

Trachoma

David Harris 2023

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What?

- keratoconjunctivitis
- caused by *Chlamydia trachomatis* infection

- Aka.
 - granular conjunctivitis
 - Egyptian ophthalmia

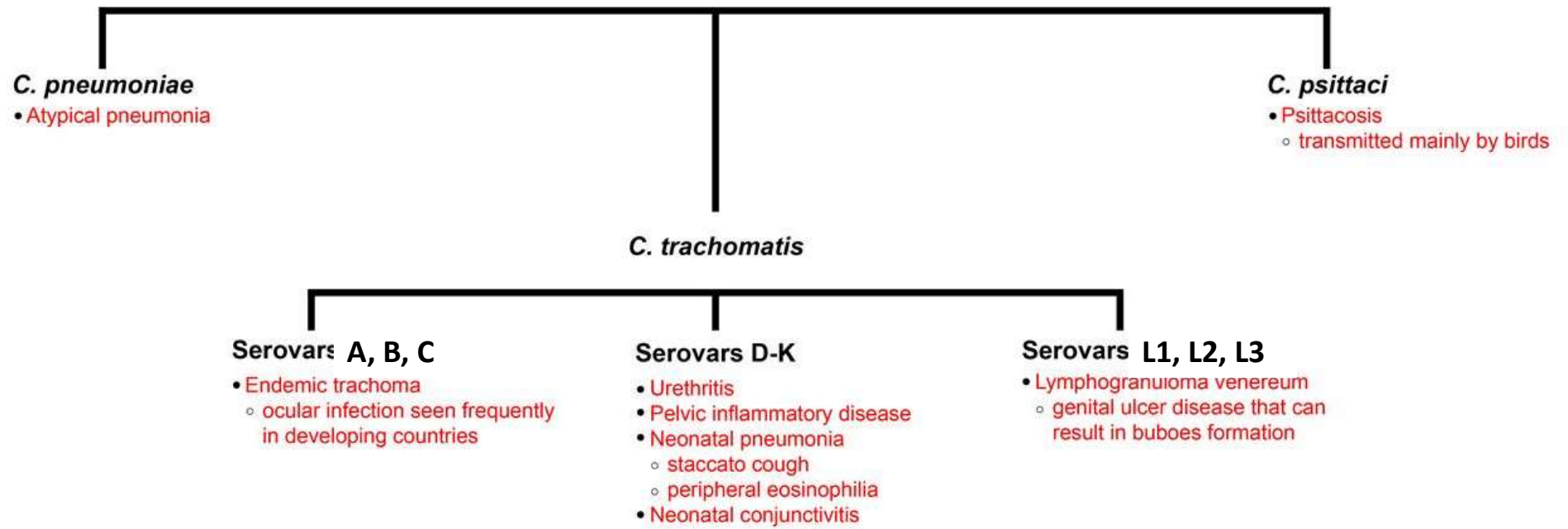
- in 1998, the WHO targeted the global elimination of trachoma as a public health problem. 2020 was the target date.
- The NTD road map 2021–2030, endorsed by the World Health Assembly set 2030 as the new target date for global elimination.

Etiology and Pathogenesis

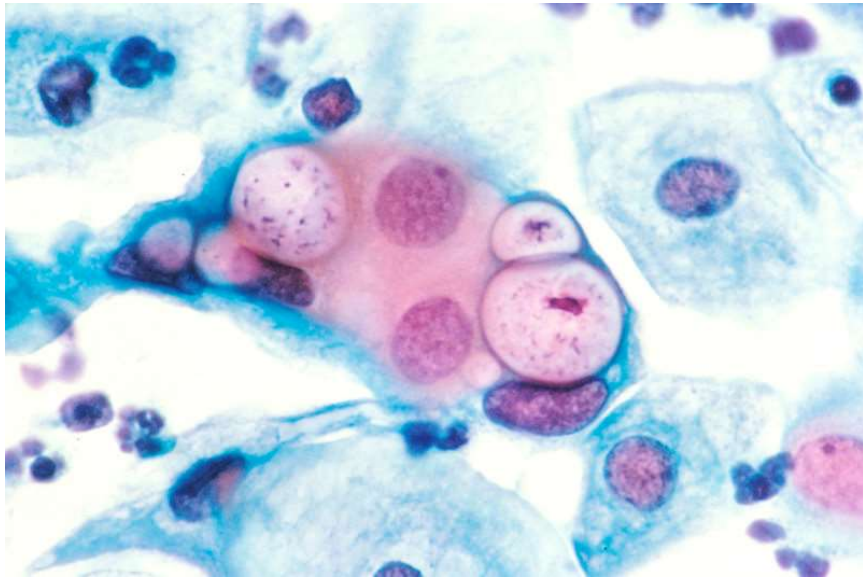
- Etiology
 - Chlamydia trachomatis serovars A, B, Ba, C
 - Chlamydia trachomatis can survive on dry inanimate surfaces for up to 3 hours in humid conditions
- Pathogenesis
 - repeated infections cause increased inflammation and damage to eyes

Chlamydia

Obligate intracellular organism



Chlamydia trachomatis

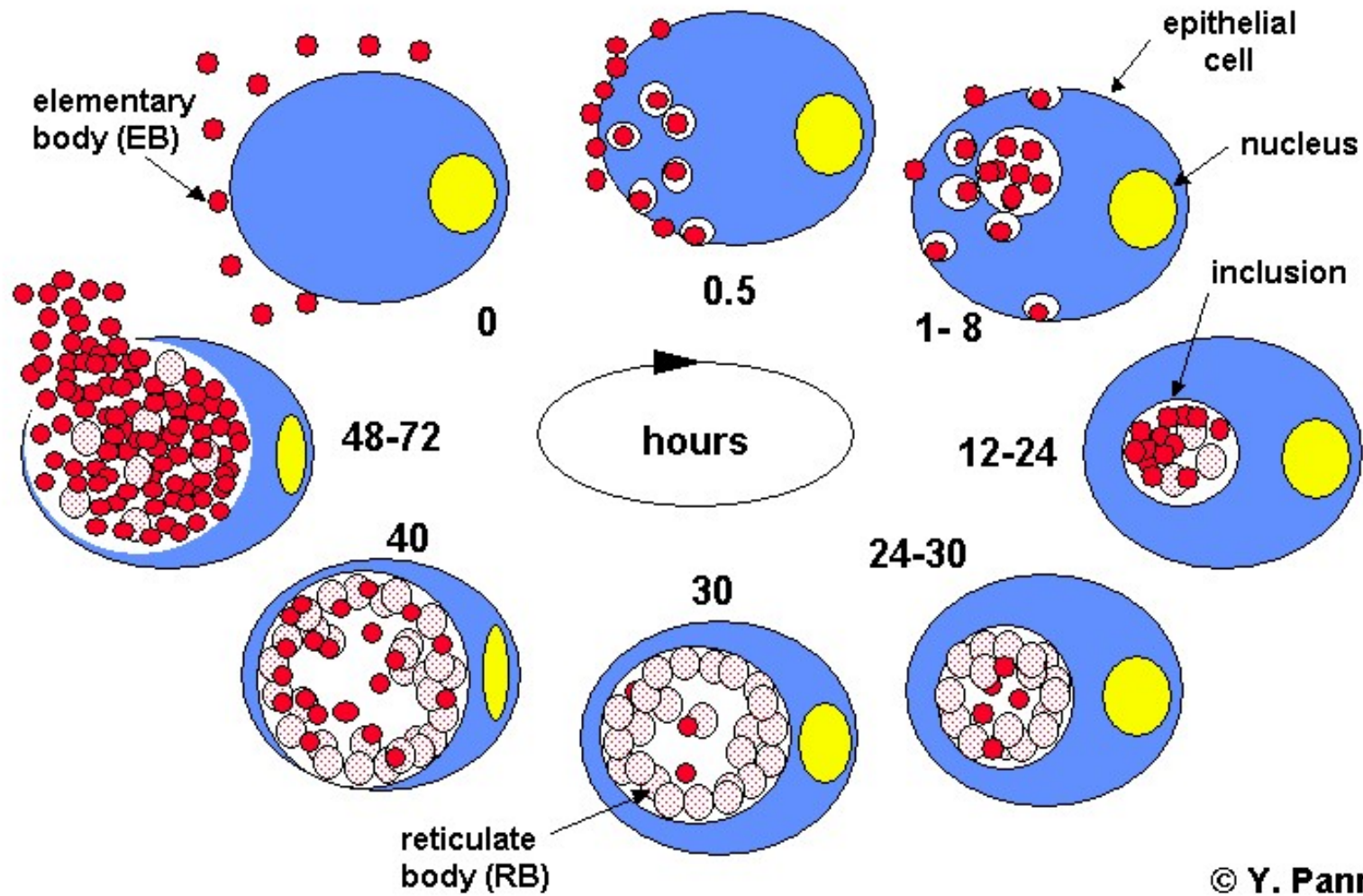


- an obligate intracellular bacterium
- mainly infects ocular and genitourinary epithelium.
- Has one of the smallest bacterial genomes (less than a fifth of the genes in *Escherichia coli*) - lost enzymes and metabolic pathways for nutrients that are readily available from the host cell
 - (Other common obligate intracellular bacteria include *Rickettsia* and *Coxiella*, which also have small genomes)

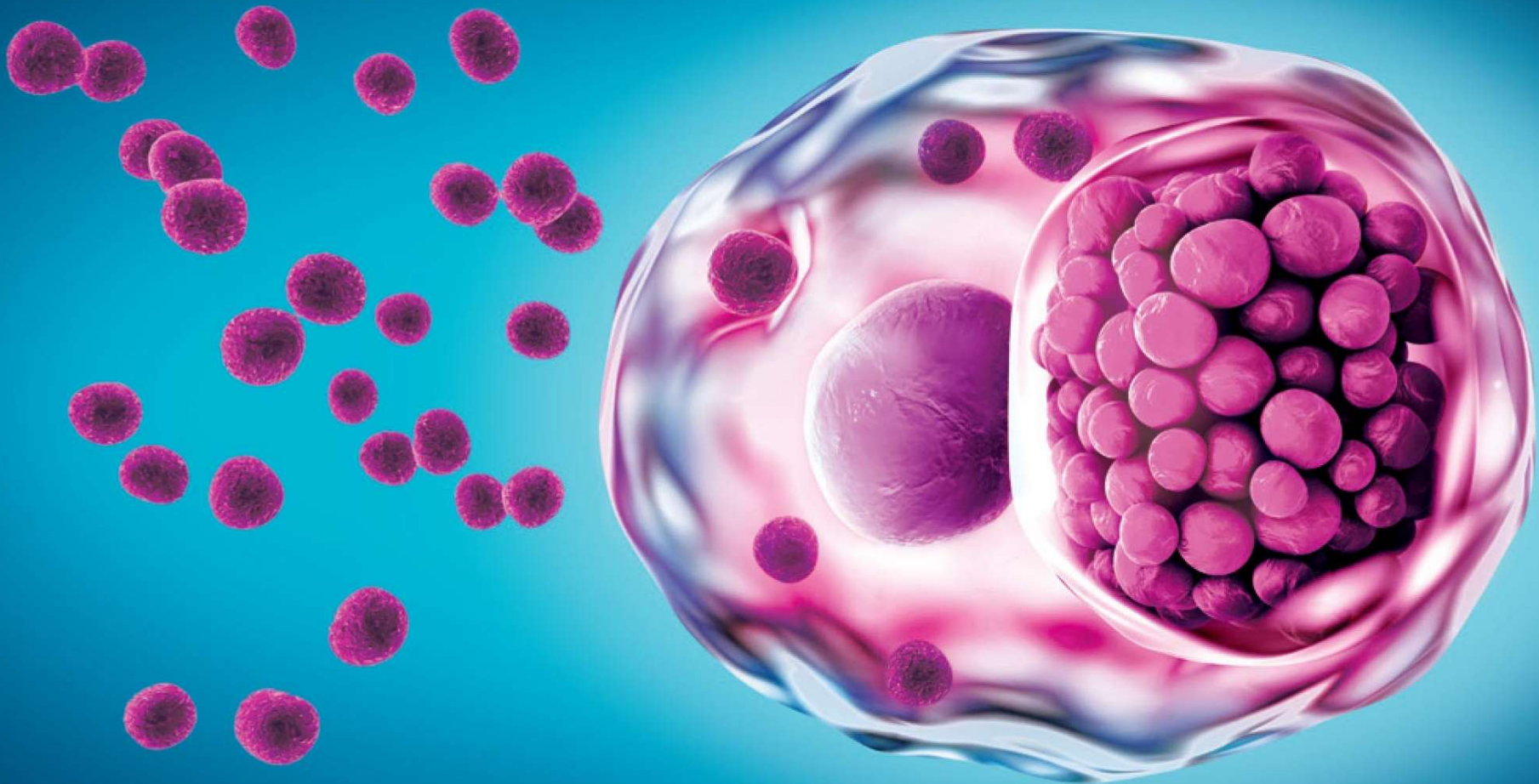
Chlamydia trachomatis

- two developmental forms
 - The elementary body (EB) is the transmissible form that attaches to and enters a susceptible epithelial cell to initiate the intracellular infection
 - Within a membrane-bound vacuole called the chlamydial inclusion, the EB converts into a reticulate body (RB) by 6 to 8 hours of entry.
 - The RB is the replicative form that divides by binary fission for a total of 8 to 10 doublings to yield 100 to 1000 progeny per infected cell.
 - Late in the infection, at about 24 hours after entry, RBs begin an asynchronous conversion into EBs for release to infect new host cells.

Developmental cycle of *C. trachomatis*

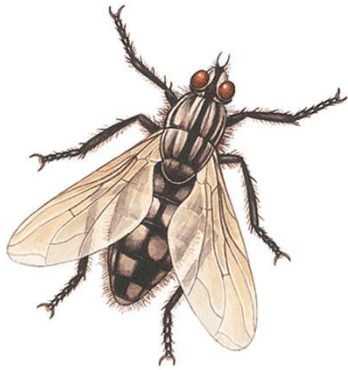


Developmental cycle of *C.trachomatis*



Transmission

- Transmission occurs by hand-to-eye contact between children and their caregivers or by contact with the feet of flies, which feed on the exudate from children with active conjunctivitis and act as a mechanical vector.

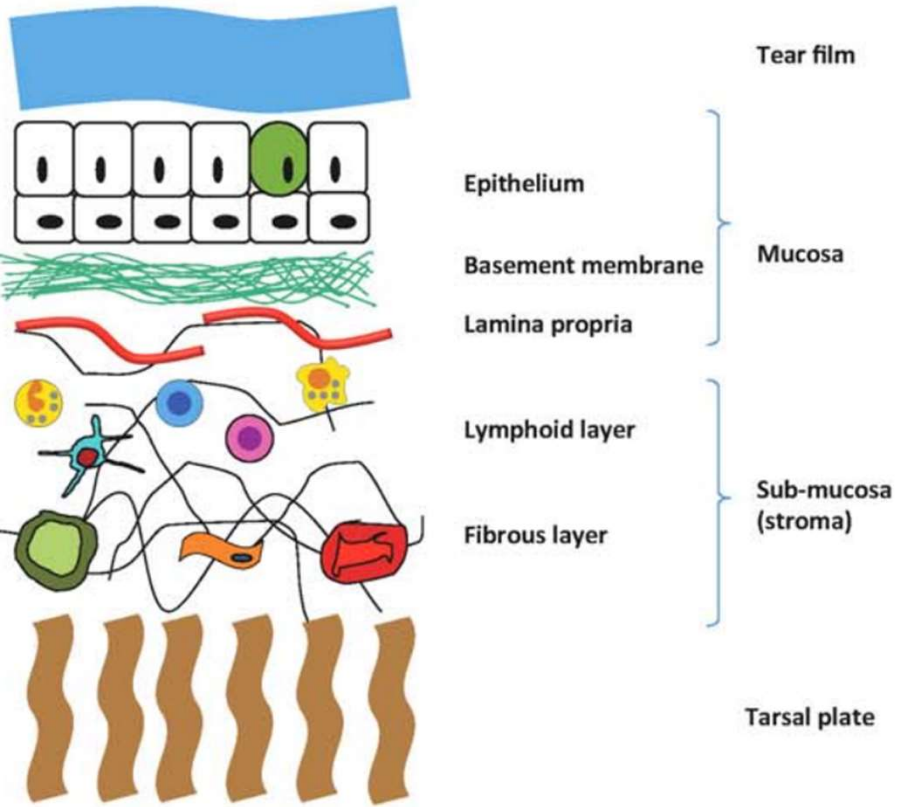


Trachoma

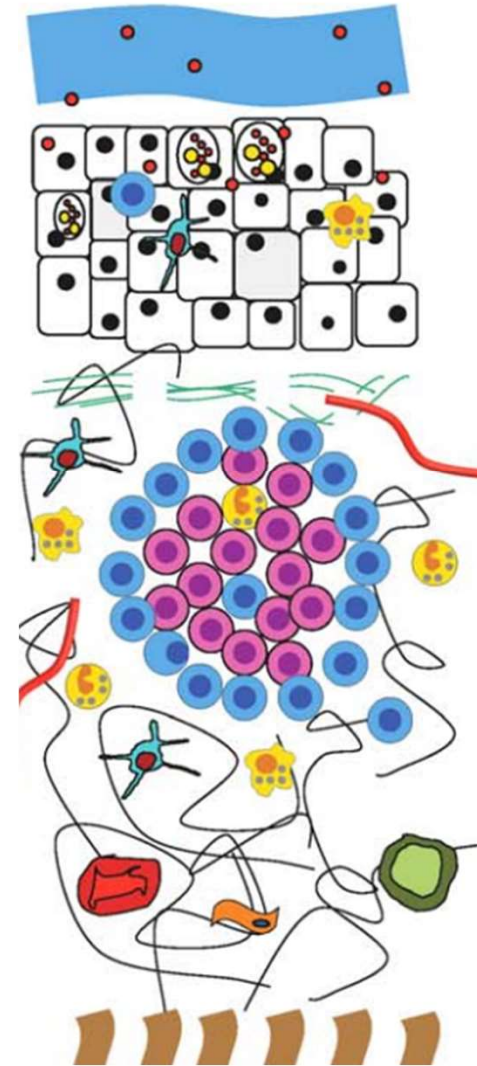
- Infection by *Chlamydia trachomatis* causes conjunctivitis
- Repeated infections causes scars on the eyelid
 - contraction and shortening of the eyelid
 - turning inward of the lid margin, touching the cornea
 - cornea trauma
 - vision is lost



A. Normal conjunctiva



B. Active disease



C. Trachomatis elementary bodies are taken up by active transport into epithelial cells where they transform into reticulate bodies and multiply by binary fission

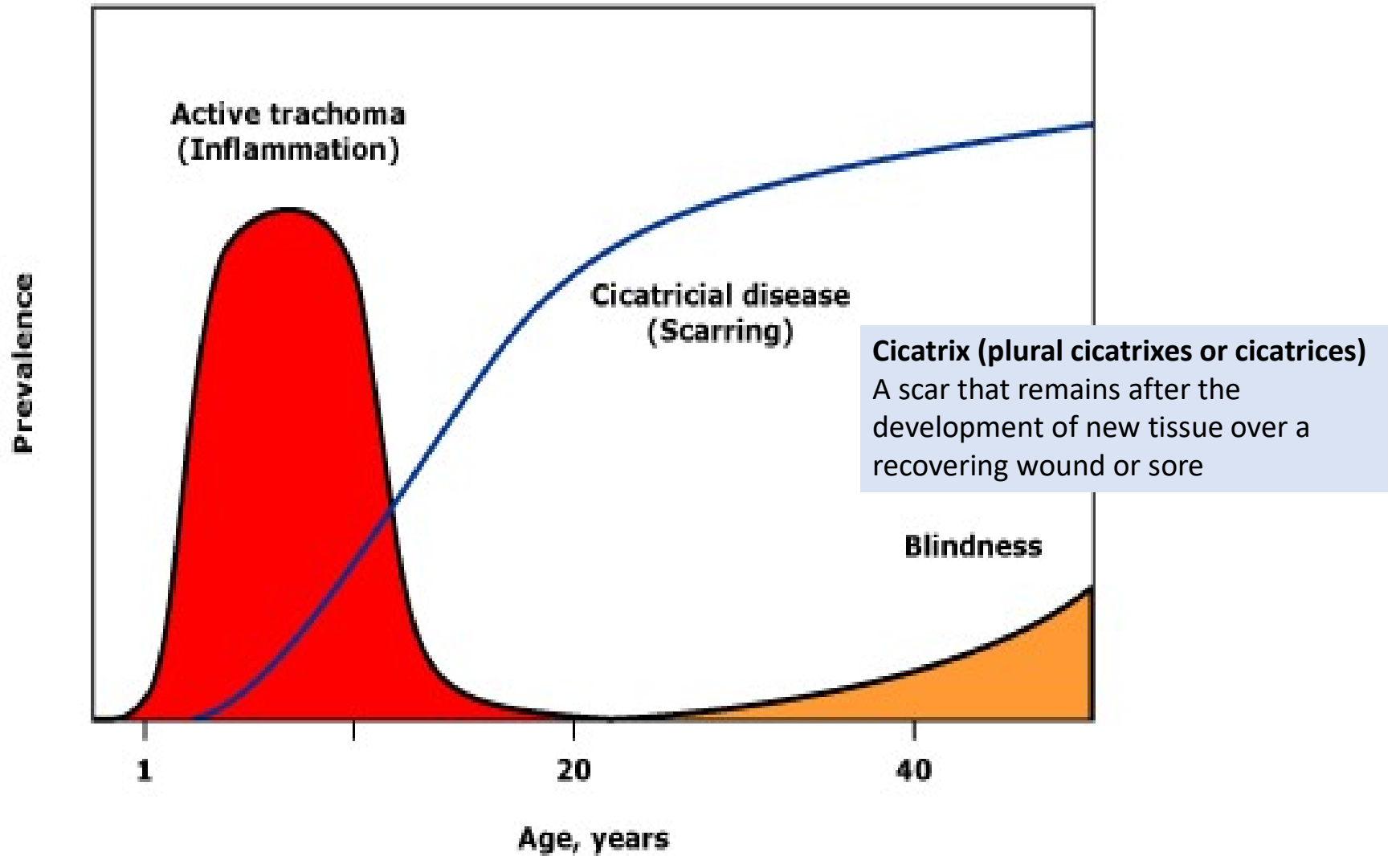
Hyperplasia of the epithelium develops and a mixed inflammatory cell infiltrate is seen within it.

The basement membrane is disrupted by MMPs released by inflammatory cells.

Lymphoid follicles form which are composed largely of B cells and are surrounded by a lymphocytic mantle. In the surrounding tissue a mixed infiltrate of leucocytes is seen.

Type V collagen, not normally seen in the conjunctiva, is deposited. There is also increased amounts of types I, III and IV collagen.

Hu VH, Holland MJ, Burton MJ (2013) Trachoma: Protective and Pathogenic Ocular Immune Responses to Chlamydia trachomatis. PLoS Negl Trop Dis 7(2): e2020.



History

- 2000 B.C. trachoma prevalent in Egypt (Egyptian ophthalmia)
- 19th century: trachoma prevalent in Europe & North America, as well as Middle East and Africa

History

- Early 20th century: trachoma was a leading exclusion criteria for immigrants coming to the North America



BROWN BROTHERS (TOP); KEYSTONE/MAST COLLECTION, UNIVERSITY OF CALIFORNIA

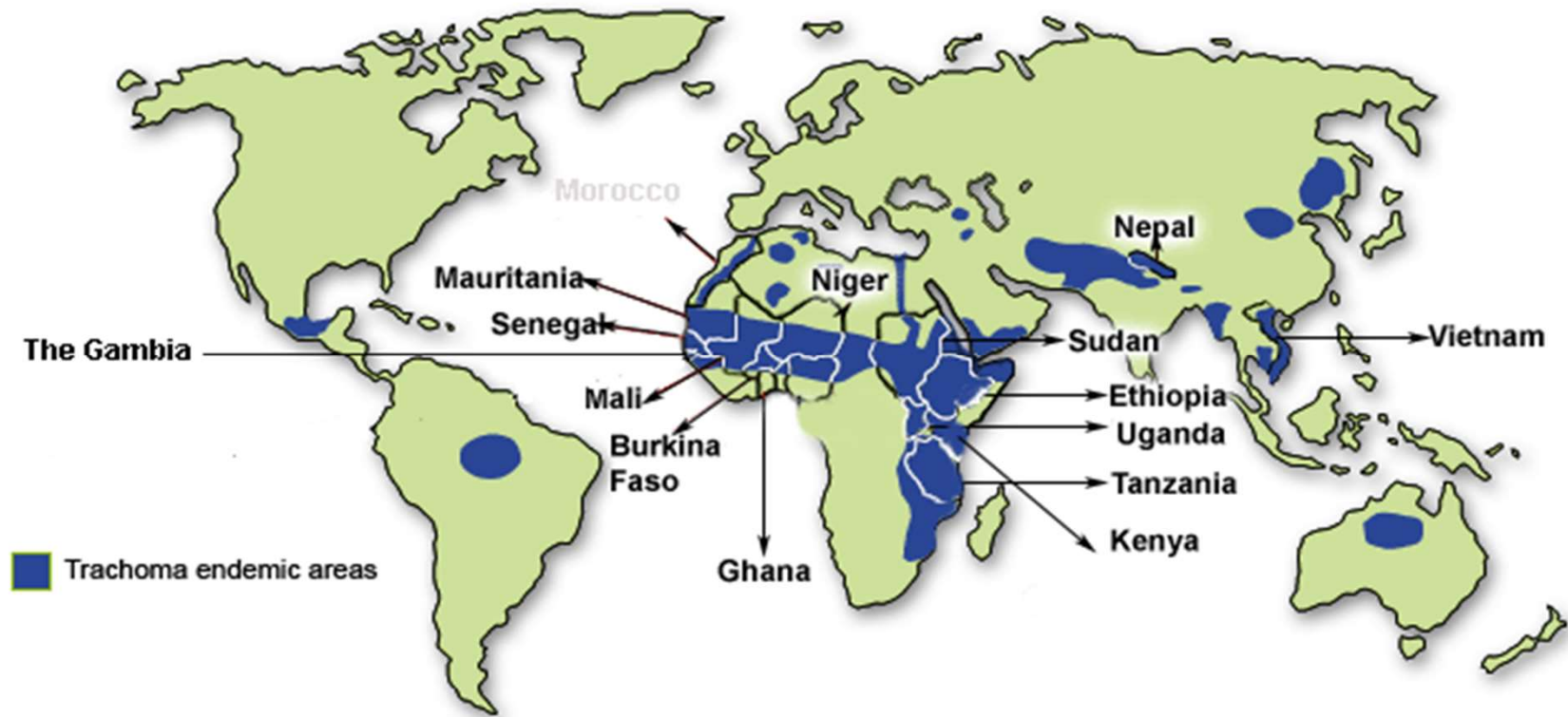
Epidemiology

- Cases worldwide, but endemic in **Africa, Middle East, parts of Asia**
- 2007 - Active trachoma affects an estimated 84 million people
 - 7.6 million have end-stage disease,
 - 1.9 million are blind
- 2021 - 137 million people live in trachoma endemic areas and are at risk of trachoma blindness



Epidemiology

- It is a public health problem in 44 countries.



Epidemiology

- Trachoma is a disease of children:
 - children < 10 years old and children with intense inflammatory trachoma may represent major source of infection in endemic communities
 - Clinically, the highest prevalence of active disease is noted in young children.
- Women blinded up to 3 times more than men

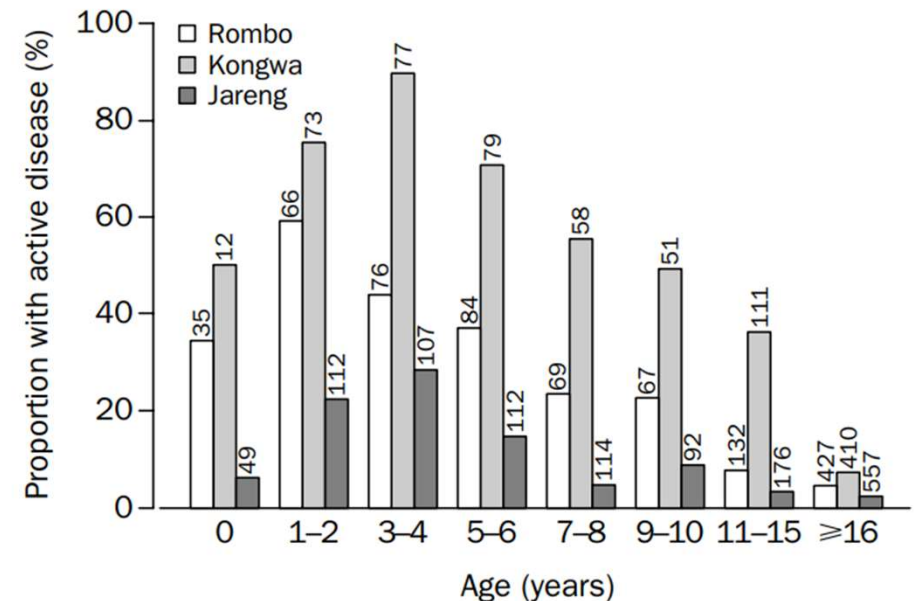
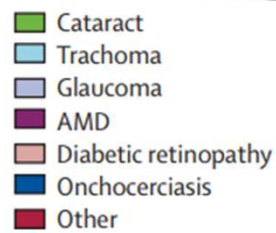
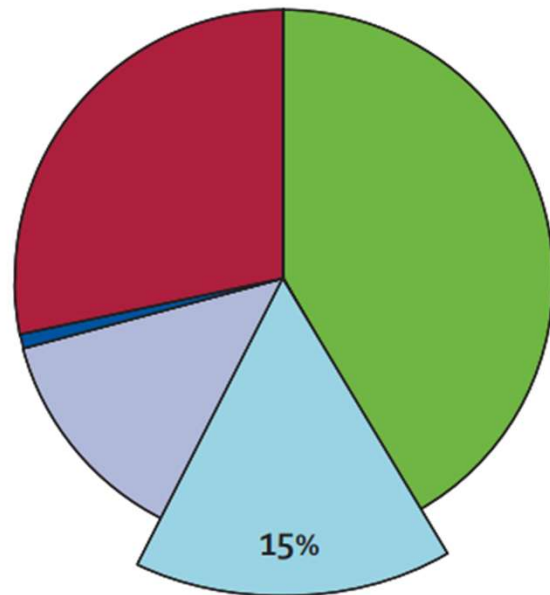


Figure 1: **Prevalence of active disease (TF, TI, or both in the swabbed eye) by age group and site**

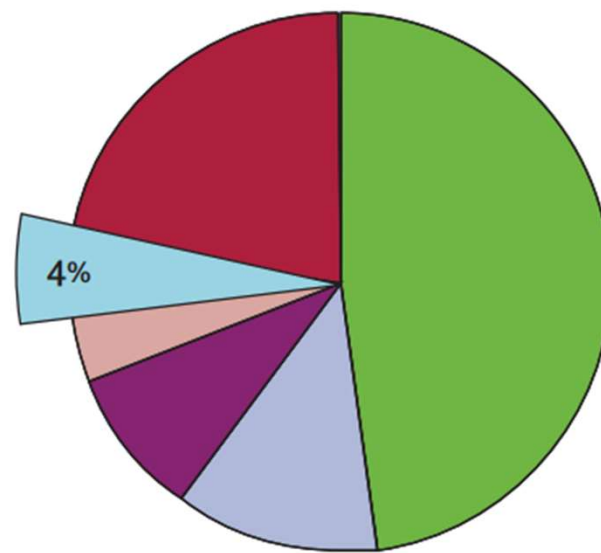
Number above every bar is the number of people sampled in that age group at that site.

Leading cause of preventable blindness

1995

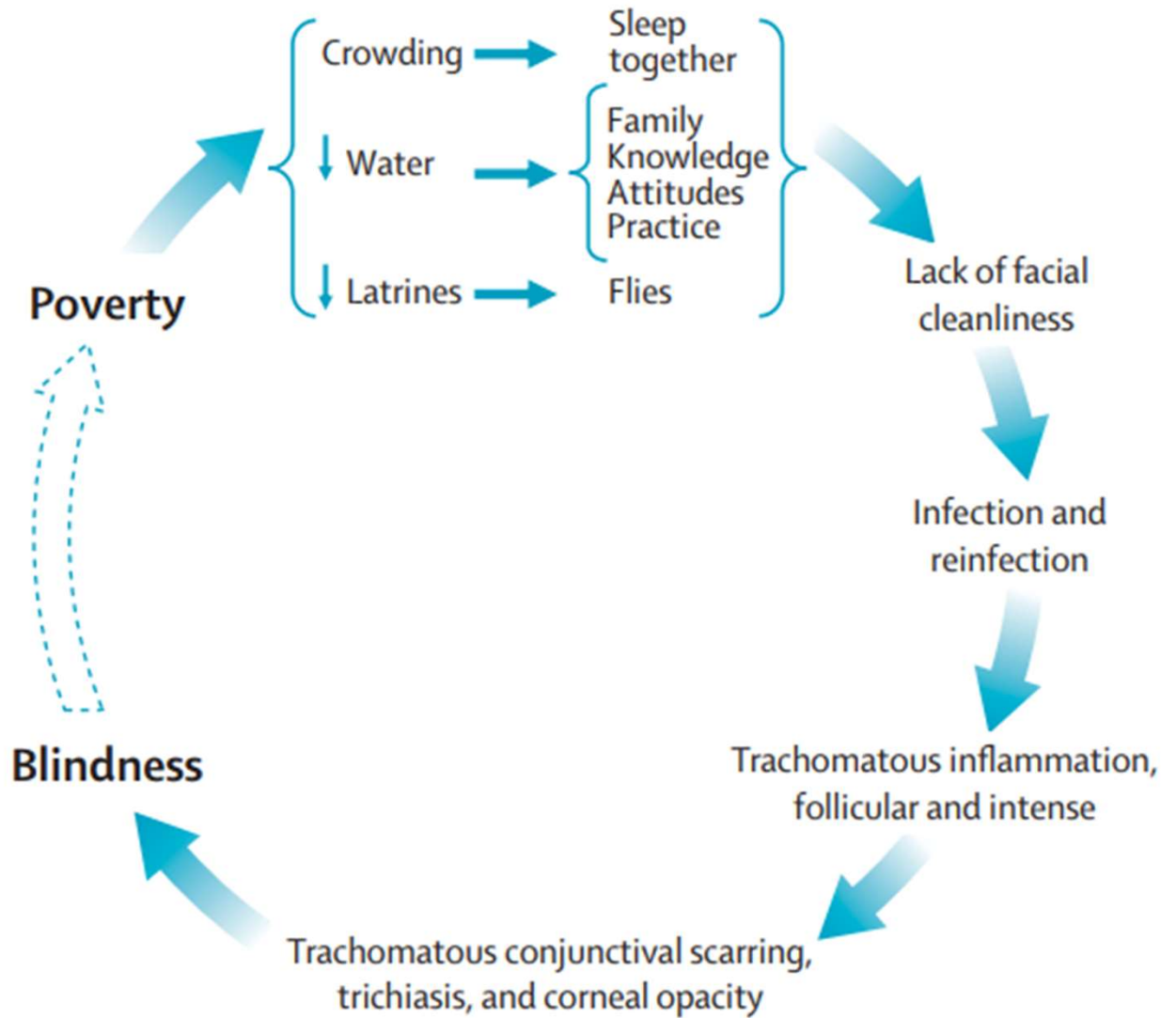


2004



Risk Factors

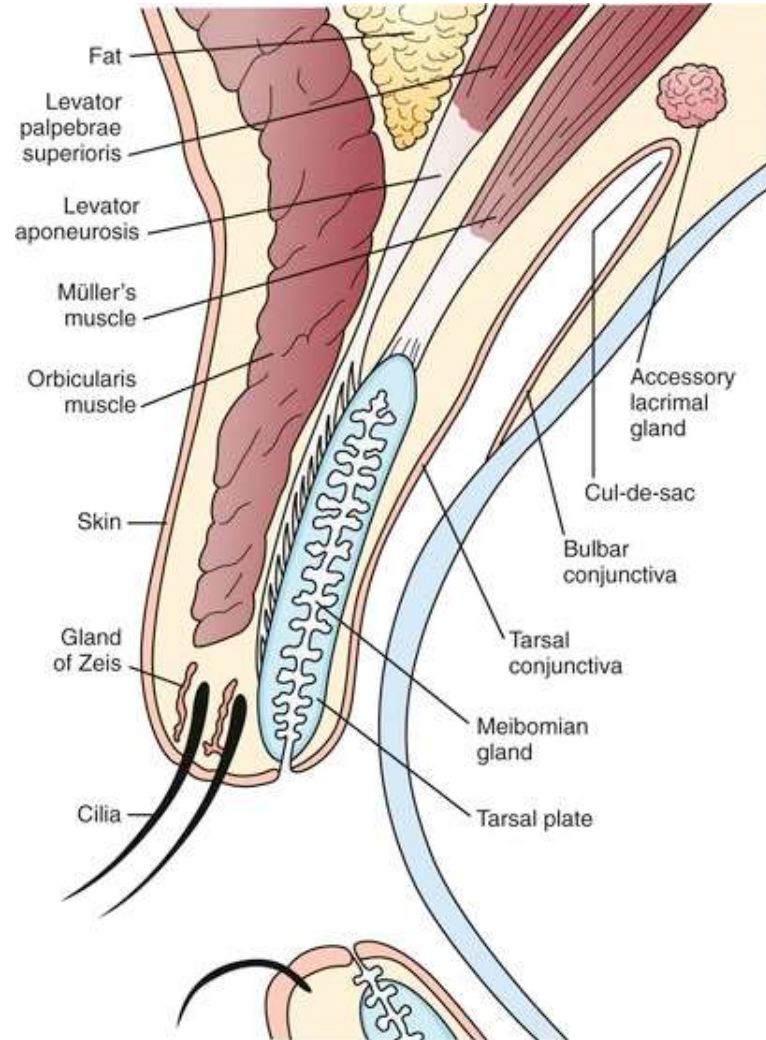
- young children in household
- poor facial cleanliness
- inadequate access to water
- poor sanitation



History and Physical

- Chief complaint (CC)
 - trachoma initially presents in childhood as red eye
 - eye pain
 - redness
 - itching eye
- Physical Exam
 - examine eyelids and cornea for evidence of in-turned lashes or corneal opacities
 - evert upper eyelid and examine tarsal conjunctiva for signs of active trachoma and/or scarring
 - presence of inflammation
 - often seen in children
 - indicates early disease
 - cicatricial (scarring) disease is second phase of trachoma
 - scarring
 - trichiasis
 - corneal opacification
 - usually seen in older individuals

Eyelid Anatomy



Classification

- World Health Organization (WHO) simplified trachoma grading system
 - normal
 - trachomatous inflammation - follicular (TF)
 - trachomatous inflammation - intense (TI)
 - trachomatous scarring - (TS)
 - trachomatous trichiasis - (TS)
 - corneal opacity - (CO)

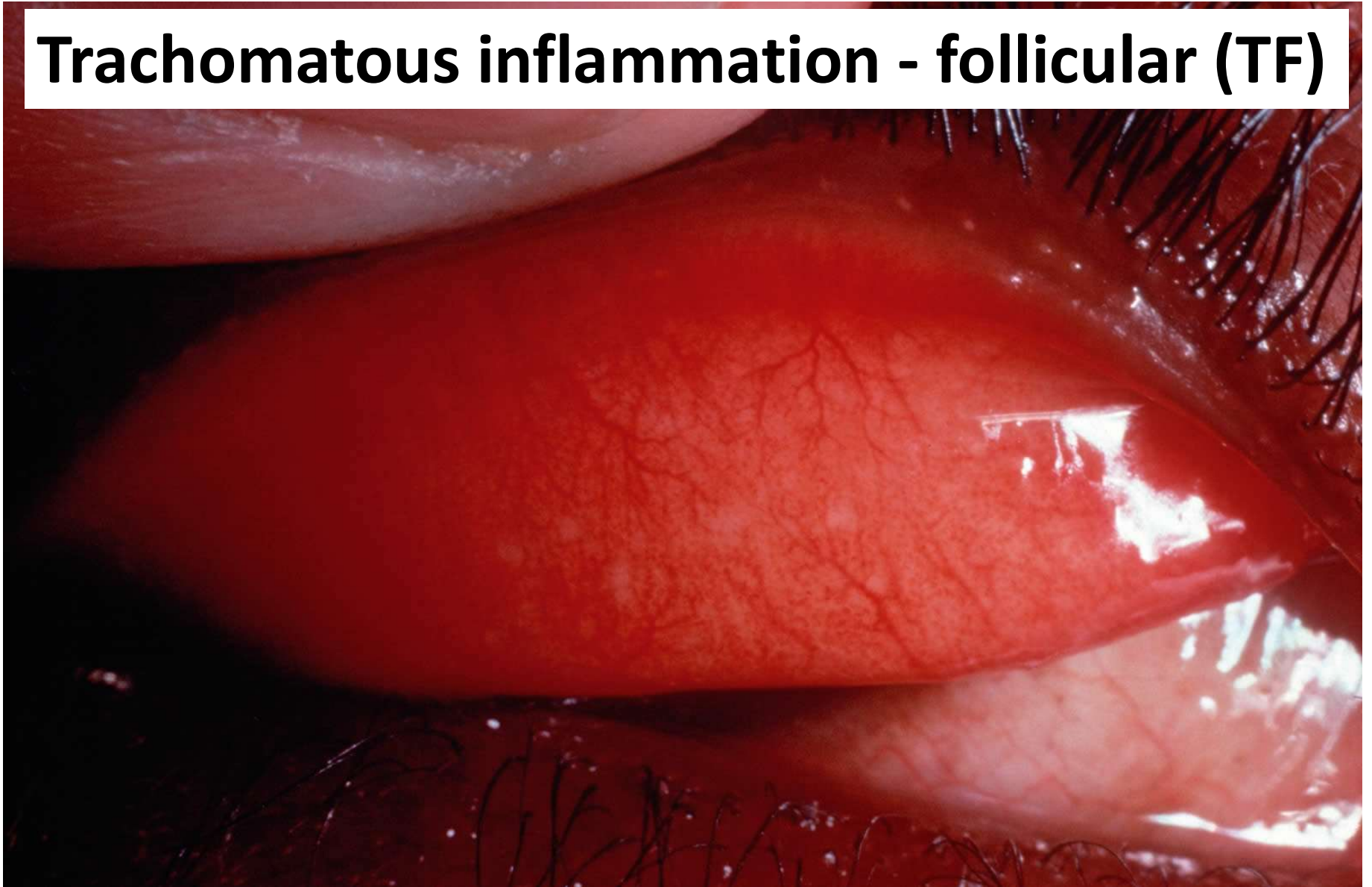
Normal



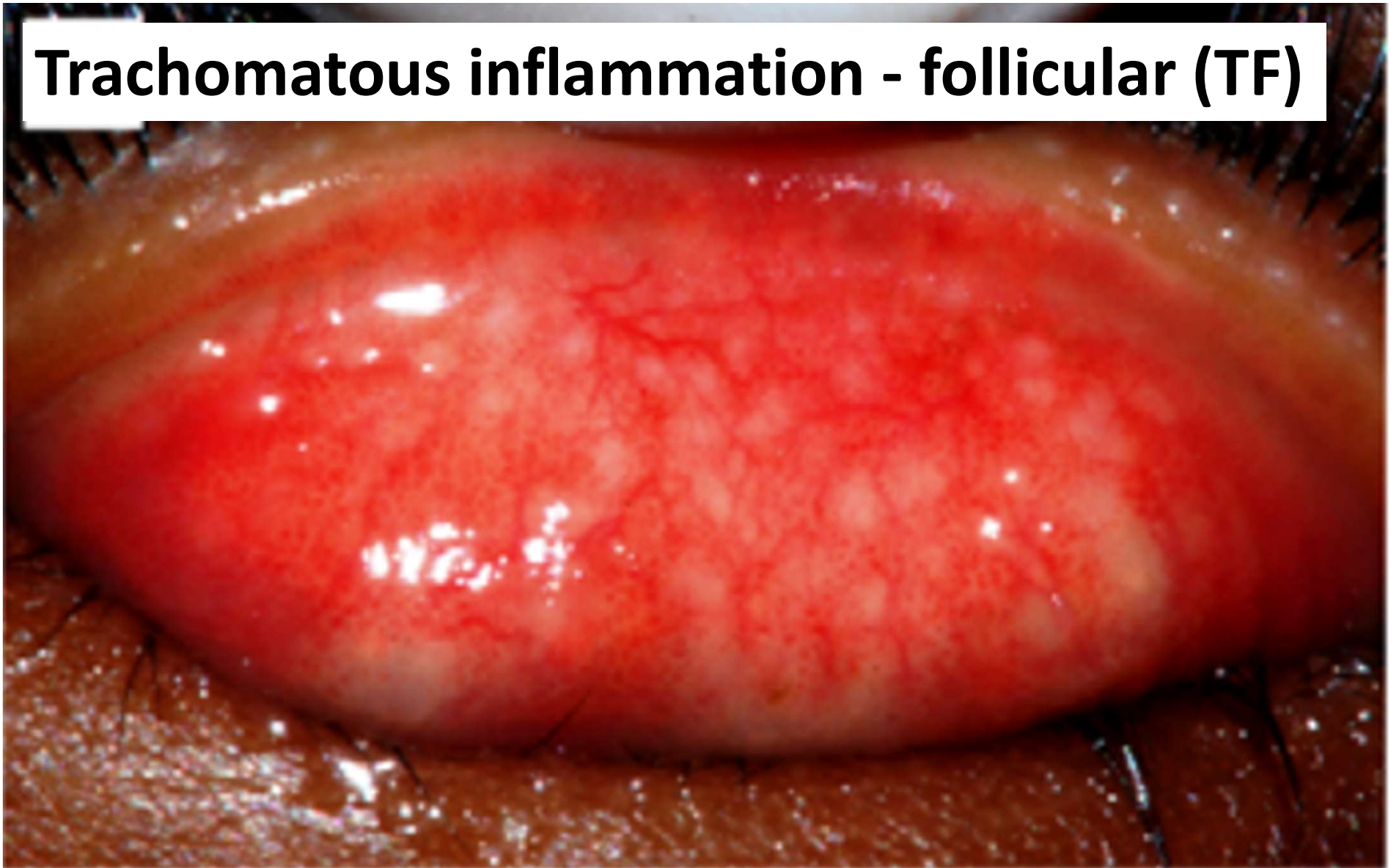
Classification

- Trachomatous inflammation - follicular (TF)
 - 5 or more follicles on the upper tarsal conjunctiva

Trachomatous inflammation - follicular (TF)



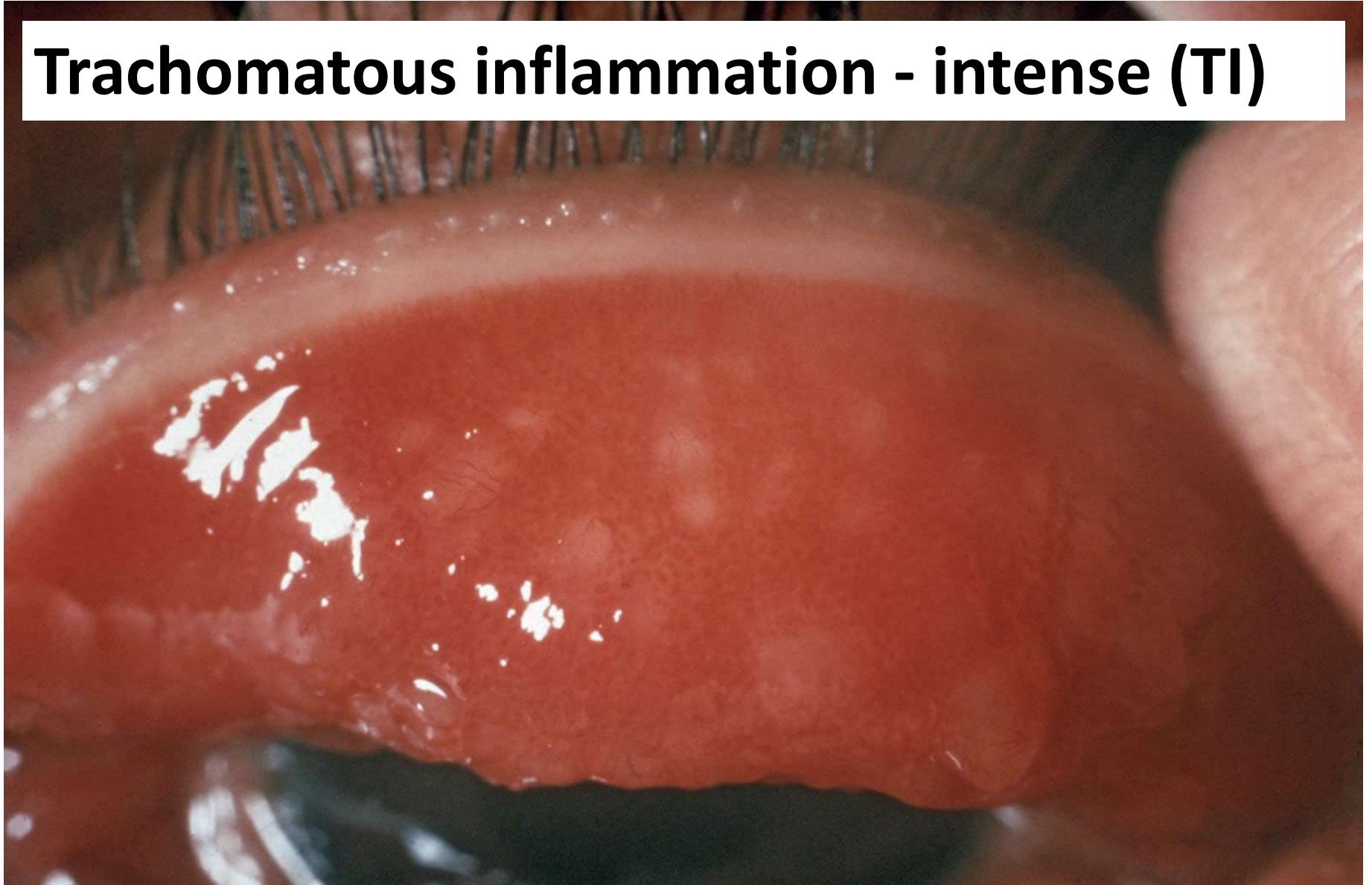
Trachomatous inflammation - follicular (TF)



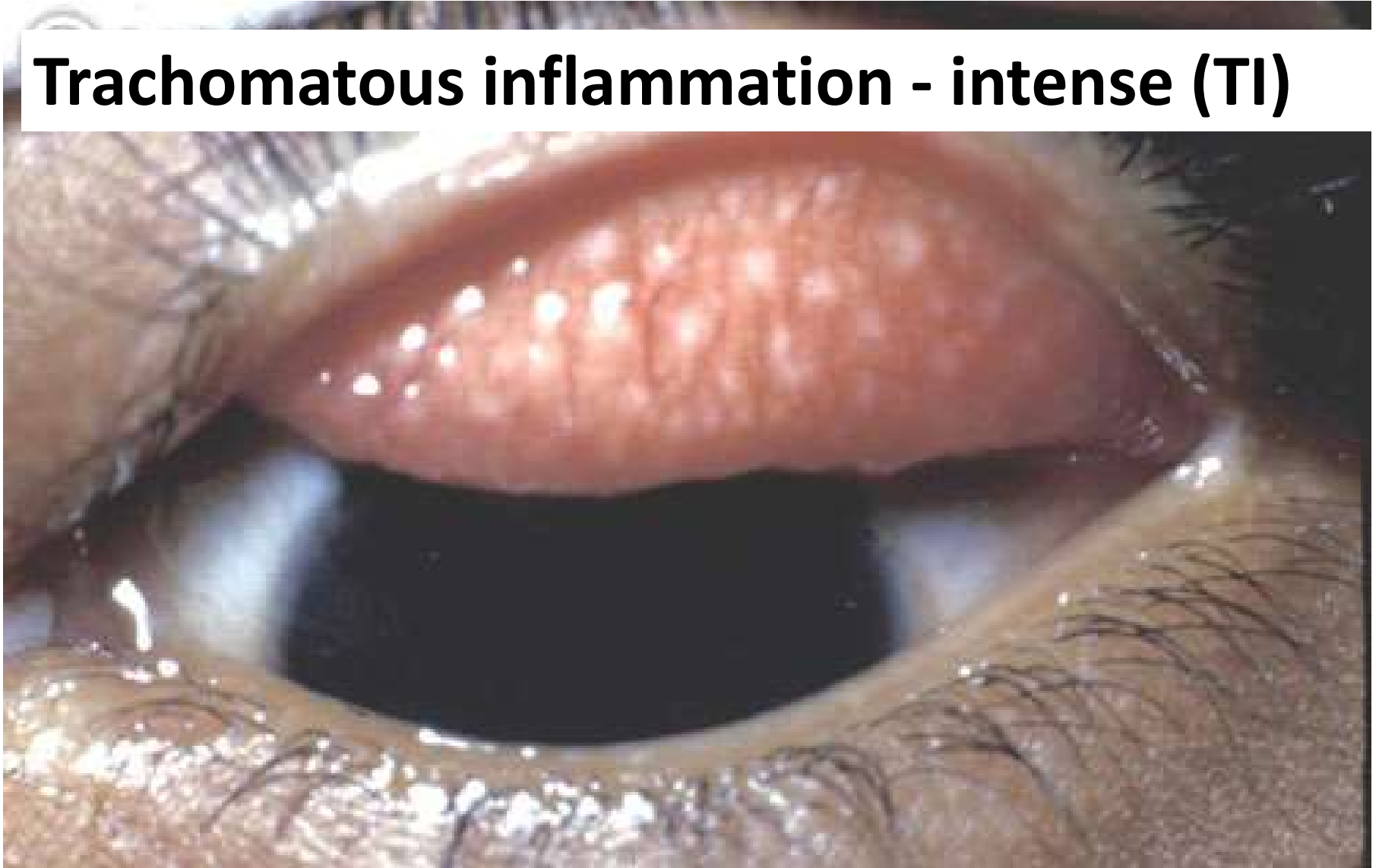
Classification

- Trachomatous inflammation - intense (TI)
 - Pronounced inflammatory thickening of the tarsal conjunctiva that obscures more than half of the normal deep tarsal
 - Papillary hypertrophy and inflammatory thickening of the upper tarsal conjunctiva

Trachomatous inflammation - intense (TI)



Trachomatous inflammation - intense (TI)



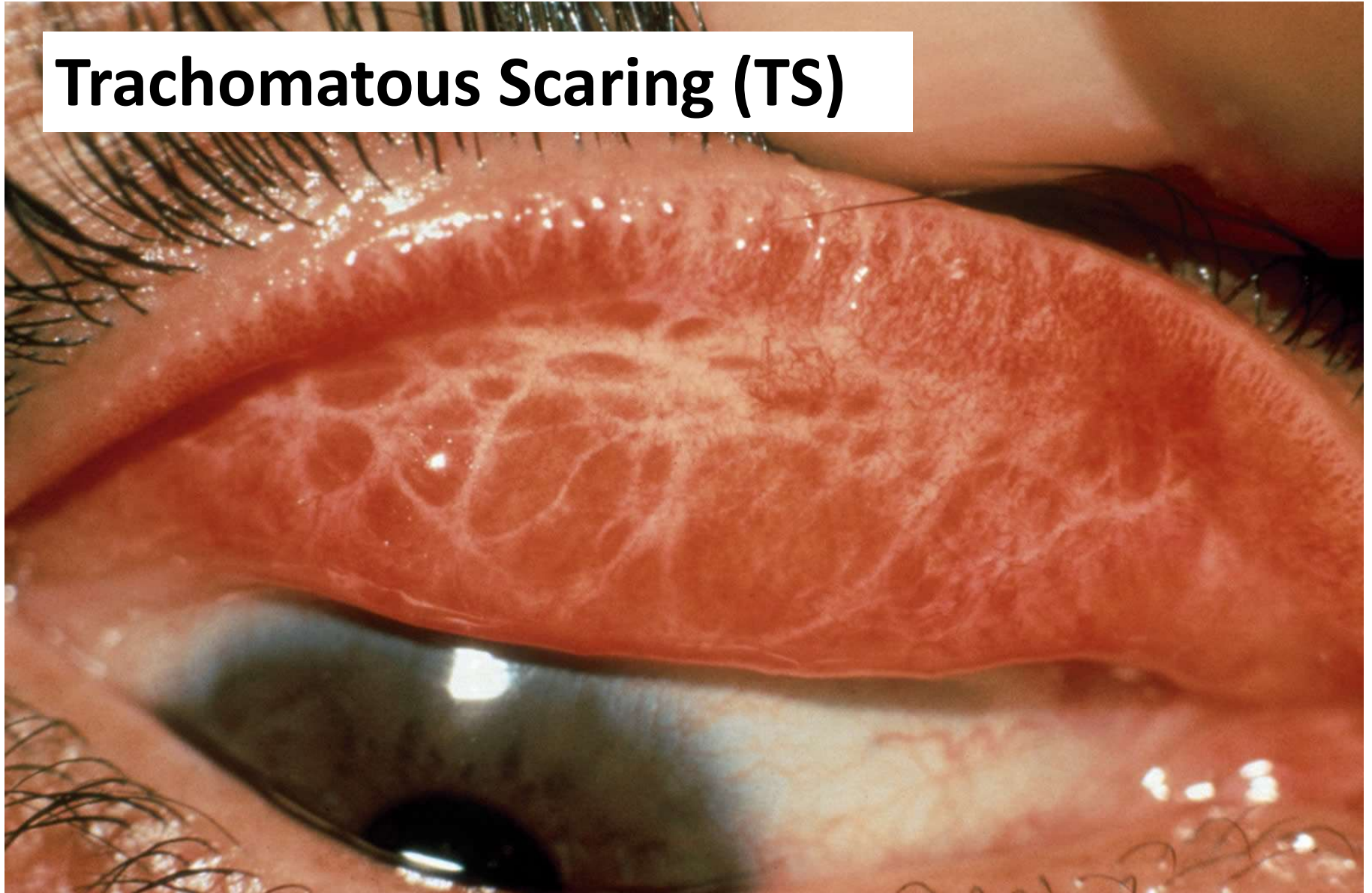
Trachomatous inflammation - intense (TI)



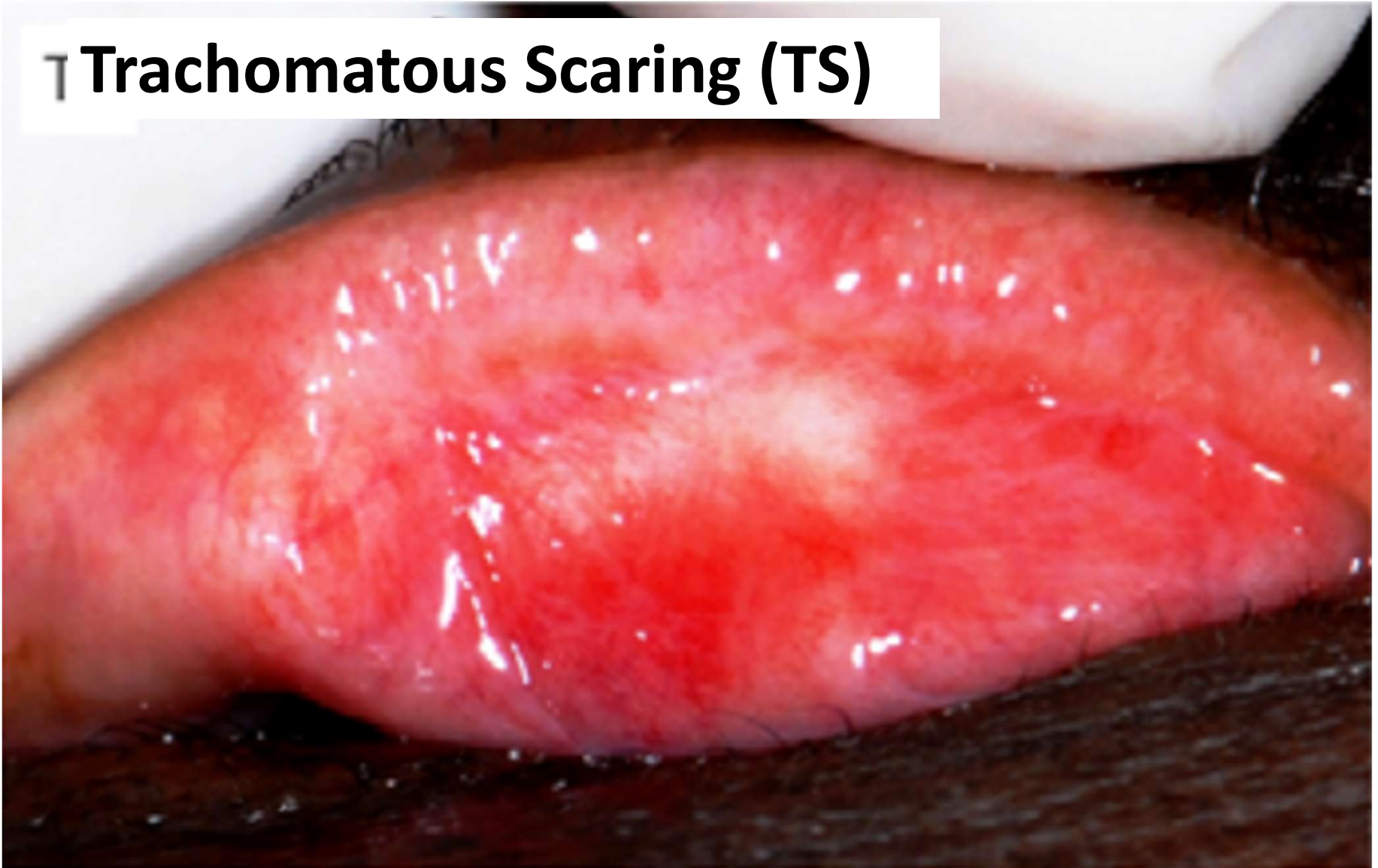
Classification

- Trachomatous Scarring (TS).
 - The presence of scarring in the tarsal conjunctiva.

Trachomatous Scarring (TS)



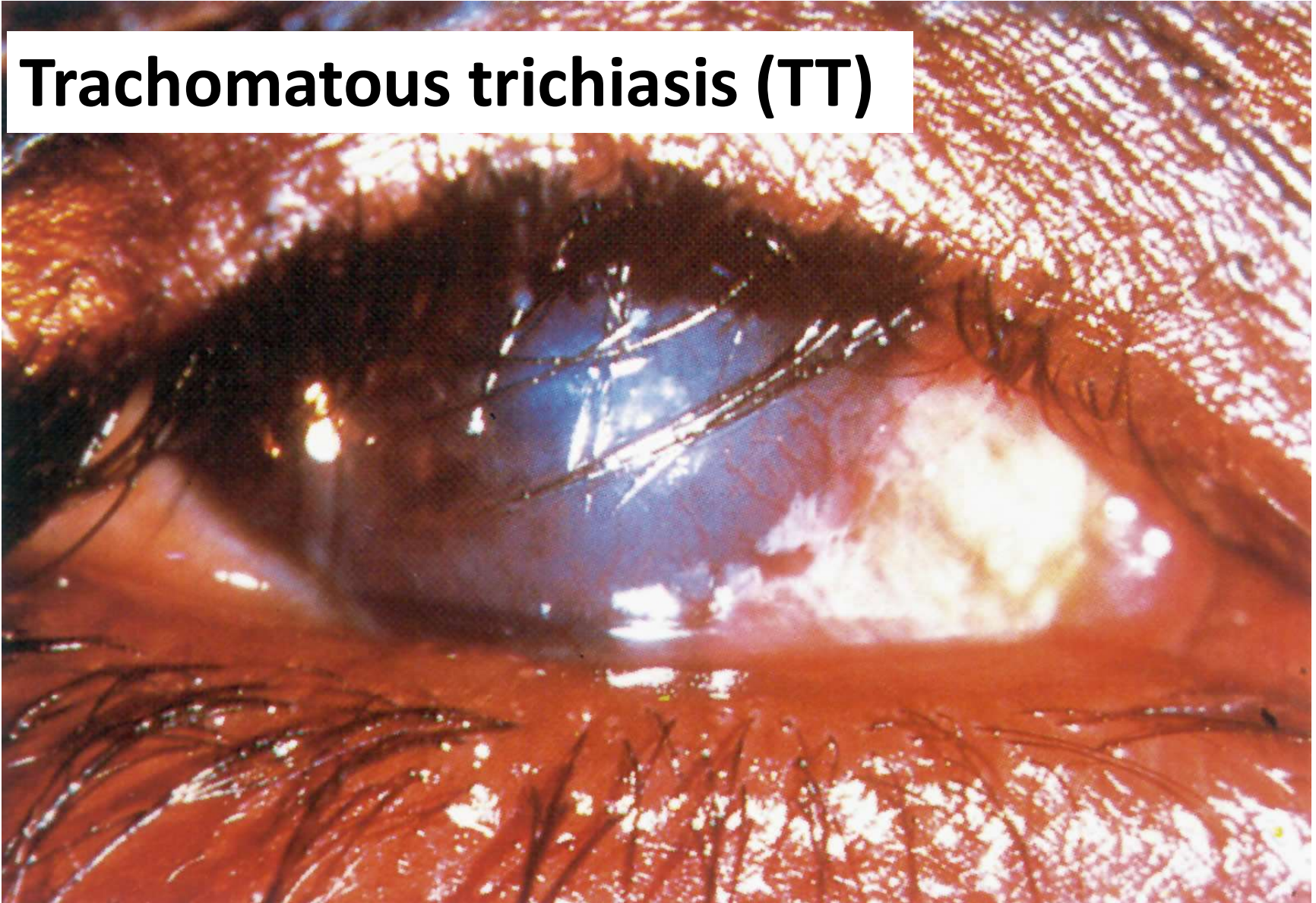
Trachomatous Scarring (TS)



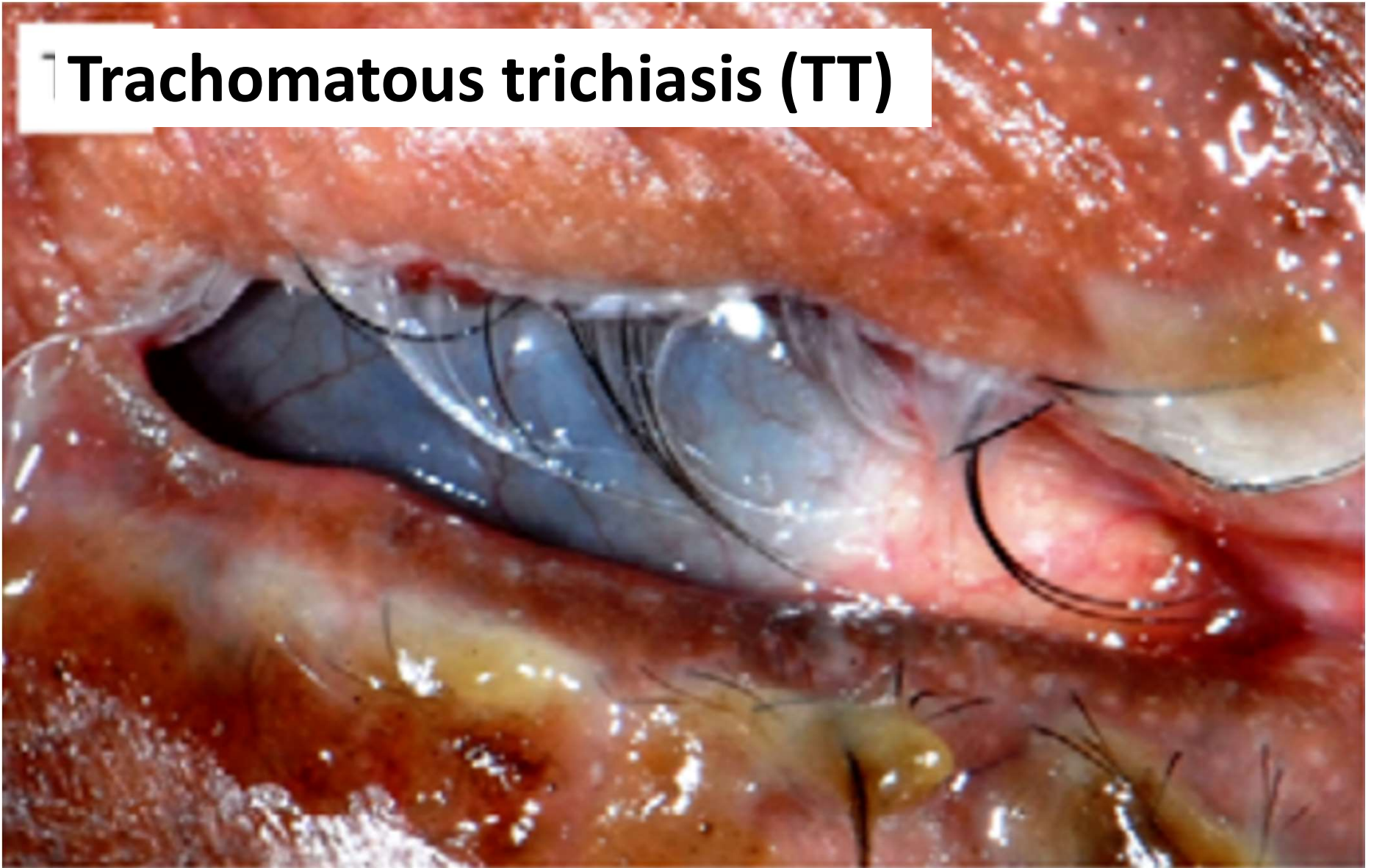
Classification

- Trachomatous trichiasis (TT)
 - At least one eyelash rubs on the eyeball or evidence of recent removal of in-turned eyelashes.
 - Trichiasis develops when scarring distorts the upper eyelid sufficiently to cause one or more lashes to abrade the cornea, scarring it in turn and causing blindness.

Trachomatous trichiasis (TT)



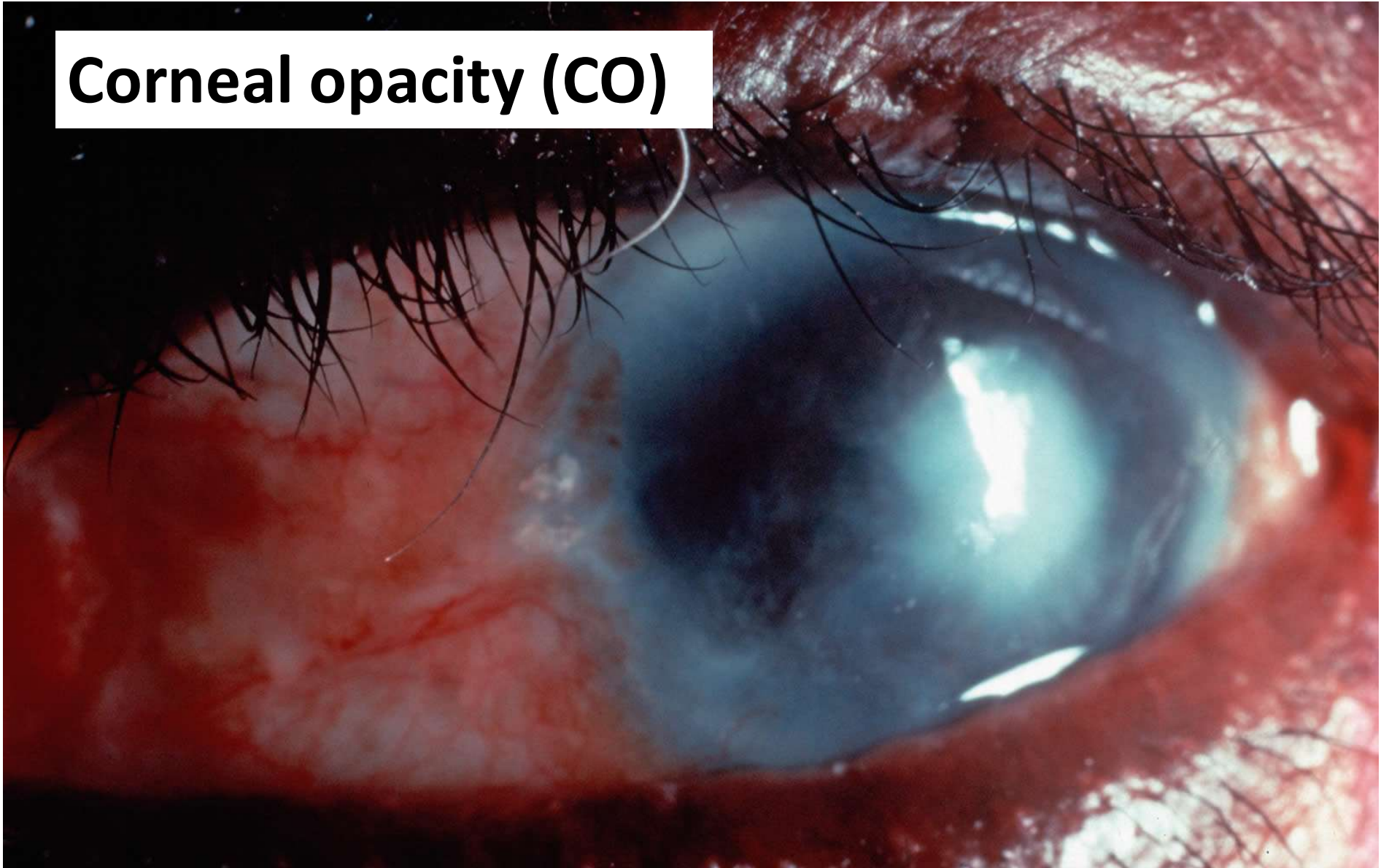
Trachomatous trichiasis (TT)



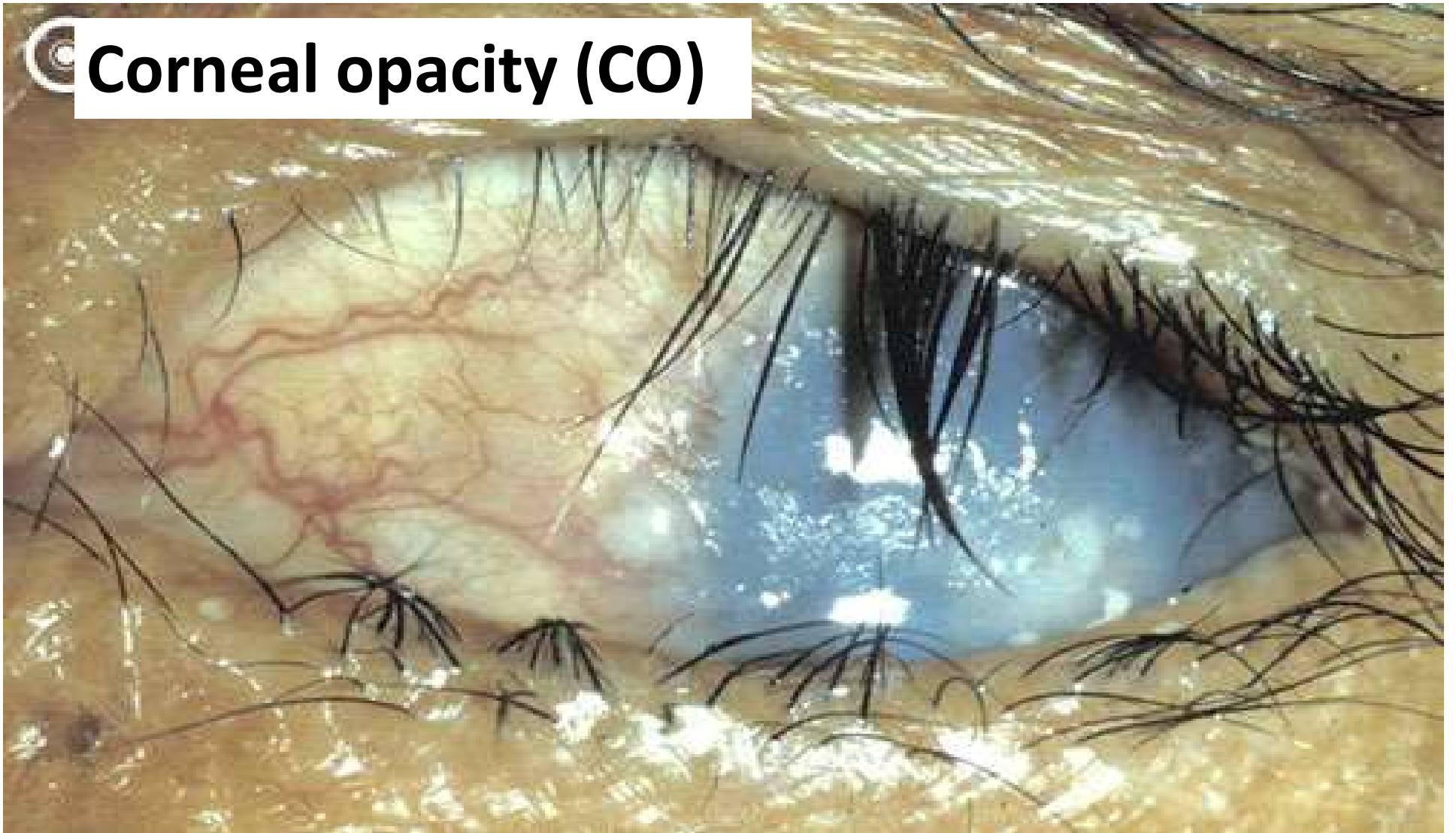
Classification

- Corneal opacity (CO)
 - Easily visible corneal opacity over the pupil.

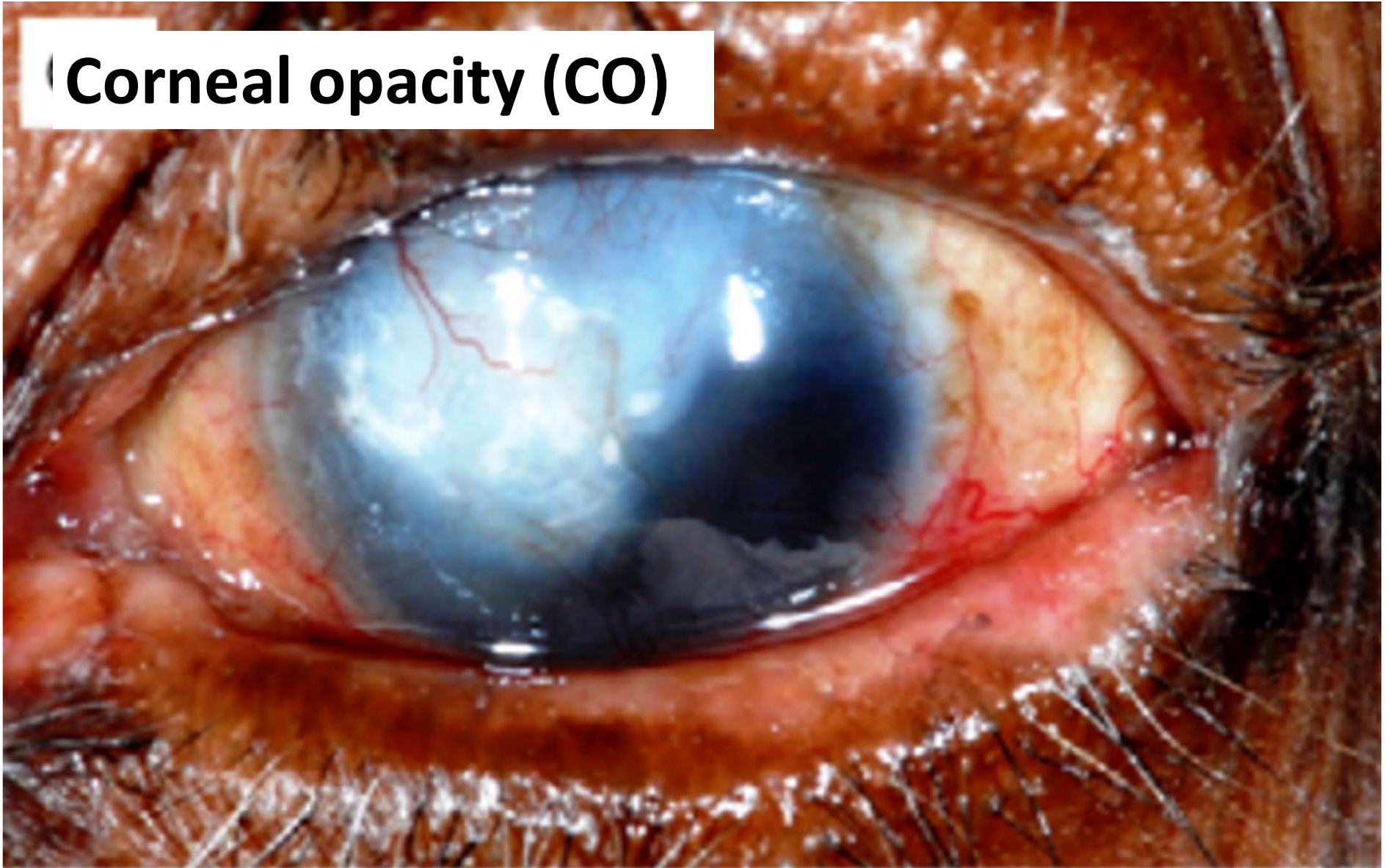
Corneal opacity (CO)



Corneal opacity (CO)



Corneal opacity (CO)



Diagnosis

- clinical diagnosis
 - diagnosed by inspecting superior tarsal conjunctiva of everted upper eyelid
 - key sign is tarsal follicle
 - 0.5-2 mm diameter
 - white to pale yellow
 - may be slightly raised
- Cytological staining (smear) for *Chlamydia trachomatis*
- Tissue culture of *C. trachomatis*
- NAT for *C. trachomatis*

- Differential diagnosis
 - infectious conjunctivitis
 - allergic conjunctivitis
 - other causes of conjunctivitis

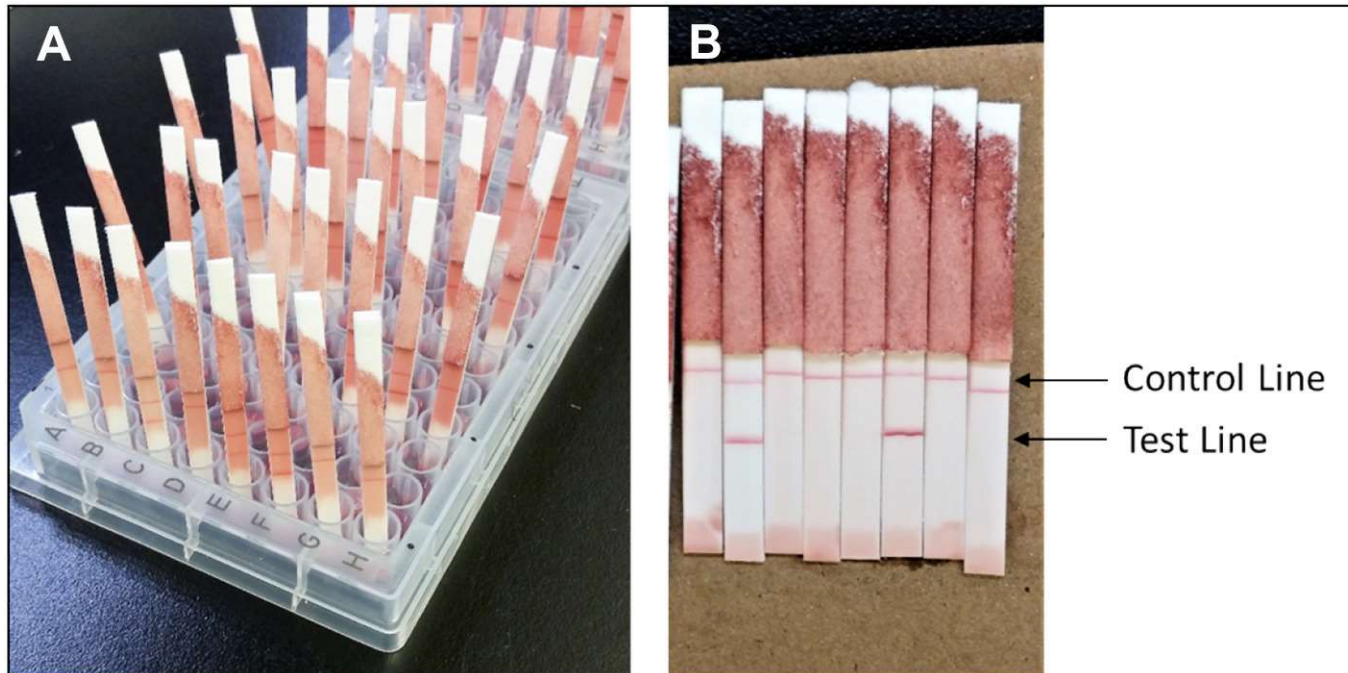
Field evaluation of a rapid point-of-care assay for targeting antibiotic treatment for trachoma control: a comparative study

Claude-Edouard C Michel, Anthony W Solomon, Jose P V Magbanua, Patrick A Massae, Ling Huang, Jonaice Mosha, Sheila K West, Elpidio C B Nadala, Robin Bailey, Craig Wisniewski, David C W Mabey, Helen H Lee

Lancet 2006; 367: 1585-90

See [Comment](#) page 1553

Diagnostics Development Unit,
Department of Haematology,
University of Cambridge,
Cambridge, UK



Field evaluation of a rapid point-of-care assay for targeting antibiotic treatment for trachoma control: a comparative study

Claude-Edouard C Michel, Anthony W Solomon, Jose P V Magbanua, Patrick A Massae, Ling Huang, Jonaice Mosha, Sheila K West, Elpidio C B Nadala, Robin Bailey, Craig Wisniewski, David C W Mabey, Helen H Lee

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Diagnostics Development Unit,
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	PCR positive				PCR negative			
	Clinical sign		POC assay		Clinical sign		POC assay	
	TF	No TF	Positive	Negative	TF	No TF	Positive	Negative
Group 1 (n=264)	65% (39/60)	35% (21/60)	83% (50/60)	17% (10/60)	30% (61/204)	70% (143/204)	2% (3/204)	99% (201/204)
Group 2 (n=200)	64% (35/55)	36% (20/55)	86% (47/55)	15% (8/55)	19% (28/145)	81% (117/145)	0% (0/145)	100% (145/145)
Group 3 (n=200)	62% (8/13)	39% (5/13)	77% (10/13)	23% (3/13)	9% (17/187)	91% (170/187)	0% (0/187)	100% (187/187)
All groups (n=664)	64% (82/128)	36% (46/128)	84% (107/128)	16% (21/128)	20% (106/536)	80% (430/536)	1% (3/536)	99% (533/536)

Table 1: Presence of *C trachomatis* DNA assessed by PCR compared with detection by the clinical sign TF and POC assay positivity

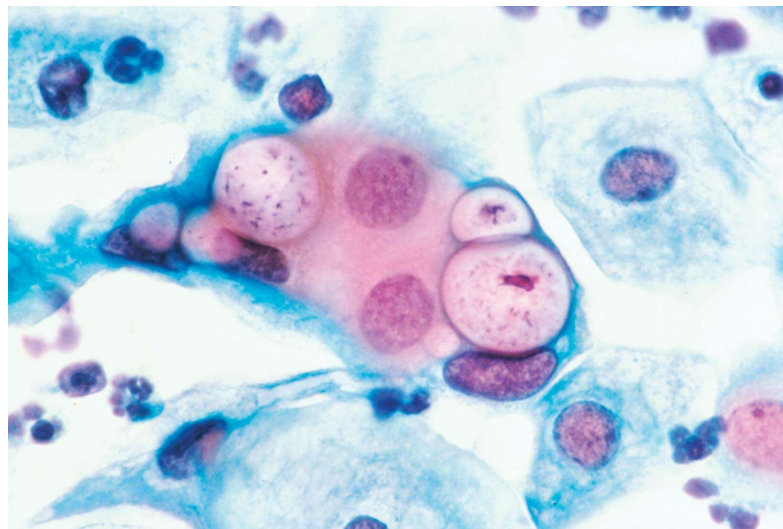
	Clinical sign (TF)				POC assay			
	Sensitivity	PPV	Specificity	NPV	Sensitivity	PPV	Specificity	NPV
Group 1 (n=264)	65.0 (52.9-77.1)	39.0 (29.4-48.6)	70.1 (63.8-76.4)	87.2 (82.1-92.3)	83.3 (73.9-92.8)	94.3 (88.1-100.6)	98.5 (96.9-100.0)	95.3 (92.4-98.1)
Group 2 (n=200)	63.6 (50.9-76.3)	55.6 (43.3-67.8)	80.7 (74.3-87.1)	85.4 (79.5-91.3)	85.5 (76.1-94.8)	100.0 (94.6-100.0)	100.0 (100-100)	94.8 (91.2-98.3)
Group 3 (n=200)	61.5 (35.1-88.0)	32.0 (13.7-50.3)	90.9 (86.8-95.0)	97.1 (94.7-99.6)	76.9 (54.0-99.8)	100.0 (77.2-100.0)	100.0 (100-100)	98.4 (96.6-100.2)
All groups (n=664)	64.1 (55.8-72.4)	43.6 (36.5-50.7)	80.2 (76.8-83.6)	90.3 (87.7-93.0)	83.6 (77.2-90.0)	97.3 (94.2-100.3)	99.4 (98.8-100.0)	96.2 (94.6-97.8)

Values in parentheses are 95% CI. PPV=positive predictive value; NPV=negative predictive value. The stratified analysis for TF indicated that the Kappa coefficients were not significantly different between groups (p=0.30). The overall agreement adjusted for group=0.346 (95% CI 0.267-0.427). Similarly, there was also no difference between groups for the POC assay (p=0.73) and the overall agreement adjusting for the groups was 0.875 (0.825-0.924).

Table 2: Performance of the clinical sign TF and the POC assay compared with PCR

Smear

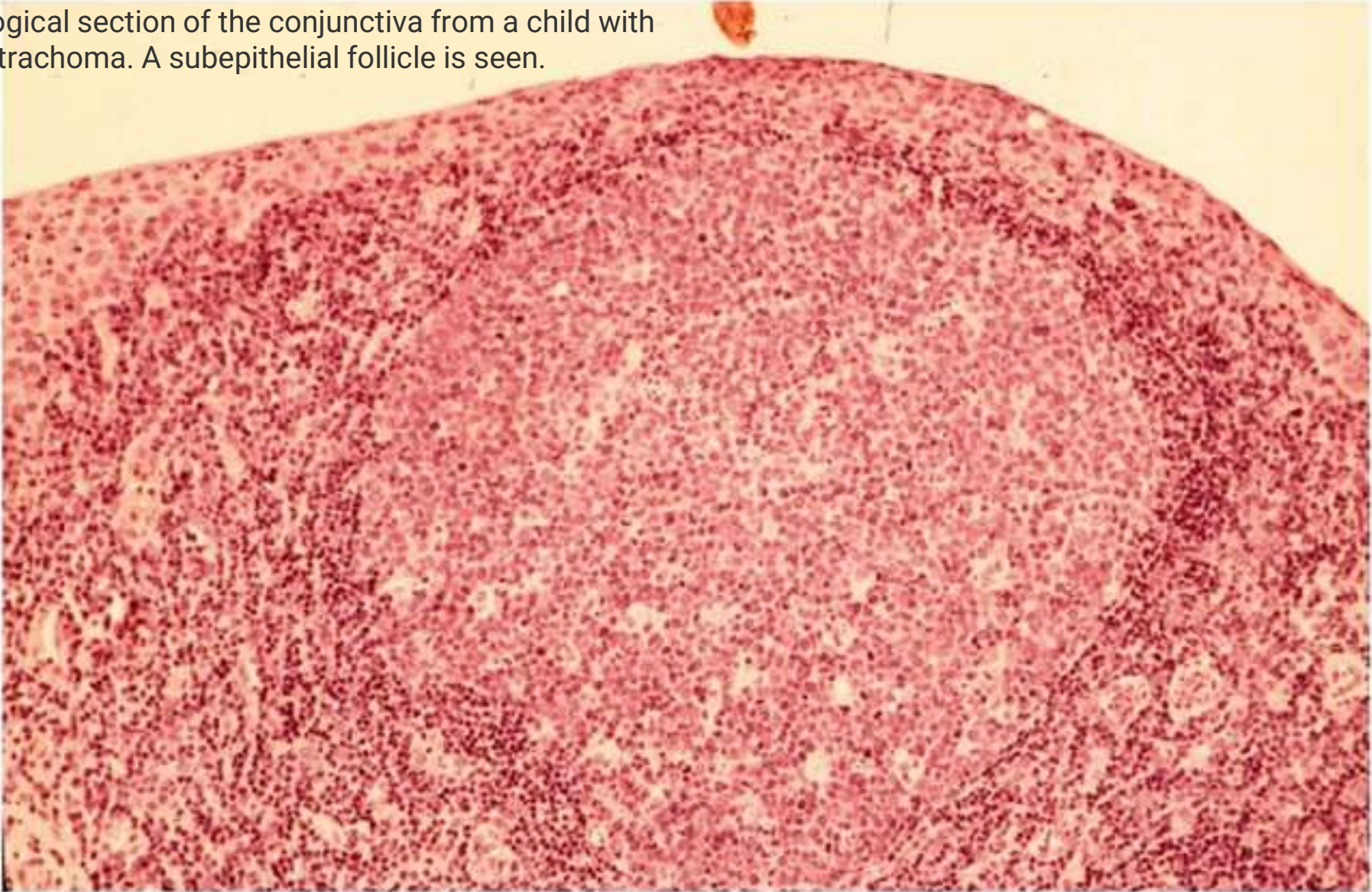
- Cytological staining (smear) for *Chlamydia trachomatis*
 - histology characterized by formation of lymphoid follicles with germinal center and parafollicular region with lymphocytes

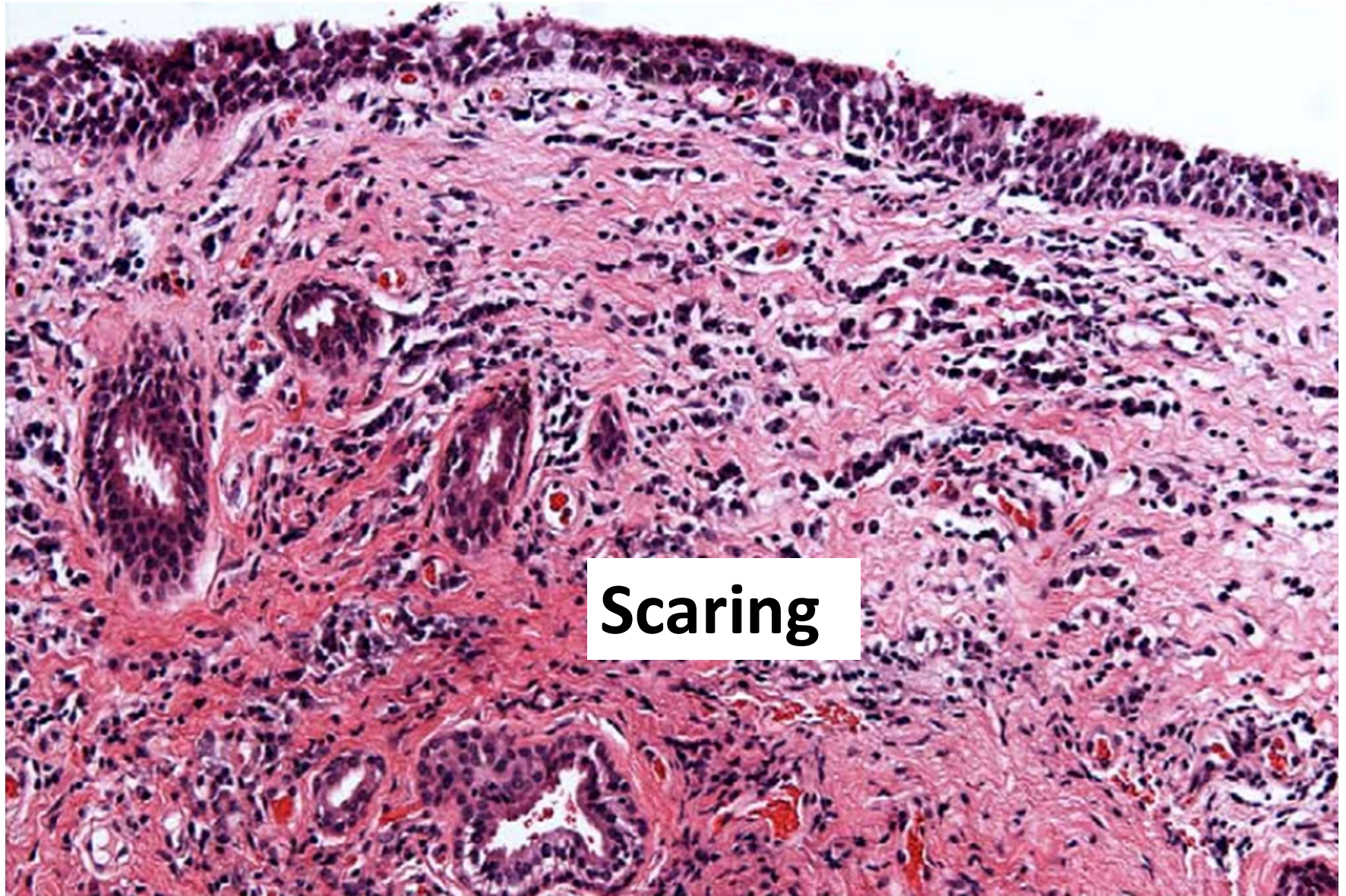


A histological micrograph showing a dense field of spindle-shaped cells with elongated nuclei, characteristic of smooth muscle or fibrous connective tissue. The cells are arranged in a somewhat organized, interwoven pattern. In the lower right corner, there are several circular structures that appear to be cross-sections of small blood vessels or ducts, containing some internal cellular detail. The overall staining is pinkish-red, typical of hematoxylin and eosin (H&E) stain.

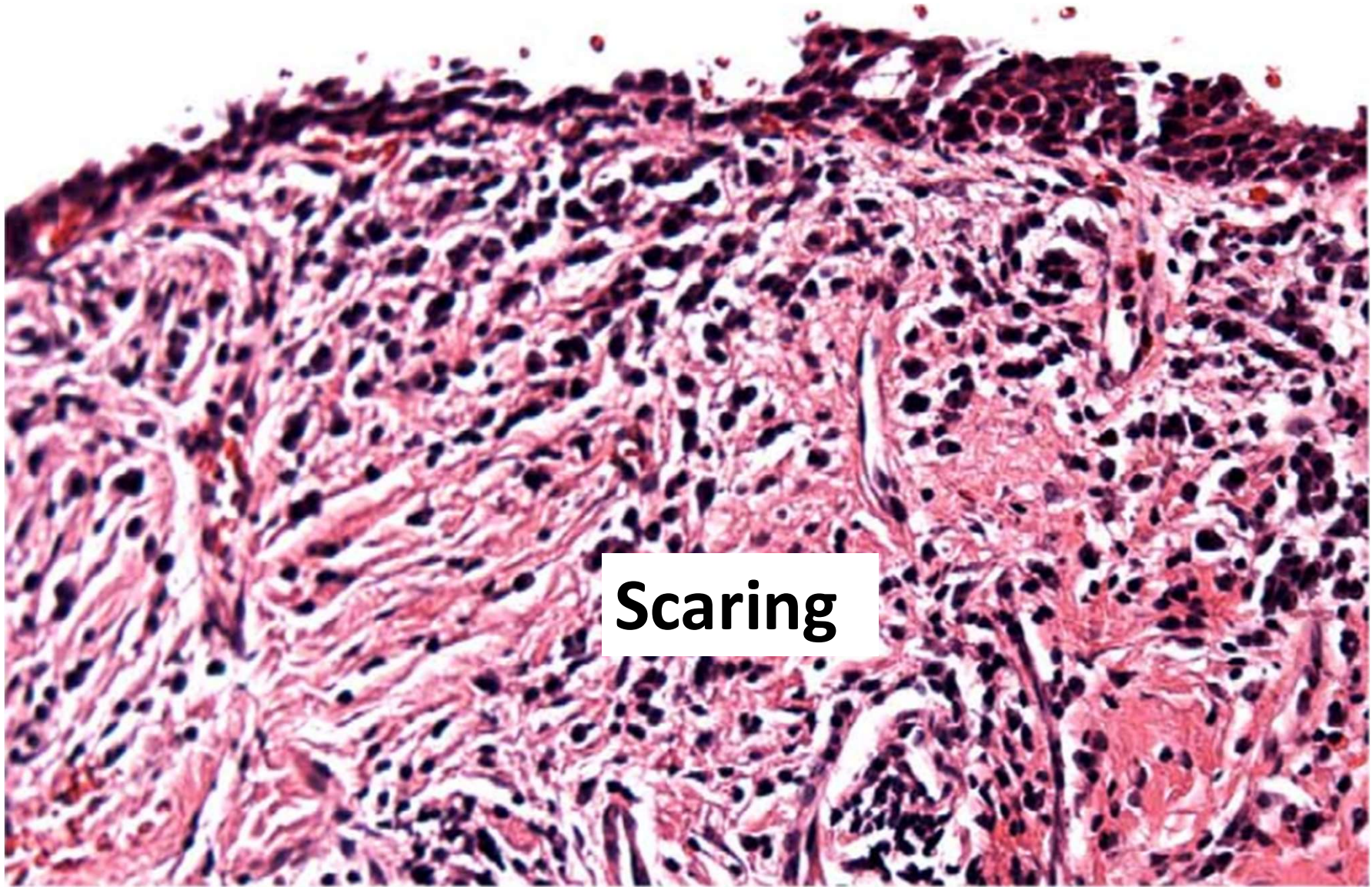
Normal Histology

Histological section of the conjunctiva from a child with active trachoma. A subepithelial follicle is seen.





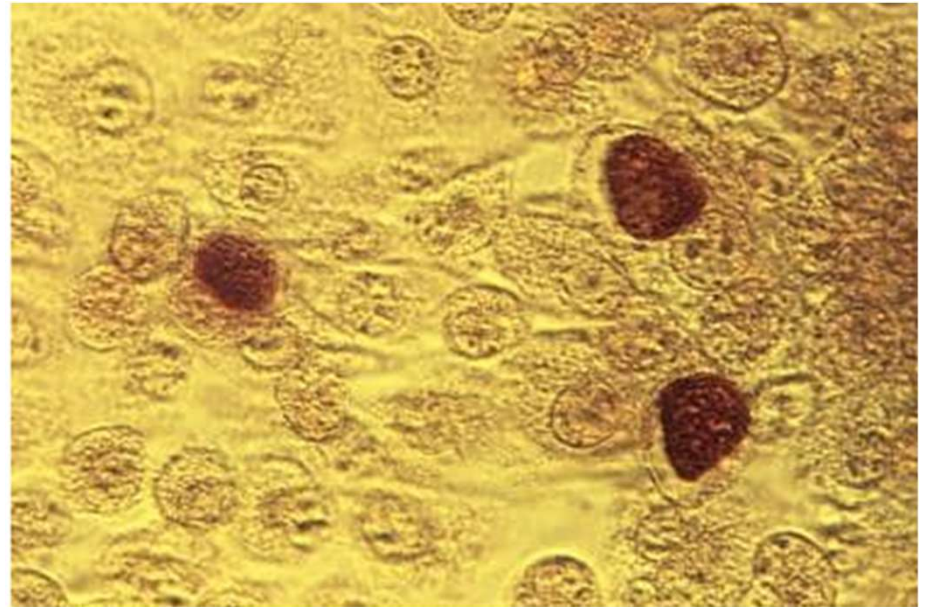
Scarring



Scarring

Cell culture

- only method to reliably identify live organism and test antibiotic sensitivity



This photomicrograph reveals McCoy cell monolayers with *Chlamydia trachomatis* inclusion bodies; magnified 200X. Image courtesy of the Centers for Disease Control and Prevention.

International Trachoma Initiative (ITI)

- Founded in 1998 in response to the WHO's call to eliminate blinding trachoma by the year 2020
- The NTD road map 2021–2030, endorsed by the World Health Assembly set 2030 as the new target date for global elimination.



SAFE strategy

SURGERY



ANTIBIOTICS

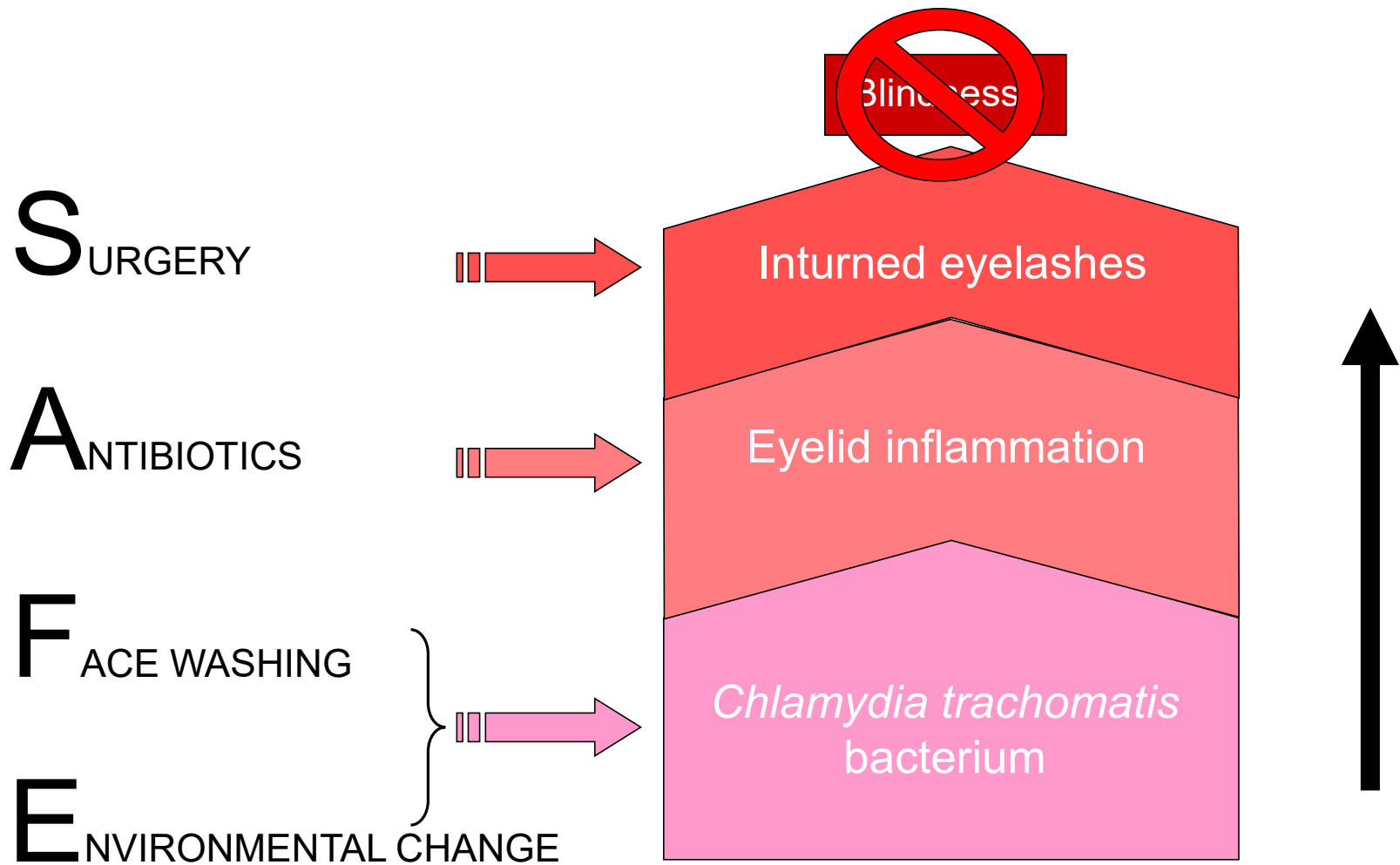


FACE WASHING



ENVIRONMENTAL CHANGE





Prevention - Environmental Improvement

- Primary prevention to eliminate risk factors
- Improve access and use of water
- Improve personal & community hygiene
- Increase use of latrines



Role of flies and provision of latrines in trachoma control: cluster-randomised controlled trial

Paul M Emerson, Steve W Lindsay, Neal Alexander, Momodou Bah, Sheik-Mafuji Dibba, Hannah B Faal, Kebba O Lowe, Keith P W J McAdam, Amy A Ratcliffe, Gijs E L Walraven, Robin L Bailey

- 21 villages randomized to
 - regular insecticide spraying vs.
 - provision of pit latrines to each household vs.
 - no-intervention control
- number of *Musca sorbens* flies caught from children's eyes reduced by 88% with insecticide spraying ($p < 0.0001$) and by 30% with latrine provision ($p = 0.04$)

Environmental sanitary interventions for preventing active trachoma (Review)

Rabiu M, Alhassan MB, Ejere HOD, Evans JR

- 2 trials that insecticides are effective in reducing trachoma, however, this effect was not demonstrated in another trial that used insecticides.
- 2 trials on latrine provision as a fly control measure have not demonstrated significant trachoma reduction.
- Health education had shown significant reduction of trachoma in 1 study but another study did not demonstrate similar findings.
- Generally, there is a little data to determine the effectiveness of all aspects of environmental sanitation in the control of trachoma.

Prevention – Face Washing

- Health education to improve facial cleanliness reduces disease prevalence
- Facial hygiene interrupts progression to blindness by extending the disease-free duration following antibiotic treatment

Face washing promotion for preventing active trachoma (Review)

Ejere HOD, Alhassan MB, Rabiu M

- 2 cluster-RCTs, which provided data from 2447 participants. Both trials were conducted in areas endemic to trachoma: Northern Australia and Tanzania. The follow-up period was 3 months in one trial and 12 months in the other
- Overall, the quality of the evidence is uncertain due to the trials not reporting many design methods.
- There is evidence from 1 trial that face washing combined with topical tetracycline may be effective in reducing severe active trachoma and in increasing the prevalence of clean faces at one year follow-up.
- Current evidence is inconclusive as to the effectiveness of face washing alone.

Effect of 3 years of SAFE (surgery, antibiotics, facial cleanliness, and environmental change) strategy for trachoma control in southern Sudan: a cross-sectional study

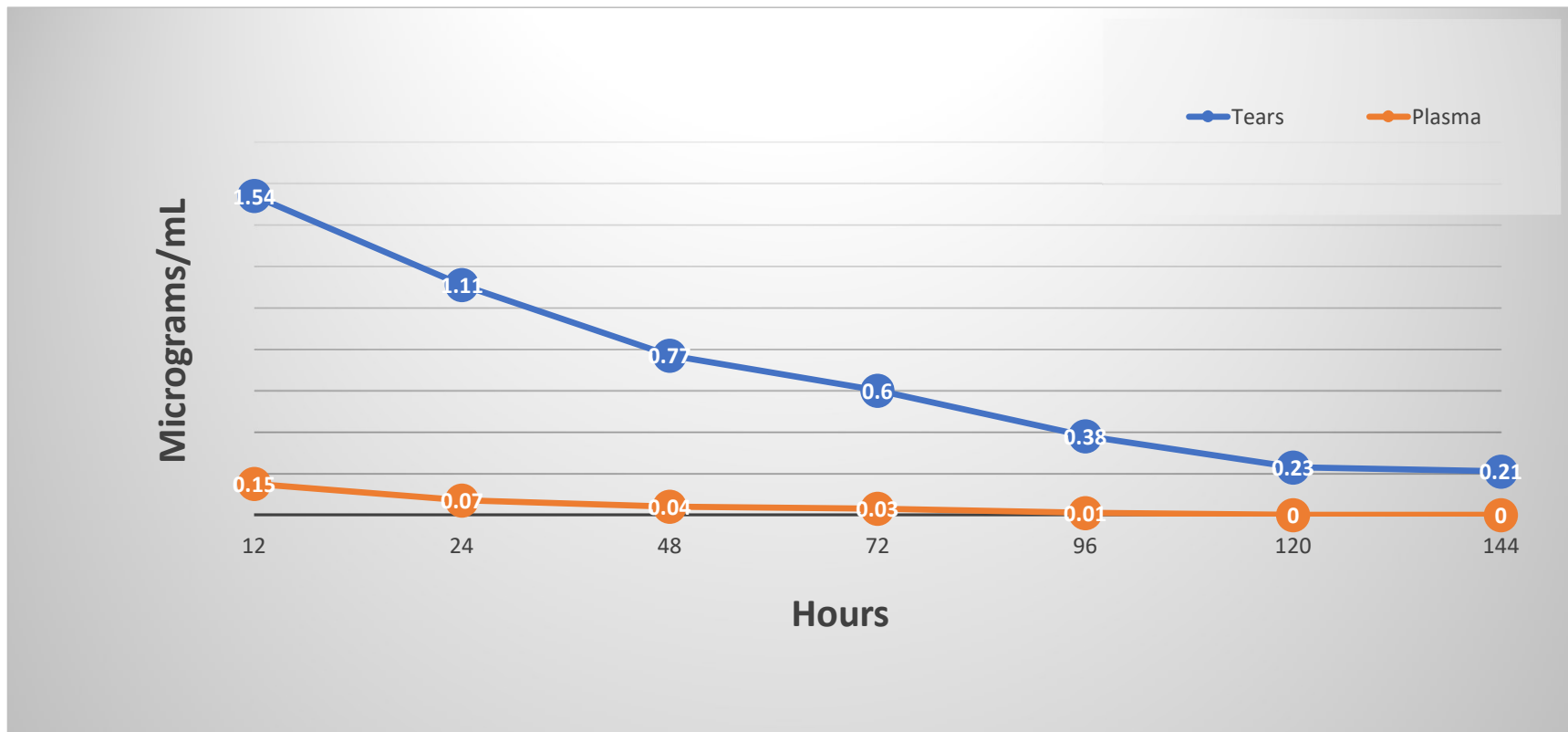
Jeremiah Ngondi, Alice Onsarigo, Fiona Matthews, Mark Reacher, Carol Brayne, Samson Baba, Anthony W Solomon, James Zingeser, Paul M Emerson

- higher uptake of antibiotics and health education associated with decline in trachoma rates

Antibiotics

- Why is Azithromycin Better?
 - Systemic—extra-ocular reservoirs of infection
 - Long half life
 - Uptake by cell—particularly infected cells
 - It works in a single dose against chlamydia, so compliance is easy

High and sustained concentrations in tears of trachoma patients



REVIEW ARTICLE

CURRENT CONCEPTS

Control of Neglected Tropical Diseases

Peter J. Hotez, M.D., Ph.D., David H. Molyneux, Ph.D., D.Sc.,
Alan Fenwick, Ph.D., Jacob Kumaresan, M.B., B.S., Dr.P.H.,
Sonia Ehrlich Sachs, M.D., Jeffrey D. Sachs, Ph.D., and Lorenzo Savioli, M.D.

- World Health Organization recommends mass antibiotic treatment annually if active trachoma prevalence >5% in children ages 1-9 years
- azithromycin 20 mg/kg (maximum 1 g) for entire at-risk population > 6 months old



Cochrane Database of Systematic Reviews

Antibiotics for trachoma (Review)

Evans JR, Solomon AW, Kumar R, Perez Á, Singh BP, Srivastava RM, Harding-Esch E

- 9 studies (1961 participants) randomized individuals with trachoma to antibiotic or control (no treatment or placebo).
 - All of these studies enrolled children and young people with active trachoma.
 - The antibiotics used in these studies included topical (oxy)tetracycline (5 studies), doxycycline (2 studies), and sulfonamides (4 studies).
 - Four studies had more than two study arms. In general these studies were poorly reported, and it was difficult to judge risk of bias.

Antibiotics for trachoma. Cochrane Database of Systematic Reviews 2019, Issue 9. Art. No.: CD001860

Antibiotics for trachoma (Review)

Evans JR, Solomon AW, Kumar R, Perez Á, Singh BP, Srivastava RM, Harding-Esch E

- Oral versus topical antibiotics (individuals)
 - There was low-certainty evidence of little or no difference in effect between oral and topical antibiotics on active trachoma at three months (RR 0.97, 95% CI 0.81 to 1.16; 953 people; 6 RCTs; I² = 63%) and 12 months (RR 0.93, 95% CI 0.75 to 1.15; 886 people; 5 RCTs; I² = 56%).
 - There was very low-certainty evidence for ocular infection at three or 12 months.
 - Antimicrobial resistance was not assessed.

Antibiotics for trachoma (Review)

Evans JR, Solomon AW, Kumar R, Perez Á, Singh BP, Srivastava RM, Harding-Esch E

- Oral azithromycin versus control (communities)
 - 4 cluster-randomised studies compared antibiotic with no or delayed treatment.
 - Data were available on active trachoma at 12 months from two studies but could not be pooled because of reporting differences.
 - 1 study found a reduced prevalence of active trachoma 12 months after a single dose of azithromycin in communities with a high prevalence of infection (RR 0.58, 95% CI 0.52 to 0.65; 1247 people).
 - There was high-certainty evidence of an increased risk of resistance of *Streptococcus pneumoniae*, *Staphylococcus aureus*, and *Escherichia coli* to azithromycin, tetracycline, and clindamycin in communities treated with azithromycin, with approximately 5-fold risk ratios at 12 months.
 - The evidence did not support increased resistance to penicillin or trimethoprim-sulfamethoxazole.
 - None of the studies measured resistance to *C trachomatis*.

Antibiotics for trachoma (Review)

Evans JR, Solomon AW, Kumar R, Perez Á, Singh BP, Srivastava RM, Harding-Esch E

- Oral azithromycin versus topical tetracycline (communities)
 - 3 cluster-randomised studies compared oral azithromycin with topical tetracycline.
 - The evidence was inconsistent for active trachoma and ocular infection at three and 12 months (low-certainty evidence) and was not pooled due to considerable heterogeneity.
- Different dosing strategies
 - 6 studies compared different strategies for dosing.
 - There was no strong evidence to support any variation in the recommended annual mass treatment.

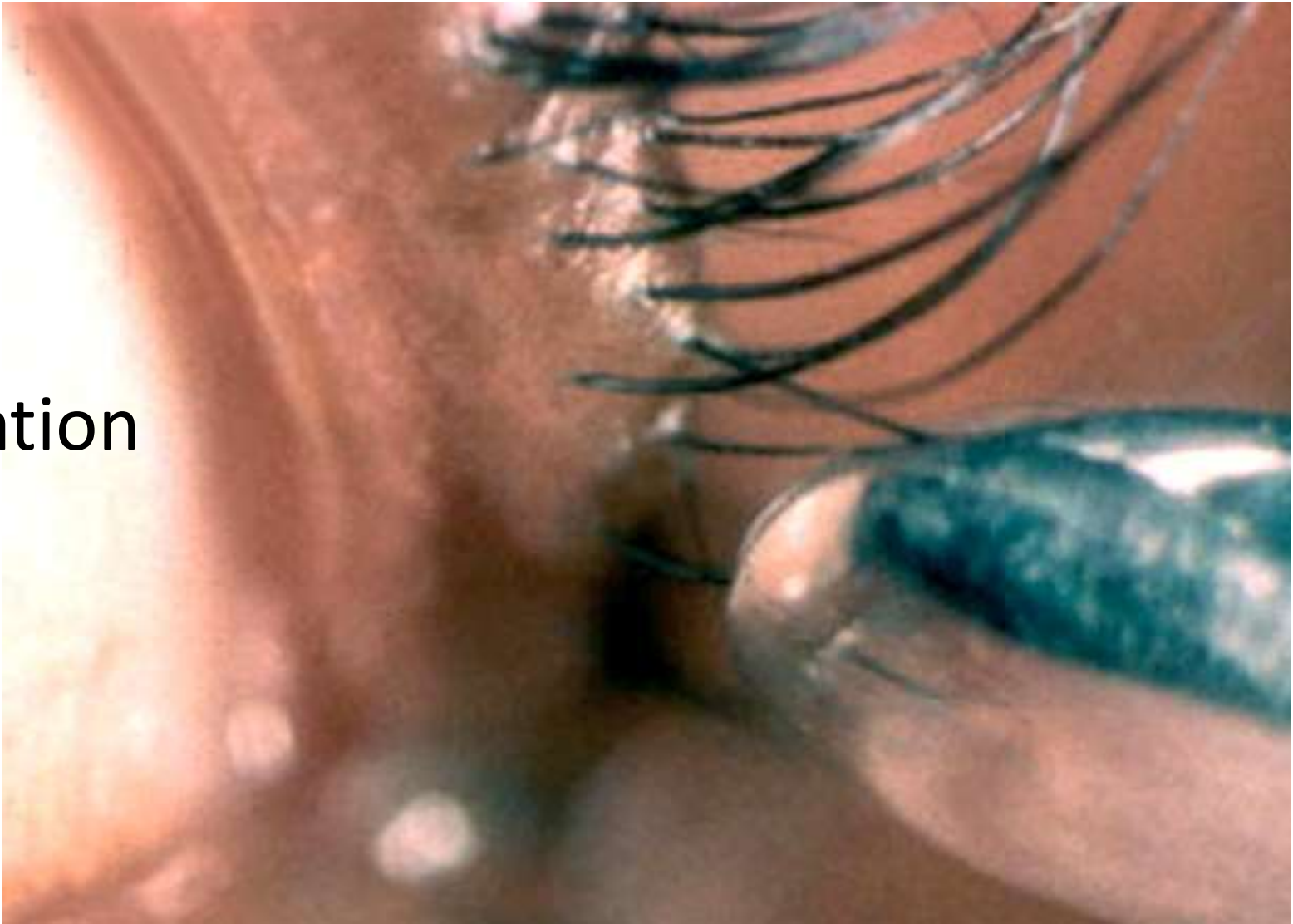
Surgery

- Epilation (the removal of hair by pulling it from the roots)
 - Simple, easy, and cheap
- Electrolysis
 - Simple, but needs the right equipment and personal training;
Not more than 4 together
- Trichiasis Surgery
 - Marginal Rotation. Eversion of superior tarsus
- In 2019, 93 thousand people received surgical treatment for advanced stage of the disease, and 95.2 million people were treated with antibiotics.

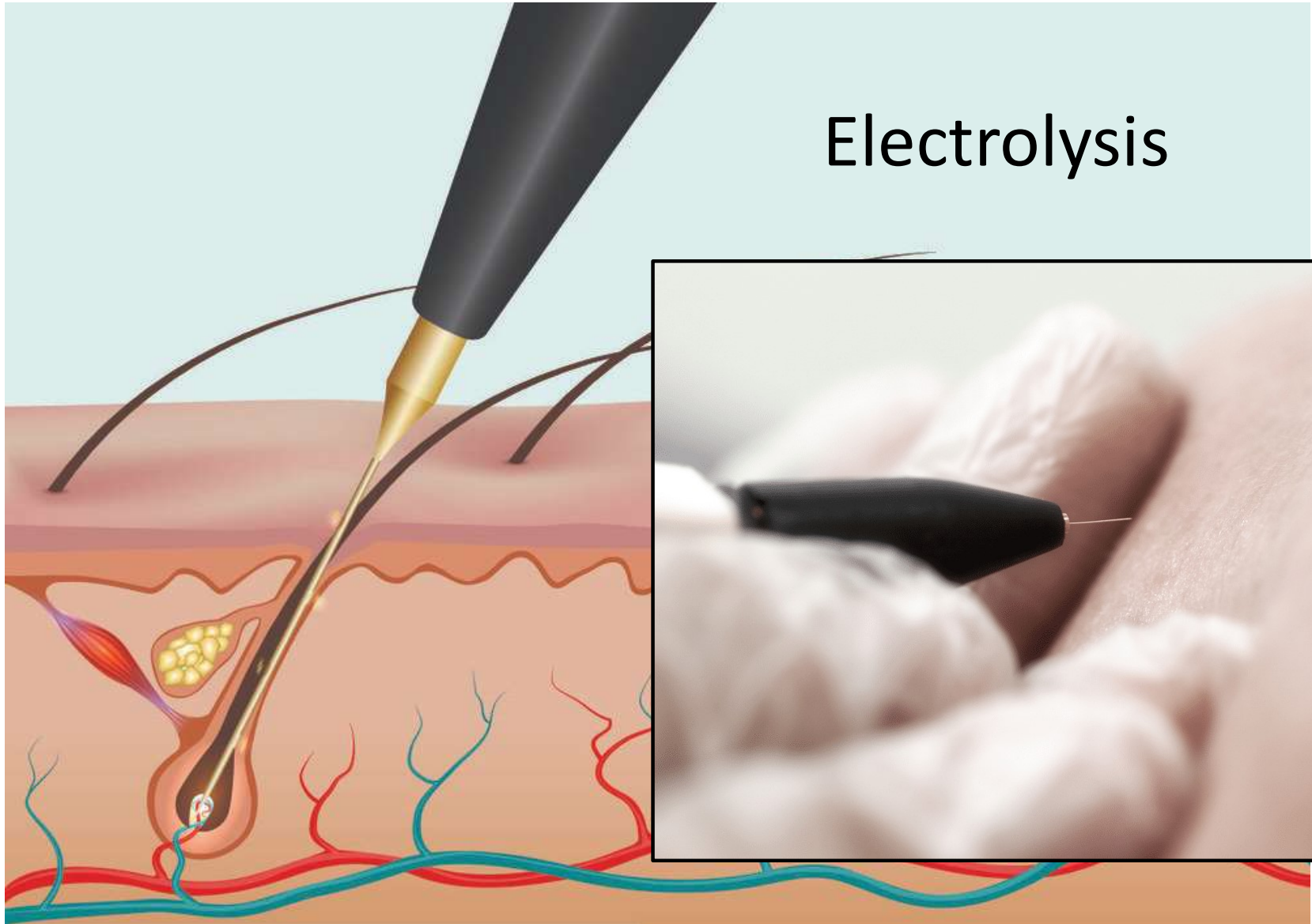
Panel 3: Barriers to acceptance of surgery

- Predictors of acceptance
- Other household member with income⁶⁷
- Symptoms that interfere with work⁶⁷
- Bilateral trichiasis⁶⁵
- Being a widow⁶⁵
- Living near the main road⁶⁵
- Low socioeconomic status⁶⁵
- Knowing someone who has had surgery⁶⁵
- Predictors of non-attendance
- Ignorance of availability of surgery^{64,67,68}
- Cost^{63,64,66-68}
- Being too busy^{63,67,68}
- Fear^{67,68}
- Transportation difficulties^{51,52,68}
- No support person to accompany them^{63,67,68}
- Having to leave children at home⁶³
- Symptoms not that bad⁶⁷
- Previous bad experience with surgery⁶⁷
- Epilation (or other treatment) fine⁶⁷
- Illiteracy⁶⁸

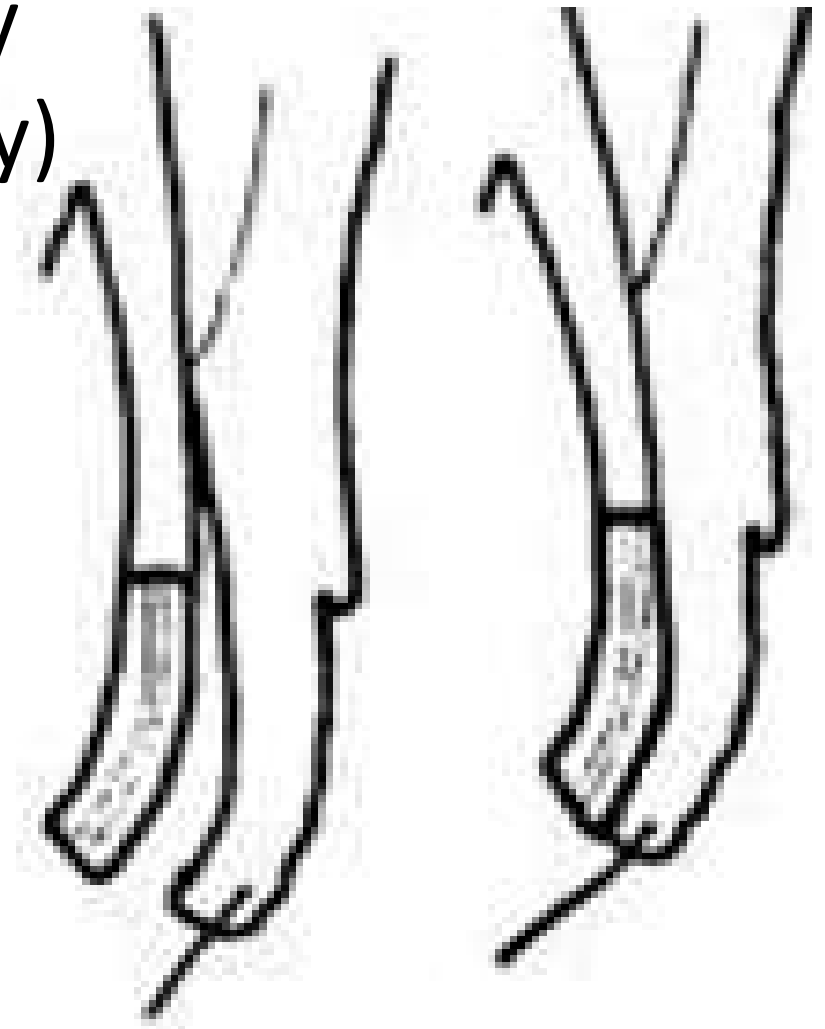
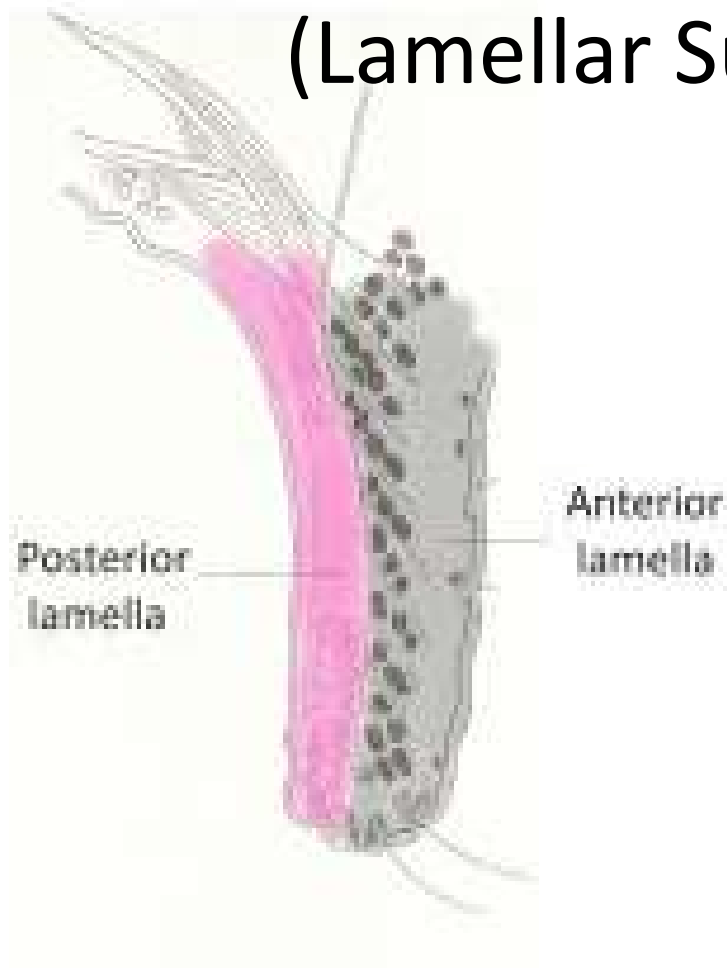
Epilation



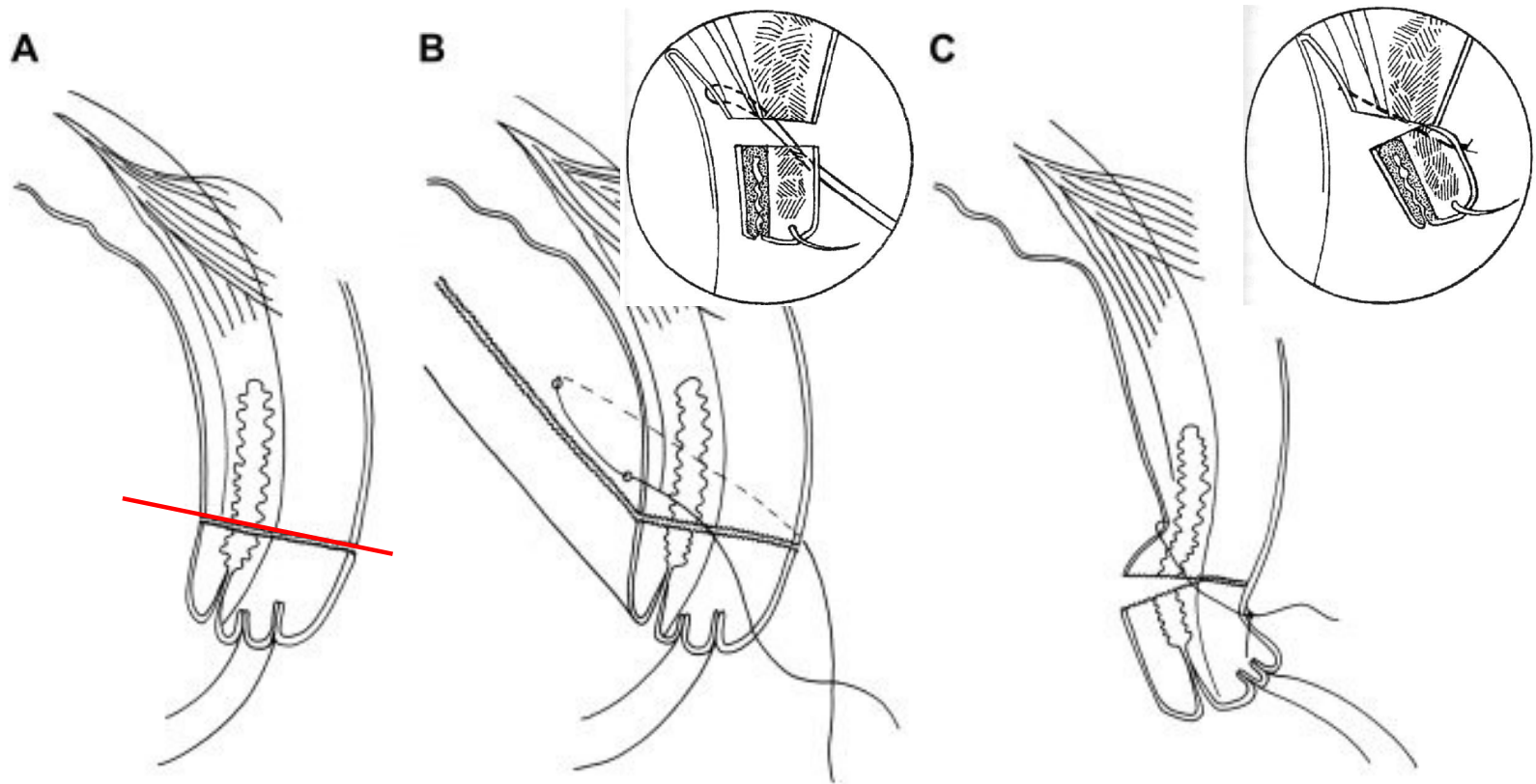
Electrolysis



Trichiasis Surgery (Lamellar Surgery)

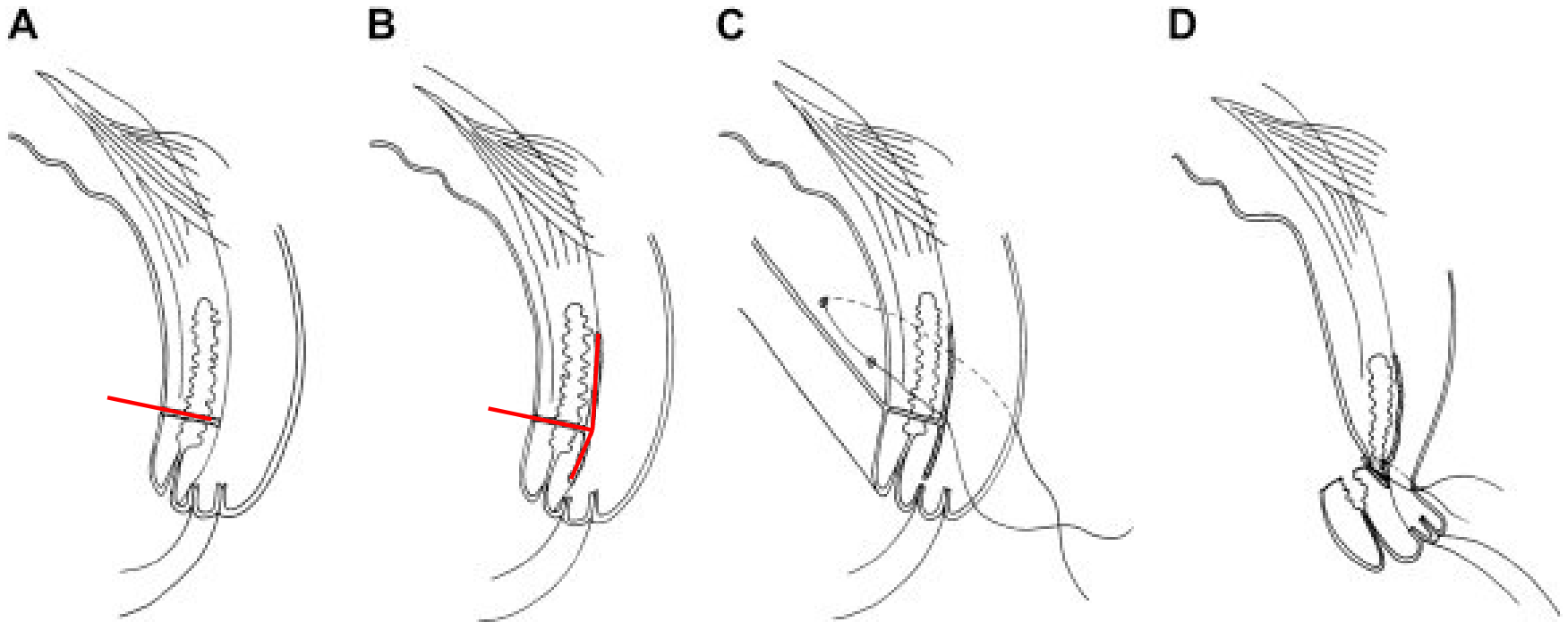


Bilamellar tarsal rotation:



A: Bilamellar incision. B: Horizontal mattress suture. C: Postoperative lid eversion.

Posterior lamellar tarsal rotation:



A: Posterior lamellar incision.

B: Dividing anterior and posterior lamellae.

C: Horizontal mattress sutures.

D: Postoperative lid eversion.

Trachoma

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