



# Trachoma

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**Abstract** | Trachoma is a neglected tropical disease caused by infection with conjunctival strains of *Chlamydia trachomatis*. It can result in blindness. Pathophysiologically, trachoma is a disease complex composed of two linked chronic processes: a recurrent, generally subclinical infectious–inflammatory disease that mostly affects children, and a non-communicable, cicatricial and, owing to trichiasis, eventually blinding disease that supervenes in some individuals later in life. At least 150 infection episodes over an individual's lifetime are needed to precipitate trichiasis; thus, opportunity exists for a just global health system to intervene to prevent trachomatous blindness. Trachoma is found at highest prevalence in the poorest communities of low-income countries, particularly in sub-Saharan Africa; in June 2021, 1.8 million people worldwide were going blind from the disease. Blindness attributable to trachoma can appear in communities many years after conjunctival *C. trachomatis* transmission has waned or ceased; therefore, the two linked disease processes require distinct clinical and public health responses. Surgery is offered to individuals with trichiasis and antibiotic mass drug administration and interventions to stimulate facial cleanliness and environmental improvement are designed to reduce infection prevalence and transmission. Together, these interventions comprise the SAFE strategy, which is achieving considerable success. Although much work remains, a continuing public health problem from trachoma in the year 2030 will be difficult for the world to excuse.

*We dedicate this article to the memory of Professor Julius Schachter, pioneering chlamydiologist, colleague, collaborator, mentor, teacher, friend; sadly lost to COVID-19 in December 2020. The world wouldn't have made it this far against trachoma without you, Julie.*

Trachoma is one of 20 diseases and disease groups designated as neglected tropical diseases by the World Health Organization (WHO)<sup>1</sup>. It is the most common infectious cause of blindness<sup>2</sup>. The disease can be conceptualized as progressing in two phases. In the first phase, repeated infection<sup>3,4</sup> with conjunctival strains<sup>5</sup> of the bacterium *Chlamydia trachomatis* (*Ct*) results in a chronic keratoconjunctivitis (inflammation of the cornea and conjunctiva), including an inflammation of the conjunctiva known as active trachoma. Rounds of severe conjunctival inflammation lead to scarring of the eyelid<sup>6,7</sup>, which is the start of the second disease phase. This scarring can cause inward rotation of the eyelashes so that they come into contact with the eyeball, a condition known as trichiasis. Trichiasis may be accompanied by a distortion of the eyelid known as entropion<sup>8</sup>, in which part or all of the eyelid margin is rolled inward. Scratching of the cornea by in-turned eyelashes predisposes to corneal opacity, vision impairment and blindness. The presence of any of

these *Ct*-induced pathological processes or clinical signs is trachoma. However, to fully grasp the nature of this disease, it is imperative to also consider the devastating effects of trichiasis and vision impairment on affected individuals, their families and their communities<sup>9</sup>. In economic terms alone, these effects combine to reduce global productivity by billions of dollars each year<sup>10</sup>.

Trachoma is a disease of poverty — it affects the poorest of the poor<sup>11</sup>. In Europe and most of North America, trachoma disappeared decades ago as living standards improved and without the implementation of specific interventions<sup>12</sup>. Similar trends have been seen in some low-income and middle-income countries with previously hyperendemic disease<sup>13–15</sup>. In addition, during the past few decades, deliberate interventions to control trachoma have been associated with dramatic declines in its global burden<sup>16,17</sup>. However, prevalence has remained high in some populations despite prolonged intensive intervention with a comprehensive, four-component strategy recommended by WHO<sup>18</sup>.

In this Primer, we provide an overview of the epidemiology, pathophysiology, clinical features and diagnosis of trachoma as well as of the management, control and elimination of disease, at both the individual and population level. We also propose key areas for future research.

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**Epidemiology**

Global trachoma prevalence data are published annually by WHO<sup>17</sup> and summarized on the [WHO Global Health Observatory](#). Data at a finer scale are available on the [Trachoma Atlas](#). As of March 2022, 44 countries were known to require interventions against trachoma, of which 26 were in the WHO African Region.

**Associations**

**Poverty.** At any spatial scale at which observations are made, trachoma is found in the poorest people. Risk of active trachoma is higher in households with crowded sleeping arrangements<sup>11,19–21</sup>; sharing a bedroom with someone else who has active trachoma doubles an individual's risk<sup>22</sup>. In trachoma-endemic communities, individuals with trachomatous trichiasis (TT) are likely to be poorer than age-matched and gender-matched peers without TT and are less likely than those peers to participate in economically productive activities even after controlling for visual impairment<sup>11</sup>. In trachoma-endemic countries, the disease affects the population groups that are poorest, most marginalized and most remote from services (particularly water and sanitation)<sup>23</sup>. At the regional and global level, concentration of trachoma in the poorest countries is evident<sup>17,24</sup>.

Poverty is both a cause and consequence of blindness<sup>25</sup>. Trachoma can trap affected individuals, families and communities in successive generations of despair.

**Age.** In trachoma-endemic populations, individuals are often first exposed to conjunctival *Ct* during the first months of life<sup>26</sup>. *Ct* infection and active trachoma occur most commonly during childhood; in infected individuals, *Ct* loads are higher at younger ages<sup>26–31</sup>. In hyperendemic areas, the frequencies with which infection and active trachoma are observed decrease with age after a peak in those aged 2–5 years. TT, corneal opacity and visual impairment are unusual before adulthood and observed frequencies increase with age<sup>27,32</sup>.

**Gender.** In childhood, boys and girls tend to be equally affected by active trachoma<sup>33,34</sup>. For TT, in pooled data, women have 1.8 times higher odds of being affected than men<sup>35</sup>, although this odds ratio can approach 4 in some settings<sup>33,36</sup>. The excess risk is generally attributed to women being exposed to conjunctival *Ct* more frequently than men as they get older because of women's disproportionate contribution to childcare duties in most societies<sup>37</sup>. More direct biological effects of oestrogen, oestrogen receptor abundance or sex-linked differences in the immune response to *Ct*<sup>38</sup> have not been ruled out.

**Mechanisms/pathophysiology*****Chlamydia trachomatis***

*Ct* is a gram-negative bacterium that infects humans at the epithelial layer of mucosal surfaces. Different *Ct* serovars, originally distinguished using micro-immunofluorescence<sup>39</sup>, have a characteristic tissue tropism and are associated with different disease complexes: A, B, Ba and C with trachoma, D through K with urogenital chlamydia, and L1, L2 and L3 with lymphogranuloma venereum (BOX 1).

*Ct* has a unique biphasic developmental cycle<sup>40</sup>. It moves between host cells as the infectious form, called the elementary body (diameter ~0.30 µm). Using mostly receptor-mediated endocytosis, the elementary body gains entry to a human epithelial cell within a vacuole formed of host cell membrane and chlamydial proteins, which then develops into a peri-nuclear inclusion<sup>41</sup>. Inside the inclusion, it reorganizes into its more metabolically active, replicating, non-infectious form, the reticulate body (diameter ~1.2 µm). After ~72 h, the reticulate body transforms into 100–1,000 elementary bodies that are released via host cell lysis. In the intracellular environment, *Ct* evades detection and dampens the host immune response via several mechanisms<sup>40</sup>.

The elementary body has a rigid cell wall, which facilitates survival under unfavourable conditions. The major outer membrane protein is the most abundant cell wall surface protein, comprising ~60% of cell wall mass. It is involved in host cell surface adhesion and is encoded by a single-copy chromosomal gene, *OmpA*<sup>42</sup>. Variation in this protein characterizes the 19 different *Ct* serovars. Whole-genome sequencing revealed that the preference of different serovars for particular anatomical niches is not absolute. Extensive recombination in the *OmpA* region has resulted in exchange of genetic material both within and between conjunctival, urogenital and lymphogranuloma venereum strains<sup>43</sup>. Urogenital strains are generally able to synthesize their own tryptophan, whereas conjunctival strains typically have inactivating mutations in the gene encoding tryptophan synthase<sup>44</sup>. One possible explanation is that ocular serovars are able to access a source of tryptophan (or one of its biosynthetic precursors) within the conjunctival sac or infected cells, and that that source is unavailable to pathogens in the urogenital tract<sup>44</sup>. Of note, tryptophan itself is not found in human tears<sup>45</sup>. The mechanism by which conjunctival *Ct* survives in this milieu and whether its peculiar biochemistry could be exploited against human disease is unknown.

Other *Ct* proteins in addition to the major outer membrane protein are produced in a complex sequence at different stages in the developmental cycle<sup>46</sup>; these include heat shock proteins that protect *Ct* in stress conditions. These proteins, such as cHsp60, are implicated in disease pathogenesis and are recognized by pathogen recognition receptors of the innate immune system, including Toll-like receptors<sup>47</sup>.

### Transmission of *Ct*

Transmission of conjunctival *Ct* infection has been the subject of considerable scrutiny, yet methods to directly investigate transmission routes in trachoma-endemic communities were not applied until 2018. Important epidemiological evidence used to generate biologically plausible hypotheses on transmission includes the focal nature of infection and disease, with spatial clustering of cases identified at bedroom, household, compound, neighbourhood and community levels<sup>31,48–56</sup>; the association of active trachoma with visible eye and nose discharge on children's faces<sup>57–59</sup>; and the association of active trachoma with observed fly-eye contact<sup>53,60–62</sup>. All of the above tend to be observed in populations that are relatively overcrowded<sup>57,62,63</sup> and have poor access to water and sanitation<sup>59,63–66</sup>. Infected eye discharge or cultured *Ct* can induce active trachoma when directly inoculated into an eye<sup>19,67</sup>, suggesting that simple mechanical transfer of infectious material from an infected to an uninfected eye may be all that is necessary to create a transmission event. Because tears drain into the nose and *Ct* can be identified in the noses of children with active trachoma<sup>68,69</sup>, nasal discharge may also be important in transmission of infection. Together, these observations implicate three principal routes of transmission: direct person-to-person transfer of infected secretions on human fingers; spread via fomites such as shared bedding or towels; and carriage on eye-seeking flies, particularly female *Musca sorbens*, which preferentially obtain protein from human exudates for egg production<sup>70</sup>. It is not yet known with certainty whether *Ct* infects and replicates within vector fly species but laboratory-based work on flies from the same genus<sup>71</sup> shows that viable *Ct* can be retrieved from flies for up to 48 h after feeding. Fingers, fomites and flies are sometimes referred to as the 'three Fs' of trachoma transmission.

Evidence now substantiates these proposed routes. *Ct* DNA can be detected on flies caught leaving the faces of children in trachoma-endemic communities<sup>55,70,72,73</sup>. In Ethiopian households in which no residents had current conjunctival *Ct* infection and which were located close to other households in which one or more residents did have conjunctival *Ct* infection, some flies caught leaving the faces of children were positive for *Ct* DNA. This implicates flies as potential carriers of conjunctival *Ct* between households as well as within them<sup>55</sup>. In a prospective trial, fly control with insecticide space spraying, which involves the creation of a liquid fog throughout community outdoor spaces, although not seen to be a sustainable intervention at scale, reduced the prevalence of active trachoma<sup>74</sup>, confirming the importance of flies as vectors.

A study published in 2020 demonstrated the presence of *Ct* DNA at other extra-ocular sites: on the skin of

human faces and hands, clothing, a sleeping surface, and a washing jug in households in which one or more residents had conjunctival *Ct* infection<sup>55</sup>. In households in which all residents had *Ct*-negative conjunctival swabs, none of these extra-ocular sites had detectable *Ct* DNA<sup>55</sup>. Experiments employing viability PCR, which uses propidium monoazide pre-treatment to prevent amplification of DNA from non-viable bacteria, suggest that at least some *Ct* remains viable on plastic, cotton cloth and skin for >24 h (REF.<sup>75</sup>), providing additional support for the roles of fingers and fomites in transmission.

### Conjunctival *Ct* infection and active trachoma

Epidemiological observations have informed mathematical models of trachoma, which suggest that >100 conjunctival *Ct* infections in an individual's lifetime are required to generate clinically significant conjunctival scarring and that 150 infections are required to precipitate TT<sup>76</sup>. As most episodes of infection occur in childhood, children who go on to develop TT later in life are likely to be re-infected several times each month, with transfer of *Ct* back and forth from one child to another.

The limited longitudinal data available indicate that a primary infection episode in a child is characterized by a short 'preclinical' phase of a few days before the development of signs of inflammation<sup>77</sup>. In adult human volunteer experiments, clinical inflammation developed ~10 days after conjunctival *Ct* inoculation<sup>78</sup>. Established infections are characterized, particularly in younger preschool age children, by a generalized follicular and papillary conjunctivitis, particularly evident in the conjunctiva of the upper eyelid. At the tissue level, the generalized papillary inflammation involves a mixed inflammatory cell infiltrate, including lymphocytes, macrophages and neutrophils. Lymphoid follicles are formed mostly of B cell aggregations in the conjunctival stroma. After the development of clinical inflammation, infection remains detectable for a few days to many weeks<sup>77</sup>. The human immune response then controls the infection, clearing it or reducing it to undetectable levels. However, conjunctival inflammation persists, and may last for many weeks after infection becomes undetectable; in untreated children aged 4–15 years, infection may be cleared after 3–8 weeks, whereas clinical signs of

#### Box 1 | Disease associations of non-ocular *Ct* serovars

Urogenital *Chlamydia trachomatis* (*Ct*) infection is sexually transmitted, causing urethritis, cervicitis, proctitis, epididymitis and pelvic inflammatory disease. In some women, scarring of the fallopian tubes occurs, presumably from repeated infections, leading to infertility or ectopic pregnancy. Lymphogranuloma venereum is also sexually transmitted, with *Ct* entering via the mucosae, affecting local lymphatic vessels and lymph nodes, and occasionally becoming disseminated<sup>292</sup>. An increasing body of both experimental and observational work challenges the notion that only lymphogranuloma venereum *Ct* strains invade beyond the epithelium of the tissue of entry, indicating that serovars A–K, which cause trachoma and urogenital infections, probably also have this ability<sup>293,294</sup>.

inflammation continue for 6–18 weeks<sup>79</sup>. Resolution of infection is thought to depend on a cell-mediated immune response, effected through IFN $\gamma$ <sup>80</sup>. Adults tend to have shorter episodes of infection and disease, although the relative frequency of exposure to reinfection in children and adults cannot be quantified<sup>77</sup>. This protection in older individuals is thought to be mediated through acquired T cell-dependent cell-mediated responses that either prevent or more rapidly resolve infection<sup>80</sup>.

The different time courses of conjunctival infection and active trachoma explain the partial mismatch observed between infection and disease at the individual level<sup>54,81–83</sup>. This disparity has important implications for trachoma programmes, as individually targeted antibiotic treatment decisions based on observable conjunctival inflammation of at least moderate intensity would miss many infected individuals with a mild clinical response. Antibiotic mass drug administration (MDA) is the most practical way of trying to treat all individuals infected with conjunctival *Ct* within large trachoma-endemic populations<sup>84</sup>.

#### **Development of scarring sequelae**

The association between increasing age and increasing prevalence of cicatricial sequelae of trachoma (conjunctival scarring, TT and corneal opacity) indicate that these signs are cumulative. Several longitudinal studies have investigated their natural history and pathophysiology<sup>85</sup>. To date, five studies have examined the rates and risk factors for progression from conjunctivae without scarring through active trachoma to the development of conjunctival scarring<sup>6,7,86–88</sup>. Their findings show a consistent and substantially increased risk of subsequent incident scarring associated with intense conjunctival papillary inflammation, particularly when observed at multiple time points<sup>6,7,86,88</sup>. Evidence linking subsequent scarring to the presence of a follicular conjunctivitis (without concomitant intense papillary inflammation) or to repeated or constant *Ct* infection is much less convincing. Only two published cohort studies of incident scarring have prospectively tested for *Ct* infection. Neither of these has identified a relationship between ongoing *Ct* infection and incident or progressive scarring after adjusting for clinical inflammation<sup>7,88</sup>.

Two large prospective studies conducted in Ethiopia and the United Republic of Tanzania have followed the progression of pre-existing conjunctival scarring in adults, including tests for the presence of *Ct*<sup>89</sup>. Both found strong evidence of a relationship between progression of scarring and the repeated observation of papillary inflammation of the conjunctiva. Conjunctival *Ct* infection was very rare in these cohorts, and the infections that were detected were not associated with progression. However, it is possible that study participants were infected occasionally for very short periods<sup>77</sup>, which multiple cross-sectional samples could easily miss.

Taken together, these studies point to a central role for chronic severe inflammation in scarring development (FIG. 1). Such severe responses are not found in all people exposed to conjunctival *Ct*, indicating that variations in the human immune response may be important

co-determinants of scarring risk although it is not possible to quantify individual exposure to repeated reinfection. At the population level, a higher prevalence of inflammatory trachoma in children correlates with a higher prevalence of trichiasis in adults<sup>90</sup>. Available data also suggest that additional pro-inflammatory stimuli, such as other bacteria and ocular surface dryness<sup>81</sup>, contribute to the progression of scarring initiated by *Ct*-related inflammation<sup>91</sup>.

#### **Immunopathological basis of scarring trachoma**

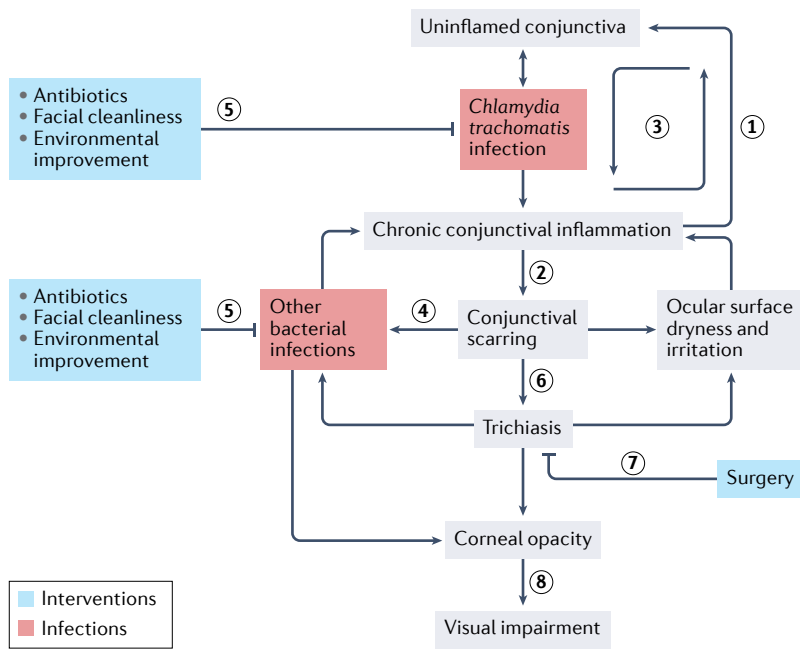
Trachoma offers an unusual opportunity to directly observe and investigate the pathophysiology of an inflammatory scarring disease process, with potential relevance to disease processes elsewhere. Multiple long-term natural history studies have been conducted, applying a range of techniques (histopathology, immunohistochemistry, in vivo confocal microscopy, human gene expression profiling or human genetics) and relating these to the clinical course<sup>80</sup>. In addition, non-human primate models have been developed as part of *Ct* vaccine development work, which have contributed substantially to our understanding of trachoma pathophysiology<sup>3,92–94</sup>.

Biopsy and in vivo confocal microscopy studies of children with active trachoma demonstrate that it is characterized by a mixed conjunctival inflammatory cell infiltrate, including macrophages, T cells, neutrophils and dendritic cells<sup>95,96</sup>. Organized lymphoid follicles are scattered throughout the conjunctival stroma, composed largely of B cells surrounded by a mantle of proliferating lymphocytes (FIG. 2).

In biopsy specimens from adults with conjunctival scarring, extensive connective tissue disruption can occur with loss of the regular stromal architecture and replacement with disorganized collagen and other elements<sup>97</sup>. Compared with controls, scarred tissue also has marked increases in CD45<sup>+</sup> inflammatory cells, whose abundance fluctuates with the intensity of clinical inflammation<sup>98</sup>. Specific staining indicates that natural killer cells are a prominent component of the cellular infiltrate in scarred conjunctivae, suggesting that innate responses may be relevant in this damaged tissue<sup>98</sup>. Staining of scarred conjunctivae against a panel of cytokines and scarring disease markers reveals prominent increases in epithelial expression of connective tissue growth factor (CTGF) and the antimicrobial peptide S100A7; in addition, expression levels of IL-1 $\beta$  are increased in the substantia propria<sup>99</sup>.

In vitro infection studies of epithelial cells have found a marked innate pro-inflammatory response, with the production of several cytokines: IL-6, IL-8, growth-regulated oncogene- $\alpha$  (GRO $\alpha$ ) and granulocyte-macrophage colony-stimulating factor (GM-CSF)<sup>100,101</sup> (FIG. 3). This finding is consistent with data from in vivo investigations into conjunctival gene expression profiles using swabs taken from the conjunctival surface<sup>102–105</sup>. The initial innate response to *Ct* is likely to be driven directly by infected epithelial cells, recognizing the presence of the organism through their pattern-recognition receptors, leading to a chronic inflammatory response. This suggestion is sometimes referred to as the cellular





**Fig. 1 | The natural history of trachoma.** Pathogenesis of visual impairment in trachoma and the SAFE strategy interventions intended to prevent or slow those processes. The two linked chronic processes that are involved in pathogenesis are shown: a recurrent, generally subclinical infectious–inflammatory disease that mostly affects children; and a non-communicable, cicatricial, increasingly painful, eventually blinding disease that supervenes in some individuals later in life. (1) Resolution of *Chlamydia trachomatis* infection and restoration of the uninflamed conjunctiva is accompanied by (2) some residual conjunctival scarring; (3) repeated reinfection drives the chronic cicatricial process. (4) Conjunctival scarring reduces the volume and alters the composition of the tear fluid, which normally acts as a mechanical barrier (via continual flow) and contains molecules that are part of the innate immune system. Where trichiatric eyelashes abrade the cornea, breaching of the epithelium (the most superficial layer of the cornea) enables penetration of bacteria into the corneal stroma. (5) Antibiotics treat prevalent *C. trachomatis* infections (and some other prevalent bacterial infections), whereas facial cleanliness and environmental improvement are intended to reduce the incidence of new infections, that is, reduce transmission intensity. (6) No specific interventions have been trialled or deployed to try to reduce the likelihood of incident trichiasis in individuals who have conjunctival scarring. Of note, SAFE strategy components are intended to reduce the accumulation of conjunctival scarring in those who do not yet have it and in those who do. (7) Surgery reduces progressive corneal opacification and ocular surface irritation, which is crucial for symptom relief. Surgery has no effect to correct existing ocular surface dryness. (8) In many conditions that blind through corneal opacification, keratoplasty (corneal transplantation) is used to reduce or reverse visual impairment. In an individual with corneal opacity due to trachoma, changes in the tear film and corneal vascularization are predicted to reduce the likelihood of long-term graft survival. In addition, populations affected by trachoma tend to have very poor access to keratoplasty services.

paradigm for the pathogenesis of *Ct*-driven scarring disease<sup>106</sup>. The alternative hypothesis, that is, the immunological paradigm, suggests that inflammation and tissue damage are driven through a cell-mediated immune or delayed-type hypersensitive response to chlamydial antigens such as cHsp60. Although well established in animal models, direct evidence from human studies corroborating this is limited<sup>80,94,106</sup>.

Resolution of *Ct* infection is thought to be dependent on IFN $\gamma$  from a CD4<sup>+</sup> T helper 1 (T<sub>H</sub>1) cell-mediated immune response. Gene expression studies in children in trachoma-endemic populations show a marked increase in conjunctival expression of IFN $\gamma$  and T<sub>H</sub>1 cell-related

factors (IL-12B and indoleamine-2,3-dioxygenase (IDO1)) and in natural killer cell pathways (characterized by NCRI, CD56 and CD247)<sup>102–104</sup>. In children with active trachoma but no detectable *Ct*, levels of IFN $\gamma$  are not particularly elevated, suggesting that this response is rapidly regulated following the resolution of infection. Infection and active trachoma are also both associated with profiles that are consistent with a prominent T<sub>H</sub>17 response, with increased expression of IL-17, IL-21 and IL-22 (REF.<sup>104</sup>). Some data indicate that T<sub>H</sub>17–IL-17 responses might contribute to a worsening of the inflammatory/scarring response in animal models<sup>107</sup>.

Intense conjunctival inflammation is the key clinical manifestation linked with the development of scarring. In cross-sectional studies, intense inflammation is associated with increased expression of a range of pro-inflammatory factors such as S100A7, defensin (DEFB4A), IL-1 $\beta$ , IL-17A, CCL18 and neutrophil chemotactic factor CXCL5 (REF.<sup>104</sup>). These often seem to persist after *Ct* infection has resolved. Interestingly, several markers (S100A7, IL-1 $\beta$ , IL-17A and CXCL5) are also consistently elevated in adults with established conjunctival scarring and visible inflammation<sup>89</sup>.

In the context of this chronic inflammatory milieu, with the recruitment and activation of a diverse population of leukocytes, the conjunctival tissue is repeatedly damaged and scar tissue is formed during healing. Matrix metalloproteinases (MMPs) are a large and diverse family of proteases that are central to the regulation of connective tissue in health and disease. Studies in trachoma-endemic populations have found increased expression of MMP7, MMP9 and MMP12 in children with intense conjunctival inflammation and adults who have established scarring with inflammation<sup>89,102,104,108</sup>. In a cohort study of Tanzanian children assessed every 3 months for 4 years, progressive scarring was strongly associated with increased proportions of follow-up points at which clinical inflammation was seen<sup>88</sup> as well as with increased expression of pro-inflammatory chemokines (CXCL5, CCL20, CXCL13 and CCL18), cytokines (IL-23A, IL-19 and IL-1B), MMP12, and S100A7 and reduced expression of SPARCL1 (REF.<sup>105</sup>).

Increased expression of several fibrogenic growth factors, including CTGF, FGF, TGF $\beta$ 1 and PDGF, has also been associated with clinical inflammation in active trachoma and scarring<sup>89,104,108</sup>. These factors have a pro-fibrotic effect, probably largely mediated through increased deposition of connective tissue elements by stromal fibroblasts. Interestingly, cultured conjunctival fibroblasts from individuals with trachomatous scarring have a markedly contractile pro-fibrotic phenotype compared with control fibroblasts, suggesting some (as-yet uncharacterized) permanent change in their behaviour<sup>109</sup>.

## Diagnosis, screening and prevention

### Diagnosis

Trachoma is diagnosed through clinical examination. This requires a trained examiner, a calm examinee, magnification (generally  $\times 2.5$  binocular magnifying loupes), and a means for the examiner to prevent iatrogenic transmission of infection from one examinee to the next

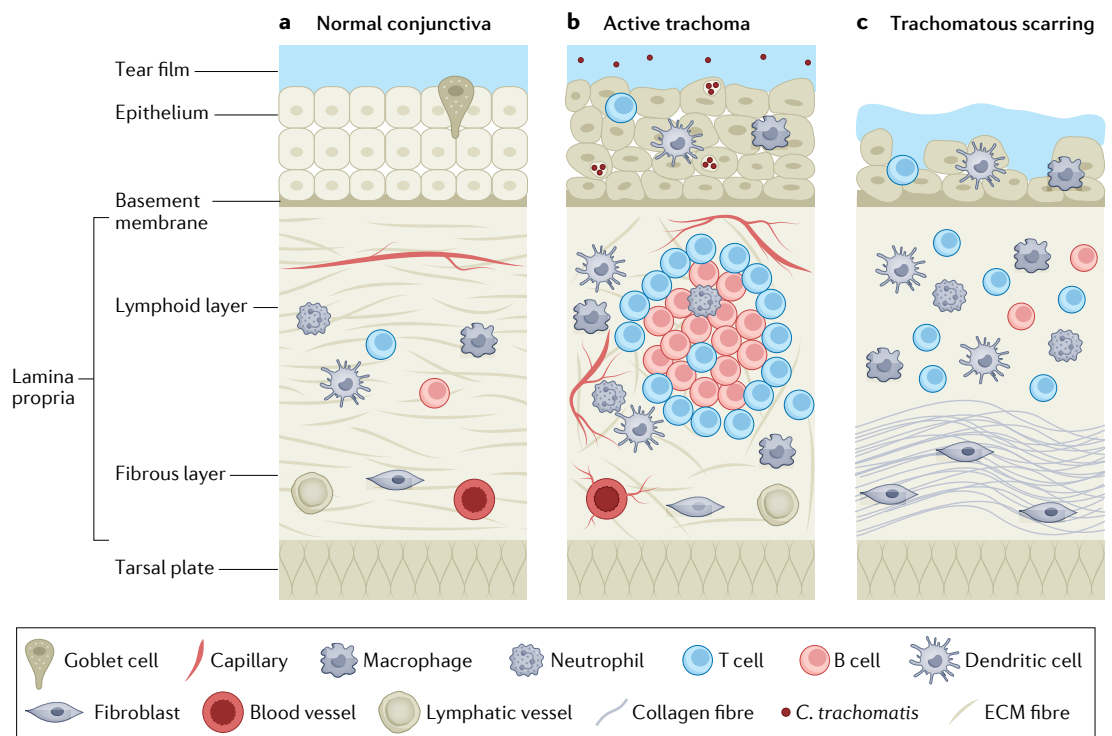
(alcohol-based hand gel, disposable examination gloves, or soap and water). Diagnosis is often (but not always) done in the field. Illumination is also important; a torch is optimal when looking for TT, whereas bright sunlight is generally adequate for examining the conjunctiva.

Most individuals with active trachoma have minimal or no symptoms. Some report eye irritation or a small amount of discharge. Individuals with TT often report a history of eye pain, blepharospasm (involuntary closure of both eyelids), light intolerance or reduced vision<sup>110</sup>. Many epilate their in-turned eyelashes using home-made forceps, clam shells or tree resin<sup>111</sup>. Poor vision may be reported even in the absence of corneal opacity. Quality of life may be severely impaired<sup>9,112,113</sup>.

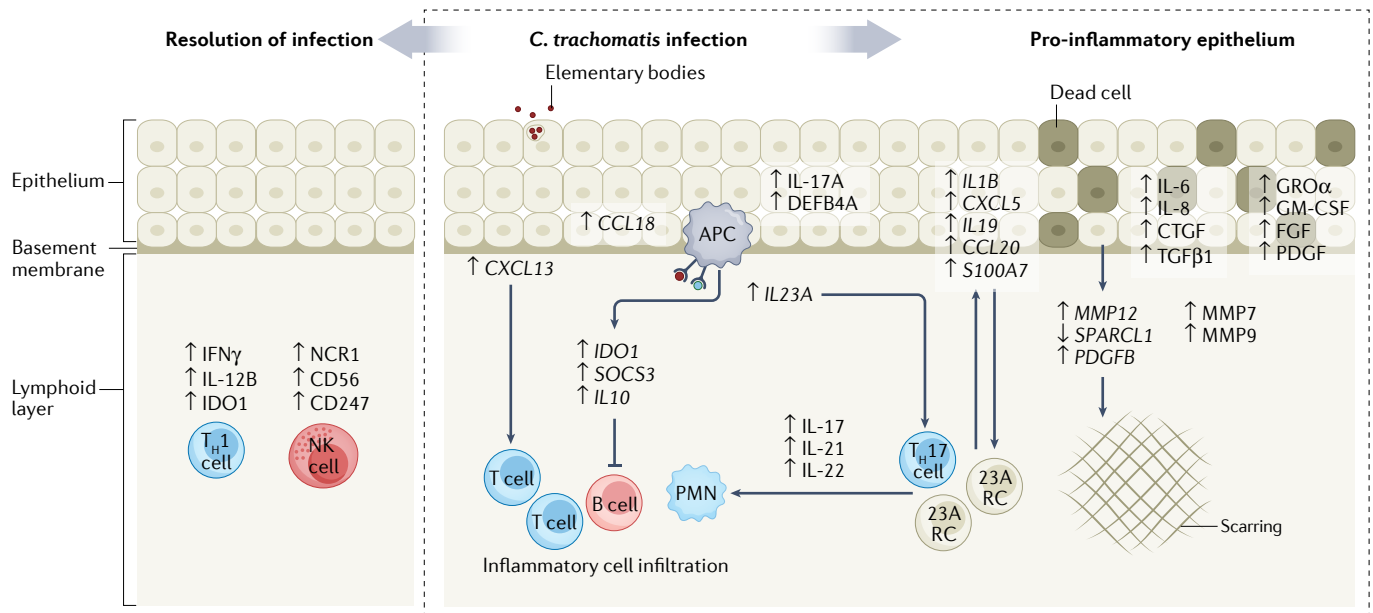
A comprehensive trachoma examination routine is ideal but, in some contexts (in particular, routine surveys conducted by public health programmes to estimate prevalence), not all of its elements are required. The examination should be guided by its purpose and context.

The comprehensive examination comprises several steps. Visual acuity is measured (for each eye separately) where possible. To reduce the risk of transposing findings in the record, routinely examining the right eye, then

the left eye, is recommended. Upper and lower eyelids are inspected for entropion, trichiasis and evidence of recent epilation; the latter includes broken or re-growing eyelashes or empty eyelash follicles. The cicatricial complications of trachoma characteristically affect the upper eyelid; in ~10% of patients, they also affect the lower eyelid but rarely in the absence of upper eyelid disease<sup>114</sup>. The cornea and limbus (border between cornea and sclera) are inspected for opacities, upper pole pannus (ingrowth of fibrovascular tissue from the limbus into the cornea) and Herbert pits (rounded depressions at the limbus resulting from regression of lymphoid follicles). If fluorescein and a slit lamp are available, superficial punctate keratitis might be detectable in some individuals with active trachoma. The upper eyelid is everted and the tarsal conjunctiva examined for central follicles, inflammatory thickening due to a papillary response, and scarring<sup>110,115</sup>. If follicles are present in the central part of the upper tarsal conjunctiva, only those with a diameter  $\geq 0.5$  mm should be regarded as being of pathological significance; follicle size guides<sup>116</sup> fixed to the examiner's thumbnails can assist in accurately assessing follicle diameter. Particularly when examining children, having an assistant to reassure and support the examinee can be invaluable<sup>117</sup>.



**Fig. 2 | Tissue changes in trachoma.** Schematic of the histology of the normal conjunctiva, the conjunctiva in the presence of active trachoma and conjunctiva in the presence of trachomatous scarring. **a** | The normal conjunctiva has a non-keratinized, stratified epithelium of 3–5 cell layers, containing interspersed goblet cells that secrete mucin. The tear film covers the epithelium. The deeper lamina propria accommodates blood vessels, lymphoid cells and other connective tissue elements. **b** | When infected with *Chlamydia trachomatis*, inflammation is manifest through telangiectasia of capillaries and small venules, and a mixed inflammatory cell infiltrate. Collections of B cells, T cells and macrophages form lymphoid follicles in the lamina propria; B cells form the core and the bulk of their mass. When sufficiently large, lymphoid follicles distort the contour of the overlying epithelium (not shown) and can be seen in the everted tarsal conjunctivae. **c** | In the scarred conjunctiva, goblet cells are depleted. The tear film is reduced in volume and changed in composition. An increasingly disorganized scar is found in the lamina propria. Scars may also be found in the tarsal plate (not shown). ECM, extracellular matrix.



**Fig. 3 | Pathophysiology of Ct infection.** Immune responses triggered by *Chlamydia trachomatis* (Ct) infection; the infection can resolve or progress to eyelid scarring. Shown are the cytokines, human cellular enzymes, growth factors and other proteins involved in the regulation of the extracellular matrix whose expression is known to be upregulated or downregulated in the presence of replicating Ct, during infection resolution or in the ongoing pro-inflammatory state leading to progressive deposition of conjunctival scar. 23A RC, IL-23A-responsive cells; APC, antigen-presenting cell; CTGF, connective tissue growth factor; DEF4A, defensin; GM-CSF, granulocyte–macrophage colony-stimulating factor; GRO $\alpha$ , growth-regulated oncogene- $\alpha$ ; IDO1, indoleamine-2,3-dioxygenase; MMP, matrix metalloproteinase; NK, natural killer; PMN, polymorphonuclear leukocyte; T<sub>H</sub>, T helper.

Other causes of conjunctival inflammation, conjunctival scarring, trichiasis, entropion and corneal opacity can have clinical signs that resemble those produced by trachoma. For example, inclusion conjunctivitis looks like active trachoma but is a self-limited inflammatory condition caused by infection of the conjunctiva with urogenital *Ct*<sup>118</sup>. Its prevalence has not been determined for any trachoma-endemic population but could be high in places where urogenital *Ct* is very common and access to water and sanitation is very poor. Non-chlamydial bacterial or viral infection may also drive follicular inflammation of the conjunctiva<sup>81,119</sup>.

The interpretation of clinical signs and their classification as being attributable (or not attributable) to trachoma can be influenced by a range of contextual impressions. For trachoma, these include the relative poverty of the patient and family, the examiner's impression of the patient's personal and family hygiene, and the trachoma endemicity of the patient's community. However, community-level endemicity status is often unknown or not known with certainty. The examiner's view on whether trachoma is endemic in a community influences the clinical interpretation of the patient, which can then (potentially inappropriately) confirm, in a circular fashion, the examiner's classification of the community<sup>120</sup>. This possible confirmation bias is important in both the diagnosis of active trachoma and in differentiating upper eyelid trichiasis that is trachomatous from that caused by other pathological processes.

To help maximize the objectivity of assessment, particularly for estimates of trachoma prevalence at the

population level, WHO developed trachoma grading systems that have subsequently evolved over decades<sup>110</sup>. Two systems are in current use. The modified WHO grading system (or FPC system, for follicles (F), papillary hypertrophy (P), cicatriciae (C)) is a specialist scale that was last updated in 1981 (REF.<sup>121</sup>) and is used principally in research studies. The simplified WHO grading system, intended for non-specialist personnel, was first published in 1987 (REF.<sup>122</sup>) and updated in 2020 (REF.<sup>115</sup>) (TABLE 1). It is in widespread use for screening and population-level assessment. The five signs are signs, not stages, and more than one can be simultaneously present in an eye. In the simplified grading system, the presence of trachomatous inflammation — follicular (TF) and/or trachomatous inflammation — intense (TI) in either eye constitutes active trachoma (FIG. 4).

The simplified system includes acknowledged imperfections<sup>115</sup>. For example, not all epilation is undertaken for trichiasis<sup>123</sup>; when epilated eyelashes have not fully regrown, it is hard to determine whether they were touching the eyeball before removal; and not all upper eyelid trichiasis is due to trachoma<sup>124</sup>.

Since 2012, standardization of grader training, grader certification and fieldwork procedures<sup>116,125–128</sup> have further contributed to comparability and confidence in trachoma prevalence data generated by national programmes. However, when assessing an individual patient, rigid adherence to grading systems and standard operating procedures may not be appropriate. This represents a fundamental difference between the diagnostic approaches needed for clinical (BOX 2) and epidemiological (BOX 3) purposes.

### Screening

In June 2021, 136 million people worldwide lived in areas in which active trachoma was thought to represent a public health problem<sup>17</sup>. Individually screening large populations for active trachoma is problematic because examining millions of people requires many examiners, and examiners without adequate training provide assessments with predictive values that are too low to be epidemiologically or programmatically useful<sup>129</sup>. Even physicians working in endemic areas may produce inaccurate screening assessments if they are not well trained<sup>130,131</sup>. Of note, the frequency of asymptomatic *Ct* infection and ease of reinfection after treatment mean that characterization and management of the population as a whole are crucial for controlling active trachoma; individual screening for the purposes of individual-level management would be unhelpful for achieving public health targets<sup>132</sup>.

For TT, active case-finding, including through mass population screening, is a recognized strategy for linking individuals who have TT with surgical services, thereby achieving agreed public health targets<sup>133</sup>. Various screening approaches are used, including centralized village-level screening conducted by eye workers and door-to-door screening by TT case finders. The limited data available suggest that the sensitivity and specificity of TT case finders are highly variable<sup>134–136</sup>. Properly training<sup>134</sup> and equipping<sup>137</sup> case finders is likely to be important.

**Population-level assessment.** A key concept in trachoma epidemiology is ‘elimination as a public health problem’, which is defined only for countries as a whole. It has three criteria: first, a prevalence of TT ‘unknown to the health system’ (that is, excluding individuals with post-surgical TT, individuals with TT who have refused surgery for it, and individuals with TT who have a surgical date set in the future) of <0.2% in those aged 15 years or more, in each formerly endemic district; second, a prevalence of TF of <5% in those aged 1–9 years, in each formerly endemic district; and, third, written evidence that the health system can identify and manage incident TT cases<sup>138</sup>.

Although validation of elimination as a public health problem can only be undertaken for a country as a whole, district-level data are needed to substantiate the claim that the first two criteria have been satisfied. Here, the term ‘district’ means the normal administrative unit for health-care management, generally a population unit of 100,000–250,000 people<sup>138</sup>. To avoid confusion with local administrative units designated as districts that may have populations outside the 100,000–250,000 range, trachoma programmes often use the term ‘evaluation units’ instead. WHO has published recommendations on estimating the prevalence of TT and TF at the level of evaluation units<sup>32,139</sup>. Although rigorous surveys undertaken according to those recommendations were determined to cost a median of US\$8,298 (in 2017) per evaluation unit<sup>140</sup>, the alternative approaches of simply continuing interventions without checking that they continue to be justified, or not eliminating trachoma at all, are likely to be considerably more expensive<sup>10,141</sup>.

Since 2012, the Global Trachoma Mapping Project (GTMP)<sup>142</sup> and its successor, Tropical Data<sup>143</sup> (TABLE 2), have together supported health ministries in 50 countries to conduct population-based trachoma prevalence surveys consistent with WHO recommendations, generating globally comparable, epidemiologically robust data<sup>125</sup>. Data from all GTMP and Tropical Data surveys are owned by the relevant health ministries, with automated linkages made available to display evaluation unit-level prevalence categories on the open-access *Trachoma Atlas* and provide the most current information to decision-makers at all levels<sup>144</sup>.

**Tests for *Ct* infection.** Sensitive molecular approaches for pathogen detection, including qualitative and quantitative nucleic acid amplification-based tests, are available<sup>110,145</sup>. In trachoma, they are generally used for research purposes and not for programmatic decision-making. However, they might find more widespread use in the future as TF prevalence is not a perfect marker in this context, for several reasons<sup>146</sup>.

First, the sign TF is reasonably specific but not particularly sensitive for conjunctival *Ct* infection. In cross-sectional surveys, a relatively high proportion of individuals who are positive in nucleic acid amplification-based tests for conjunctival *Ct* do not have TF<sup>147</sup>. The prevalence of *Ct* tends to be higher in those with TI than in those with TF, and higher in those with TF than in those with less florid signs of trachoma<sup>54,83,104</sup>. Some of this discrepancy is due to variation between the natural history of infection and the natural history of disease in the individual<sup>3,110</sup>. In particular, *Ct* infection is present for days to weeks before TF or TI develops, and is cleared days to weeks before TF or TI resolves.

Second, the specificity of TF for conjunctival *Ct* infection varies between contexts. In trachoma-endemic populations, less than half of those with TF are PCR-positive for *Ct*<sup>147</sup>. Again, some of this discrepancy will be due to the natural history of infection versus that of disease in the individual<sup>110</sup>, including the effect of frequent reinfection in accelerating *Ct* clearance after each infection episode<sup>3</sup>. In addition, other processes also cause follicular conjunctivitis. Although in antibiotic MDA-naive

Table 1 | The WHO simplified trachoma grading system<sup>115</sup>

Sign <sup>a</sup> (abbreviation)	Definition
Trachomatous trichiasis (TT)	At least one eyelash from the upper eyelid touches the eyeball, or evidence of recent epilation of in-turned eyelashes from the upper eyelid
Corneal opacity (CO)	Easily visible corneal opacity that is so dense that at least part of the pupil margin is blurred when viewed through the opacity
Trachomatous inflammation — follicular (TF)	The presence of five or more follicles, each at least 0.5 mm in diameter, in the central part of the upper tarsal conjunctiva
Trachomatous inflammation — intense (TI)	Pronounced inflammatory thickening of the upper tarsal conjunctiva that obscures more than half of the normal deep tarsal vessels
Trachomatous scarring (TS)	The presence of easily visible scarring in the upper tarsal conjunctiva

WHO, World Health Organization. <sup>a</sup>Listed in the order for which they are examined.



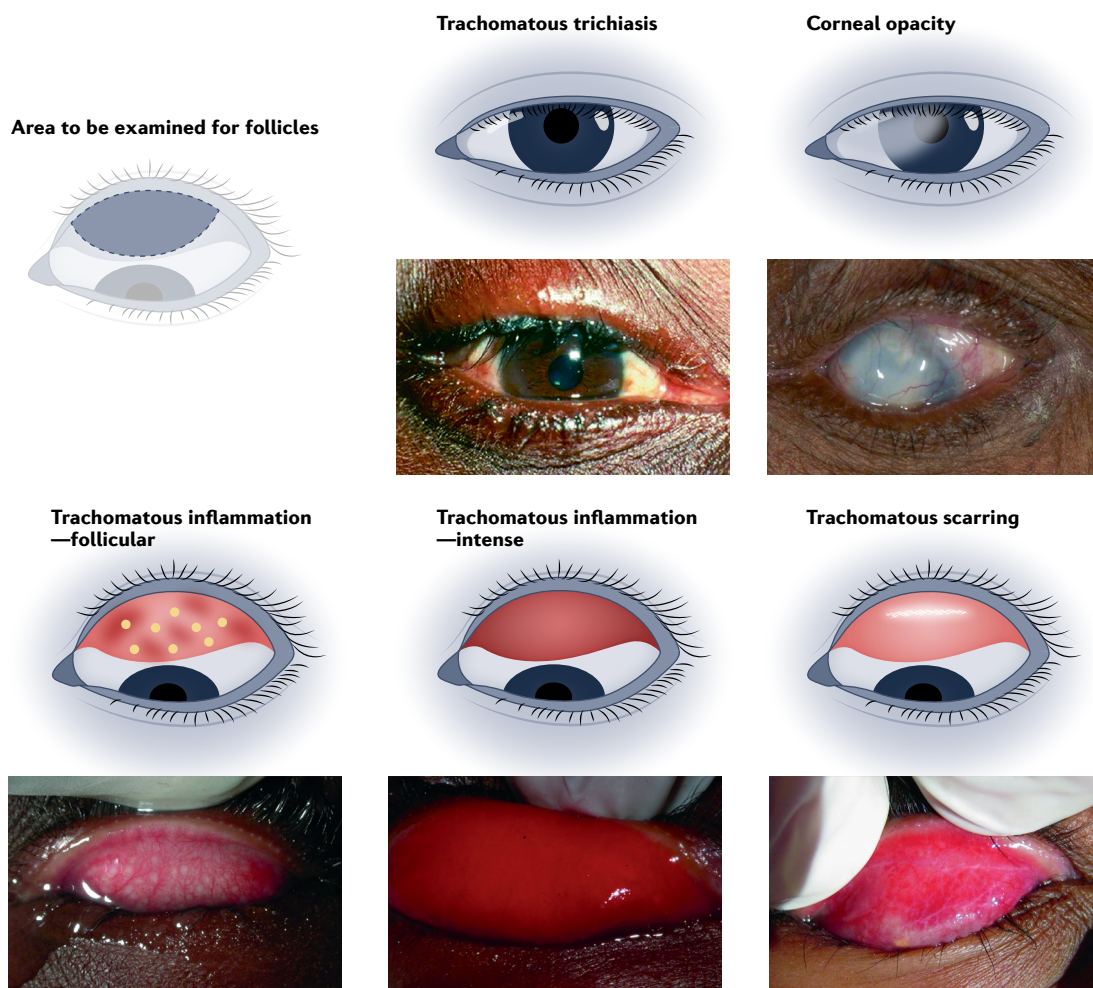


Fig. 4 | **The WHO simplified trachoma grading system**<sup>115</sup>. The World Health Organization (WHO) simplified trachoma grading system defines five signs that are indicative of trachoma. The shaded area indicates the area of the conjunctiva to be examined for follicles. Follicles found outside this area may be normal<sup>122</sup>. Trachomatous inflammation — follicular and trachomatous inflammation — intense are signs of active trachoma<sup>122</sup>. Adapted from REF.<sup>115</sup>, CC BY 4.0 (<https://creativecommons.org/licenses/by/4.0/>).

communities in Africa, the prevalence of TF (or TI) tends to reflect the underlying prevalence of conjunctival *Ct*<sup>147</sup>, this relationship weakens after antibiotic MDA, presumably because reductions in the prevalence of *Ct* infection give other causes of follicular and intense conjunctival inflammation greater relative importance, and/or because of reduced sensitivity of tests for *Ct* where *Ct* bacterial loads are lower<sup>147</sup>. In some countries in the Western Pacific, even before antibiotic MDA, children have moderately high prevalences of TF despite the extremely low prevalence of or absent conjunctival *Ct* infection<sup>148–152</sup>.

Third, falling TF prevalences globally make the appropriate training of graders both more difficult and more important. High-quality photographs and centralized photograph grading<sup>153,154</sup> might help but would not solve the problem of the mismatch between the natural histories of disease and infection.

An appropriately designed<sup>155</sup> diagnostic test for current conjunctival *Ct* infection, deployed to help estimate infection at the evaluation unit level, could avoid misclassification from all three of these issues. Efforts have been made

to develop rapid point-of-care diagnostics for the detection of current conjunctival *Ct* infection<sup>156–158</sup>. However, the principal programmatic use case is to determine whether or not interventions are indicated at the population level; therefore, high-quality tests for infection do not need to be performed next to the individuals recruited to participate in a survey. Alternatively, although open to misinterpretation in the assessment of a single individual, anti-*Ct* antibody data, based in particular on the presence of antibodies to the *Ct* antigen Pgp3, can be used to generate age-seroprevalence curves and seroconversion rates that are likely to be informative at the population level. This holds considerable promise for programmes<sup>159</sup>.

### Prevention

*Ct* vaccine research is an important topic for basic and translational research<sup>160</sup>. From 2016 to 2017, a phase I, first-in-human, randomized, placebo-controlled trial was undertaken of recombinant *Ct* protein CTH522, adjuvanted with either CAF01 liposomes or aluminium hydroxide, as a potential vaccine against urogenital *Ct* infection. Both preparations seemed to be safe and

## Box 2 | The diagnostic approach in a clinical encounter

In making a diagnosis for an individual patient, the clinician's primary responsibility is to that patient. Ancillary ethical or legal responsibilities may exist towards the clinician's own safety and well-being, the patient's contacts, the health system, or society as a whole, but bearing those other responsibilities in mind, a good clinician focuses all their diagnostic acumen to gain the greatest possible understanding of the patient's problems to help provide solutions. In formulating one or more diagnoses, the clinician, therefore, ideally takes all available information into account, including a complete history, general and specific examination findings, the epidemiological context, and the clinician's previous experience of the present and other patients.

For example, two preschool-age children are brought to the eye clinic of a district hospital, where a parent reports that each child has a history of a week or more of small amounts of eye discharge with crusting of the eyelashes and slightly swollen eyelids. The examining clinician notes the family's residence in an area known to be highly endemic for trachoma and their impoverished appearance. The clinician does not specifically look for trichiasis, as the probability of finding it is very low given the patients' ages and history. In both eyes of the first child, the clinician finds trachomatous inflammation — follicular and trachomatous inflammation — intense. The clinician diagnoses active trachoma and prescribes antibiotics to treat active trachoma. In each eye of the second child, there is inflammation, but neither the definition of trachomatous inflammation — follicular nor that of trachomatous inflammation — intense is met. The clinician prescribes antibiotics to treat active trachoma anyway, on the basis that the second child is in close contact with the first, and is highly likely to be developing active trachoma even if the current clinical appearance does not meet the criteria given in the World Health Organization (WHO) simplified system.

immunogenic, with CTH522:CAF01 showing particular promise<sup>161</sup>. Currently, however, no vaccine is commercially available that protects against conjunctival or urogenital *Ct* infection. Therefore, preventing blindness from trachoma relies on interventions intended to limit *Ct* transmission, treat *Ct* infection and re-shape eyelids with TT so that eyelashes no longer touch the eyeball. These interventions are designed to achieve primary, secondary and tertiary prevention of trachomatous visual impairment.

### Management

Interventions against trachoma are grouped together as the SAFE strategy: surgery (S) for TT, antibiotics (A) to clear infection, and facial (F) cleanliness and environmental (E) improvement to reduce transmission<sup>162</sup>. The components of the SAFE strategy are delivered at different scales: surgery is offered to individuals, while antibiotics, facial cleanliness and environmental improvement are generally offered to whole evaluation units of 100,000–250,000 people. However, 'surgery' conceptualized as a public health-level intervention entails measures, sometimes including painstaking house-to-house case searches, to reduce the evaluation unit-level prevalence of TT to below the threshold for elimination as a public health problem. Equally, it is critical that, while delivering the A, F and E components, the principles of non-maleficence and autonomy for every individual are respected; as Addiss has written so powerfully for another global health programme, we must continue to "see both the faces and the numbers"<sup>163</sup> of the people that we serve.

### Surgery

The S of SAFE comes first not just because it makes a good acronym. Individuals with TT are at continuous risk of progressive visual impairment and are often in

considerable pain<sup>9</sup>. Management to interrupt contact between eyelashes and the eyeball is urgent.

Many different surgical procedures have been used to correct TT, with varying success<sup>164</sup>. The two procedures recommended by WHO<sup>165</sup> are the bilamellar tarsal rotation procedure (BLTR) and the posterior lamellar tarsal rotation procedure (PLTR or modified Trabut). Both involve an incision across the upper eyelid, parallel to the eyelid margin, to release the trachomatous scarring-induced tension in the tarsus that draws eyelashes inwards, followed by placement of sutures to rotate the eyelashes outwards towards their normal anatomical position. Long-term surgical success is principally evaluated by assessing the cumulative incidence of post-operative TT (PTT), which is caused by either immediate surgical failure or longer-term disease progression resulting in eyelashes touching the eyeball again. Other adverse surgical outcomes include pyogenic granuloma and eyelid contour abnormalities<sup>166</sup>. A pyogenic granuloma is a small, round, highly vascularized growth on the conjunctival surface of the eyelid that develops as a result of injury or to protect against a foreign body such as a suture fragment left in the eyelid. Eyelid contour abnormalities are defined as any deviation >1 mm from the normal curvature of the eyelid. These can range in severity from a slight change in the contour to substantial deviation in the form of a gap between the eye and eyelid, which can often lead to the development of a pyogenic granuloma.

PTT rates vary by procedure, geographical location and type of study, with a cumulative incidence at 1 year after surgery ranging from below 10% to above 40%<sup>167</sup>. Surgeon skill level is an important predictor of outcome<sup>168</sup> but non-physician surgeons can be as successful as ophthalmologists<sup>169</sup>. A head-to-head trial showed that PLTR was superior to BLTR in reducing the cumulative incidence of PTT, both in the short term and 3 years after surgery<sup>170,171</sup>. This trial included surgeons originally trained in PLTR who then converted to deliver BLTR, which could have influenced outcomes. Work to investigate whether BLTR-experienced surgeons should convert to PLTR is ongoing<sup>172</sup>. Currently, WHO recommends that new surgeons should be trained in PLTR<sup>173</sup>, but existing surgeons trained in BLTR may continue to employ that procedure. Use of absorbable sutures and the TT clamp, which enables a single, safe, guided incision in the eyelid, have both been shown to reduce the incidence of pyogenic granuloma formation<sup>174,175</sup>. The TT clamp is also successful at reducing eyelid contour abnormalities<sup>175</sup>. In settings where surgeons are highly skilled, a single dose of azithromycin reduces PTT incidence by about one-third<sup>176</sup>; however, this effect is diminished in settings with increased rates of PTT<sup>177</sup>. Doxycycline does not reduce the incidence of PTT<sup>178</sup>. TT severity can range from a single eyelash touching the eye to the entire eyelid having cicatricial entropion with all eyelashes in contact with the eye. The number of trichiatic eyelashes present pre-operatively and surgeon skill are the most consistent predictors of PTT, with more trichiatic eyelashes increasing the risk of developing PTT<sup>168,179</sup>. An analysis of multiple clinical trials also showed that peripheral trichiatic eyelashes

were a risk factor for PTT regardless of the surgical procedure used<sup>180</sup>. The evidence on best approaches for the management of TT at first presentation is relatively clear but very little is known about how best to manage PTT. Individualized management by highly skilled surgeons is probably required<sup>181</sup>.

Since 2013, training programmes for TT surgery have evolved to maximize the skill levels of new surgeons. WHO now recommends that surgical simulation should be included in both new and refresher training programmes and that periodic monitoring of surgical quality after training is advisable<sup>124</sup>. Standard checklists are available to evaluate the skills required for each of the main surgical procedures<sup>165</sup>.

In trachoma-endemic communities, surgery is typically provided free of charge, either through outreach campaigns or static services. Uptake of surgical services varies both within and between countries. Patients' understanding of what the surgery involves, distance to the location at which surgery is available and access to domestic help after surgery all affect uptake<sup>182,183</sup>. Surgical productivity is also affected by surgeons' access to surgical supplies and a supervisor<sup>184</sup>.

The removal of eyelashes with forceps is referred to as epilation, and this provides temporary pain relief. Cross-sectional studies suggest that eyes with evidence of previous epilation have a lower prevalence of corneal opacity<sup>185,186</sup>. Epilation is widely used in trachoma-endemic communities by individuals who have TT or their caregivers (with caregiver involvement being particularly important for individuals with TT and impaired vision). A trial evaluating epilation versus surgery for eyelids with  $\leq 5$  trichiatric eyelashes showed that epilation was non-inferior for vision outcomes but less successful at preventing eyelashes from touching the eye<sup>187</sup>. Epilation using high-quality forceps and with regular follow-up is recommended where an individual with TT either declines surgery or has no immediate access to it<sup>124</sup>. Some countries have been reluctant to

incorporate advice to epilate into their trachoma programmes based on concerns that it might further reduce surgical uptake. Evidence from Ethiopia suggests that programmatic support for epilation does not adversely affect the willingness of patients to consider future surgical management for TT<sup>188</sup>.

Although surgery is expected to primarily limit further loss of vision owing to ongoing corneal opacification, high-quality surgery can actually improve visual acuity compared with the pre-operative baseline<sup>177,189</sup>, presumably by reducing corneal oedema and tearing. TT surgery leads to marked decreases in pain, discharge and photophobia, improving both self-reported physical functioning and quality of life<sup>190,191</sup>, even in the absence of an improvement in visual acuity. Most PTT occurs within the first 12 months after surgery and subsequent incidence is low, suggesting that the longer-term prognosis for patients who have good outcomes at 1 year is relatively positive<sup>171,192</sup>.

### Antibiotics

Antibiotics are used to clear conjunctival *Ct*. Two alternative antibiotic regimens are recommended by WHO: 1% tetracycline eye ointment, instilled into the lower conjunctival sac of both eyes twice daily for 6 weeks, or a single oral dose of 20 mg azithromycin/kg body weight, to a maximum of 1 g (REF.<sup>117</sup>). Evidence for the effect of oral azithromycin is stronger than that for topical tetracycline<sup>193</sup>. Topical tetracycline treatment also has several disadvantages that limit adherence, including a prolonged treatment course, which cannot be completely observed by health-care workers. In addition, instillation into the conjunctival sac is difficult, and the ointment stings slightly on application and briefly blurs the vision after each administration. Oral therapy has the additional benefit of treating extra-ocular *Ct* infections that might otherwise be reservoirs for conjunctival recurrence<sup>68</sup>. Tetracycline eye ointment remains on the recommended list because it is very cheap, used in children aged <6 months of age, and is nearly universally available, whereas azithromycin is comparatively expensive if it is not donated.

The high intracellular concentration and long half-life of azithromycin are beneficial for single-dose treatment of *Ct*, which can only replicate intracellularly. Initial trials showed that oral azithromycin was at least as effective as topical tetracycline for clearing infection in individuals<sup>194,195</sup>. Efficacy in a single dose and the excellent safety profile enabled consideration of its use in MDA. The Azithromycin in Control of Trachoma trial in Egypt, Gambia and the United Republic of Tanzania demonstrated that azithromycin MDA led to greater reductions in *Ct* prevalence than topical tetracycline MDA<sup>84</sup>. This finding was supported by cohort studies demonstrating dramatic reductions in the prevalence and load of conjunctival *Ct* following azithromycin MDA<sup>29,196–198</sup>.

The goal of the A component is to clear infection from as much of the community as possible, rather than merely treating individuals with clinically apparent active trachoma. Annual<sup>199</sup> MDA is employed, with a target of  $\geq 80\%$  coverage of the population at each treatment

### Box 3 | The diagnostic approach in an epidemiological investigation

In a population-based survey or other epidemiological investigation, the clinician's primary responsibility to the individual survey examinee is to do no harm. Where diagnoses are made, the survey team has the responsibility of providing service or a pathway to service, but generating a comprehensive assessment of each examinee is generally not practical. A comprehensive assessment is also very difficult to fully standardize and is, therefore, inadmissible if trying to generate reproducible data. Thus, unlike the diagnostic process for an individual patient, information that is not in the survey protocol should not be used to weigh positive or negative findings.

In the morning of the day that the parent in the example provided in BOX 2 had intended to take the children to the eye clinic, a team undertaking a population-based survey visits the household. The team is only surveying districts suspected or known to be endemic for trachoma and no weight is therefore given to the presumed epidemiological status of the population. Individuals resident in the household are asked to consent to examination; demographic data but no individual histories are recorded. The first child is examined: the findings are recorded as right eye negative for trachomatous trichiasis (TT<sup>-</sup>), positive for trachomatous inflammation — follicular (TF<sup>+</sup>) and positive for trachomatous inflammation — intense (TI<sup>+</sup>); left eye TT<sup>-</sup>, TF<sup>+</sup>, TI<sup>+</sup>. The second child is examined: the findings are right eye TT<sup>-</sup>, TF<sup>-</sup>, TI<sup>-</sup>; left eye TT<sup>-</sup>, TF<sup>-</sup>, TI<sup>-</sup>. Both children could still be given antibiotics for active trachoma by the survey team as both have eye problems that are likely to benefit from treatment, but it is critically important for the integrity of the data collection exercise and the most accurate estimate of population-level prevalence that the second child is not recorded as having TF, TI or active trachoma.

Table 2 | GTMP and Tropical Data

Characteristic	GTMP	Tropical Data <sup>a</sup>
Dates of operation	December 2012–January 2016	February 2016 onwards
Survey types supported	Baseline	Baseline, impact, surveillance and TT-only
Funding	UK Department for International Development and US Agency for International Development	Core Tropical Data funding from the International Trachoma Initiative, Sightsavers and RTI International; countries are responsible for funding the surveys themselves with support from partners
Primary unit of reporting to funding agencies	Districts, as defined by the country, resulting in different population sizes and geographical areas	EUs, each comprising a population of ~100,000–250,000 people <sup>288</sup> , making process data more comparable
QA and QC	Developed and implemented globally standardized methodologies for epidemiologically robust population-based trachoma prevalence surveys with QA and QC at every step of the survey process <sup>125,126</sup>	Developed GTMP QA and QC methods further, including the incorporation of 3D goggles for TT training <sup>289,290</sup> ; incorporation of follicle size guides to aid TF diagnosis <sup>116</sup> ; and longer data recorder training, data recorder reliability test and greater emphasis on supervision <sup>128</sup>
Number of countries supported	29	45
Number of people examined	>2.6 million	>6.8 million
Number of evaluation units surveyed	905	2,200
Impact	Baseline mapping of all accessible suspected trachoma-endemic countries; active trachoma was confirmed to be a public health problem in 341 of 905 EUs (38%) surveyed; TT was confirmed to be a public health problem in 473 of 905 EUs (52%)	445 baseline, 1,036 impact, 491 surveillance and 141 TT-only surveys supported; helped confirm that MDA should be started or continued in 586 EUs; MDA was not needed in 332 EUs; MDA could be stopped in 638 EUs; and trachoma no longer a public health problem in 416 EUs

EU, evaluation unit; GTMP, Global Trachoma Mapping Project; MDA, mass drug administration; QA, quality assurance; QC, quality control; TF, trachomatous inflammation — follicular; TT, trachomatous trichiasis. <sup>a</sup>Data presented are for the first 5 years (February 2016–February 2021) of operation only.

round<sup>117</sup>. Azithromycin (specifically Zithromax, Pfizer, NY, USA) is donated to trachoma-endemic countries through the [International Trachoma Initiative](#)<sup>200</sup> and is offered as tablets to individuals who are both  $\geq 120$  cm tall and aged  $\geq 7$  years. Azithromycin suspension is given to children aged  $\geq 6$  months and  $< 7$  years and individuals  $< 120$  cm tall; suspension can also be taken by those older and taller than these thresholds if they have difficulty swallowing tablets<sup>201</sup>. The 20 mg/kg body weight dose of azithromycin is approximated using a dosing pole, up to the adult dose of 1 g (REFS<sup>129,201,202</sup>). Children aged  $< 6$  months are offered tetracycline eye ointment.

Determination by trachoma programmes of the need for antibiotic MDA is based on evaluation unit-level prevalence of TF in those aged 1–9 years. If prevalence is  $\geq 30\%$ , the evaluation unit is offered five annual rounds of antibiotics and then re-evaluated with a repeat population-based survey undertaken at least 6 months after the last round. If prevalence is 10–29.9%, the evaluation unit is offered three annual rounds, and if prevalence is 5.0–9.9%, a single round. Antibiotic MDA should be discontinued in evaluation units in which the TF prevalence, estimated through adequately powered prevalence surveys, is  $< 5\%$ .

The incidence of adverse events, such as local irritation or skin reactions, with the use of tetracycline eye ointment is extremely low. Azithromycin is also very well

tolerated. In MDA programmes, the overall incidence of reported adverse events following single-dose azithromycin treatment is  $< 10\%$ <sup>203,204</sup>. Most symptoms are minor and gastrointestinal, including abdominal pain, nausea, vomiting and diarrhoea<sup>18,19</sup>. In general, the incidence of adverse events increases with increasing age; in children aged  $< 6$  months participating in a study of azithromycin MDA for prevention of mortality, the prevalence of adverse events did not significantly differ between children receiving azithromycin or placebo<sup>205</sup>. Azithromycin MDA may have additional benefits for children, including reducing all-cause mortality (by 13.5% in the largest cluster-randomized trial<sup>206</sup>) and the burden of some specific pathogens beyond *Ct*, including *Streptococcus pneumoniae*, *Campylobacter* spp., *Treponema pallidum* subsp. *pertenue* (the causative agent of yaws) and *Plasmodium* spp.<sup>206–216</sup>. Although observational studies have suggested a relationship between azithromycin use and risk of cardiovascular death in adults in the USA<sup>217</sup>, a randomized study of MDA in Ethiopia found no increase in adult mortality in communities receiving azithromycin compared with those receiving placebo, nor did it find a difference in mortality between individuals aged  $\geq 30$  years who took azithromycin and those who did not<sup>218</sup>.

To date, substantial macrolide resistance in *Ct* has not been documented following azithromycin MDA for trachoma<sup>219–221</sup>. Some evidence of selection for



resistance in non-target organisms exists<sup>193,222</sup>. In nasopharyngeal *Streptococcus pneumoniae* collected from population-based samples of children, an increase in macrolide resistance has been found following azithromycin MDA, followed by a reduction in resistance when MDA was discontinued, removing selection pressure<sup>223,224</sup>. Selection for resistance in other potentially pathogenic organisms, including *Escherichia coli* and *Staphylococcus aureus*, has also been documented<sup>224–228</sup>.

#### Facial cleanliness and environmental improvement

The goal of the F and E components of the SAFE strategy is to reduce the transmission of conjunctival *Ct*. For F, the ‘theory of change’ holds that clean faces reduce the amount of infected eye and nose discharge available for transfer to fingers, fomites and flies, and reduce the attractiveness to female *M. sorbens* of both infected and uninfected eyes. Like the disappearance of trachoma from Europe and North America<sup>12</sup>, the elimination of trachoma as a public health problem in the Islamic Republic of Iran has been attributed to improvements in hygiene and environmental health<sup>229</sup>. Multiple cross-sectional studies consistently show an association between a lack of facial cleanliness and the increased probability of having active trachoma<sup>57–59</sup>. However, these studies are limited both in temporality and by the potential for unmeasured confounding.

The evidence base for the efficacy of interventions to improve facial cleanliness is not strong. A pair-matched, community randomized trial in the United Republic of Tanzania found no significant evidence that a hygiene promotion intervention designed to improve face washing among children reduced TF prevalence<sup>230</sup>. In this trial, the hygiene promotion intervention did reduce the prevalence of a marker of very severe active trachoma, the key driver to scarring, and having a clean face on multiple visits was protective against active trachoma. There is potential for reverse causality or unmeasured confounding between sustained facial cleanliness and active trachoma outcomes. A more recent cluster-randomized trial in Ethiopia found no evidence of an effect of hygiene promotion on the prevalence of conjunctival *Ct* infection in young children<sup>231</sup>. Interventions promoting facial cleanliness may be limited by difficulties in achieving sustained behaviour change, which is unlikely to be achieved using the approaches employed by most contemporary trachoma programmes<sup>232,233</sup>. Because evidence of efficacy for any particular intervention is weak, it is difficult to offer programmes an evidence-based recommendation to alter their approach; instead, it is only possible to observe that current approaches are not in accordance with established theory on behaviour change<sup>234</sup>.

Environmental improvement interventions attempt to increase access to water and the means to safely dispose of human faeces. Theoretically, increased water access could improve personal hygiene, including face and hand cleanliness, and thereby decrease transmission, while improved sanitation could reduce the abundance of *M. sorbens*, which lays eggs on human faeces left exposed on soil<sup>70</sup>. The water used for personal hygiene does not necessarily have to be potable: seawater, for

example, would (at least in theory) also be effective. Unfortunately, community randomized trials in Ethiopia and the Gambia have not provided evidence that the provision of latrines reduces the prevalence of active trachoma or conjunctival *Ct* infection<sup>235–237</sup>. Similarly, evidence for the effectiveness of improving access to water on trachoma markers is inconclusive, lacking support from community randomized trials<sup>231,237</sup>.

Although a firm evidence base for the F and E components of SAFE is lacking<sup>237,238</sup>, access to water and sanitation is thought to be important for the management of many other neglected tropical diseases<sup>239</sup> as well as being a fundamental human right. A rights-based approach mandates us to continue to promote the F and E components of SAFE while simultaneously encouraging further research on specific interventions designed to reduce transmission of conjunctival *Ct*.

#### Quality of life

Active trachoma does not impair vision. Individuals with active trachoma tend to report mild eye irritation, perhaps accompanied by a small amount of eye discharge that may cause eyelash crusting. Because these symptoms are common in trachoma-endemic populations and because the peak prevalence of active trachoma is in young children, these symptoms often go unremarked<sup>110</sup>.

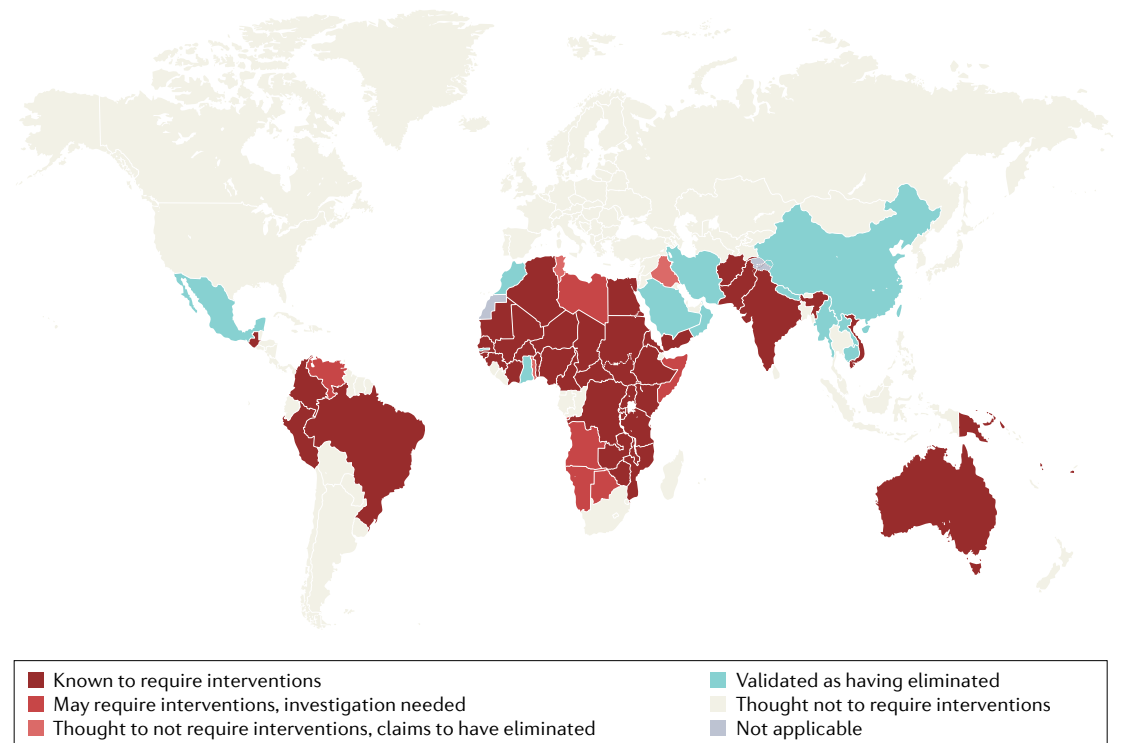
Conjunctival scarring causes progressive drying of the eyes<sup>240,241</sup>. This is associated with pervasive eye discomfort and fluctuating visual disturbances that can affect daily activities. Paradoxically, scarring of the lacrimal canaliculi can also lead to epiphora (apparent excessive watering of the eyes), as the normal drainage of the conjunctival sac is impaired and tear fluid escapes onto the cheeks<sup>242</sup>. Either dry eye or epiphora can have a considerable negative impact on quality of life<sup>243,244</sup>.

TT is painful to the point of being debilitating, even without objective loss of visual acuity. It has profoundly negative effects on quality of life, psychological health, productivity and social standing<sup>9,112,113</sup> that persist for as long as TT is present. For example, when assessed using WHO-recommended instruments, individuals with TT in Amhara Region, Ethiopia, had a substantially lower overall quality of life (mean 34.5 versus 64.6;  $P < 0.0001$ ) and health satisfaction (mean 38.2 versus 71.7;  $P < 0.0001$ ) compared with control individuals matched for age, gender and location. These associations are present even in subgroups of patients and control individuals with normal visual acuity<sup>112</sup>. Surgery for TT improves the quality of life regardless of whether it improves vision<sup>9,113,191</sup>.

#### Outlook

##### Progress against trachoma to date

From 2002 to 2021, the estimated number of people with trichiasis worldwide fell from 7.6 million to 1.8 million, a decrease of 77%. In the same period, the estimated number of people living in areas that warranted treatment with the A, F and E components of the SAFE strategy for trachoma elimination purposes fell from 1.5 billion people to 136 million, a decrease of 91%<sup>17,245</sup>. Of the 2021 total, 116 million lived in the WHO African region. Ethiopia was the most affected country, where



**Fig. 5 | Trachoma endemicity status of WHO Member States.** As of March 2022, 44 countries were known to require interventions to eliminate trachoma as a public health problem, 7 required investigation to determine whether interventions are required, 3 claimed to have eliminated trachoma as a public health problem, and 12 had been validated as having eliminated trachoma as a public health problem. The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the authors or the institutions with which they are affiliated concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Adapted with permission from REF.<sup>291</sup>, World Health Organization (WHO).

67 million people were at risk of trachomatous blindness. As of March 2022, WHO had validated 12 countries as having eliminated trachoma as a public health problem: Cambodia, China, Gambia, Ghana, the Islamic Republic of Iran, Lao People's Democratic Republic, Mexico, Morocco, Myanmar, Nepal, Oman and Saudi Arabia<sup>17,246</sup> (FIG. 5). Despite this undoubtedly encouraging progress, it is important to acknowledge that the December 2020 deadline for the global elimination of trachoma as a public health problem, agreed in 1996 (REF.<sup>247</sup>), was missed; the target date has now been reset to 2030 (REF.<sup>1</sup>). Of note, progress has been heterogeneous and elimination has proven difficult to achieve in some areas. This is further discussed below.

#### **Future progress against trachoma**

Elimination as a public health problem is a considerably more modest public health goal than eradication, which requires the permanent reduction to zero of the worldwide incidence of an infection<sup>248</sup>. At an international meeting in 2019, most of the trachoma stakeholders who were present and surveyed believed trachoma could actually be eradicated at some future date<sup>249</sup>. Others believe that setting such a goal would not be in the best overall interest of global health, since the opportunity cost might be considerably greater than the immediate public health benefit<sup>250</sup>. This issue (like all other issues related to future progress against trachoma) will benefit

from continuing input from all relevant stakeholders, particularly national programme managers. If eradication was to be targeted, improvements in surveillance systems, increased funding, enhanced community engagement and the absence of emergent antibiotic resistance (or development of an infection-blocking vaccine) may be pre-requisites<sup>249</sup>.

An effective *Ct* vaccine would certainly change the landscape for trachoma. Although 100 years of work on chlamydial vaccines have not yet generated an effective product, encouraging data have emerged from a phase I trial of a recombinant protein subunit vaccine targeting the major outer membrane protein of *Ct*<sup>161</sup>. The lack of established immunological correlates of protection<sup>161</sup> and the relative difficulty of determining disease-related outcomes in the urogenital tract suggest that future partnership of vaccine developers with trachoma programmes may be rewarding: the protection offered by an effective vaccine will be easier to observe in the conjunctivae.

In addition to the further efforts to develop and make available an efficacious future vaccine, weaknesses of current programmes need attention, as several types of measurement error put further progress at risk.

The imperfect predictive power of TF prevalence as a marker for *Ct* infection at the population level hampers progress; evaluation of indicators of conjunctival *Ct* transmission intensity other than TF prevalence is

an area of growing interest. Serological indicators may have an application in monitoring for recrudescence after antibiotic MDA has been discontinued, including in post-validation surveillance<sup>251–253</sup>. Programmes need guidance on optimal strategies to detect possible recrudescence but evidence on which to base this guidance is currently limited. Serosurveys would be one possible approach. However, currently assayed anti-*Ct* antibodies are not specific for trachoma *Ct* strains; thus, serosurveillance approaches using these antibodies would need to be driven primarily by data from children who have cleared maternal antibodies and not yet reached the age of sexual debut and would need to accept the contribution of inclusion conjunctivitis to population-level seropositivity. Identification of an anti-*Ct* antibody specific to trachoma strains would be a major step forward in the utility of serosurveillance.

Another measurement issue arises from the difficulty of estimating the prevalence of a rare condition. Despite assiduous attention to epidemiological principles in survey design and implementation of quality control and quality assurance tools<sup>126</sup>, prevalence estimates generated by surveys remain estimates, subject to error. This becomes particularly important when public health decisions are made against fine margins as is inevitably the case when measuring progress against the elimination prevalence threshold (0.2%) for TT. The use of a geospatial rather than traditional frequentist statistical approach enables the harnessing of spatial correlation in prevalence data and may therefore improve the accuracy of TT prevalence estimates<sup>254</sup>.

In addition, important questions about each component of the SAFE strategy remain to be answered. For the S component, data on the best approaches for managing PTT are needed as, even in the best hands, at least 10% of individuals who receive surgery for TT will commonly develop PTT<sup>167</sup>. Based on available global data, at least 180,000 individuals who had TT in June 2021 (REF.<sup>17</sup>) will need further surgical management after their primary operations. In most settings, patients with PTT are currently managed with the same procedure that they initially received to manage their TT. Two surgical approaches for correcting PTT are currently being investigated in a clinical trial<sup>255</sup>, PLTR and the Bevel-Rotation Advancement Procedure (B-RAP)<sup>256</sup>. PLTR involves a partial-thickness incision followed by rotation of the distal fragment to return eyelashes to their normal anatomical position. In doing so, the distal and proximal tarsal fragments are overlapped, creating a thicker tarsus, which may be more likely to result in an eyelid contour abnormality. B-RAP is a new procedure designed to overcome this issue by creating a bevelled incision of the tarsus, dissecting between the anterior and posterior lamellae and removing scar tissue. This approach enables the marginal rotation to be combined with a posterior lamellar advancement and a reduction in eyelid thickness. Additionally, some countries are beginning to recommend epilation as a definitive management strategy for PTT in which just one or two eyelashes touch the sclera temporal or nasal to the cornea<sup>257</sup>.

For countries to clear their TT surgery backlogs, efficient case-finding strategies are needed. The use

of machine learning to develop image recognition software for TT identification is currently under way, which has the potential to improve broad-scale screening for TT. Similar programmes are also being developed for the identification of active trachoma<sup>258</sup>. As TT becomes less common, strategies for ensuring access to high-quality surgery for all who need it will continue to be important. This will require surgeons to maintain their skills through regular practise on simulators, and potentially other creative solutions for delivering integrated, people-centred services<sup>259</sup> to a progressively more scattered population in need.

For the A component, research priorities depend on local epidemiology. In areas where *Ct* transmission persists despite years of implementation of A, F and E, such as some areas of Ethiopia<sup>260</sup>, new strategies (within the A, F or E components) for reducing community transmission of conjunctival *Ct* are needed<sup>18</sup>. In these areas, multiple rounds of annual azithromycin MDA may have produced a new equilibrium wherein transmission continues but at lower levels than at baseline. Although increased antibiotic pressure, such as through more frequent MDA or a higher target antibiotic coverage, could hypothetically reduce infection prevalence, community randomized trials in Ethiopia and Niger have not consistently found empirical support for this theory<sup>261–265</sup>. However, in one trial in Ethiopia, quarterly treatment offered only to those aged 1–10 years achieved lower conjunctival *Ct* prevalence than annual MDA to people of all ages<sup>266</sup>, and evidence of a herd protection effect was noted with reduced *Ct* prevalence in untreated older children and adults<sup>267</sup>. This is likely to be a demonstration of a ‘core group’ effect in local transmission dynamics, in which suppression of transmission from and between children prevents infection from sustaining an equilibrium level in the population as a whole<sup>268</sup>. Further studies are needed.

Work is also required to determine how to identify where (or even whether) antibiotic MDA is needed in evaluation units in which the TF prevalence is around the 5% elimination threshold. In communities in the United Republic of Tanzania with a baseline TF prevalence of 5.0–9.9% randomized to a single round of antibiotic MDA or no treatment, no difference in TF prevalence after 12 months was observed between study arms<sup>269</sup>. Longer-term study of the need for antibiotics in evaluation units where trachoma is disappearing or where the prevalence of TF seems to be rising again after antibiotic MDA discontinuation would provide greater insight into where and how antibiotics should be used for trachoma<sup>270</sup>. Tests for *Ct* infection need further exploration as potential guides for decision-making<sup>271</sup>.

For the F and E components, a better understanding of *Ct* transmission and reliable markers of sustained facial cleanliness would help in the testing of candidate interventions and assessment of programme effectiveness<sup>272–274</sup>. A community randomized trial of combined facial cleanliness and environmental improvement interventions did not prevent recrudescence in conjunctival *Ct* infection prevalence after antibiotic MDA was discontinued in a trachoma hyperendemic population<sup>231,275</sup>, but it is important to note that

coverage of interventions fell short of the 80–90% that models indicate might be a threshold for effectiveness<sup>65</sup>. Randomized controlled trials of WASH interventions are challenging to undertake, both logistically and in terms of achieving the transformative change in WASH access and use that is probably important<sup>276</sup>. However, such trials are essential to evaluate how best to deliver the F and E components to achieve sustained progress against trachoma. When washing the face, the use of soap may be important<sup>277</sup>.

The SAFE strategy is a combination of measures intended to prevent visual impairment from trachoma at multiple levels. Prevention of iatrogenic harm is also important and can be achieved through maintaining high-quality surgery and exercising good antibiotic stewardship. Surgical quality should be maximized through improvements in training, support, supervision and audit<sup>184,278,279</sup> of surgeons as well as consideration of who to operate on<sup>188</sup>. Good antibiotic stewardship involves avoidance of unnecessary antibiotic distribution<sup>280</sup>. Minimization of pressure driving the development of antimicrobial resistance<sup>222</sup> is growing in importance. Developing better tools for characterizing the population-level need for anti-*Ct* antibiotics for trachoma elimination purposes should help. Greater attention to

visual rehabilitation and disability inclusion for those whose sight has already been affected by trachoma<sup>281</sup> also needs to be built into programmes. The effects of COVID-19-related interruptions to community-based work on trachoma have yet to be empirically determined; models suggest that these may be considerable<sup>282,283</sup>.

### Beyond trachoma

In January 2021, WHO published the road map for neglected tropical diseases 2021–2030 (REF.<sup>1</sup>). A neglected tropical disease research and development blueprint, to be published as a companion document, is being prepared. Research needs for trachoma, including some of the questions identified above, will form part of this. A common issue for all neglected tropical diseases will be how best to integrate what have often been relatively disease-specific programmes to achieve maximum efficiency, and how to further combine those efforts into a whole-of-health-system approach in collaboration with other sectors<sup>284–287</sup>. It is our hope that further characterizing the research needs of trachoma in this way, and then fulfilling those needs, will lead to a 2030 world in which trachoma is no longer a public health problem.

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