ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Sept. 2003, p. 2765–2769 Vol. 47, No. 9
0066-4804/03/$08.00+0 DOI: 10.1128/AAC.47.9.2765–2769.2003

Impact of Azithromycin Administration for Trachoma Control on the Carriage of Antibiotic-Resistant *Streptococcus pneumoniae*

Sarah L. Batt,[1] Bambos M. Charalambous,[1] Anthony W. Solomon,[2,3,4] Charles Knirsch,[5] Patrick A. Massae,[3] Salesia Safari,[3] Noel E. Sam,[4] Dean Everett,[1] David C. W. Mabey,[2] and Stephen H. Gillespie[1]*

Department of Medical Microbiology, University College London, Royal Free Campus, London NW3 2PF,[1] and London School of Hygiene and Tropical Medicine, London WC1E 7HT,[2] United Kingdom; Huruma Hospital, Huruma,[3] and Clinical Laboratory, Kilimanjaro Christian Medical College, Moshi,[4] Tanzania; and Pfizer Inc., New York, New York 10017-5755[5]

Received 13 February 2003/Returned for modification 4 March 2003/Accepted 9 June 2003

Community distribution of azithromycin has an important role to play in trachoma control. Previous studies have suggested that this may increase the prevalence of macrolide-resistant *Streptococcus pneumoniae*. *S. pneumoniae* was isolated from children under 7 years of age in Rombo District, northern Tanzania, before and 2 and 6 months after community-wide administration of azithromycin. Overall carriage rates were 11, 12, and 7%, respectively. Only one macrolide-resistant isolate carrying the *mef* gene was obtained 6 months after azithromycin administration. This contrasted with cotrimoxazole and penicillin resistance, both of which were common (cotrimoxazole resistance, 42, 43, and 47%, and penicillin resistance, 21, 17, and 16% at baseline, 2 months, and 6 months, respectively). There was a significant association between cotrimoxazole and penicillin resistance ($P < 0.0001$, Fisher's exact). These data suggest that in communities where macrolide resistance is rare, azithromycin distribution for trachoma control is unlikely to increase the prevalence of resistant organisms.

Trachoma is the most common infectious cause of blindness in the world. It is caused by *Chlamydia trachomatis*, an obligate intracellular bacterium. Possible strategies to control this disease, which predominantly affects poor, marginalized and displaced peoples, include the distribution of azithromycin on a community-wide basis (14). Azithromycin should be given as one element of the World Health Organization (WHO)-recommended SAFE strategy (surgery for in-turned lids, antibiotics for active disease, and face washing and environmental improvement to reduce transmission) (26). Community-wide application of single-dose oral azithromycin has been shown to be as effective as 6 weeks of once- or twice-daily tetracycline eye ointment administered under supervision (3, 6, 22). Under operational conditions, where tetracycline ointment must be administered by the patient or a family member, azithromycin is significantly more effective than tetracycline (4). Azithromycin is the antibiotic of choice for the control of trachoma in programs supported by the International Trachoma Initiative (D. Mabey and N. Fraser-Hurt, Cochrane database, Syst. Rev, CD001860, 2002).

Studies in the northern hemisphere have suggested an association between the widespread community use of antibiotics and a rise in antibiotic resistance in *Streptococcus pneumoniae* (2, 20). In an Australian aboriginal community, Leach's group conducted a prospective study of the impact of azithromycin given to children with trachoma and their household contacts who were children, on carriage and resistance of *S. pneumoniae*. Two weeks after azithromycin treatment, the prevalence of *S. pneumoniae* carriage had fallen compared to baseline; it recovered rapidly and was at normal levels 2 and 6 months after treatment. The proportion of *S. pneumoniae* isolates recovered that were-resistant to azithromycin was 1 of 54 (1.9%) before treatment and 6 of 11 (54.5%), 10 of 29 (34.5%), and 2 of 34 (5.9%) at 2 weeks, 2 months, and 6 months after treatment, respectively (13). The application of azithromycin also appeared to influence the serotype profile among those sampled. In contrast to the distribution strategy in the Leach study, many trachoma control programs advocate mass treatment of all community residents when the prevalence of disease is above locally defined thresholds. Fry et al. reported a surveillance study in a region of Nepal where trachoma is not hyperendemic. The design mixed retrospective collection of treatment information with prospective isolation and susceptibility testing of *S. pneumoniae* from nasopharyngeal swabs (7). Given that the majority of blinding trachoma occurs in countries with hyperendemic patterns of disease, we conducted a prospective study of *S. pneumoniae* colonization before and after treatment with azithromycin in a area of Tanzania where trachoma is mesoendemic.

Acute lower respiratory tract infections are one of the most important causes of death in children under 5 years old in developing countries (9). Though azithromycin for trachoma control is only available through a drug donation scheme and is unlikely to be used against lower respiratory tract infections in endemic countries because of its expense, the possibility of selection of pathogens cross-resistant to other macrolides or the spread of azithromycin-resistant strains may occur. It is important, therefore, that the impact of community-wide azithromycin treatment on antibiotic resistance should be evaluated. In this paper we report the results of antimicrobial

* Corresponding author. Mailing address: Department of Medical Microbiology, University College London, Royal Free Campus, Rowland Hill Street, London NW3 2PF, United Kingdom. Phone: 020 7794 0500, ext 3539. Fax: 020 7794 0433. E-mail: stepheng@rfc.ucl.ac.uk.

susceptibility testing of *S. pneumoniae* isolates obtained from children in a trachoma-endemic village in Tanzania before and 2 and 6 months after community-wide distribution of azithromycin.

MATERIALS AND METHODS

Ethics. This study was approved by the ethics committees of the Kilimanjaro Christian Medical College, Moshi, Tanzania, and the Tanzanian National Institute of Medical Research. Extensive consultation was undertaken with opinion leaders in the study village prior to the commencement of research. A village meeting approved the sampling protocol after discussion of the study's aims. Informed consent was obtained from parents or caregivers before samples were taken.

Description of study population. Fieldwork was undertaken in Kahe Village, Rombo District, northern Tanzania. Kahe lies on the northeast slopes of Mount Kilimanjaro at an elevation of between 1,300 and 1,600 m above sea level. There are two rainy seasons, the short rains in November-December, and the long rains in March through July; in recent years, rainfall has been considerably lower than historical averages. The economy is dominated by subsistence farming, though coffee and bananas are grown as cash crops by many families. Trachoma is endemic in Rombo; in a whole village survey conducted from April to June 2000, active disease was found in 1,096 of 5,527 people examined (19.8%). There is a dispensary in Kahe village that provides basic medical care to village residents as well as the people of adjoining villages. In addition, a variety of antibiotics but not macrolides are available over the counter in village shops. The designated district hospital, Huruma, is approximately an hour away by local bus.

A trachoma research program was initiated in Kahe village in 1999. As part of this research, all available nonpregnant resident individuals over 12 months of age were offered a single oral dose of azithromycin at 20 mg/kg (Zithromax; Pfizer) in August 2000. Women who thought they might be pregnant and children less than 12 months of age were given two tubes of tetracycline ointment (1%) instead of azithromycin, with instructions to apply it to the lower conjunctival fornices of both eyes twice daily for 6 weeks. Ointment was self-administered at home by the recipients or their caregivers. All azithromycin treatments were directly observed.

Sample collection. To investigate the impact of this antibiotic distribution on *S. pneumoniae* in children, we undertook cross-sectional surveys prior to the distribution and at 2 and 6 months after it. Throat swabs were chosen as the means of collecting samples as it was believed that they would be more acceptable to the local population. The first survey took place in August 2000, the second in October 2000, and the third in February 2001.

Throat swabs were obtained from each child aged 7 or below for whom consent was given. Between 300 and 400 samples were obtained on each day by three teams, and sampling was completed after 5 days. Swab tips were placed in a skim milk-glucose-glycerol (SGG) transport medium contained in bijoux bottles (1 ml). This method has been evaluated previously and shown to support *S. pneumoniae* survival better than direct plating and permits samples to be freeze-thawed at least five times without loss of viability (13, 17; S. L. Batt, B. M. Charalambous, N. E. Sam, and S. H. Gillespie, Abstr. 3rd Int. Symp. Pneumococci Pneumococcal Dis., 2002, abstr. P-01 21B). Samples were transported at ambient temperature to the local laboratory each evening, where the cotton tips were removed and discarded, and the liquid was aseptically transferred to sterile cryotubes and then stored at −70°C for between several weeks and several months.

Sample processing. Transport broth samples were processed in batches by inoculation on 5% sheep blood agar plates made selective by the addition of 5 μg of gentamicin per ml. For isolation, swabs were thawed and mixed and a 10 μl loop of SGG plated onto blood agar plates with gentamicin. When total bacterial numbers were small, the inoculation was repeated with 100 μl of transport broth. Suspect colonies were chosen for identification as *S. pneumoniae* on the basis of α-hemolysis and characteristic morphology. Identification was confirmed by optochin susceptibility. The identity of optochin-resistant colonies with pneumococcal morphology was confirmed by the bile solubility test. The theoretical lower limit of detection is 10 CFU/ml, although in reality it may be lower than this.

Susceptibility testing. The MICs of penicillin, cotrimoxazole, and erythromycin for all isolates were determined by means of the E-test (AB Biodisk, Solna, Sweden) with the manufacturer's instructions. Strains with a penicillin MIC of ≤0.1 mg/liter were called susceptible, those with an MIC of >0.1 to <2.0 were defined as intermediate, and those with an MIC of ≥2.0 mg/liter were defined as resistant. The relevant values for erythromycin were ≤0.25 and ≥1.0 mg/liter, and for cotrimoxazole they were ≤0.5 mg/liter for susceptible, >0.5 to <4.0 for intermediate, and ≥4.0 for resistant. Serotyping was performed by slide agglutination with antipneumococcal capture antibodies (Staten Serum Institute, Copenhagen, Denmark). This typing set included all of the serotypes that are contained in the 23-valent pneumococcal vaccine; other strains were defined as not typeable. The Danish system of serogroup nomenclature (10) was used throughout.

TABLE 1. Serotype distribution of *S. pneumoniae* isolated from children under the age of 7 years in Kahe village, Rombo district, in relation to the azithromycin donation program

Serogroup[a]	No. (%) of isolates		
	Pretreatment (n = 141)	2 mo (n = 149)	6 mo (n = 92)
1	2 (1.4)	1 (0.7)	0 (0)
3	8 (5.6)	9 (6.0)	7 (7.6)
4	4 (2.8)	3 (2.0)	4 (4.3)
5	1 (0.7)	0 (0)	1 (1.0)
6	20 (14.2)	26 (17.4)	8 (8.8)
7	6 (4.2)	4 (2.7)	2 (2.2)
8	1 (0.7)	1 (0.7)	0 (0)
9	15 (10.6)	12 (8.1)	6 (6.5)
11	4 (2.8)	7 (4.7)	4 (4.3)
12	1 (0.7)	0 (0)	3 (3.3)
14	1 (0.7)	1 (0.7)	0 (0)
15	8 (5.7)	3 (2.0)	7 (7.6)
17	1 (0.7)	2 (1.3)	0 (0)
18	5 (3.5)	7 (4.7)	8 (8.7)
19	29 (20.6)	33 (22.1)	9 (9.8)
20	0 (0)	0 (0)	1 (1.1)
22	1 (0.70)	0 (0)	0 (0)
23	18 (12.8)	10 (6.7)	12 (13.0)
Nontypeable	16 (11.3)	30 (20.1)	20 (21.8)

[a] Strains defined as not typeable were those that did not fall into the serotypes contained within the 23-valent vaccine. There were no significant differences in the numbers of different serotypes isolated.

RESULTS

Community surveillance. Overall treatment coverage for the village, including azithromycin and tetracycline, was 5,001 of 5,838 (85.7%). Of those treated, a total of 76 of 2,176 males and 143 of 2,825 females received tetracycline ointment, and the others received azithromycin. Coverage figures quoted represent the number of people treated (5,001) divided by the number of people actually living in the village at the time of the distribution (5,838), which was determined by a house-to-house census conducted by the research team.

A total of 1,315 samples were obtained at baseline, 1,225 at 2 months and 1,402 at 6 months. The prevalences of *S. pneumoniae* carriage at these time points were 11% (141 of 1315), 12% (149 of 1,225), and 7% (92 of 1,402), respectively. All of the *S. pneumoniae* isolates were serotyped. The most prevalent serotypes isolated were 6, 9, 19, and 23. It is notable that between 11.3 and 21.8% of the isolates did not fall into the serogroups contained in the 23-valent vaccine and were designated not typeable. A total of 60% would have been covered by the heptavalent vaccine. It is also striking that serotype 14, a frequent cause of invasive disease in children, was rare, with only two isolates identified during the study (<1%). The complete serotype data are given in Table 1.

The prevalence of *S. pneumoniae* carriage in study subjects was considerably lower than expected. To investigate whether this low carriage rate was due to methodological problems, we performed a parallel study in children of similar age in a local

TABLE 2. Susceptibility of isolates of *S. pneumoniae* obtained from children under the age of 7 years in Kahe village, Rombo district, Tanzania

Agent and susceptibility	No. (%) of isolates		
	Baseline (n = 141)	2 mo (n = 149)	6 mo (n = 92)
Penicillin			
Sensitive	111 (79)	125 (84)	77 (84)
Intermediate	30 (21)	24 (16)	15 (16)
Resistant	0	0	0
Cotrimoxazole			
Sensitive	82 (58)	85 (57)	49 (53)
Intermediate	20 (14)	25 (17)	20 (22)
Resistant	39 (28)	39 (26)	23 (25)
Erythromycin (any resistance)	0	0	1 (1)

sugar plantation, with the same protocols for obtaining throat swabs and for subsequent sample processing. The prevalence of *S. pneumoniae* carriage at this site was found to be 50% between October and December 2000.

The most striking feature of the data is the almost complete absence of macrolide resistance. During this study, only one erythromycin-resistant isolate was identified. This isolate was obtained from a specimen collected 6 months after antibiotic distribution. This isolate belonged to serotype 23 and was resistant to cotrimoxazole and intermediately resistant to penicillin. By specific PCR, it was demonstrated to possess the *mef* gene, indicating the presence of resistance due to an efflux pump. The methylase or *erm* gene could not be detected by PCR.

It was also noted that there were no children carrying penicillin-resistant strains, although intermediate resistance was common. Resistance and intermediate resistance to cotrimoxazole was very common. These data are summarized in Table 2. There was no significant change in the prevalence of penicillin or cotrimoxazole over the period of study.

Penicillin resistance was more common among isolates that were intermediate or resistant to cotrimoxazole. Of the 71 penicillin-resistant strains isolated during the study. 53 were resistant and 18 were sensitive to cotrimoxazole; of the 311 penicillin-sensitive strains, 113 were resistant and 198 were sensitive to cotrimoxazole. The association between intermediate penicillin resistance and any cotrimoxazole resistance was statistically significant (Fisher's exact, $P < 0.0001$).

DISCUSSION

The impact of antibiotic use on resistance is of considerable clinical importance. There is a growing threat from primary pathogens which have developed resistance to first-line therapeutic agents. Studies in Finland have shown an association between a reduction in erythromycin use and a fall in macrolide resistance in isolates of *Streptococcus pyogenes* (23). A study compared the effect of azithromycin and amoxicillin-clavulanate treatment of otitis media on *S. pneumoniae* nasopharyngeal colonization. Selection for antibiotic-resistant strains was not observed in children who received amoxicillin-clavulanate but was observed in two who received azithromycin (8). Azithromycin has been shown to select for macrolide-resistant *S. pneumoniae* when used for eradication of *S. pyogenes* carriage in elementary school children (15).

Adegbola et al. studied the impact of three doses of azithromycin (20 mg/kg) given as part of a trachoma control campaign. Oropharyngeal swabs were taken before treatment and 1 month later. There was a significant reduction in the carriage of *S. pneumoniae,* but the susceptibility patterns were not reported (1). A study based in Nepal took conjunctival swabs for bacterial culture from 121 children before and 14 days after treatment with azithromycin at 20 mg/kg. A control group was given the same dose at the 14-day review visit. In this study, azithromycin significantly reduced the number of bacterial pathogens isolated from the conjunctiva overall but significantly increased the number of macrolide-resistant *S. pneumoniae* (5). Leach et al.'s small study performed in the Australian Northern Territory among aboriginal children demonstrated selection of macrolide-resistant organisms after administration of azithromycin for the treatment of trachoma (13). Fry et al. reported macrolide resistance occurring in 2 of 92 (4.3%) colonized children after two annual doses of azithromycin for trachoma and suggested the need for resistance monitoring. Unfortunately, baseline carriage data from these children were not available to know whether this rate indicated a change over time (7).

Macrolide resistance may emerge through acquisition of genes which encode an efflux pump (*mef*) or a methylase (18). Additionally, resistance may emerge through point mutation in the 50S ribosomal subunit (21). Antibiotic resistance may emerge in a population of pneumococci because treatment eradicates susceptible organisms, favoring the survival of resistant strains. Alternatively, exposure of organisms to antibiotics may allow organisms which have developed point mutations in critical genes to survive (21). There is evidence that this can occur in *S. pneumoniae* during the treatment of patients with pneumonia (16).

Our study is the largest evaluation to date of the impact of an azithromycin distribution campaign on *S. pneumoniae* resistance. It gave us the opportunity to see whether community distribution of azithromycin changed the prevalence of resistance. No macrolide-resistant *S. pneumoniae* were found in Kahe village before antibiotics were given, and there are similar reports of a low prevalence of macrolide resistance in East Africa (19, 12), although there are reports that macrolide resistance is increasing rapidly in South Africa (11). There was no reduction seen in the prevalence of *S. pneumoniae* carriage after azithromycin distribution, as has been observed in other studies (13), possibly because our posttreatment sampling was performed after 2 months, when the initial clearing effect of azithromycin had passed. The 6-month point was chosen to detect the long-term impact of a pulse of azithromycin on the carriage of resistant organisms. At the 2-month and 6-month points, macrolide-resistant isolates were 0% and 1%, respectively. A single strain possessed the *mef* gene. This fact, together with the absence of 50S ribosomal subunit mutants, suggests that the resistance that was seen was already present in the community at a low prevalence or had been introduced into the community during the course of the study. Thus, when azithromycin selection pressure was applied, the prevalence of resistance did not increase significantly, probably because of the initial low prevalence of resistance. In the setting we stud-

ied, community-wide azithromycin administration for trachoma control did not affect the prevalence of macrolide-resistant *S. pneumoniae* in areas where such resistance is rare.

In this community, the prevalence of *S. pneumoniae* carriage was much lower than expected. We chose to use oropharyngeal swabs in this study because local discussions suggested that these would be more acceptable to children. This swabbing method is associated with a lower detection rate than nasopharyngeal swabs. However, we believe that the low carriage rate is a genuine finding because studies with the same swabbing technique in a nearby area at lower altitude and with higher humidity noted carriage rates of 50% throughout the year. Inefficiencies of specimen collection technique could only influence the result we obtained if resistant isolates were less likely to colonize the throat than the nasopharynx. There is no evidence in the literature to support this, and thus we believe that the organisms that we have described here form a representative sample of the *S. pneumoniae* carried by children in this village.

The prevalence of macrolide resistance differs very significantly from that of cotrimoxazole and penicillin in this community. This reflects the relative availability of these antibiotics (24). Macrolides were rarely used in the local district hospital and were not available in kiosks where antibiotics can be purchased without prescription. In contrast to the low level of macrolide resistance, cotrimoxazole resistance was common, and many of these strains were also penicillin intermediate resistant. There was a statistically significant relationship between cotrimoxazole resistance and penicillin resistance. This suggests that if a selection pressure in favor of cotrimoxazole were applied, penicillin-intermediate strains would be coselected. Such a selection pressure could arise if cotrimoxazole prophylaxis was used widely in patients with human immunodeficiency virus infection to reduce the incidence of opportunistic infections, as has been proposed (25).

The data presented in this study suggest that the impact of community-wide application of azithromycin is unlikely to increase the prevalence of macrolide resistance in communities where this type of resistance is rare before administration. This contrasts with the conditions pertaining in Australia, where the preadministration rate of macrolide-resistant *S. pneumoniae* was higher (13). In the district that we studied, it appears that there were so few macrolide-resistant strains before administration and the prevalence of carriage was so low that they were unable to take advantage of the selective pressure applied. Further studies are under way to evaluate the impact of azithromycin mass treatment on a wide range of infections, including clinical syndromes and changes in susceptibility.

ACKNOWLEDGMENTS

This study was funded by a grant from Pfizer Corporation.

We are grateful to the nursing and laboratory staff of Huruma Hospital and the Kilimanjaro Christian Medical Centre for their assistance and to Therese Donnelly for secretarial help. We are also grateful to David Farrell, who identified the molecular mechanism of macrolide resistance.

REFERENCES

1. **Adegbola, R. A., E. K. Mulholland, R. Bailey, O. Secka, T. Sadiq, K. Glasgow, and D. Mabey.** 1995. Effect of azithromycin on pharyngeal microflora. Pediatr. Infect. Dis. J. **14:**335–337.
2. **Arason, V. A., K. G. Kristinsson, J. A. Sigurdsson, G. Stefansdottir, S. Molstad, and S. Gudmundsson.** 1996. Do antimicrobials increase the carriage rate of penicillin-resistant pneumococci in children? Cross sectional prevalence study. Br. Med. J. **313:**387–391.
3. **Bailey, R. L., P. Arullendran, H. C. Whittle, and D. C. Mabey.** 1993. Randomised controlled trial of single-dose azithromycin in treatment of trachoma. Lancet **342:**453–456.
4. **Bowman, R. J., A. Sillah, C. Van Dehn, V. M. Goode, M. Muquit, G. J. Johnson, P. Milligan, J. Rowley, H. Faal, and R. L. Bailey.** 2000. Operational comparison of single-dose azithromycin and topical tetracycline for trachoma. Investig. Ophthalmol. Vis. Sc. **41:**4079.
5. **Chern, K. C., S. K. Shrestha, V. Cevallos, H. L. Dhami, P. Tiwari, L. Chern, J. P. Whitcher, and T. M. Lietman.** 1999. Alterations in the conjunctival bacterial flora following a single dose of azithromycin in a trachoma endemic area. Br. J. Ophthalmol. **83:**1332–1335.
6. **Dawson, C. R., J. Schachter, S. Sallam, A. Sheta, R. A. Rubinstein, and H. Washton.** 1997. A comparison of oral azithromycin with topical oxytetracycline/polymyxin for the treatment of trachoma in children. Clin. Infect. Dis. **24:**363–368.
7. **Fry, A. M., H. C. Jha, T. M. Lietman, J. S. Chaudhary, R. C. Bhatta, J. Elliott, T. Hyde, A. Schuchat, B. Gaynor, and S. F. Dowell.** 2002. Adverse and beneficial secondary effects of mass treatment with azithromycin to eliminate blindness due to trachoma in Nepal. Clin. Infect. Dis. **35:**395–402.
8. **Ghaffar, F., L. S. Muniz, K. Katz, J. Reynolds, J. L. Smith, P. Davis, I. R. Friedland, and G. H. McCracken, Jr.** 2000. Effects of amoxicillin/clavulanate or azithromycin on nasopharyngeal carriage of *Streptococcus pneumoniae* and *Haemophilus influenzae* in children with acute otitis media. Clin. Infect. Dis. 31:875–880.
9. **Greenwood, B. M.** 1999. The epidemiology of pneumococcal infection in children in the developing world. Phil. Trans. R. Soc. Lond. B **354:**777–785.
10. **Henrichsen, J.** 1979. The pneumococcal typing system and pneumococcal surveillance. J. Infect. **1:**31–37.
11. **Huebner, R. E., A. D. Wasas, and K. P. Klugman.** 2000. Trends in antimicrobial resistance and serotype distribution of blood and cerebrospinal fluid isolates of *Streptococcus pneumoniae* in South Africa, 1991–1998. Int. J. Infect. Dis. **4:**214–218.
12. **Joloba, M. L., S. Bajaksouzian, E. Palavecino, C. Whalen, and M. R. Jacobs.** 2001. High prevalence of carriage of antibiotic-resistant *Streptococcus pneumoniae* in children in Kampala, Uganda. Int. J. Antimicrob. Agents **17:**395–400.
13. **Leach, A. J., T. M. Shelby-James, M. Mayo, M. Gratten, A. C. Laming, B. J. Currie, and J. D. Mathews.** 1997. A prospective study of the impact of community-based azithromycin treatment of trachoma on carriage and resistance of *Streptococcus pneumoniae*. Clin. Infect. Dis. **24:**356–362.
14. **Mabey, D., and R. Bailey.** 1999. Eradication of trachoma worldwide. Br. J. Ophthalmol. **83:**1261–1263.
15. **Morita, J. Y., E. Kahn, T. Thompson, L. Laclaire, B. Beall, G. Gherardi, K. L. O'Brien, and B. Schwartz.** 2000. Impact of azithromycin on oropharyngeal carriage of group A *Streptococcus* and nasopharyngeal carriage of macrolide-resistant *Streptococcus pneumoniae*. Pediatr. Infect. Dis. J. **19:**41–46.
16. **Musher, D. M., M. E. Dowell, V. D. Shortridge, R. K. Flamm, J. H. Jorgensen, P. Le Magueres, and K. L. Krause.** 2002. Emergence of macrolide resistance during treatment of pneumococcal pneumonia. N. Engl. J. Med. **346:**630–631.
17. **O'Brien, K. L., M. A. Bronsdon, R. Dagan, P. Yagupsky, J. Janco, J. Elliott, C. G. Whitney, Y. H. Yang, L. G. Robinson, B. Schwartz, and G. M. Carlone.** 2001. Evaluation of a medium (STGG) for transport and optimal recovery of *Streptococcus pneumoniae* from nasopharyngeal secretions collected during field studies. J. Clin. Microbiol. **39:**1021–1024.
18. **Okamoto, H., K. Tateda, Y. Ishii, T. Matsumoto, T. Kobayashi, S. Miyazaki, and K. Yamaguchi.** 2002. High frequency of erythromycin A resistance and distribution of *mefE* and *ermB* genes in clinical isolates of *Streptococcus pneumoniae* in Japan. J. Infect. Chemother. **8:**28–32.
19. **Paul, J., J. Bates, J. Kimari, and C. Gilks.** 1996. Serotypes and antibiotic susceptibilities of *Streptococcus pneumoniae* in Nairobi, Kenya. J. Infect. **32:**139–142.
20. **Pedersen, G., H. C. Schonheyder, F. H. Steffensen, and H. T. Sorensen.** 1999. Risk of resistance related to antibiotic use before admission in patients with community-acquired bacteraemia. J. Antimicrob. Chemother. **43:**119–126.
21. **Pihlajamaki, M., J. Kataja, H. Seppala, J. Elliot, M. Leinonen, P. Huovinen, and J. Jalava.** 2002. Ribosomal mutations in *Streptococcus pneumoniae* clinical isolates. Antimicrob. Agents Chemother. **46:**654–658.
22. **Schachter, J., S. K. West, D. Mabey, C. R. Dawson, L. Bobo, R. Bailey, S. Vitale, T. C. Quinn, A. Sheta, S. Sallam, H. Mkocha, D. Mabey, and H. Faal.** 1999. Azithromycin in control of trachoma. Lancet **354:**630–635.
23. **Seppala, H., T. Klaukka, J. Vuopio-Varkila, A. Muotiala, H. Helenius, K. Lager, and P. Huovinen.** 1997. The effect of changes in the consumption of macrolide antibiotics on erythromycin resistance in group A streptococci in Finland. Finnish Study Group for Antimicrobial Resistance. N. Engl. J. Med. **337:**441–446.
24. **Stronge, R. L.** 2002. The epidemiology of *Streptococcus pneumoniae* infection

in young children in an area of Tanzania: a geographical perspective. Ph.D. thesis. Edinburgh University, Edinburgh, Scotland.

25. **Wiktor, S. Z., M. Sassan-Morokro, A. D. Grant, L. Abouya, J. M. Karon, C. Maurice, G. Djomand, A. Ackah, K. Domoua, A. Kadio, A. Yapi, P. Combe, O. Tossou, T. H. Roels, E. M. Lackritz, D. Coulibaly, K. M. De Cock, I. M. Coulibaly, and A. E. Greenberg.** 1999. Efficacy of trimethoprim-sulphamethoxazole prophylaxis to decrease morbidity and mortality in HIV-1-infected patients with tuberculosis in Abidjan, Côte d'Ivoire: a randomised controlled trial. Lancet **353:**1469–1475.
26. **World Health Organization.** 1996. Future approaches to trachoma control: report of a global scientific meeting. WHA/PBL/96.56. World Health Organization, Geneva, Switzerland.