reduction in the number of people at risk of trachoma blindness, from 1.5 billion to 125 million, alongside a 78% reduction in individuals with TT from 7.6 million to 1.7 million *(8)*. However, some EUs continue to have TF prevalences above the elimination threshold despite years of MDA ("persistent active trachoma"), while in other EUs the TF prevalence has returned to above the elimination threshold following the cessation of antibiotic pressure ("recrudescent active trachoma") *(9)*.

4. Available diagnostic tools

In trachoma prevalence surveys, trachoma is diagnosed using the WHO simplified grading system, which was designed for use by non-specialist personnel *(10)*. The key signs for programmatic decision-making

are TF, which is associated with ocular *C. trachomatis* infection, and TT, where eyelashes from the upper eyelid touch the eyeball (or where there is evidence of recent epilation of in-turned eyelashes from the upper eyelid), which can threaten sight. Concerted efforts have been made to standardize and ensure the quality of assessment of these clinical signs in population-level surveys *(11–14)*. However, a growing body of evidence highlights their limitations, including poor sensitivity and specificity of TF as a marker for *C. trachomatis* infection (especially post-MDA *(15)*), inherent subjectivity of grading clinical signs, and difficulty of training graders as trachoma prevalence falls and cases become rarer *(2)*.

Nucleic acid amplification and serological testing have been used in multiple research studies and have also been used as part of some countries' post-validation surveillance for programmatic purposes *(2, 16–19)*. Nucleic acid amplification testing of ocular swab samples detects current *C. trachomatis* infection with high sensitivity and specificity, but the assays are relatively expensive, and require laboratory infrastructure and trained personnel *(20)*. Serological testing of antibodies to *C. trachomatis* is reflective of cumulative exposure to infection, with age–seroprevalence curve and seroconversion rate calculations at the population level being informative for programmatic decision-making *(2)*. However, serology cannot be considered a diagnostic tool for current infection, because it can be positive in the face of prior exposure; furthermore, diagnostic accuracy is affected by the contribution of urogenital *C. trachomatis* infection to overall seroprevalence *(18, 21)*. WHO has now recommended that, where data on *C. trachomatis* antibodies or ocular infection are available, they should be used to inform programmatic decision-making in EUs in which there is persistent or recrudescent active trachoma *(9)*.

5. Diagnostic Technical Advisory Group for Neglected Tropical Diseases

The WHO Global Neglected Tropical Diseases Programme (WHO/NTD) manages a diverse portfolio of 21 diseases and disease groups, each with its own unique epidemiological and diagnostic challenges. The principal advisory group to WHO on the control, elimination and eradication of NTDs is the Strategic and Technical Advisory Group for Neglected Tropical Diseases, which determined that a single WHO working group would help ensure a unified approach to identifying and prioritizing diagnostic needs, and to informing WHO strategies and guidance on the subject *(22)*.

In response, the Diagnostic Technical Advisory Group for Neglected Tropical Diseases was created as an advisory group to WHO/NTD. The Group recommended the establishment of several disease-specific diagnostic subgroups, including one to advise on trachoma surveillance activities, as well as the development of TPPs to help test developers focus energies appropriately on tests needed by programmes. A subgroup of trachoma technical experts was formed, and first met virtually on 8 September 2022.

6. Purpose of the target product profile

The purpose of this TPP is to communicate platform-agnostic recommendations of what a diagnostic should have. It presents the minimum and ideal characteristics for diagnostics needed to detect evidence of past and/or present *C. trachomatis* infection for trachoma surveillance purposes at EU level. The subgroup identified the need for TPPs in three epidemiological contexts: (i) newly suspected endemic EUs, to confirm the aetiology of the follicular conjunctivitis, and to measure epidemiological progress at population level

following intervention; (ii) after discontinuation of antibiotic MDA (i.e. for use in impact and surveillance surveys, and for post-validation surveillance); and (iii) in EUs in which the epidemiology of trachoma is unusual, such as EUs in which there is persistent or recrudescent active trachoma, or EUs/countries where a high proportion of children have active trachoma but there is little evidence of TT in adults, such as in certain countries in the Pacific.

7. TPP development process

These TPPs were developed in accordance with the processes outlined in *WHO target product profiles, preferred product characteristics, and target regimen profiles: standard procedures (second edition) (23)*.

Decisions were made by the trachoma subgroup by consensus, defined as an absence of any further objections during a series of teleconferences specifically convened to develop these TPPs, and subsequent confirmation by subgroup members of agreement with the written text. External peer review was undertaken by members of the public, advertised on the WHO website (https://www.who.int/news-room/articles-detail/call-for-public-consultation--target-product-profiles-(tpp)-for-trachoma-surveillance) and requested from members of the WHO Alliance for the Global Elimination of Trachoma via email.

8. Management of conflicts of interest

All subgroup members acted independently and in a personal capacity. Declarations of Interest were submitted by all members, and these were reviewed by two members of the technical unit. Potential conflicts of interest were further assessed with the technical unit team leader. No significant interests were identified. Nominations were approved by the WHO Assistant Director-General, Universal Health Coverage/Communicable and Noncommunicable Diseases.

9. Characteristics of a needed diagnostic test for trachoma surveillance

The TPPs have been designed for the three different use cases, but the minimum and ideal characteristics have only been presented for the first use case (newly suspected endemic, Table 1) unless a difference was identified as being needed for the other use case(s) (Tables 2 and 3).

The TPPs also present minimum and ideal characteristics for both a field-based "point-of-care" test and a laboratory-based test, to account for different countries' infrastructures and population accessibility, and how diagnostics could inform programmatic decision-making in these different contexts. For instance, since trachoma interventions are implemented at the EU level, it is not necessary to know an individual's infection status and laboratory-based tests would be acceptable in a large proportion of cases. However, certain populations are difficult or expensive to access (for example, due to insecurity or remoteness)*(24)*, and therefore a population-based decision could be made in the field based on point-of-care, field-based, test results.

Table 1. TPP for newly suspected endemic evaluation units

	Ideal	Minimum
1. Product use summary		
1.1 Intended use	**For both field- and laboratory-based test:** In EUs that are newly-suspected of being trachoma-endemic, to measure prevalence of a *Chlamydia trachomatis* infection biomarker	Same
1.2 Targeted population	**For both field- and laboratory-based test:** All ages[1]	**For both field- and laboratory-based test:** 1–5-year-olds[2]
1.3 Lowest infrastructure level	**Field-based test:** The test will be performed under "zero-infrastructure" conditions, including but not limited to schools, community health centres, households and outdoor conditions **Laboratory-based test:** The test can be performed in a district, regional or national diagnostic testing laboratory	**Field-based test:** The test will be performed under "minimum-infrastructure" conditions, including but not limited to schools, community health centres, households and outdoor conditions **Laboratory-based test:** Same
1.4 Lowest level user	**Field-based test:** Surveillance teams, health personnel and community health workers **Laboratory-based test:** Trained laboratory technicians	Same
1.5 Training requirements	**Field-based test:** One day or less for health personnel and community health workers; testing job aid/instructions/instructional videos for use should be made available via the Internet for download (i.e. are publicly available). Training includes certification of competency **Laboratory-based test:** < 1 week for trained laboratory technicians and competent health personnel; testing job aids/instructions/ instructional videos for use should be made available via the Internet for download (i.e. are publicly available) in addition to the instructions included with the test. Training includes certification of competency	Same

EU: evaluation unit; GDP: gross domestic product; GHTF: Global Harmonization Task Force; IVDR: in vitro diagnostic regulation; KFDA: Korean Food and Drug Administration; MDA: mass drug administration; MSDS: material data safety sheet; N/A: not applicable.

[1] An ideal test could be applied to everyone but it does not have to be (i.e. depending on context, it could be applied to the age group suspected of having peak infection prevalence).

[2] Studies to date suggest that the 1–5-year-old age range captures most of the information around infection and antibody responses. In addition, younger children represent more recent infection and are easier to find in household-based surveys because they are not at school and, therefore, the sample is less subject to biases of incomplete enrolment.

Table 1. TPP for newly suspected endemic evaluation units (cont'd)

	Ideal	Minimum
2. Design		
2.1 Portability	**Field-based test:** Highly portable with no specialised transport needs[3] **Laboratory-based test:** There are no special requirements regarding portability of the test itself	Same
2.2 Instrument/ power requirement	**Field-based test:** Self-contained kit, independent of any power source, including battery or generator power **Laboratory-based test:** Access to plug-in power (mains or generator) is acceptable. There are no other special requirements regarding instrument/power requirements of the test itself	Same
2.3 Water requirement	**Field-based test:** Independent of any water supply **Laboratory-based test:** Access to a source of laboratory-grade water is acceptable	Same
2.4 Maintenance and calibration	**Field-based test:** No maintenance required (i.e. disposable) and no calibration required **Laboratory-based test:** Periodic maintenance and calibration of any instrumentation required to be available in the countries and should not be needed more frequently than once a year	Same
2.5 Sample type/ collection	**For both field- and laboratory-based test:** Biomarker that is a minimally invasive sample type, such as ocular swab, finger-prick, tears, buccal swab, etc.[4]	Same
2.6 Sample stability	**For both field- and laboratory-based test:** Analytes stable during collection chain	Same
2.7 Sample preparation/ transfer device	**Field-based test:** Sample preparation should not exceed transfer of sample to the testing device, either directly or by use of a predefined and provided device **Laboratory-based test:** Sample preparation should not exceed transfer of specimen to a suitably designed sample transport device, either directly or by use of a predefined and provided device for final processing at a laboratory	Same

[3] Portability implies those characteristics described in 2.2–2.4, as well as no locational limitations to where the test can be performed.
[4] The laboratory-based test will need to function with samples that have been collected up to 1 day before. A dried blood spot sample lends itself to integration more than other sample types do.

Table 1. TPP for newly suspected endemic evaluation units (cont'd)

	Ideal	Minimum
2.8 Sample volume	**For both field- and laboratory-based test:** As little as is practically necessary, determined by sample type[5]	Same
2.9 Target analyte	**For both field- and laboratory-based test:** *C. trachomatis* biomarker, serovar-specific	**For both field- and laboratory-based test:** *C. trachomatis* biomarker
2.10 Type of analysis	**For both field- and laboratory-based test:** Semi-quantitative[6]	**For both field- and laboratory-based test:** Qualitative
2.11 Detection	**Field-based test:** High contrast, clear result for naked eye; indoor and outdoor reading of a signal that provides unambiguous determination of the output **Laboratory-based test:** May include instrument-based detection of a signal that provides unambiguous determination of the output	Same
2.12 Quality control[7]	**For both field- and laboratory-based test:** Internal process control (e.g. control line). External performance control (e.g. negative and positive controls to verify test line is working appropriately). Colorimetric or other indicator to identify excessive heat/humidity exposure	**For both field- and laboratory-based test:** Internal process control (e.g. control line). External performance control (e.g. negative and positive controls to verify test line is working appropriately)
2.13 Supplies needed	**For both field- and laboratory-based test:** All reagents and supplies included in kit, with minimal import restrictions (e.g. animal-free)	Same
2.14 Safety	**For both field- and laboratory-based test:** No additional risk to usual practice	Same
3. Performance		
3.1 Species differentiation	**For both field- and laboratory-based test:** *C. trachomatis* species-specific antigen (serovars A–K)[8]	**For both field- and laboratory-based test:** *C. trachomatis*

[5] Sample volume represents that volume which is introduced to the test device itself. It is determined by the sample type and test requirements. It should be a volume that does not limit participant adherence.

[6] Detection of *C. trachomatis* infection for monitoring and evaluation shall be independent of load of infection. However, it may be desirable to have the ability to gain some degree of information regarding load of infection.

[7] There would need to be a definition of how external positive controls should/would be used if they are to be included with a test. Controls should have a shelf-life consistent with that of the test. A test for the adequacy of sample collection may also be considered.

[8] The ideal would enable differentiation between ocular and genital infection.

Table 1. TPP for newly suspected endemic evaluation units (cont'd)

	Ideal	Minimum
3.2 Diagnostic/ clinical sensitivity[9,10]	**For both field- and laboratory-based test:** For a hypothetical prevalence threshold of 5%: > 60% For a hypothetical prevalence threshold of 10%: > 85%	Same
3.3 Diagnostic/ clinical specificity[11,12]	**For both field- and laboratory-based test:** > 98%	Same
3.4 Time to results[13]	**Field-based test:** Same day result (< 1 hour) **Laboratory-based test:** Hours	Same
3.5 Result stability	**Field-based test (with visual detection):** Developed test result remains stable for 1–2 hours **Laboratory-based test (with instrument detection):** N/A	Same
3.6 Throughput	**For both field- and laboratory-based test:** sufficient throughput to turn results around in time required by trachoma programme	Same
3.7 Target shelf-life/stability	**Field-based test:** ≥ 24 months, 2–40 °C, 75% relative humidity (no cold chain required); temperature excursion/prolonged deviation of 50 °C for 2 weeks acceptable **Laboratory-based test:** ≥ 18 months, 2–40 °C, 75% relative humidity; temperature excursion/ prolonged deviation of 50 °C for 2 weeks acceptable	**Field-based test:** Same **Laboratory-based test:** ≥ 18 months, 2–40 °C, 75% relative humidity (cold chain acceptable); temperature excursion/prolonged deviation of 50 °C for 2 weeks acceptable

[9] Tool sensitivity is crucial to correctly implement antibiotic MDA when it is needed.

[10] Calculations conducted to provide guidance that is agnostic with respect to a particular diagnostic/biomarker; the 5% and 10% thresholds are simply illustrative of biomarker prevalence that a diagnostic might measure in suspected trachoma-endemic EUs. Assumptions made for sensitivity calculations: (i) hypothetical prevalence threshold of 5% (with assumed true prevalence of 1%) or threshold of 10% (with assumed true prevalence of 5%); (ii) a population-based sample of 20–30 clusters, with approximately 50 children per cluster (i.e. approximately 1000 children in total). WHO recommendations for cluster, household and individual sampling in population-based prevalence surveys are described in: *Design parameters for population-based trachoma prevalence surveys* https://www.who.int/publications/i/item/who-htm-ntd-pct-2018.07; (iii) the minimum specificity identified for this scenario in Table section 3.3 (> 98%); (iv) type 1 error (α) ≤ 5%. This means that using the diagnostic, the survey would incorrectly conclude that prevalence in a defined population is below the 5–10% threshold < 5% of the time. The source code used for the calculations is available from the *WHO trachoma TPP sensitivity and specificity calculations*: https://osf.io/bezv4/.

[11] High specificity is required to avoid unnecessarily implementing antibiotic MDA.

[12] Calculations conducted to provide guidance that is agnostic with respect to a particular diagnostic/biomarker; the 5% and 10% thresholds are simply illustrative of biomarker prevalence that a diagnostic might measure in suspected trachoma-endemic EUs. Assumptions made for specificity calculations: (i) hypothetical prevalence threshold of 5% (with assumed true prevalence of 1%) or threshold of 10% (with assumed true prevalence of 5%); (ii) a population-based sample of 20–30 clusters, with approximately 50 children per cluster (i.e. approximately 1000 children in total). WHO recommendations for cluster, household and individual sampling in population-based prevalence surveys are described in: *Design parameters for population-based trachoma prevalence surveys* https://www.who.int/publications/i/item/who-htm-ntd-pct-2018.07; (iii) power (1–Type II error) was set to 90% to correctly conclude prevalence is below the threshold at a given level of true prevalence: 1% to 5% (suspected endemic). The source code used for the calculations is available from the *WHO trachoma TPP sensitivity and specificity calculations*: https://osf.io/bezv4/.

[13] This is the test turnaround time (test run-time, not time since sample collection).

Table 1. TPP for newly suspected endemic evaluation units (cont'd)

	Ideal	Minimum
3.8 Ease of use	**Field-based test:** One timed step; ten or fewer user steps, instructions for use should include diagram of method and results interpretation. Must be able to use in an unprotected external environment **Laboratory-based test:** No minimum number of steps; must be able to be competently run by a trained professional	**Field-based test:** One timed step; 10 or fewer user steps, instructions for use should include diagram of method and results interpretation **Laboratory-based test:** Same
3.9 Ease of results interpretation	**Field-based test:** Interpretation by unaided eye, does not require discrimination of one colour from another **Laboratory-based test:** Results can be interpreted by a suitable instrument	Same
3.10 Operating temperature	**Field-based test:** 15–40 °C **Laboratory-based test:** May have to control temperature	Same
3.11 Operating humidity	**Field-based test:** 10–75% relative humidity **Laboratory-based test:** May have to control humidity	Same
3.12 Real-time connectivity	**For both field- and laboratory-based test:** Connectivity capability in order to support surveillance and monitoring activities within the trachoma elimination programme	N/A
4. Product configuration		
4.1 Shipping conditions of the test from place of manufacture to place of testing	**Field- and laboratory-based test:** Conformance to applicable requirements of ASTM D4169-05 and ISO 11607-1:2006 (or equivalent); no cold-chain shipping required	**Field-based:** Same **Laboratory-based test:** Conformance to applicable requirements of ASTM D4169-05 and ISO 11607-1:2006 (or equivalent); cold-chain shipping (e.g. 0–4 °C) is acceptable
4.2 Storage conditions	**Field-based test:** Ambient storage conditions, 2–40 °C; 10–90% relative humidity; no cold storage required. Colorimetric or other indicator of temperature deviation to indicate excessive heat/humidity exposure. It is recommended that the indicator be placed inside the carton **Laboratory-based test:** Cold storage is acceptable; 10–90% relative humidity. Colorimetric or other indicator of temperature deviation to indicate excessive heat/humidity exposure. It is recommended that the indicator be placed inside the carton	**Field-based test:** Same, but 40–60% relative humidity **Laboratory-based test:** Same, but 40–60% relative humidity

Table 1. TPP for newly suspected endemic evaluation units (cont'd)

	Ideal	Minimum
4.3 Service and support	**Field-based test:** Not required, or to be determined **Laboratory-based test:** Support must be available from manufacturer	Same
4.4 Waste disposal	**Field-based test:** Minimal or no hazardous materials, per WHO and country standards. Daily throughput needs are considered in the packaging so as to minimize waste, including use of biodegradable or recyclable materials in test and packaging **Laboratory-based test:** Does not include material that cannot be disposed of in normal laboratory biohazard waste streams	Same
4.5 Labelling and instructions for use (IFUs)	**For both field- and laboratory-based test:** Compliance required per IVDR requirements and WHO prequalification (PQ) guidance (see WHO TGS-5: *Designing instructions for use for in vitro diagnostic medical devices*); Product insert shall be available in relevant local language(s) and shall include IFUs for the test. Must provide accurate MSDS information on components that are potentially toxic. WHO PQ label/IFU guidance should be applied, regardless of whether test is prequalified by WHO or not	Same
5. Product cost and channels[14]		
5.1 Target pricing per test (US$)[15]	**For both field- and laboratory-based test:** < $5 per test	**For both field- and laboratory-based test:** < $10 per test
5.2 Capital cost	**Field-based test:** None **Laboratory-based test:** Zero cost (using existing instrumentation)[16]	**Field-based test:** Same **Laboratory-based test:** Low[17]

[14] No statement is made regarding pooling of samples to reduce the cost of testing; rigorous research would need to be done before any such strategy was recommended.

[15] Calculating an optimal test cost is complex, as many variables need to be taken into account, cost values change and are context specific. The ideal and minimum target pricings per test are the best estimates we are able to make. In order to benchmark against the cost of distributing MDA, you may use the costing calculator available at TPP v0.1, which uses the App published by Fitzpatrick et al., 2016: https://healthy.shinyapps.io/benchmark/. The context-specific values can be entered for the different variables, including: EU population size, MDA coverage, national or subnational MDA, whether doing school-based delivery, whether volunteers are used, whether other diseases are integrated, number of MDA rounds per year, number of previous MDA rounds, median GDP per capita, population density, whether a small island developing state, whether medicines donated, the discount rate, and whether calculating financial or economic costs.

[16] The tool should be something that can be brought into the existing workflow, so there should be zero capital cost because it uses existing instrumentation.

[17] The unit cost per test is dependent on the existing instrumentation's finite shelf-life and the number of tests that can be processed on it across diseases, geography and time. Costs to establish a laboratory de novo will require considerable cost not reflected in this document. The cost would be to the provider (e.g. health ministry, nongovernmental organization supporting the health ministry, external donor, etc.), not to the person in the community.

	Ideal	Minimum
5.3 Product lead times[18]	**For both field- and laboratory-based test:** < 4 weeks	**For both field- and laboratory-based test:** < 6 weeks
5.4 Target launch countries	**For both field- and laboratory-based test:** WHO prioritized countries	Same
5.5 Product registration (i.e. substantiation to regulatory body of product claims)[19]	**For both field- and laboratory-based test:** Please see footnote[19]	Same
5.6 Procurement	**For both field- and laboratory-based test:** Available for procurement by all endemic countries with no restriction	Same
5.7 Cost	**For both field- and laboratory-based test:** Standardised pricing quoted by manufacturer available to all stakeholders. Absence of distributor or third-party mark up	Same

[18] Lead time includes fulfilment and delivery of ordered tests to procurer. NB: May be adjusted to longer lead times provided shelf-life is of sufficient duration (e.g. 2 years). Purpose for information is to address design decisions that can impact line/process design for production, and hence impact lead times.

[19] Registration options include: CE Mark or IVDR; any registration required for export from country of origin (e.g. KFDA); WHO PQ (in due course), Expert Review Panel for Diagnostics, or evidence from stringent regulatory assessment (GHTF founding members); country-level registration (if required/ applicable for target countries).

Table 2. TPP differences for post-MDA evaluation units

(Where ideal and minimum characteristics are the same as for the first use case [newly suspected endemic evaluation units, Table 1], they are not repeated here.)

	Ideal	Minimum
1. Product use summary		
1.1 Intended use	**For both field- and laboratory-based test:** After discontinuation of antibiotic MDA (i.e. for use in impact and surveillance surveys and for post-validation surveillance)[20]	Same
1.2 Targeted population	**For both field- and laboratory-based test:** 1–9-year-olds[21]	**For both field- and laboratory-based test:** 1–5-year-olds
3. Performance		
3.2 Diagnostic/ clinical sensitivity[22,23]	**For both field- and laboratory-based test:** > 50%	Same
3.3 Diagnostic/ clinical specificity[24,25]	**For both field- and laboratory-based test:** > 99.5%	Same

[20] The recommended timing of impact and surveillance surveys may need to be revisited, depending on the diagnostic tool used and its performance characteristics.

[21] Since we know this area was formerly endemic, the target population is children born since interruption of transmission/the age group of peak infection prevalence (1–9-year-olds).

[22] Tool sensitivity is crucial to correctly implement antibiotic MDA when it is needed.

[23] Calculations conducted to provide guidance that is agnostic with respect to a particular diagnostic/biomarker; the 1% threshold is simply illustrative of biomarker prevalence that a diagnostic might measure in post-MDA EUs. Assumptions made for sensitivity calculations: (i) hypothetical prevalence threshold of 1% (with assumed true prevalence of 0%); (ii) a population-based sample of 60 clusters, with approximately 50 children per cluster (i.e. approximately 3000 children in total). WHO recommendations for cluster, household and individual sampling in population-based prevalence surveys are described in: *Design parameters for population-based trachoma prevalence surveys* https://www.who.int/publications/i/item/who-htm-ntd-pct-2018.07. Deviation for the recommended maximum number of 30 clusters is needed to reach the required sample size (details in footnote 25); (iii) the minimum specificity identified for this scenario in Table section 3.3 (> 99.5%); and (iv) type 1 error (α) ≤ 5%. This means that using the diagnostic, the survey would incorrectly conclude that prevalence in a defined population is below the 1% threshold < 5% of the time. The source code used for the calculations is available from the *WHO trachoma TPP sensitivity and specificity calculations*: https://osf.io/bezv4/.

[24] In post-elimination settings, the diagnostic will need to measure very low prevalence with good precision. To have the adequate power to make a correct decision, either a very large sample size is needed, or a test with very high specificity is needed. If the true prevalence falls below an elimination threshold, false positives will bias the estimated prevalence upwards, and thus reduce the survey's power to make a correct decision.

[25] Calculations conducted to provide guidance that is agnostic with respect to a particular diagnostic/biomarker; the 1% threshold is simply illustrative of biomarker prevalence that a diagnostic might measure in post-MDA EUs. Assumptions made for specificity calculations: (i) hypothetical prevalence threshold of 1% (with assumed true prevalence of 0%); (ii) given the larger required sample size (approximately 3000 children in total) to achieve ≥ 90% power to correctly determine prevalence was < 1% if true prevalence is 0%: a population-based sample of 60 clusters, with approximately 50 children per cluster. WHO recommendations for cluster, household and individual sampling in population-based prevalence surveys are described in: *Design parameters for population-based trachoma prevalence surveys* https://www.who.int/publications/i/item/who-htm-ntd-pct-2018.07. Deviation for the recommended maximum number of 30 clusters is needed to reach the required sample size; and (iii) power (1- Type II error) was set to 90% to correctly conclude that prevalence is below the 1% threshold given the true prevalence of 0% (post-elimination). The source code used for the calculations is available from the *WHO trachoma TPP sensitivity and specificity calculations*: https://osf.io/bezv4/.

Table 3. TPP differences for evaluation units with unusual epidemiology

(Where ideal and minimum characteristics are the same as for the first use case [newly suspected endemic evaluation units, Table 1], they are not repeated here.)

	Ideal	Minimum
1. Product use summary		
1.1 Intended use	**For both field- and laboratory-based test:** In EUs in which the epidemiology of trachoma is unusual. This includes EUs in which there is persistent or recrudescent active trachoma, and EUs/countries where a high proportion of children have active trachoma but there is little evidence of TT in adults, such as in certain countries in the Pacific	Same
1.2 Targeted population[26]	**For both field- and laboratory-based test:** All ages	**For both field- and laboratory-based test:** 1–5-year-olds
3. Performance[27]		
3.2 Diagnostic/ clinical sensitivity[28,29]	**For both field- and laboratory-based test:** For a hypothetical prevalence threshold of 1%: > 50% For a hypothetical prevalence threshold of 5%: > 60% For a hypothetical prevalence threshold of 10%: > 85%	Same
3.3 Diagnostic/ clinical specificity[30,31]	**For both field- and laboratory-based test:** For a hypothetical prevalence threshold of 1%: > 99.5% For a hypothetical prevalence threshold of 5–10%: > 98%	Same

[26] Having all ages for the ideal test provides the historical data in order to understand the unusual epidemiology, but the minimum target population of 1–5-year-olds is sufficient for a basic understanding.

[27] Populations with unusual epidemiology may fall into any of the hypothetical prevalence threshold categories (10%, 5%, 1%), as the unusual epidemiology may include scenarios such as: persistent or recrudescent trachoma despite years of ongoing MDA (therefore, likely 5–10% threshold); active trachoma in the absence of TT, suggesting non-*C. trachomatis* aetiology (therefore, likely 1% threshold).

[28] Tool sensitivity is crucial to avoid not implementing antibiotic MDA when it is needed.

[29] Calculations conducted to provide guidance that is agnostic with respect to a particular diagnostic/biomarker; the thresholds are simply illustrative of biomarker prevalence that a diagnostic might measure in unusual epidemiology EUs. Assumptions made for sensitivity calculations: (i) hypothetical prevalence of 5–10% for suspected endemic and prevalence of 1% for post-elimination; (ii) a population-based sample of 20–30 clusters, with approximately 50 children per cluster (i.e. approximately 1000 children in total). For a prevalence of 1%, 60 clusters (approximately 3000 children) would be required. WHO recommendations for cluster, household and individual sampling in population-based prevalence surveys are described in: *Design parameters for population-based trachoma prevalence surveys* https://www.who.int/publications/i/item/who-htm-ntd-pct-2018.07; (iii) the minimum specificity identified for this scenario; and (iv) type 1 error (α) ≤ 5%. This means that using the diagnostic, the survey would incorrectly conclude that prevalence in a defined population is below the 1–10% threshold < 5% of the time. The source code used for the calculations is available from the *WHO trachoma TPP sensitivity and specificity calculations*: https://osf.io/bezv4/.

[30] High specificity is required to avoid unnecessarily implementing antibiotic MDA.

[31] Calculations conducted to provide guidance that is agnostic with respect to a particular diagnostic/biomarker; the thresholds are simply illustrative of biomarker prevalence that a diagnostic might measure in unusual epidemiology EUs. Assumptions made for specificity calculations: (i) hypothetical prevalence threshold of 5–10% for suspected endemic (with assumed true prevalence of 1–5%) and prevalence threshold of 1% (with assumed true prevalence of 0%) for post-elimination; (ii) a population-based sample of 20–30 clusters, with approximately 50 children per cluster (i.e. approximately 1000 children in total). For a prevalence threshold of 1%, 60 clusters (approximately 3000 children) would be required. WHO recommendations for cluster, household and individual sampling in population-based prevalence surveys are described in: *Design parameters for population-based trachoma prevalence surveys* https://www.who.int/publications/i/item/who-htm-ntd-pct-2018.07; and (iii) power (1- Type II error) was set to 90% to correctly conclude that prevalence is below the threshold at a given level of true prevalence: 5–10% (suspected endemic) or 1% (post-elimination). The source code used for the calculations is available from the *WHO trachoma TPP sensitivity and specificity calculations*: https://osf.io/bezv4/.

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Global Neglected Tropical Diseases Programme
World Health Organization
20 avenue Appia
1211 Geneva 27
Switzerland

Website: https://www.who.int/teams/control-of-neglected-tropical-diseases

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