# TRACHOMA

## The business case for new diagnostics

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# Executive summary

A key component of the global effort to eliminate trachoma has been reducing transmission using mass drug administration (MDA) with azithromycin. MDA is made possible by a large-scale drug donation by Pfizer.

Currently, clinical examination to assess the prevalence of disease indicators is the sole method used to inform elimination program decisions regarding MDA. However, there has been increasing recognition within the international trachoma stakeholder community of the need for improved diagnostic tools to support control program decisions given the limitations of using clinical disease indicators to accurately inform late-stage decisions, such as when to stop MDA.

PATH is seeking to assess diagnostic needs, survey potential solutions, and determine an appropriate strategy to support improvement of diagnostic testing in support of trachoma elimination efforts. Based upon previous input from experts in the trachoma community, including input obtained during a Diagnostics Working Group meeting convened by the Bill & Melinda Gates Foundation in London in 2013, two diagnostic use cases for trachoma were prioritized for further exploration: informing decisions to stop MDA and conducting post-MDA surveillance. The purpose of this report is to identify the point in the cycle of trachoma transmission, infection, and elimination that would best be targeted for a new diagnostic technology and to articulate the business case for developing that diagnostic. Current technologies including clinical diagnosis of trachoma infection may be sufficiently sensitive for monitoring disease prevalence and the efficacy of MDA in early stages of population-based treatment, but the development of more sensitive and accurate tests that are low-cost may be beneficial. In particular, the decision to stop MDA, which may both conserve drug and reduce likelihood of the emergence of drug resistance, could be optimized by more sensitive and simple-to-use diagnostics. More immediately, the most sensible investment may be in immune-based diagnostics with improved sensitivity deployed for post-elimination surveillance to prevent disease re-emergence.

# Disease overview

Trachoma is the world's leading preventable cause of blindness. An estimated 7.2 million people are already suffering from the disease, and as many as 320 million are at risk for infection. Populations at risk are primarily concentrated in impoverished areas where unsanitary, crowded conditions promote the spread of infection.[1–3]

Trachoma is a painful and debilitating disease in which inflammation in response to repeated infections with the bacterium *Chlamydia (C.) trachomatis* can lead to progressive damage, including scarring of the eyelid, trachomatous trichiasis (TT), corneal opacity, and ultimately blindness (Figure 1). In response to this unresolved global health issue, the Alliance for the Global Elimination of Trachoma by the year 2020 (GET 2020)—a group led by the World Health Organization (WHO)—set a goal to eliminate the disease as a public health problem. To accomplish this goal, the alliance works to mobilize resources to support a strategy known by the acronym "SAFE," which stands for **S**urgery, **A**ntibiotics, **F**acial cleanliness, and **E**nvironmental improvement. A key element of this strategy is reducing transmission and the risk of trachoma disease through the use of mass drug administration (MDA) campaigns, enabled through global donations of antibiotics. To date, Pfizer has donated more than 340 million doses of the antibiotic azithromycin (Zithromax®), distributed through the International Trachoma Initiative.[2–5]

**Figure 1.** Life cycle of Chlamydia trachomatis.[6] The Carter Center/A. Granberg.
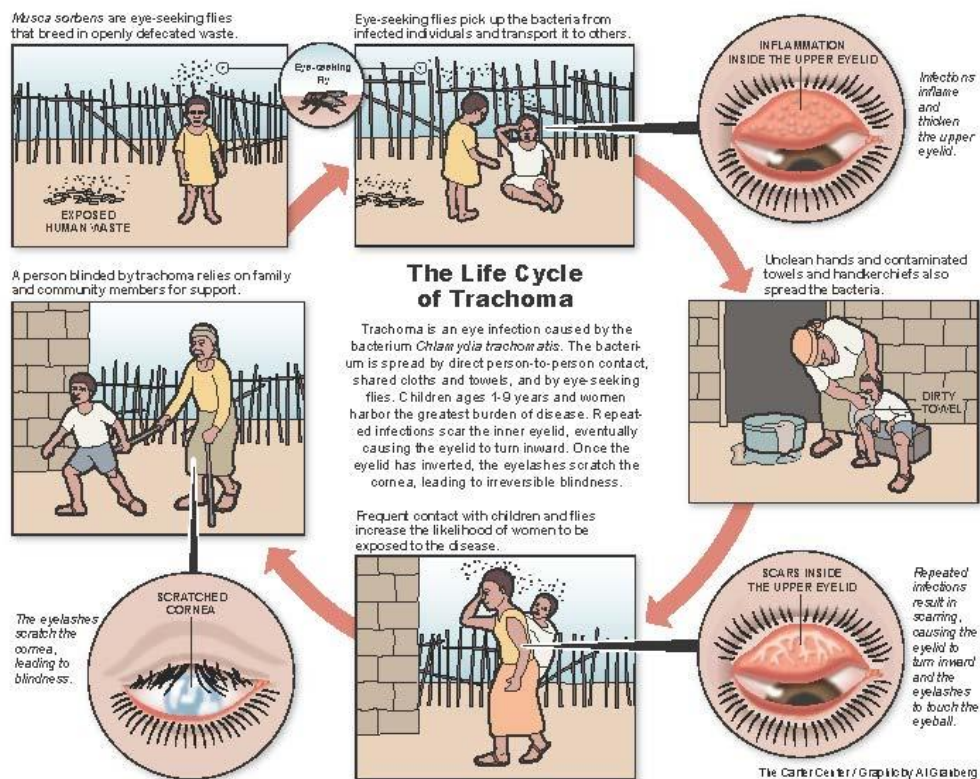
Accurate surveillance to inform decisions by trachoma elimination programs remains critical to the success of the interventions outlined in the SAFE strategy, especially MDA. Currently, clinical examination of the eye for signs of disease using a simplified grading system is the only WHO-approved method for use by national trachoma elimination programs. Decisions on whether to start or stop MDA are made based on the prevalence of the clinical signs for trachomatous inflammation–follicular (TF) in children 1 to 9 years old.[7] If the prevalence of TF in this group is above 10%, MDA is initiated (or re-started, if previously stopped). Once prevalence falls below 10%, more targeted interventions (including MDA) and surveillance may be considered at the discretion of the program. Finally, a TF prevalence of less than 5% signals that MDA should be stopped and post-MDA surveillance initiated. Elimination may eventually be considered if TF stays below 5% in children 1 to 9 years old and the burden of severe disease in the adult population is reduced to a maximum of 1/1,000 as measured by the prevalence of TT.[1,3,7]
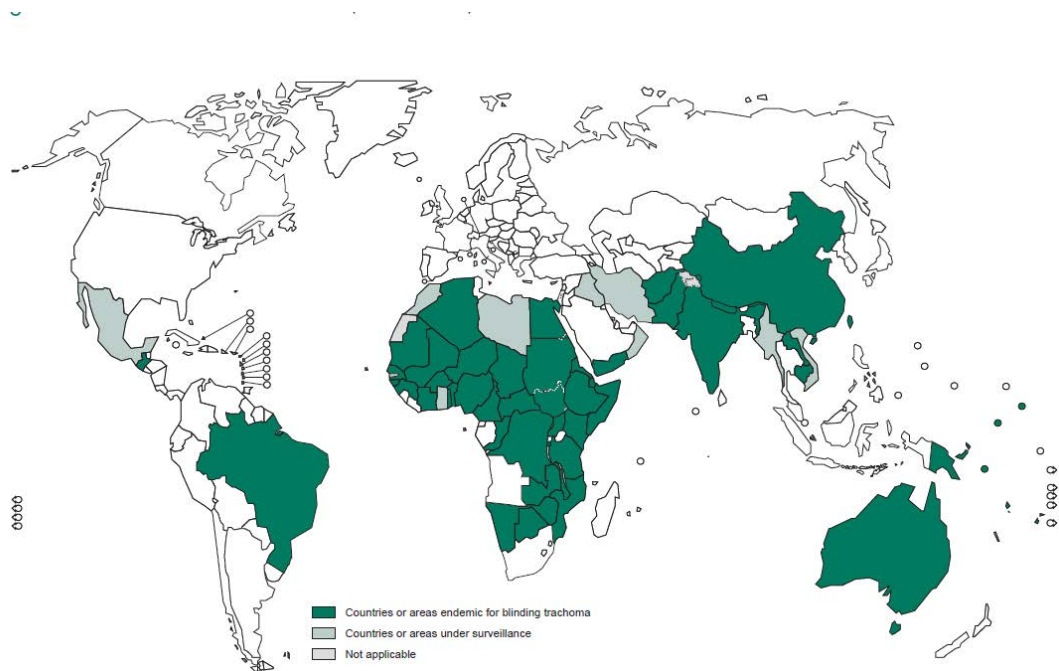
Clinical grading is not without its problems. It can be somewhat subjective; it is prone to false positives (in relation to ocular *C. trachomatis* infection), particularly after interventions have begun; and it misses some cases of subclinical infection. Additionally, MDA is intended to treat the reservoir of active infection in populations to reduce further transmission. As trachoma prevalence becomes low, which may occur after multiple rounds of MDA, the correlation between clinical signs and active infection becomes weaker.[8–12]

Research has shown that disease measures do not always correlate to active infection as determined by sensitive molecular assays for *C. trachomatis*. Previous studies have found that only 18% to 40% of individuals with less severe active disease (WHO classification of TF) were positive by nucleic acid amplification test (NAAT), whereas 50% to 70% of those with severe inflammation (WHO classification of trachomatous inflammation–intense [TI]) were positive.[13] Additionally, clinical signs of trachoma can lag long after infection has cleared and DNA is undetectable.[11] Thus, clinical signs may lead to over- or underestimation of trachoma prevalence and may ultimately lead to inappropriate program decisions to prolong or halt MDA. Given these limitations and the current availability of high-performance laboratory tests to directly measure infection, there has been growing debate on the need to use improved methods to monitor the impact of MDA. This need is particularly great during the final stages of elimination, when prevalence is low and key decisions to halt MDA are considered.[8–10,14–17]

## Geographic distribution

Figures 2 and 3 illustrate the global distribution of trachoma in 2012 and the number of people treated with azithromycin by WHO region in 2008–2012, respectively.

**Figure 2.** Distribution of trachoma worldwide, 2012.[18]



Legend:
- Countries or areas endemic for blinding trachoma
- Countries or areas under surveillance
- Not applicable

**Figure 3.** Number of people treated and global coverage of azithromycin for trachoma, by WHO region, 2008–2012.[18]



Legend:
- African Region
- Region of the Americas
- Eastern Mediterranean Region
- South-East Asia Region
- Western Pacific Region
- Global coverage
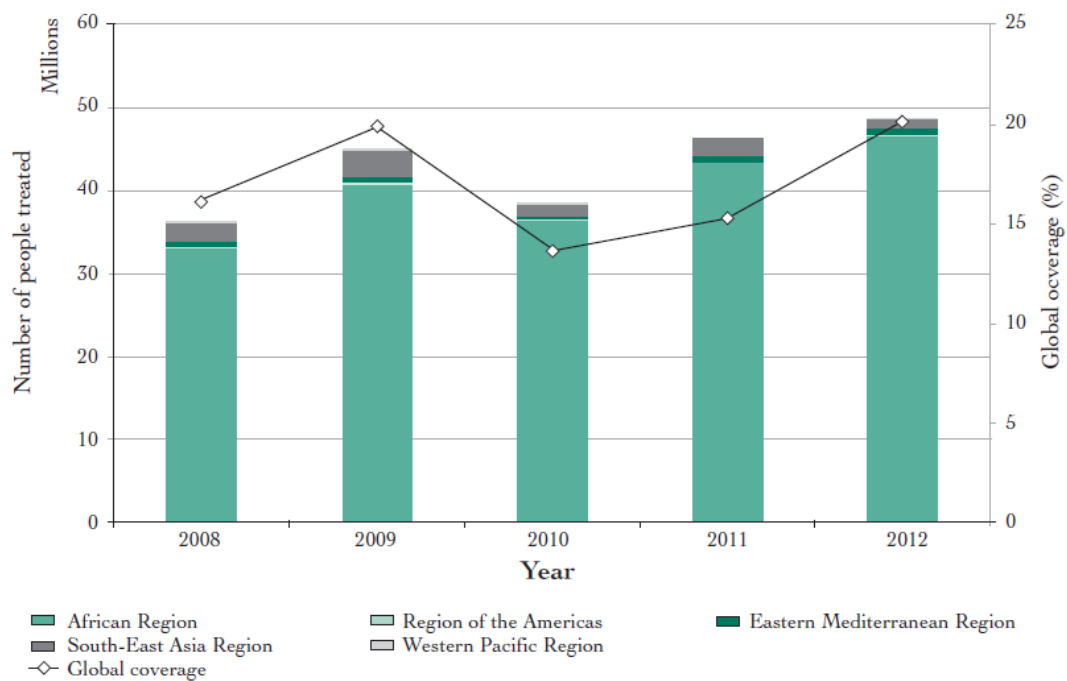
# Control strategy

Figure 4 depicts WHO's SAFE strategy to eliminate blindness from trachoma infection. The strategy is designed to incorporate community involvement and targets the community with a primary health care approach. It was adopted during a November 1996 meeting on the prevention of blindness and deafness held at WHO's Geneva headquarters. Importantly, multiple international nongovernment entities—including the key manufacturer of a drug treatment for trachoma (Pfizer; azithromycin) were represented at the meeting. The migration of standard drug treatment of trachoma from tetracycline to azithromycin, a trail blazed by Morocco between 1997 and 1999 when it implemented the first large-scale nationwide elimination program for trachoma, is expanding and is a key part of the SAFE strategy globally. Thus, political as well as private-sector efforts have been coordinated in the development of the current approach to elimination of trachoma as a blinding disease.

**Figure 4.** World Health Organization guidelines for treatment of trachoma.[19]
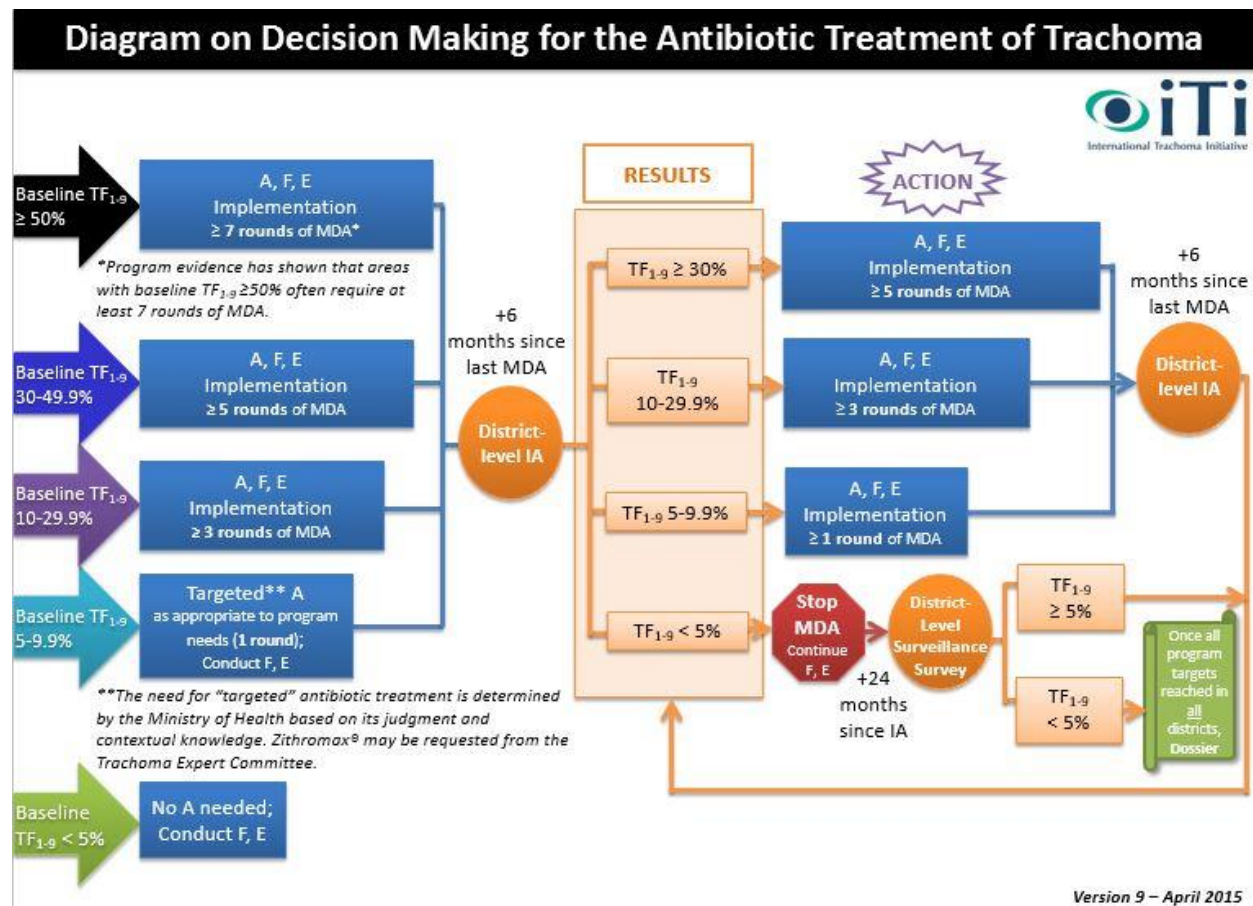


**Note: A=antibiotics; E=environmental improvements; f=facial cleanliness; MDA=mass drug administration; TF=trachoma follicles (presence of); UIG=ultimate intervention goal.**

Under current WHO guidelines (Figure 4) the prevalence of clinical disease indicators remains the sole measure for informing control program decisions including the use of MDA. However, clinical signs do not

always correlate directly with active trachoma infection and often can persist long after the resolution of the current infection. Nonetheless, clinical indicators remain the standard methodology used by control programs, with cases positive for signs of TF indicative of the need for treatment or as evidence of recent infection.

The results from recent disease modeling to determine the effect of diagnostic performance on prevalence estimates for trachoma indicate that the reduced sensitivity of current measure of TF (as a proxy for confirmed active infection) may result in the overestimation of the true prevalence and prolong reaching the required threshold (5%) needed to consider stopping MDA (Figure 5B).[20] This suggests that basing MDA decisions solely on TF may delay MDA stopping by 3 to 4 years, resulting in extra rounds of treatment and over-administration of antibiotics. In contrast, a diagnostic measure that provides improved performance (Figure 5C and 5D) with sensitivity similar to what has previously been demonstrated with NAATs (Figure 5A), would potentially result in a more accurate assessment of when the prevalence of confirmed infections falls below the required threshold of 5% to suspend MDA—thus informing a decision to suspend MDA multiple years earlier and conserving programmatic resources, including donated antibiotics.

**Figure 5.** Trachomatous inflammation–follicular (TF) is a lagging indicator.[20]
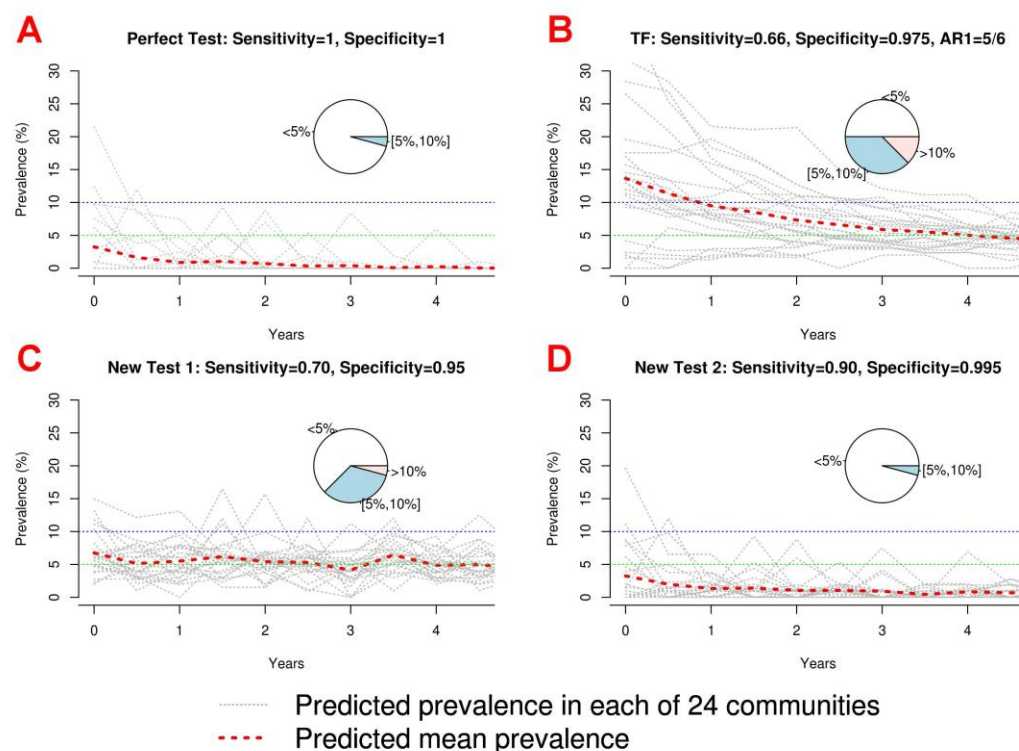


Red dotted trace represents what each diagnostic test would indicate in the given population to be the mean prevalence of trachoma infection, where: A, theoretical perfect diagnostic; B, clinical observation of trachoma follicles; C and D, modeled diagnostics with the indicated sensitivity and specificity.

# Diagnostics to detect trachoma disease

## Current diagnostic tools and their shortcomings

*C. trachomatis* is the causative agent of ocular trachoma and chlamydia, which is one of the most prevalent sexually transmitted infections in the world. Most current tests for trachoma are diagnostics developed for the detection of urogenital chlamydia infection that have been adapted for use with ocular specimens.

Health workers have used a multitude of test types for detection of chlamydia, from highly technical microbiologic and molecular assays to low-complexity, rapid immunoassay tests intended for use at or near the point of care (POC). Assays previously used in trachoma research have included microscopy of conjunctival scrapings, isolation in cell culture, direct fluorescent antibody tests, enzyme immunoassays including enzyme-linked immunosorbent assay (ELISA) serology, nucleic acid hybridization probes, and nucleic acid amplification tests (NAATs).[21] Although there is currently no designated gold standard laboratory test for trachoma, NAATs are generally regarded as being the most sensitive and specific due to their superior performance when compared to other methodologies.[21–23] However, only moderate-to-high-complexity chlamydia NAATs have been evaluated for trachoma. Many of these tests, including commercial assays prioritized for introduction and use by international trachoma stakeholders, allow some level of automation for hands-off batch testing but often require significant infrastructure investment and advanced personnel training.[23–24] Consequently, their appropriateness for sustained use by control programs in low-resource settings remains to be determined.

Diagnostic tests for trachoma typically use biomarkers that are specific to either genus or species. The exceptions are serologic and genotypic research methods designed specifically to type *C. trachomatis* serovars using specific reagents typically targeted against serovar-specific peptide regions within the major outer membrane protein (MOMP) or variable genetic regions (*ompA* or *omp1*). Serovars of *C. trachomatis* are considered to be tissue-selective rather than tissue-specific, with trachoma serovars A, B, Ba, and C mainly localized to epithelial surfaces in the eye and serovars D through K localized to epithelial surfaces in the urogenital tract. Although there are cases where trachoma serovars have been detected in urogenital infections and conjunctivitis has been caused by chlamydia serovars,[21,1] these infections may not be critical for surveillance tests using ocular swabs given the vast predominance of trachoma serovars expected with chlamydial eye infections in endemic settings. Antibody tests against species-specific antigens are currently considered to be sufficient unless evidence later shows that high background prevalence of urogenital chlamydial or other exposures confound survey results and interpretation. More importantly, use of biomarkers should be able to adequately discriminate against other common bacterial pathogens that may be found in ocular samples and, in the case of antibody tests, able to exclude other closely-related chlamydial species including *C. pneumoniae,* which is a highly prevalent infection globally.[25]

For infection detection, ribosomal RNA (either 16SrRNA or 23SrRNA), which is the target of the commercial Aptima tests (Hologic), represents the most sensitive biomarker for trachoma, with a theoretical limit of detection of less than 1 elementary body per test given the high target copy number per cell. However, molecular tests using DNA detection have been shown to be adequate for accurate detection of trachoma infection in prior research and may provide a less costly approach. Among DNA targets, the cryptic plasmid (pCT) may be preferable because it is often present in multiple copies per cell and may thus impart improved sensitivity.[21,22] Alternatively, the use of chromosomal gene targets, such as *ompA* or *omp1*, either alone or in

conjunction with pCT, could be advantageous in the event of the emergence and widespread circulation of trachoma variants that are missing the plasmid. To date, no trachoma strains have been described that lack pCT, although this has been reported for urogenital chlamydial strains.[26,27] For antigen detection, monoclonal antibodies are used to detect genus-specific regions within the chlamydial lipopolysaccharide (LPS), including rapid diagnostic tests (RDTs) produced by Alere (Quickview) and Quidel (Clearview) as well as the low-cost POC rapid test developed by Diagnostics for the Real World (Chlamydia Rapid Test). However, potential performance issues have been noted when current tests have been evaluated under field conditions in trachoma-endemic regions.[28,29] MOMP has also been used for antigen detection tests with the potential added advantage of being able to use monoclonal antibodies that may target serovar-specific epitopes in the antigen.[21,30,31]
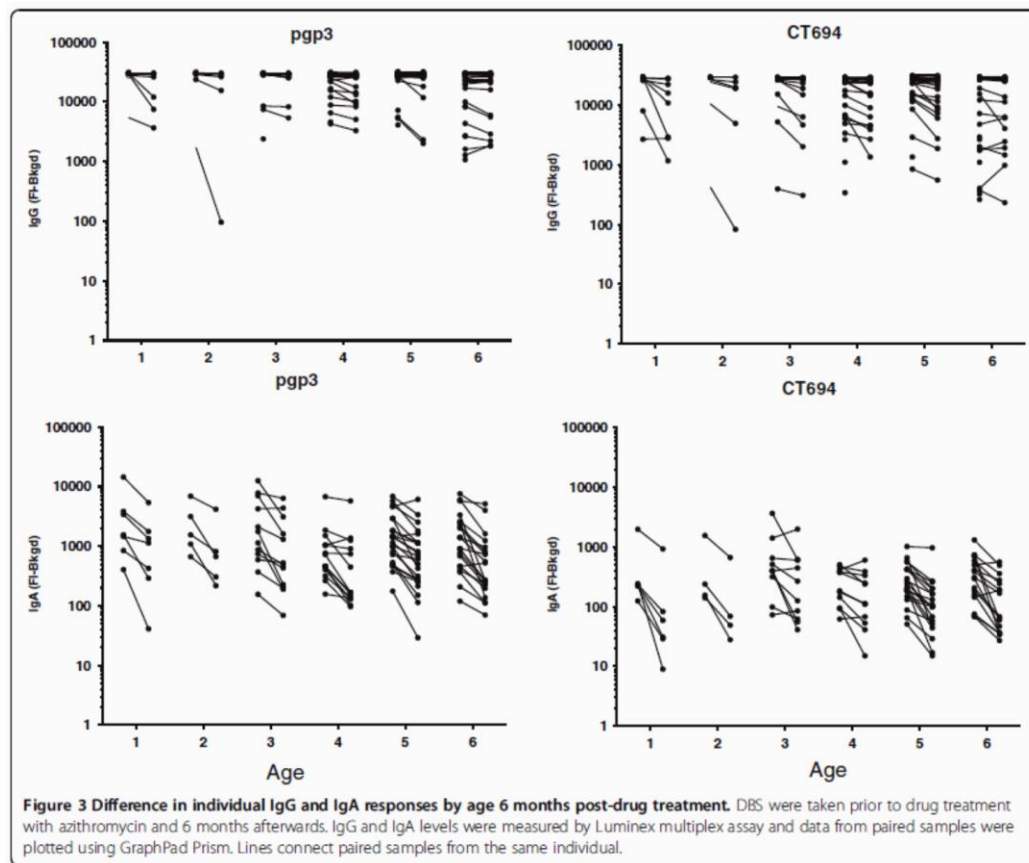
Until recently, serological tests were generally not considered a useful tool for the diagnosis of trachoma infection due in part to the long-lived nature of serum antibodies elicited by chlamydial infection and thus the inability to distinguish active and past infections.[32,33] However, the potential to incorporate trachoma diagnostic tests into low-cost test formats and/or highly multiplexed serologic assays has renewed interest, particularly for post-elimination surveillance activities.[34] A recent array-based study identified promising candidate antigens based on their specific immunodominance in cases of severe disease (trachomatis trichiasis).[35] Among the ten chlamydial antigens that were selectively reactive in more than 50% of trachoma patient sera, three were prioritized for further assay development and evaluation by the Centers for Disease Control and Prevention (CDC)—CPAF, pgp3, and CT694.[36] CPAF was later de-prioritized by the CDC for further evaluation due to technical difficulties incorporating it into the current microsphere immunoassay (D. Martin [CDC], personal communication). Thus, pgp3 and CT694 have been carried forward and evaluated in multiple studies within trachoma-endemic countries, including the current multisite study led by the Task Force for Global Health (TFGH).[33,37,38] Recently published studies have already demonstrated the potential value of using these serologic markers as a more standardized tool for assessing transmission during post-MDA surveillance, particularly in the key indicator group of 1 to 9 year olds.[38] Development of these immunoassays in other formats such as ELISA and lateral flow tests is also currently being explored (D. Martin [CDC], personal communication). Finally, although MOMP is not currently being evaluated in the CDC-developed assays, it has been shown in previous research to be an immunodominant antigen.[21] It has the added advantage of potentially providing target regions that could be used to provide further specificity for trachoma serovars if background seroreactivity with urogenital chlamydia serovars is determined to be problematic. However, given the current efforts to characterize pgp3 and CT694 in trachoma epidemiologic research, it is likely that if antibody tests are later prioritized, then these biomarkers would be the strongest candidates based upon relevant evidence and their stage of development.

Although most current research is primarily focused on collecting evidence to further support the adoption and expansion of existing lab-based NAATs, the development of more field-deployable test options for trachoma may still have value to ensure the testing needs of all country programs can be met. Although no field-deployable POC molecular test is currently widely available for chlamydia, new assays and platforms are emerging with potential opportunities for development of future test solutions for trachoma. Field-deployable NAAT platforms are becoming available, including the Alere-i and -q and Quidel's Savanna. Polymerase chain reaction (PCR) assays for chlamydia are already available, and multiple isothermal assays have been described in the literature that use isothermal chemistries that are proprietary to the commercial developers of these platforms, such as Recombinase Polymerase Amplification (RPA) and Helicase-Dependent Amplification (HDA).[39,40] Additionally, other test developers including Ustar Diagnostics (http://www.bioustar.com/en/) and Atlas Genetics (http://atlasgenetics.com/systems/io-system) are currently

developing molecular assays for *C. trachomatis* detection for sexually transmitted diseases (STDs) using their own proprietary technology. The tests may one day have utility for trachoma detection as well. Finally, while NAATs remain prioritized, it is important to remember that advances in technology and methodology with enzyme immunoassays may warrant further consideration for the use of antigen and antibody-detection tests. Simple, low-cost readers such as the Veritor (BD) have shown an ability to improve the performance over RDTs for other diseases as well as simplify interpretation of test results.[41] Meanwhile, the potential of immunoassays to be highly multiplexed to integrate testing for many diseases and conditions, sometimes using the same sample, continues to be an attractive quality that could be leveraged for trachoma along with many other high-priority neglected tropical diseases.[33,34,42]

While the technology to detect and diagnose trachoma infections is advancing, the more fundamental problem of the indicators against which it is directed may be difficult to circumnavigate. Skillful tracking of antibody serotypes against the bacterium is feasible and informative, but may not be suitable as a comprehensive diagnostic solution. Basic research into the immunologic response (generation of antibodies) to trachoma infections has shown that, though potentially tractable differences in the kinetics of antibody serotypes exist (e.g., IgG vs IgA), the presence of these antibodies never returns to zero (seroconversion) following azithromycin treatment (Figure 6). This suggests that the most certain utility of a test for antibodies against trachoma antigens will be for the detection of any lifetime exposure to the bacterium, and therefore may make serological testing most effectively deployed in post-elimination surveillance in an ostensibly naïve population. Their high sensitivity and amenability to low-tech, RDT applications make antibodies attractive tools in this context.

**Figure 6**. IgA and IgG levels against trachoma antigens persist following azithromycin treatment in children of various ages.[37]



Figure 3 Difference in individual IgG and IgA responses by age 6 months post-drug treatment. DBS were taken prior to drug treatment with azithromycin and 6 months afterwards. IgG and IgA levels were measured by Luminex multiplex assay and data from paired samples were plotted using GraphPad Prism. Lines connect paired samples from the same individual.
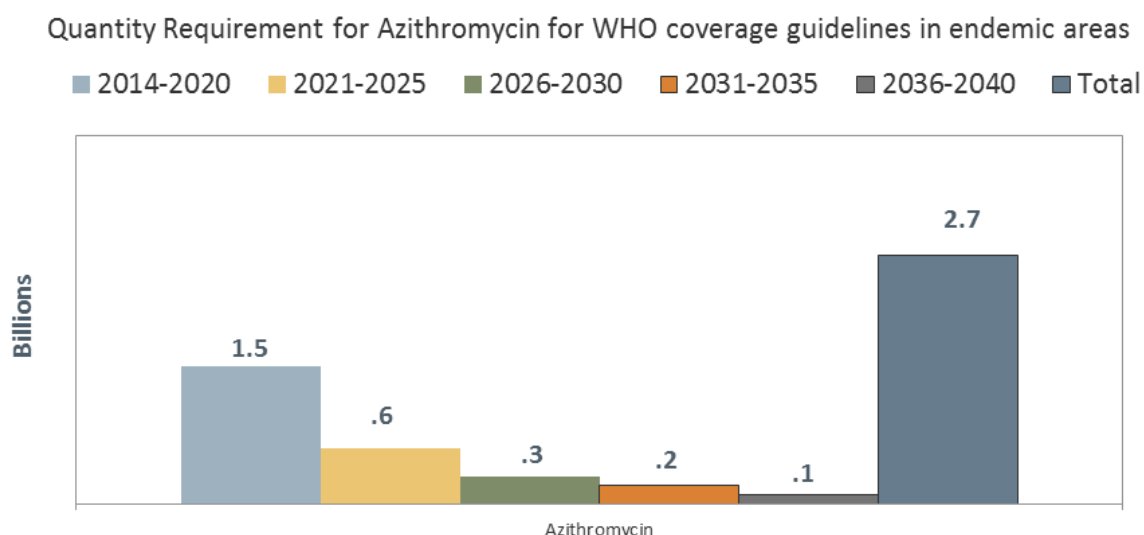
**Note: Dried Blood Spots (DBS) were taken prior to drug treatment and six months afterward. IgG and IgA levels were measured by Liminex multiplex assay and data from paired samples were plotted using GraphPad Prism. Lines connect paired samples from the same individual.**

## Prioritized uses for new, improved diagnostics

There is a clear need for a more effective way to determine when to initiate azithromycin MDA and when to discontinue it. From a cost/benefit perspective, improved decisions regarding MDA could provide significant value because the estimated cost per treatment is US$0.35 per person, with some estimates as high as $1.50 per person for remote locations.[43] Thus, reducing even one unnecessary round of MDA for a district of 250,000 people would provide substantial cost savings ($80,000 at $0.35/person). Given that up to five rounds of MDA may be required, depending on trachoma prevalence, the cost of decisions based on inaccurate survey data can be very significant. Especially during the next decade, the projected quantities of azithromycin to be needed are massive (Figure 7).

**Figure 7.** Estimated quantities of azithromycin (treatments) required over time to meet World Health Organization coverage guidelines in trachoma-endemic areas.[52]

Quantity Requirement for Azithromycin for WHO coverage guidelines in endemic areas

■ 2014-2020   ■ 2021-2025   ■ 2026-2030   ■ 2031-2035   ■ 2036-2040   ■ Total



In the longer term, there is a real risk of developing antibiotic resistance with over- and mis-administration of azithromycin. The cost of this could be far greater than calculable in terms of disability-adjusted life-years (DALYs) but would extend to other infections treated with the drug and to the billions of dollars typically spent in developing each drug that gets to market. A population study in Nigeria reported the emergence of azithromycin-resistant pneumococcal clones in Nigeria following four rounds of MDA that reached 5% of total isolates following treatment. The MDA reduced the diversity of clones of the bacterium, indicating expansion of select, resistant clones.[44, 47]

There is considerable economic and health imperative to develop better measures to accurately monitor the progress of current control efforts for trachoma. However, the diagnostic landscape previously outlined does not reveal obvious points before and during MDA where it makes great business sense to insert new diagnostic technologies. The most immediate and economically feasible opportunity may be establishing diagnostics tools to provide robust measures during post-elimination surveillance to help reduce the risk that widespread disease re-emergence into an area where elimination has been previously achieved does not undo substantial national gains. It makes economic sense to capitalize on the persistence of multiple antibody immune responses to trachoma infections by deploying serological assays for surveillance of transmission among children, ostensibly a naïve population.

## Key considerations in diagnostic investment choice

- **Intended use is for population-based surveillance**. For trachoma surveillance, diagnostic tools will be used primarily to inform decisions by control programs on whether to treat entire populations with MDA and not for individual diagnosis and patient management. Thus, operational requirements such as the

ability to perform the test at the POC and provide a rapid result may take on lesser importance *if* specimens can be transported effectively to allow for testing within an external location. Conversely, the capacity to easily batch-test large numbers of samples collected during surveys may increase the value of a specific option.[34, 21-22]

- **Targeted use cases**. Clinical examination and monitoring of disease indicators are considered by stakeholders to be adequate for monitoring trachoma when prevalence is high, such as when determining baseline prevalence (mapping) or assessing of effects of early rounds of MDA in reducing burden (impact monitoring). Thus, the targeted use cases for new diagnostic tools do not prioritize the early stages of trachoma control but rather late stages when decisions need to be made on when to stop MDA and then monitor for possible re-emergence.[48] Additionally, it is likely that the measure (infection or exposure) used in tools for informing both of these late-stage use cases will need to be the same or extremely well-correlated, since data will be used longitudinally in these stages.

- **New diagnostic tools for trachoma must offer substantial improvement over current methods.** If new diagnostic tools do not provide substantial benefit over clinical examination for informing decisions by control programs, justifying their approval by WHO and use by control programs for surveillance will be difficult. Ideally, a new diagnostic test will offer improvement in terms of accuracy and operational characteristics to justify the increased cost versus relatively inexpensive clinical exams. Molecular tests for detection of trachoma infection remain a prioritized option due to their superior analytical performance as demonstrated through prior research. Because operationalizing and implementing current NAAT options raises legitimate concerns, alternative platforms with lower cost and complexity, such as immunoassays for antigen or antibody detection, may warrant further consideration. However, many older, outdated methodologies and technologies that have been used in prior trachoma research, such as those based on classic microbiologic methodology, were beyond the scope of this landscape report and were omitted in detailed analysis. Their cost, complexity, and, in many cases, inferior performance compared to newer tests make them unlikely to be viable solutions for late-stage uses.

## Preferred product characteristics and promising solutions

The low cost of an RDT is one strong reason for adopting such a technology (see Figure 8). This is in contrast to the more expensive NAAT and ELISA-based laboratory assays. The negotiated average price for an NAAT test in low-resource settings is approximately US$10 to $11 per test, including ancillary supplies. However, additional costs are incurred with this assay, including those related to sample transportation, laboratory staff, and technology delivery and maintenance. ELISA tests may vary, but one manufacturer agreement is $2.50 for a single test, and then $0.20 for each additional test (source: unpublished PATH data).

**Figure 8.** Average unit prices of malaria rapid diagnostic tests, 2007–2012.
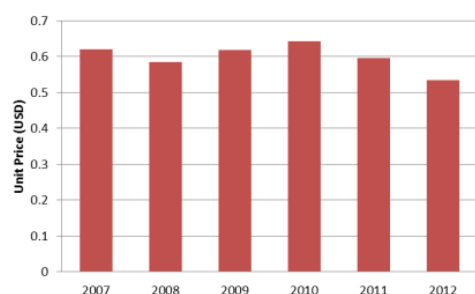


The RDT must detect *C. trachomatis* antibodies. Although the targets would ideally be specific to ocular trachoma serovar to ensure optimal specificity, current research has demonstrated promise using species-specific targets. Two antigens have been identified as potential candidates for a lateral flow immunoassay: *C. trachomatis* antigens pgp3 (pCT03) and CT694. PGP3 is encoded as an ORF5 of the eight total ORFs on the highly-conserved cryptic plasmid and is rarely found in *C. pneumonia* isolates.[45] CT694 is a secreted protein involved in pathogenesis that manipulates host proteins by acting as a T3S-dependent substrate.[46] These two antigens were first identified as part of a chlamydia antigen mapping project that assessed antibody responses in women with urogenital chlamydia infections. They were two of the 27 antigenic proteins that were recognized by more than 50% of women's antisera, thereby receiving the designation *immunodominant antigens*.[47] They were then reported to elicit antibody responses in blood samples taken from children in trachoma-endemic regions, with stronger antibody responses elicited from children greater than three years old with evidence of active infection or PCR positive results, thereby suggesting they may play an active role in ocular trachoma.[36]

Table 1 compares various assays for the diagnosis of active infection.

**Table 1.** Comparison of assays for the diagnosis of active *Chlamydia trachomatis* infection.[a,21]

| Test | | | | |
|---|---|---|---|---|
| Culture | Infectious organism | Conjunctival swab | 50–70 | 100 |
| Enzyme immunoassay | | | | |
| Lab based | Antigen | Conjunctival swab | 60–85 | 80–95 |
| Rapid test[1] | Antigen | Vaginal, cervical, urethral swabs, and first void urine | 50–80[b] | 97–99 |
| Nucleic acid hybridization | DNA | Conjunctival swab | 60–80 | 95–100 |
| Nucleic acid amplification | DNA or RNA | Conjunctival swab | 90–100 | 95–100 |

[a] Performance compared against a reference standard of culture and/or nucleic acid amplification test.
[b] One study showed that sensitivity of a urogenital chlamydia RDT decreased from 65% to 25% when conducted in a high-prevalence population versus a low-prevalence population.

# Potential markets for improved diagnostic tools

Trachoma is endemic in 53 countries, including countries in Africa, Asia, Central and South America, Australia, and the Middle East (see Figure 9). Worldwide in 2011, an estimated 325 million people lived in endemic areas. However, this could be an underestimate since not every endemic country has done a complete assessment of the burden of disease. In 2012, a consortium of nongovernmental organizations (NGOs) and academic institutions launched the Global Trachoma Mapping Project (GTMP), which is scheduled for completion in 2015.[48] To meet WHO's definition of global elimination, *all* endemic regions must be controlled, and thus the test must be applicable across a broad array of geographies.

**Figure 9.** Estimates of the population at risk of trachoma: potential markets in selected countries. [49]
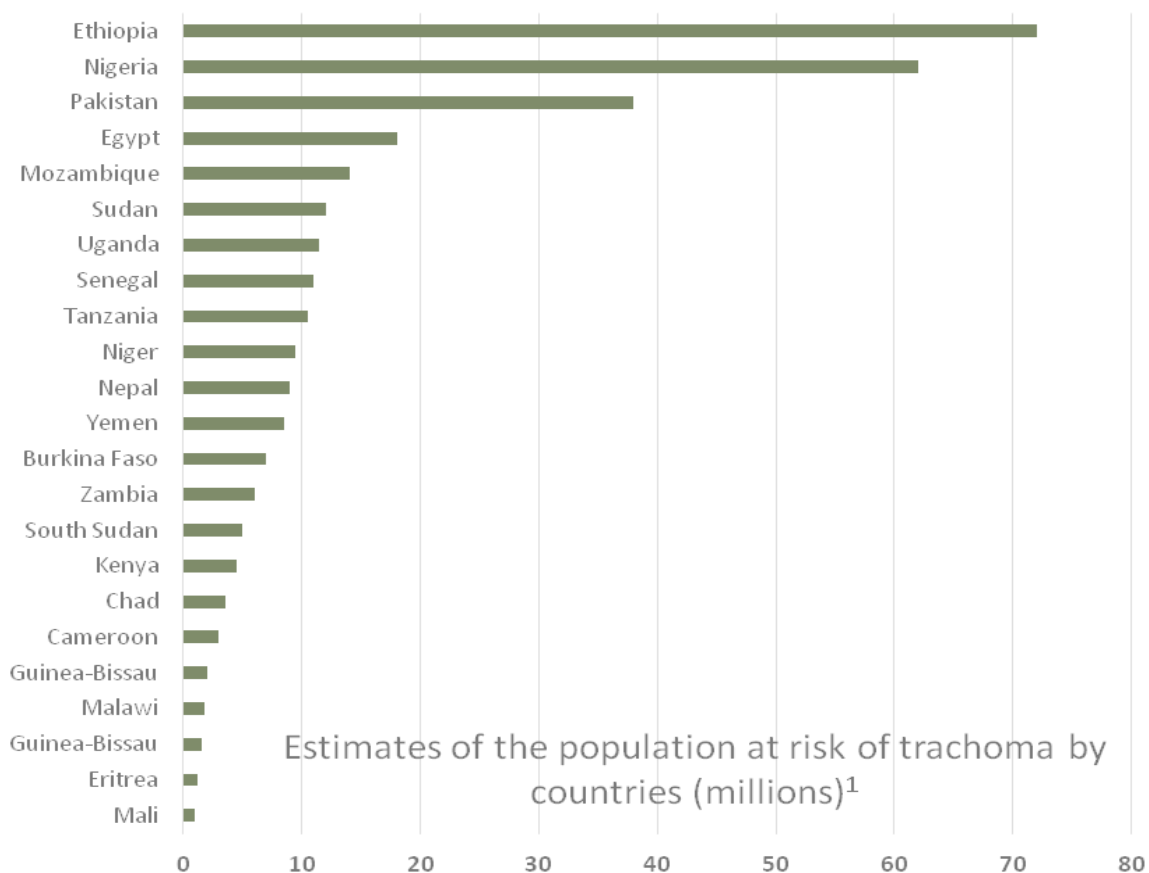


**Not shown are Brazil (1–3 million), China (455 million), India (425 million), and 16 other endemic countries with fewer than 700 at risk.**

# Projected health and economic impacts of new diagnostics

In addition to the projected and known cost savings from azithromycin conservation articulated previously, there are some estimates of DALYs (Table 2)[50] and other trachoma-related loss. Countries with known or suspected blinding trachoma have 3.8 million cases of blindness and 5.3 million cases of low vision and a potential productivity loss of US$2.9 billion (in 1995 dollars). Prevalent cases of trachomatous visual loss yield 39 million lifetime DALYs.[51]

**Table 2.** Disability-adjusted life-years associated with eight eye conditions.[50]

| Ophthalmologic Condition | No. of Systematic Reviews and Protocols in the CDSR | Cochrane Group Contributions | % of Total 2010 DALY (Of 291 Conditions) | DALY % Change of DALY From 1990 to 2010 | 2010 DALY Rank (Of 176 Conditions) |
|---|---|---|---|---|---|
| Other vision loss | 26 (23 reviews, 3 protocols) | 19 Eyes and Vision, 5 Neonatal, and 2 Stroke | 0.25 | +2 | 67 |
| Refraction and accommodation disorders | 15 (12 reviews, 3 protocols) | 15 Eyes and Vision | 0.23 | +1 | 68 |
| Cataracts | 19 (16 reviews, 3 protocols) | 16 Eyes and Vision and 3 Anesthesia | 0.19 | -30 | 74 |
| Macular degeneration | 20 (19 reviews, 1 protocol) | 20 Eyes and Vision | 0.054 | +56 | 132 |
| Glaucoma | 30 (20 reviews, 10 protocols) | 30 Eyes and Vision | 0.038 | +31 | 147 |
| Trachoma | 4 (4 reviews, 0 protocols) | 4 Eyes and Vision | 0.013 | +48 | 165 |
| Onchocerciasis | 1 (1 review, 0 protocols) | 1 Eyes and Vision | 0.02 | -31 | 163 |
| Vitamin A deficiency | 1 (1 review, 0 protocols) | 1 Acute Respiratory Infections | 0.032 | -9 | 153 |

**Abbreviations: CDSR, Cochrane Database of Systemic Reviews; DALY, disability-adjusted life-year; GBD, Global Burden of Disease; ª Arranged in order of decreasing percentage of total 2010 DALY.**

Given that the primary entry point for a new diagnostic technology will impinge on new infections and hopefully prevent re-emergence and widespread transmission in areas where trachoma has been eliminated in the population, one would estimate that the health and economic impacts of this approach would encompass all the above-referenced figures going forward.

# Investment and value proposition

New, improved diagnostics for trachoma infection should be integrated along with improvements that are responsive to the negative impact that less-sensitive diagnostics have had. Trachoma infection has been overtreated at the population level in accordance with inaccurate data (Figure 10).

**Figure 10.** Overtreatment of people for trachomatous inflammation-follicular (TF) even though they do not harbor the infection.[20]
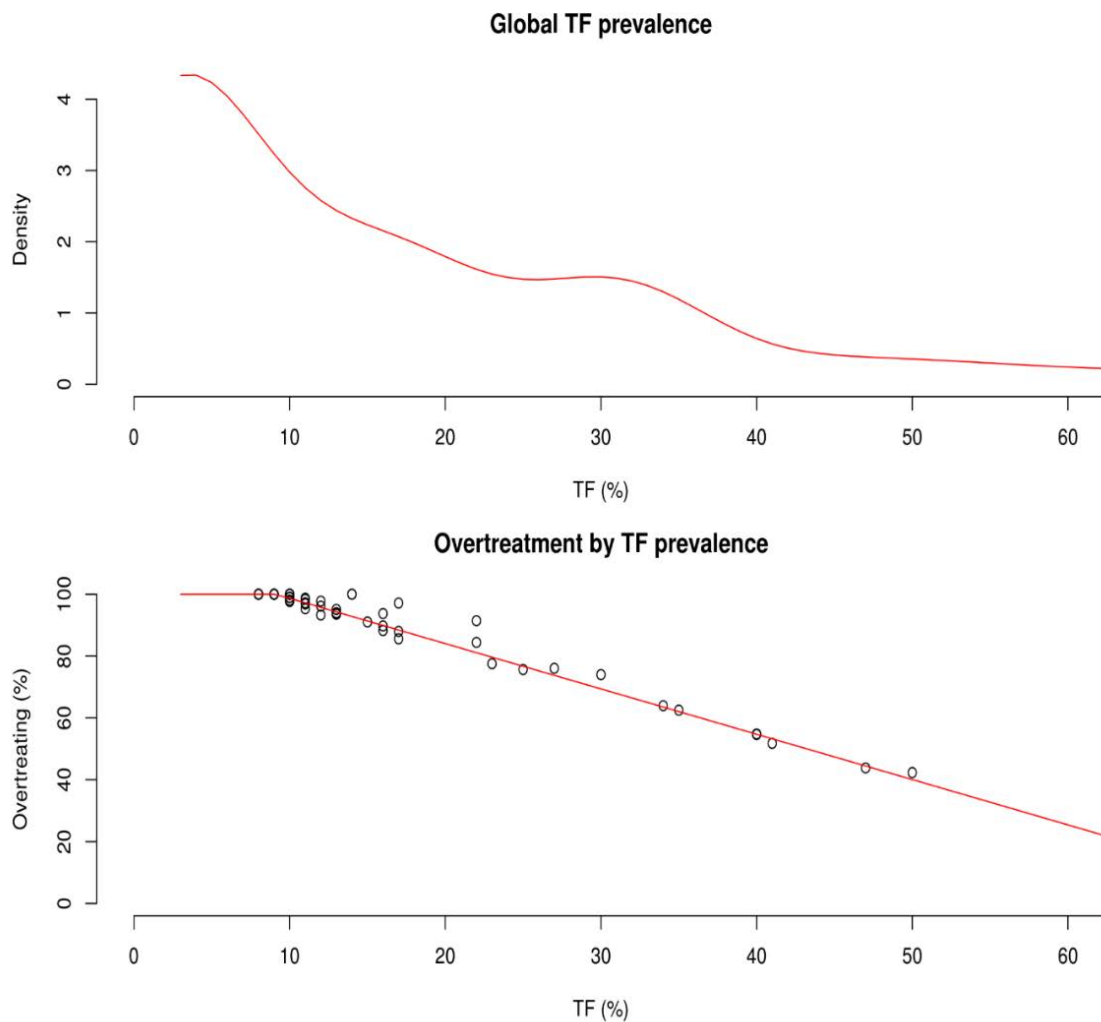


It is therefore important to note both the immediate economic impact that informed discontinuation of MDA can have, as well as the downstream impact that prudent surveillance post-elimination will have. From a cost/benefit perspective, improved decisions regarding MDA could provide significant value, since, as mentioned earlier, reducing even one unnecessary round of MDA for a district of 250,000 people would provide substantial cost savings (US$80,000 at $0.35/person). Given that up to five rounds of MDA may be required depending on trachoma prevalence, the cost of decisions based on inaccurate survey data can be very

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significant. The value of judicious administration of azithromycin in the current environment of overtreatment is perhaps inestimably high, considering the emergence of resistant strains of bacteria in Africa, referred to in this report. Apart from the compounding impact on DALY that could arise from azithromycin-resistant trachoma, one must consider the same in patients with other bacterial infections—multiple infections—where azithromycin is indicated. Finally, in the context of informing MDA decisions, the cost to Pfizer or another company of developing a replacement for azithromycin could be prohibitive.

In conclusion, the current primary tool for trachoma diagnosis—clinical examination—can lead to false-positives due to unrelated infections, tends to lag behind the actual rate of infection clearance, and is not especially sensitive. From the perspective of population-based treatment, this can lead to overestimation of prevalence and poorly informed MDA stopping decisions, and it does not provide a sensitive method of surveillance once infections are eliminated. The spectrum of infection detection tests in development improve upon the simple clinical exam and may be adaptable to short-term needs, but they risk becoming increasingly expensive and complex, particularly in the case of NAAT. There may be a commercial rationale for expanding existing chlamydial STD NAAT to include CT diagnosis as a cost-consolidating approach but, in the long run, a low-complexity, POC-adaptable test for antigen/antibody would be more useful for directing MDA stopping decisions.

The commercial frontier for development of improved diagnostics of trachoma infection is likely in post-elimination surveillance, where the guidelines and measures for their implementation should be improved. Lack of guidance and available tools to support this development could be a critical gap to meeting the London Declaration LD2020 goals—the measure of successful elimination needs to be defined so that these new tools can be deployed to prevent the loss of public health gains made by successful elimination.

From a purely commercial point of view, such new standards will enable the development of other biomarkers and antibody-based tests to be optimized for both efficiency and cost and to be multiplexed into diagnostics for multiple infections and further cost savings. It is the integration of commercial development of new antibody/antigen-based tests with the adjustment of standards for their use that will truly drive the success of this technology both from a commercial standpoint and in terms of its impact on global health.

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