Mass Azithromycin Distribution and Emerging Resistance: Taking a Minimum Harms Approach

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(See the Major Article by Coles et al on pages 1519–26.)

Trachoma is the leading cause of infectious blindness in the world affecting approximately 21.4 million people, causing visual impairment in 2.2 million and clinical blindness in 1.2 million individuals [1]. Blinding trachoma is endemic in 53 countries covering predominantly sub-Saharan Africa, the Middle East, and Asia, where children under 10 years of age are the core reservoir of the causative organism, Chlamydia trachomatis, and also most vulnerable to infection. The International Coalition on Trachoma Control was established in 2004 (http://www.trachomacoalition.org), which, together with the World Health Organization (WHO), has successfully engaged international governmental and nongovernmental agencies in trying to eliminate blinding trachoma by advocating and implementing the Surgery, Antibiotics, Face-washing, and Environmental change (SAFE) strategy. Mass administration of azithromycin (MDA) to children <10 years of age in endemic areas is an integral part of the SAFE program, and a recent Cochrane review assessing the evidence supporting the antibiotic arm of the SAFE strategy concluded that mass antibiotic treatment with single-dose oral azithromycin was associated with a 20% reduced relative risk of active trachoma and ocular infection [2]. Furthermore, MDA also decreased overall mortality in children 1–5 years of age by 65% [3], possibly because of azithromycin’s activity against common respiratory and gastrointestinal pathogens that often have a lethal outcome in children in trachoma-endemic areas. However, any ancillary benefits of MDA should outweigh the risks. Azithromycin use is not only associated with the emergence of macrolide resistance, but also with selection of strains resistant to β-lactams [4–6] that represent the most commonly used antibiotic group for respiratory infections.

In this issue of Clinical Infectious Diseases, Coles et al [7] analyze the impact of the WHO-recommended annual MDA on the emergence and persistence of macrolide resistance (MAC-R) in 1015 children aged <5 years from 8 communities in central Tanzania that have poor access to potable water. Four communities showing trachoma prevalence of ≥10% received annual MDA according to the Tanzanian government mandate and were compared with 4 neighboring communities that, having <10% trachoma prevalence, were ineligible for the annual MDA and served as the control group. Coles and colleagues identified a clear association between MDA exposure and MAC-R development in Streptococcus pneumoniae, a nontarget pathogen also commonly harbored by children. Proportion of total MAC-R isolates studied by Etest increased 2- to 3-fold, and among these, the highly resistant MAC-R isolates (minimum inhibitory concentration [MIC] ≥16 μg/mL) increased by up to 17-fold till the 6-month postprophylaxis study period. We have also previously shown that a single course of azithromycin has a significant impact on resistance in the oral streptococcal flora of healthy volunteers, in whom MAC-R proportions rose by up to 60% and remained 14% higher even at 6 months after therapy compared to the placebo-treated group [4].

MAC-R in streptococci occurs by 2 main mechanisms. The first is active drug efflux mediated by a pump encoded by the mef (macrolide efflux) gene that confers low to moderate resistance against macrolides (erythromycin MICs from 0.5 μg/mL to 32 μg/mL). In the second mechanism, a methylase encoded by the erm(B) gene modifies the macrolide binding site on the bacterial ribosome, generally conferring a high degree of resistance (MICs typically ranging from 32 μg/mL to >512 μg/mL). Interestingly, the increased prevalence of highly resistant MAC-R S. pneumoniae observed by Coles and colleagues from the 3-month postprophylaxis period onward corroborates our previous results [4].
wherein we showed an amplification of the lower resistance conferring mef efflux mechanism following azithromycin use as well as a phenotypic shift toward higher erythromycin MICs (8–16 μg/mL), observed approximately 1.5 months after therapy, among the selected mef-harbor- 
ing commensal streptococci [4]. While a larger reservoir of MAC-R genes in commensal streptococci increases the transfer potential to S. pneumoniae under antibiotic pressure, persistence of such organisms is highly dependent on the biological cost of the resistance mechanism to the bacterium in the absence of antibiotic pressure [8, 9]. Recent research suggests that maintaining antibiotic use below a critical threshold would not only facilitate stabilization of low levels of resistance but also of “milder” resistance mechanisms that have lower fitness costs for the bacterium [9]. Harboring and expressing mef, compared to erm(B), is less burdensome for S. pneumoniae [10], and would allow mef-harbor- 
ing S. pneumoniae to persist even once antibiotic pressure is low. In the long term, such community-wide shifts toward S. pneu- 
moniae clones with higher MICs increase the risk of potential treatment failures during empirical macrolide therapy [4, 11], and highlight the need to monitor the long-term impact of MDA on treatment options for pediatric infections.

Results from Coles and colleagues’ study also provide interesting insights on differences in resistance selection that exist between β-lactams and macrolides. More than 50% of the children included in the study received amoxicillin for acute lower respiratory tract infections during the baseline and 6-month study period. However, percentages of penicillin-resistant S. pneumoniae remained as low as 0%–1.9% during the study period. Selection of resistance by amoxicillin and its persistence in streptococci follows a much shorter trajectory than the macrolides [12], and might explain why resistance to this antibiotic remains relatively low despite several years of use. In contrast, high levels of co-trimoxazole resistance at baseline (exhibited by >40% of S. pneumoniae isolates screened) were not surprising, as co-trimoxazole pro- 
phylaxis is a fundamental aspect of care for human immunodeficiency virus (HIV)–infected adults and children living in resource-limited settings [13]. Co-trimoxazole resistance might also be selected by the frequent use of the antimalarial agent sulfadoxine-pyrimeth- 
amine, as both target enzymes in the folic acid synthesis pathway [14]. Its co- 
selection with MAC-R, however, is worrisome because such S. pneumoniae clones are likely to be maintained and enriched by frequent co-trimoxazole use in HIV patients, also prevalent in Africa.

Considered on its own, an annual MDA offers a “minimum harms” approach, with the selected MAC-R S. pneumoniae likely eliminated by the next treat- 
ment round [15], and importantly, is also not inferior to a more frequent MDA in decreasing infection prevalence [16, 17]. However, antibiotics alone cannot eliminate trachoma. Where possible, facial cleanliness and environmental improvement, the other important elements of the SAFE strategy, are seminal for breaking the transmission chain of C. trachomatis acquired through contact with eye discharge from infected persons and eye-seeking flies. Of note, Coles and colleagues also observed higher education levels and closer access to water re- 
sources in their non-MDA villages, which had a <10% prevalence of the disease. Taken together, these results un- 
derscore the need for basic health education and water availability and its use in sustaining the advancements achieved by MDA in combating this terrible disease.

Note

Potential conflicts of interest. Both authors: No reported conflicts.

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