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An Index of Community Ocular *Chlamydia trachomatis* Load for Control of Trachoma

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The World Health Organization (WHO) has set a target of global elimination of trachoma as a blinding disease by the year 2020. The WHO simplified grading scheme (Thylefors et al., 1987), used by trachoma control programmes to assess and monitor progress, has been shown to have limitations. Clinical signs of active disease may be absent in the early (incubation) stages of infection and in “mild” infections; these signs are not pathognomonic and may occur with other infections; and they persist long after the organism can no longer be detected (Baral et al., 1999). An index which accurately reflected the impact of control programmes on the infecting organism, rather than on clinical signs, would therefore be beneficial.

Experience with onchocerciasis has demonstrated the utility of indices related to the average intensity of infection, in particular the community microfilarial load (CMFL; Remme et al., 1986). This is obtained by adding 1 to each microfilarial count, taking the geometric mean, then subtracting 1 from the result (the Williams mean, 1937). The geometric mean itself — the nth root of the product of the n data values — is zero whenever any single person’s count is zero. The CMFL prevents this, but has the disadvantage of being dependent on the units of the original data. For example, if a skin snip has 2mg of skin, the CMFL per snip is not double the CMFL per mg, even though both units are used (Remme et al., 1986; Marshall et al., 1986).

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Conflict of Interest

The authors have received research support from the International Trachoma Initiative, a non-profit organisation which receives funds from Pfizer Inc, the manufacturer of azithromycin.

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The advent of real-time quantitative polymerase chain reaction (Q-PCR) for *Chlamydia trachomatis* (Solomon et al., 2003) raises the possibility of an index of infection intensity for trachoma control. The scale-dependence of the CMFL can be avoided by adding and subtracting a number with the same units as the actual measurements, as opposed to a dimensionless value of 1. The smaller the value added and subtracted, the closer the index is to the geometric mean. We propose the value of 1 organism per ml of swab eluate, and call the resulting index the 'community ocular *Chlamydia trachomatis* load' (COCTL). This concentration of 1 per ml equals 0.0288 per Q-PCR capillary, or 0.55 per swab, so the COCTL is closer to the geometric mean than the Williams (CMFL) mean: very close, if no-one in the sample is negative. More commonly, there will be at least one negative person, in which case the COCTL is — like the Williams mean — somewhat arbitrary, but has the benefit of being comparable between studies, as well as subgroups of a single study, due to its scale-independence.

We assessed the COCTL in a large longitudinal study of azithromycin in Kahe Mpya, Rombo District, Tanzania (Solomon et al., 2003). At baseline, 956 of the 978 population contributed eye swabs for Q-PCR, and 955 were given a single oral dose of azithromycin. Follow-up surveys were done at 2, 6 and 12 months (Solomon, 2003). Ethical approval was given by the London School of Hygiene & Tropical Medicine and the Kilimanjaro Christian Medical Centre.

Using the Williams (CMFL) method, the Rombo infection intensities per swab at 2, 6 and 12 months, as percentages of the baseline value, are 13.8%, 8.6% and 4.6% respectively. When expressed per Q-PCR capillary, the corresponding values are 11.7%, 7.0% and 2.9%, showing a strong dependency on the units used, especially when there are many zeroes. Using a value of 1 per ml to add and subtract avoids this problem, yielding COCTL values of 13.9%, 8.7% and 4.7%, as a percentage of baseline, whether per capillary or per swab. If a different sample volume had been used in different surveys, then comparability could have been maintained by multiplying the value of 1/ml by the same factor as the volume.

In most settings, infection is concentrated in children, so a more efficient index could be obtained by concentrating on them. The table shows the COCTL by age and disease status. In practice, we would intend the overall index value in children, or in all ages, to be key: in our data, these are 1.1 and 0.4 organisms per swab, respectively. The concentration in children shows how the COCTL could be used to identify target groups for treatment.

Other possible statistical measures are problematic, largely because of extreme skewness. The two highest values (491,708 and 451,554 per swab) constitute 60% of the total estimated number of *Chlamydia trachomatis* organisms found in conjunctival swabs from the entire community, making the arithmetic mean highly dependent on them. For some applications, the arithmetic mean may be appropriate even with very skewed data (Barber & Thompson, 2000). If someone with half the community's *Chlamydia trachomatis* organisms was responsible for half the onward transmission, the arithmetic mean might be useful. However, the importance of within-house trachoma transmission makes this unlikely. The median is often used for skewed data but is not practical for trachoma because, except in the most severely affected areas, the majority of the community have no infection and therefore

the median is zero. Higher, eg 90th, percentiles are also limited by their dependence on extreme values, and lack of sensitivity in identifying low prevalence communities. Finally, measures such as the trimmed mean and other M-estimators require parameter choices which are either arbitrary or based on complicated criteria.

Clinical signs are imperfect indicators of *Chlamydia trachomatis* infection, and, as control programmes progressively reduce infection prevalence, they will become less useful in defining whether, and whom, to treat (Baral et al., 1999). Compared to prevalence of infection, quantifying the infective load has the advantage of identifying communities and sub-groups with heavier infections, which are more likely to maintain transmission. The COCTL is based on quantitative PCR and therefore requires sophisticated technology, expertise and significant expense. Its role would therefore seem to be in sentinel sites, in operational research to identify the most cost-effective strategies for reducing and eliminating the organism in various settings, and in calibrating disease measures such as the prevalence of active disease.

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Table

The community ocular *Chlamydia trachomatis* load per swab (COCTL) according to age, and presence or absence of active trachoma (ie TF, follicular trachoma, or TI, trachoma intense, or both).

	baseline COCTL per swab (*n*), according to age and trachoma status					
	aged 6 months to 10 years			**whole population**		
	uninfected	**infected**	**overall**	**uninfected**	**infected**	**overall**
clinical signs of active trachoma (TF or TI or both)	0 (*91*)	1069 (*45*)	6.2 (*136*)	0 (*116*)	853 (*58*)	5.8 (*174*)
neither TF nor TI	0 (*198*)	52 (*10*)	0.1 (*208*)	0 (*749*)	20 (*33*)	0.1 (*782*)
total	0 (*289*)	618 (*55*)	1.1 (*344*)	0 (*865*)	220 (*91*)	0.4 (*956*)