Age, Sex, and Cohort Effects in a Longitudinal Study of Trachomatous Scarring

Meraf A. Wolle,1 Beatriz Muñoz,1 Harran Mkocha,2 and Sheila K. West1

PURPOSE. To determine the 5-year incidence rate of scarring, and associated factors, in the population of Maindi, Tanzania.

METHODS. A census of every resident was obtained at baseline, and ocular examinations for the presence and severity of trachoma were performed. Images of the upper eyelid were taken and graded for the presence and severity of scarring, according to a four-step severity scale based on photographs. Five years after baseline, a second series of images was taken and graded for scarring. Incident scarring was defined as new scars in those without scarring at baseline; progression was defined as those with scars that worsened by one step or more at 5 years.

RESULTS. The rate of scarring at baseline increased with age, from 1% in the <6-year to 38% in the 41+-year age group. Females at any age had more scarring than did males. The 5-year incidence rate of scarring was 0.20 (95% confidence interval [CI], 0.16–0.25), but varied with age up to 0.43 in the 41+-year group. There was a striking cohort effect, with those aged less than 16 years at baseline having more prevalent scarring and incidence rates comparable to those aged 16 to 40. Progression rates averaged 0.47 (95% CI, 0.36–0.58).

CONCLUSIONS. In this trachoma-endemic community, incident scarring was high, especially in the younger cohorts. A dramatic increase in risk of trachomatous scarring occurred approximately 15 years ago and appears to be unabated. Trachoma control programs to reduce risk of scarring are urgently needed to avoid blinding complications in this community.

TRACHOMA, ocular infection caused by Chlamydia trachomatis, is the leading infectious cause of blindness worldwide. Approximately 150 million children have active trachoma, and approximately 1.3 million people, mainly adults, are blinded from the late sequelae.

Communities in which trachoma is endemic show typical age-specific patterns of various manifestations of the disease. Active follicular and severe inflammatory trachoma (active trachoma) occur primarily in young children, of whom up to 60% or more may have clinical signs in hyperendemic communities. In young adults, there is less active disease, and conjunctival scarring may occur as a consequence of repeated or prolonged bouts of active trachoma. After age 30, the prevalence of scarring increases and up to 10% of adults have trichiasis and entropion, which if untreated, places them at high risk of blinding corneal opacification.

The lengthy course involved in the transition from active trachoma to scarring has led to an incomplete understanding of the specific factors associated with this transition. In one prospective study, children with constant severe trachoma were at increased risk of incident scarring. Case–control studies have identified specific immunologic markers of scarring. However, there are no prospective population-based studies of incidence or progression of scarring in whole communities at high risk of trachoma.

In a population-based cohort of village residents, we determined the 5-year incidence of scarring across the population and evaluated the effects of age, gender, active disease status, and treatment history. In addition, we evaluated cohort effects in this population.

METHODS

The population was enrolled in a 5-year longitudinal study of trachoma and ocular C. trachomatosis infection in the village of Maindi, Kongwa district, Tanzania. The study has been described in detail elsewhere.

In short, a baseline census of every household was taken, a baseline survey was performed that included an examination for clinical trachoma, ocular swabs were taken to determine infection status, and images were obtained of the right upper tarsal conjunctiva. A follow-up survey was performed at 5 years after baseline, with the same methods used and the same data collected. To be eligible for this study, all residents of the village had to be present at baseline and 5 years.

At each survey, a trained trachoma grader (HM) classified the trachoma status of the everted upper eye lid using the World Health Organization (WHO) simplified grading scheme. In this scheme, the presence of TF (trachoma follicular, or at least five follicles of size 0.5 mm) is noted, and the presence of TI (trachoma intense, or inflammation so severe as to obscure 50% of the deep tarsal vessels). A digital camera (990; Nikon, Tokyo, Japan) was used to obtain an image of the everted upper eyelid of the right eye of each person.

Grading the baseline images for the presence of active trachoma was performed by two graders using the WHO simplified grading scheme. The graders also assessed the presence and severity of scarring on images at baseline and at 5 years, using a grading scale system based on photographs (Fig. 1). Scarring grades were subdivided into four levels of severity, with representative images having been chosen for each level. The definitions were as follows:

1. S1, a single line of scarring no more than 3 mm in length and some stellate scars, but not as severe as S2.
2. S2 (part of the WHO trachoma training set for scarring), multiple lines of scarring of more than 3 mm in length with or without convergence that occupy approximately one eighth of the eyelid, but not as severe as S3.
3. S3, a linear pattern of scarring occupying at least one third of the upper lid with clear conjunctiva between, but not as severe as S4.
4. S4, more than 90% of the conjunctiva obliterated by scarring.

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We considered using the fine grade for scarring published in the 1981 Guide to Trachoma Control, but the definitions included a measure of tarsal distortion, which is difficult to see on photographs, and there was no clear definition in that system of “severe” scarring or “fine” scarring.14

The images were graded for scarring at 5× magnification, by comparison with standards also assessed at 5× magnification. Interobserver agreement in using this system of grading on a set of 84 images was unweighted \( \kappa = 0.74 \). Images were assessed by two graders, and any disagreements that arose were openly adjudicated.

Azithromycin was offered to every resident of the village at baseline and again at 18 months after baseline. Treatment was a single dose, 20 mg/kg up to 1 gram. Coverage overall was high at baseline (86%) but lower at 18 months (64%); 94% of the overall population received at least one dose of treatment.15

We determined the incidence of scarring in those who at baseline had no scars (defined as grade less than S1). The population was divided by age at baseline, in 5-year increments, until the age of 20. This categorization permitted us to determine the direct observation of any cohort effects. The remaining population was divided into two cohorts of age 21 to 40 and 41+ years to accommodate the smaller number of adults who were not scarred at baseline. We did not include children younger than 6 months in this study, as they are not eligible for azithromycin and were not part of the original survey. We used the Fisher exact test or \( \chi^2 \) test to compare differences between the groups. All analyses were performed with commercial software (SAS; SAS Institute, Cary, NC). The research complied with the tenets of the Declaration of Helsinki. Research conducted with approval from the Johns Hopkins Institutional Review Board and the National Institute of Medical Research of the United Republic of Tanzania.

**RESULTS**

A total of 990 people were present in the village at baseline. However, due to the highly mobile nature of this community, only 487 (49%) of them were in the village at the 5-year follow-up. Of the 487, 453 (93%) had gradable images at both time points. The baseline characteristics of those examined at 5 years and those that were not are shown in Table 1. Residents in the 16- to 20-year age group at baseline were less likely to be present at 5 years and those less than 10 or greater than 40

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Examined at 5 y (( n = 487 ))</th>
<th>Not Examined at 5 y (( n = 503 ))</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age group in years</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1–5</td>
<td>22.2</td>
<td>18.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>6–10</td>
<td>18.9</td>
<td>15.1</td>
<td></td>
</tr>
<tr>
<td>11–15</td>
<td>12.5</td>
<td>15.1</td>
<td></td>
</tr>
<tr>
<td>16–20</td>
<td>7.8</td>
<td>17.9</td>
<td></td>
</tr>
<tr>
<td>21–40</td>
<td>24.4</td>
<td>24.4</td>
<td></td>
</tr>
<tr>
<td>41+</td>
<td>14.2</td>
<td>9.2</td>
<td></td>
</tr>
<tr>
<td>% Female</td>
<td>52.8</td>
<td>56.3</td>
<td>0.17†</td>
</tr>
<tr>
<td>Active disease*</td>
<td></td>
<td></td>
<td>0.04†</td>
</tr>
<tr>
<td>None</td>
<td>61.0</td>
<td>66.7</td>
<td></td>
</tr>
<tr>
<td>TF only</td>
<td>29.1</td>
<td>21.5</td>
<td></td>
</tr>
<tr>
<td>TI +/- TF</td>
<td>9.9</td>
<td>11.8</td>
<td></td>
</tr>
<tr>
<td>% Treated at baseline</td>
<td>86.9</td>
<td>86.1</td>
<td>0.56†</td>
</tr>
</tbody>
</table>

* Missing active disease status: \( n = 2 \) and 19, respectively.
† Age adjusted.

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**Figure 1.** Trachomatous scarring reference images.
years of age were more likely to be present. After adjustment for age, those who had left the village were slightly less likely to have trachoma than were those who remained. There were no significant differences in the other baseline variables between those who were in this study and those who were not.

The rate of active trachoma and the prevalence of scars by age group in the 487 person cohort are shown in Table 2. Active trachoma significantly declined with age. In the 1- to 5-year age group, 60% had TF only and 18% had TI (with or without TF) while in the 41+ year age group, active trachoma dropped to 1.5% and 2.9%, respectively. The percentage of people with scars at baseline, on the other hand, increased with age. In the 1 to 5-year age group, only one child had evidence of scarring, whereas in the 41+ age group, 58% were scarred. Severity of scarring increased with age, with all those having scarring of severity 4 in the age group aged 41+ years (Fig. 2). At baseline, the females had substantially more scarring and more severe scarring than did the males in all groups up to the group aged 41+ years.

The overall 5-year incidence rate of scarring was 0.20, with the highest rate in those aged 41+ years (Table 3). Progression rates of those with scars did not differ by age but reflect the small samples the younger age groups. There was no effect of treatment twice versus treatment once with azithromycin on scarring in any of the age groups (data not shown).

The baseline data suggested higher rates of scarring in those aged <16 years than might be predicted from those ages 16 to 40 years. The finding was not entirely explained by the sex of the subject. There was an absence of any scarring in the males aged 16 to 20 at baseline, partially explaining why the overall rates in that age group were so low (Fig. 2). However, even the females in the 16- to 20-year age group had less scarring than did the age group 11 to 15 years. The incidence rates of scarring in those <16 were also not significantly different from for those aged 16 to 40 years (P = 0.62), suggesting high rates in this young age group.

We examined a potential cohort effect by graphing the starting and 5-year ending prevalences of scarring in each 4-year age group up to age 25 (Fig. 3). It is noteworthy that the end points of the previous age group become the starting points of the next age group, as expected, until the 16- to 20-year age group. For this age group, the starting prevalence was much lower, where the 1- to 5-year-olds ended and became lower where the 11- to 15-year-olds began. Similarly, the starting and ending prevalences of scarring for the age group 21 to 25 mimicked those who were 10 years younger.

### DISCUSSION

In this trachoma hyperendemic community, there was evidence of a cohort effect of increased scarring that began in the children about 15 years ago. The active trachoma and infection rates were high at baseline in the children in this population, which matches the increased risk of scarring observed in their cohort. However, the young adults aged 16 and up to age 40 or so had less scarring at baseline. Incidence rates of scarring were high and similar across age groups until the 41+ group. After age 40, the prevalence and incidence of scarring was higher as expected with age.

We have no data from 15 years ago to describe the trachoma rates in this population when the cohort now aged 16 were infants, but the data suggest that trachoma rates were most likely lower. This finding is at variance with

### TABLE 2. Baseline Active Trachoma and Trachomatous Scarring Rates of the Cohort

<table>
<thead>
<tr>
<th>Age at Baseline</th>
<th>TF Only (n/N) %</th>
<th>TI ± TF (n/N) %</th>
<th>Scars† (n/N) %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1–5</td>
<td>65 (108)/193</td>
<td>20 (108)/193</td>
<td>1 (89)/100</td>
</tr>
<tr>
<td>6–10</td>
<td>49 (92)/132</td>
<td>12 (92)/125</td>
<td>11 (90)/122</td>
</tr>
<tr>
<td>11–15</td>
<td>19 (61)/31.2</td>
<td>6 (61)/9.8</td>
<td>15 (57)/26.3</td>
</tr>
<tr>
<td>16–20</td>
<td>4 (38)/10.5</td>
<td>4 (38)/10.5</td>
<td>4 (37)/10.8</td>
</tr>
<tr>
<td>21–40</td>
<td>3 (118)/2.5</td>
<td>4 (118)/3.4</td>
<td>24 (111)/21.6 41+†</td>
</tr>
<tr>
<td>Test for trend</td>
<td></td>
<td></td>
<td>P &lt; 0.001</td>
</tr>
</tbody>
</table>

* Two missing active trachoma grade at baseline.
† 34 missing scars grades at baseline or five years.

### TABLE 3. Five-Year Incidence and Progression Rates of Scars by Age Group

<table>
<thead>
<tr>
<th>Age at Baseline (y)</th>
<th>Incidence</th>
<th>Progression</th>
</tr>
</thead>
<tbody>
<tr>
<td>1–5</td>
<td>98 15.3</td>
<td>11 63.4</td>
</tr>
<tr>
<td>6–10</td>
<td>79 24.1</td>
<td>15 46.7</td>
</tr>
<tr>
<td>11–15</td>
<td>42 9.5</td>
<td>4 50.0</td>
</tr>
<tr>
<td>16–20</td>
<td>35 18.2</td>
<td>4 50.0</td>
</tr>
<tr>
<td>21–40</td>
<td>87 21.8</td>
<td>24 53.3</td>
</tr>
<tr>
<td>41+</td>
<td>28 42.9</td>
<td>31 51.6</td>
</tr>
<tr>
<td>Total</td>
<td>367 20.4</td>
<td>85 47.1</td>
</tr>
<tr>
<td>Test for trend with age</td>
<td>P = 0.038</td>
<td>P = 0.39</td>
</tr>
</tbody>
</table>

* Only one person was at risk of progression, a boy who did progress.
investigators who suggest that trachoma disappears over time\textsuperscript{16}; this does not appear to be the case in this population. The findings were not explained by differential loss of persons aged 16 to 20 years at the 5-year follow-up, as they had even less trachoma compared with those who remained in the study. This suggests that, if anything, the differences by age would be even more marked.

It is unlikely that differences in the host response to infection among younger children compared with that in older children or young adults could explain these differences, as younger children were often siblings of the older children, or children of the young adults. There is no reason to propose that they have a different immune response compared with their immediate family members at the same age. Although differential immune response may explain some of the variation in scarring seen in previous studies, it is not a likely explanation for this cohort effect.\textsuperscript{4–10}

Kari et al.\textsuperscript{17} have postulated that different genovars of \textit{Chlamydia} may have differential virulence. It is conceivable that the serovars of \textit{Chlamydia} have changed over time in this village, but we have no data on this intriguing potential factor.

There would have had to be a rapid introduction of a new, more virulent strain that quickly (within a few years) supplanted the old strain to produce the cohort effects in our study.

Atik et al.\textsuperscript{18} have postulated that treatment of \textit{C. trachomatis} may increase the risk of more frequent infection and decrease the likelihood of developing an immune response. However, the study in which this was postulated is problematic in that few persons with infection were in fact actually treated, and so the likelihood of reinfection or re-emergence from inadequate community treatment was high. In our study, we found no evidence that two treatments either increased or decreased the risk of scarring compared with one treatment. Too few persons were not treated at all to study the effect of lack of treatment on risk of scarring.

It may also be likely that the cohort effects in our study were due to changes in the environment in the village. We tried to ask the village elders what was different in the village about 15 years ago compared with those in 2000 (when we did the 5-year follow-up), but there was no clear cut answer. We suggest two possible explanations: First, the village conditions were very harsh after the enforced villagization in the 1960s in Tanzania, with few services and high child mortality. Trachoma has been associated with chronic malnutrition,\textsuperscript{19} and in one small study, severe inflammatory trachoma has been linked to mortality.\textsuperscript{20} If, in the older cohorts, children with severe trachoma were also those most likely to have chronic malnutrition and die, they would leave behind a “healthier” cohort of children who may be at less risk of scarring. In this scenario, conditions would have improved in the mid-1980s to -1990s so that the younger cohorts with severe trachoma would be more likely to survive to develop scarring. However, we have some data from 1986 in Kongwa to suggest that even in the mid-1980s conditions in general in villages were difficult, with environments that fostered high trachoma rates.\textsuperscript{21} Thus, it is not clear that conditions improved in the mid-1980s. Certainly, food shortages were common after inadequate harvests even into the 1990s. Noticeable improvements in the Kongwa area, and any effect of the National trachoma program, were not evident until well into 2002 and later.

Another possibility is that with the growth of the village population, conditions simply became more crowded with more likelihood of spread of trachoma over time. Even after treatment, reinfection across households occurs by 12 months.\textsuperscript{22} In this population, the prevalence and incidence rates of scarring were greatest in the 41+ age group, as expected from other cross-sectional surveys.\textsuperscript{2} Moreover, the rates were greatest in the females, especially in the younger cohorts. These findings are similar to our previous findings and those reported elsewhere.\textsuperscript{21,23–24} It will be interesting to follow this cohort of children as they progress into adulthood to determine whether the same rate of scarring will occur; the introduction of mass treatment into these communities on a regular basis will probably perturb the scarring rate, but at present the younger cohort is on target to achieve a rate of 40% by the age of 20. Of interest, the progression rates of those with scars did not vary much by age.

There are limitations to our study. The loss of the population over the 5-year period to migration was unavoidable, but decreased the sample size and power to detect differences. There may have been follow-up biases other than in the variables of trachoma and age that we were unable to account for.

In summary, the incidence of scarring in this Kongwa village demonstrated interesting cohort effects that suggest possible effects of crowding, or a competing risk of mortality in these cohorts. Further longitudinal follow-ups of these children are warranted to determine whether potential projections for scarring are realized and the effect of multiple rounds of mass treatment under the Tanzania National Program.

Acknowledgments

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