

## SCIENTIFIC CORRESPONDENCE

Community treatment with azithromycin for trachoma is not associated with antibiotic resistance in *Streptococcus pneumoniae* at 1 year

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**Aims:** To determine if macrolide resistant *Streptococcus pneumoniae* will be a major concern in areas that receive annual mass azithromycin distributions for trachoma.

**Methods:** A cross sectional survey was conducted of nasopharyngeal *S pneumoniae* isolates for susceptibility to azithromycin 1 year after administering a single dose of azithromycin to treat trachoma in a village in Nepal.

**Results:** *S pneumoniae* was isolated from 50 (86%) of 57 nasopharyngeal cultures and no resistance to azithromycin was detected.

**Conclusion:** The authors were unable to demonstrate that mass azithromycin therapy for trachoma produced macrolide resistant *S pneumoniae* that persists until the next scheduled annual treatment.

Mass, community-wide distributions of azithromycin have been shown to be effective in reducing the prevalence of ocular chlamydial infection in a population.<sup>1–6</sup> Given the World Health Organization's (WHO) initiation of a worldwide programme using azithromycin to eradicate trachoma by the year 2020,<sup>7</sup> the recommendation for mass treatment,<sup>1</sup> and the likely requirement for repeated treatments,<sup>8</sup> additional consequences of this systemic treatment should be explored.

Potential disadvantages of systemic treatment include allergic or other reactions and the selection and propagation of macrolide resistant bacteria in treated populations. Determining macrolide resistance in *Chlamydia trachomatis* is not standardised and rarely pursued, although there is well documented resistance to both azithromycin and erythromycin in *Streptococcus pneumoniae*.<sup>9–11</sup> After a single dose of azithromycin for trachoma, pneumococcal resistance has appeared in conjunctival isolates<sup>12</sup>; however, it is unclear that their presence alone presents clinical concerns. In a longitudinal study, a low level baseline prevalence of macrolide resistant pneumococcus in a community increased after a single dose of azithromycin for trachoma.<sup>13</sup>

Given that annual treatment may be needed in trachoma endemic areas,<sup>8</sup> timely assessments of nasopharyngeal *S pneumoniae* isolates would provide insight into the threat of burgeoning resistance. If no resistance exists 1 year after treatment, then perhaps annual azithromycin treatment will not have a significant impact on the prevalence of azithromycin resistant *S pneumoniae* in a population. In this study, the prevalence of macrolide resistant *S pneumoniae* was assessed 1 year after treatment with azithromycin, immediately before retreatment.

## MATERIALS AND METHODS

In a rural village in western Nepal, all children age 1–10 years were examined for the presence of trachoma on 1 December 1998 (visit 1). Clinical activity was assessed during examination, based on the WHO simplified trachoma grading scale,<sup>14</sup> and utilising a 2.5× loupe by trained personnel. All children with clinically active trachoma and all household members of these children were treated with a single dose (20 mg/kg in children; 1 g in adults) of oral azithromycin (Zithromax, Pfizer, New York, NY, USA).

Approximately 1 year later, on 15 November 1999 (visit 2), all village children were re-examined for the presence of trachoma. In addition, nasopharyngeal specimens were collected, using a calcium alginate swab, from a random cross section of children aged 1–10 years. Randomisation was achieved by assigning each child a pseudorandom number between 0 and 1 (Microsoft Excel “rand” function), and selecting all those with a value <0.3.

Nasopharyngeal specimens were immediately placed on selective streptococcus agar (blood agar with neomycin and polymixin B; Hardy Diagnostics, Santa Maria, CA, USA) and processed using standard microbiological techniques. Isolates were confirmed *S pneumoniae* by growth on streptococcus selective media, α haemolysis, susceptibility to optochin, and bile salt solubility. MIC values for azithromycin and trimethoprim/sulfamethoxazole were determined using Etest (AB Biodisk, Piscataway, NJ, USA). Control isolates confirmed the reliability of antibiotic susceptibility testing.

## RESULTS AND DISCUSSION

At visit 1, a total of 243 children were examined and 94 (39%) were found to have clinically active trachoma. On visit 2, 21 of 175 (12%) of the village children were found to have clinically active trachoma. Nasopharyngeal cultures were performed on 57 (median age 6 years, range 1–10) of the 175 children. Fifty of the 57 nasopharyngeal swabs were positive for *S pneumoniae* (prevalence 86%; 95% CI, 76% to 95%). None of these isolates (0%; 95% CI, 0% to 15%) were resistant (MIC ≥2 µg/ml) to azithromycin. Four of the 50 isolates (8%; 95% CI, 2% to 20%) were resistant (MIC ≥4 µg/ml) to trimethoprim/sulfamethoxazole.

There is a high prevalence of nasopharyngeal colonisation with *S pneumoniae* in the children of this rural Nepali village (86%). The 8% resistance to trimethoprim/sulfamethoxazole in *S pneumoniae* is not surprising as this antibiotic is one of the most widely available antibiotics in the area. Macrolide resistant *S pneumoniae* were not present in this sample of children 1 year after community-wide treatment with azithromycin. However, because of the low expected frequencies of macrolide resistance and the small sample size, these data lack power—even if as many as 15% of infections (or colonisations) with *S pneumoniae* in this village were resistant to macrolides,

there would still be a 5% chance of having recorded no resistance in our sample.

There was no control village that had not received azithromycin. However, the government sub-health posts in this area prescribe amoxicillin and trimethoprim/sulfamethoxazole, but not macrolides. Thus, the chance of de novo resistance in villages that did not receive azithromycin may be quite low.

In the study by Leach *et al*, azithromycin resistance was found in 1.9% of the pneumococcal isolates at baseline, 55% at 2–3 weeks, 35% at 2 months, and 6% at 6 months after azithromycin treatment.<sup>13</sup> Resistant serotypes that were found at 2–3 weeks, were less prevalent at 2 months and 6 months, perhaps because they were replaced by sensitive wild types. It is tempting to speculate that prevalence of these resistant strains might have returned completely to the baseline level at 1 year, which would be consistent with the current study's data.

Infectious diseases are transmissible, so if an individual in a village acquires a drug resistant strain, others in the same village are more likely to be infected with the same strain; samples taken from different villages will not correlate as well as samples taken from the same village. Thus, the above confidence intervals account for the sampling error of the prevalence within that particular village only, and do not reflect what would be expected by assessing other (even identical) villages which had undergone similar treatments. More villages, rather than just more people from a single village, need to be monitored before the risk for unacceptable levels of drug resistance can be discounted with confidence.

This study did not definitively prove the absence of resistance at 1 year. Nevertheless, the data are encouraging. Effective therapy for trachoma has not produced an unanticipated amount of macrolide resistant *S pneumoniae* in these children. If little or no resistance is found 1 year after treatment, the chance of establishing a permanent population of resistant bacteria is probably low. However the effect of repeat treatment is unknown, and assessment after multiple treatments is necessary. Resistance in villages where the entire population is treated with macrolides should be assessed. Only about 50% of the children were treated in both this study and in Leach's study.<sup>2 13</sup> Finally, even if a significant increase in the prevalence of resistant pneumococcus had been found 1 year after mass antibiotic administration, the benefit of trachoma eradication would probably outweigh the potential risks associated with the presence of resistant pneumococcus in these populations. Resistant organisms tend to be less fit than the wild type. Their presence is transitory and probably would reverse when treatment programmes conclude.<sup>15</sup> Larger longitudinal studies of multiple villages and multiple treatments are currently under way to address the limitations of this pilot study.

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