WHO's mandate is to provide technical leadership and coordination to the international efforts aiming to eliminate trachoma as a public health problem. The recommended elimination strategy, known as "SAFE", was adopted by WHO in 1996, and is a combination of interventions implemented as an integrated approach. SAFE is an acronym for:

- **S**urgery for *trachomatous trichiasis*
- **A**ntibiotics to clear ocular *C. trachomatis* infection
- **F**acial cleanliness to reduce transmission of ocular *C. trachomatis*
- **E**nvironmental improvement, particularly improved access to water and sanitation.

The summaries on this page are related to **Antibiotics to clear ocular *C. trachomatis* infection**

Titles included in this document:

1. Relationship between Community Drug Administration Strategy and Changes in Trachoma Prevalence, 2007 to 2013.
2. A Cluster-Randomized Trial to Assess the Efficacy of Targeting Trachoma Treatment to Children
3. Prevalence of Active and Latent Yaws in the Solomon Islands 18 Months after Azithromycin Mass Drug Administration for Trachoma
4. Treating village newcomers and travelers for trachoma: Results from ASANTE cluster randomized trial.
5. Effectiveness of expanding annual mass azithromycin distribution treatment coverage for trachoma in Niger: a cluster randomised trial
6. Comparative efficacy of low-dose versus standard-dose azithromycin for patients with yaws: a randomised non-inferiority trial in Ghana and Papua New Guinea
7. One round of azithromycin MDA adequate to achieve the active trachoma elimination threshold in districts with prevalence of trachomatous inflammation—follicular of 5.0-9.9%: evidence from Malawi.
8. A Longitudinal Analysis of Chlamydial Infection and Trachomatous Inflammation Following Mass Azithromycin Distribution
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10. Antimicrobial resistance following mass azithromycin distribution for trachoma: a systematic review

1. **Relationship between Community Drug Administration Strategy and Changes in Trachoma Prevalence, 2007 to 2013.**

Liu B, Cowling C, Hayen A, Watt G, Mak DB, Lambert S, Taylor H, Kaldor JM.
PLoS Negl Trop Dis. 2016 Jul 6;10(7):e0004810. doi: 10.1371/journal.pntd.0004810. eCollection 2016 Jul.

Australia is the only high income country with persisting endemic trachoma. It is found primarily in small, remotely located Aboriginal communities. A national control program has been in place since 2006. From 2006 to 2013, the program involved annual screening of 5-9 year old children for trachoma in communities designated to be at high risk of disease and treatment of those affected with the antibiotic azithromycin. Depending on the level of trachoma detected in children, antibiotic treatment was also given to households and other community members.

In this study, data collected annually from 2007 to 2013 was used to examine what effect the extent of azithromycin treatment had on subsequent levels of trachoma in children aged 5-9 years. We found that in communities with high levels of trachoma (>=20%), when all community members received azithromycin (community-wide treatment), the greatest reduction in trachoma levels was achieved. However in communities with moderate levels of trachoma (5% to <20%), either community-wide treatment or more targeted (household) treatment resulted in similar reductions in trachoma (11% and 7% respectively).

While the findings suggest that in communities with moderate trachoma prevalence, either community-wide treatment (mass drug administration) or more targeted treatment may be equally effective, the unique nature of the trachoma problem in Australia (very small remotely located communities) and the nature of the Australian surveillance program, means that the relevance of these findings to settings outside of Australia is uncertain. Until the observation is confirmed in other settings, program managers should continue to adhere to current WHO recommendations regarding trachoma control strategies.

2. **Prevalence of Active and Latent Yaws in the Solomon Islands 18 Months after Azithromycin Mass Drug Administration for Trachoma**

Michael Marks, Oliver Sokana, Eli Nachamkin, Elliot Puiahi, Georgina Kilua, Allan Pillay, Christian Bottomley, Anthony W Solomon, David C Mabey
PLoS Negl Trop Dis 2016, **10**:e0004927.
http://dx.doi.org/10.1371/journal.pntd.0004927

Yaws is a bacterial infection closely related to syphilis. The WHO has launched a worldwide campaign to eradicate yaws by 2020. This strategy relies on mass treatment of the whole community with the antibiotic azithromycin. Mass treatment with azithromycin is also a major part of the SAFE strategy recommended by WHO to treat trachoma, but the dose used for trachoma is lower than that recommended for yaws. Both yaws and trachoma are endemic in many countries in the Pacific. In an earlier study in the Solomon Islands it was demonstrated that a trachoma control programme significantly reduced the prevalence of both clinical yaws and infection. A follow-up survey was conducted to see if this benefit persisted at 18 months.

A total of 1,284 children were examined in the study. Amongst children aged 5–14 years, 223 (27.5%) had blood test evidence of previous infection and thirty five children (4.3%) had blood test evidence of current infection. The coverage of MDA in each village was the strongest predictor of infection in children. The number of yaws cases notified to the Ministry of Health had remained significantly lower following MDA than the 3 proceeding years. Amongst children aged 1–4 years had evidence of infection 16 (3.5%) suggesting that transmission had not been completely interrupted.

Both yaws and trachoma are endemic in a number of countries, which has implications for the roll out of the SAFE strategy in these countries. Yaws interventions are recommended to occur every six months compared to annually for trachoma. Our data suggest that a trachoma control programme has a significant impact on yaws that lasts at least 18 months. This suggests that it might be possible to align the timing of trachoma and yaws interventions. A WHO sponsored study formally comparing lower and higher doses of azithromycin for the treatment of yaws is due to finish in 2016/2017. If the lower dose is shown to be equally effective then integration of trachoma and yaws control programmes may be possible in co-endemic countries.

3. A Cluster-Randomized Trial to Assess the Efficacy of Targeting Trachoma Treatment to Children

Abdou Amza[1], Boubacar Kadri,[1] Beido Nassirou,[1] Sun Y. Cotter,[2] Nicole E. Stoller,[2] Zhaoxia Zhou,[2] Robin L. Bailey[3], David C. Mabey[3], Travis C. Porco [2,4,5], Jeremy D. Keenan [2,4] Bruce D. Gaynor [2,4,] Sheila K. West [6], and Thomas M. Lietman [2,4,5]

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[3]Clinical Research Unit, Department of Infectious and Tropical Diseases, London School of Hygiene and Tropical Medicine, London, United Kingdom; Departments of [4]Ophthalmology and [5]Epidemiology and Biostatistics, University of California, San Francisco; and [6]Dana Center for Preventive Ophthalmology, Wilmer Eye Institute, Johns Hopkins University, Baltimore, Maryland

The World Health Organization recommends annual treatment of entire communities where trachoma is endemic. However, children typically have a higher bacterial load and higher probability and duration of infection compared to adults.

We conducted a cluster randomized trial to assess the efficacy of biannual treatment of children only compared to annual mass azithromycin distribution to all members of the community. Forty-eight communities in Matamèye, Niger were randomized to annual oral azithromycin treatment of the entire community or biannual treatment of children aged 0-12 years only. Both children and adults were monitored for ocular chlamydia infection by PCR. The prevalence of childhood infection was reduced in the annually treated arm from **21.2%** (95% CI 15.2%—28.0%) at baseline to **5.8%** (95% CI 3.2%—9.0%) at 36 months (p<0.001) and in the biannual arm from **20.2%** (95% CI 15.5%—25.3%) to **3.8%** (95% CI 2.2%—6.0%, p<0.001). Adult infection in the annual arm was reduced from **1.7%** (95% CI 0.9%—2.7%) to **0.3%** (95% CI 0.0%—0.7%) and in the biannual arm from **1.2%** (95% CI 0.5%—2.2%) to **0.0%** (95% CI 0.0%—0.7%, p=0.005).

The effect of biannual treatment of children compared to annual treatment of the entire community in both children (95% CI - 0.04%—0.02%) and adults (95% CI 0.9%—2.7%) excluded pre-specified non-inferiority threshold of **6%** (p=0.003 and <0.001 respectively). Periodic distribution of antibiotics to children in trachoma-endemic communities reduces chlamydial infection in both children and untreated adults, suggesting a form of herd protection.

Biannual treatment of children was comparable to (specifically, non-inferior to) annual treatment of the entire community, and may offer lower antibiotic use and other logistical advantages.

4. **Treating village newcomers and travelers for trachoma: Results from ASANTE cl uster randomized trial.**

PLoS One. 2017 Jun 29;12(6):e0178595. doi: 10.1371/journal.pone.0178595. eCollection 2017.

West SK, Munoz B, Mkocha H, Dize L, Gaydos CA, Swenor B, Ervin AM, Quinn TC.

Some Trachoma control programs have found that when districts have relatively low trachoma rates, despite ongoing rounds of Mass Drug Administration, it is harder to achieve a continual decline in trachoma. Investigators have found that newcomers to villages may have higher trachoma rates than longer term residents, and others have found that residents who travel outside the village, potentially to areas of greater risk for trachoma, may bring back trachoma. These sources of trachoma-newcomers and travelers-may contribute to higher rates of trachoma in surveys and potential may bring trachoma to other residents.

The ASANTE trial was a cluster randomized trial designed to test the hypothesis that a surveillance system (intervention) would result in more villages in the intervention arm with low rates of infection and trachoma compared to villages in the arm without such a program (control). The surveillance system consisted of Community Monitors, residents recruited at village level, who would identify and treat with azithromycin the newcomers and travelers every week.

In Kongwa district, 52 communities were enrolled in the trial and randomized to the intervention arm or the control arm. In addition, regularly scheduled MDA was provided annually to all communities in the trial, unless infection was ≤1% or TF was <5%. The communities were followed with 6 monthly surveys in a random sample of children age 1-9 years for trachoma and infection with ocular chlamydia.

Newcomers and travelers to these villages were frequent events. The 26 Intervention communities experienced an average of 110 surveillance events per month. At 24 months, 7 (27%) of 26 intervention communities achieved a prevalence of infection ≤1% compared to 4 (15%) of the 26 control communities. Although a difference was observed, it was not statistically significant. The estimated yearly change in trachoma in the control communities was -·04%, compared with -0·9% in the intervention communities, and this difference in the rate of change between control and intervention communities was borderline significant (p=0·05).

The study had one Community Monitor per 20-30 households, who visited their households once per week. This required a time commitment of less than the equivalent of a single day so as to not seriously compromise other work, and they were paid the equivalent of $1 per week to do this. At scale, without consideration of supervision or training, this would require around 3200 community monitors for Kongwa district alone. Outside of a research setting, a more practical approach would likely be targeting villages where in-migration from known endemic areas was greatest. Nevertheless, West et al concluded that the difference in infection rates would need to be sizable, at least the 30% as anticipated from previous data, to justify such an effort. The difference between 27% of communities with infection ≤1% compared to 15% of

communities in the control arm may not be sufficient justification to undertake such an approach.

5. Effectiveness of expanding annual mass azithromycin distribution treatment coverage for trachoma in Niger: a cluster randomised trial

Abdou Amza, Boubacar Kadri, Beido Nassirou, Sun Y Cotter, Nicole E Stoller, Sheila K West, Robin L Bailey, Travis C Porco, Bruce D Gaynor, Jeremy D Keenan, Thomas M Lietman, Catherine E Oldenburg. Br J Ophthalmol. 2017 Sep 11. pii: bjophthalmol-2017-310916. doi: 10.1136/bjophthalmol-2017-310916

The World Health Organization recommends 3-5 years of annual mass azithromycin distribution with at least 80% treatment coverage to districts with active trachoma prevalence over 10% among children. However, trachoma control has been difficult to achieve in some communities under the current guidelines. Alternative antibiotic strategies, such as expanding azithromycin coverage, may be beneficial for trachoma control. We assessed the efficacy of an enhanced azithromycin coverage strategy that involved three follow-up visits to achieve coverage of 90% or greater compared to the standard single day azithromycin treatment with a coverage target of 80% or greater in a mesoendemic region of Niger.

Twenty-four communities were randomised to a single day of azithromycin distribution with a coverage target of 80% of the community or up to 4 days of treatment, aiming for greater than 90% coverage. Distributions were annual and individuals above 6 months of age were treated. Children under 5 years of age were monitored for ocular chlamydia infection and active trachoma. We compared ocular chlamydia prevalence in communities in the standard versus enhanced coverage arms at 36 months.

At baseline, ocular chlamydia prevalence was 20.5% (95% CI 9.8% to 31.2%) in the standard coverage arm and 21.9% (95% CI 11.3% to 32.5%) in the enhanced coverage arm, which reduced to 4.6% (95% CI 0% to 9.5%, p=0.008) and 7.1% (95% CI 2.7% to 11.4%, p<0.001) at 36 months, respectively. There was no significant difference in 36-month ocular chlamydia prevalence between the two arms (p=0.21).

We found no benefit of expanding azithromycin coverage for annual mass azithromycin distribution strategies in this region of Niger, which was consistent with previous reports in Tanzania and the Gambia. Taken together, these three studies indicate that expanding coverage beyond the WHO target yields little if any additional benefit for trachoma control.

6. **Comparative efficacy of low-dose versus standard-dose azithromycin for patients with yaws: a randomised non-inferiority trial in Ghana and Papua New Guinea***.*

Marks, M., et al. (2018). Lancet Global Health 6(4): e401-e410.

Yaws is a bacterial infection of the skin, cartilage and bone. WHO has launched a worldwide campaign to eradicate yaws by 2020. This strategy relies on mass treatment of the whole community with the antibiotic azithromycin. Mass treatment with azithromycin is also a major part of the SAFE strategy recommended by WHO to eliminate trachoma, but the dose used for trachoma is lower than that recommended for yaws. Both yaws and trachoma are endemic in many countries in the Pacific.

This was a multi-county study run in Ghana and Papua New Guinea to evaluate the relative efficacy of a 30mg/kg dose of azithromycin (max 2gm, "standard dose") and a 20mg/kg dose of azithromycin (max 1gm, "low dose") for the treatment of yaws. Treatment was evaluated in both patients with active yaws (patients with a skin lesion from which *T. pallidum* DNA was detected) and patients with latent yaws (patients with positive blood tests but whose skin lesion did not contain *T. pallidum* DNA).

A total of 583 children were enrolled; 292 patients were assigned a low dose of azithromycin and 291 patients were assigned a standard dose of azithromycin. 191 participants had active yaws and 392 had presumed latent yaws. Complete follow-up to 6 months was available for 157 (82·2%) of 191 patients with active yaws. In cases of active yaws, cure was achieved in 61 (80·3%) of 76 patients in the low-dose group and in 68 (84·0%) of 81 patients in the standard-dose group. Amongst patients with latent yaws, cure was achieved in 59% in the low-dose group and 51% in the standard-dose group. Only a single participant (with presumed latent yaws) had definitive serological failure.

Although further data are needed to unequivocally establish the non-inferiority of low-dose azithromycin, the data in this study, together with existing observational data, suggest that 20 mg/kg of azithromycin is an effective treatment for yaws. In co-endemic countries planning mass drug administration for trachoma, the current results provide reassurance that this will also have a beneficial effect on the prevalence of yaws.

7. **One round of azithromycin MDA adequate to achieve the active trachoma elimination threshold in districts with prevalence of trachomatous inflammation—follicular of 5.0-9.9%: evidence from Malawi.**

Khumbo Kalua[1, 2, *], Alvin Chisambi[2], David Chinyanya[2], Michael Masika[3], Rebecca Willis[4], Paul M Emerson[4], Anthony W Solomon[5,6], Robin L Bailey[6]

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Author Synopsis

As highly trachoma-endemic countries approach elimination, some districts will have prevalences of trachomatous inflammation–follicular in 1–9-year-olds (TF1-9) of 5.0–9.9%. The World Health Organization (WHO) previously recommended that in such districts, TF prevalence be assessed in each sub-district (groupings of at least three villages), with three rounds of azithromycin treatment offered to any sub-district in which TF≥10%. Given the large number of endemic districts worldwide and the human and financial resources required to conduct surveys, this recommendation may not be practical, as countries approach end stage. To explore alternative recommendations, researchers identified a group of 8 Malawi districts with baseline TF prevalences of 5.0–9.9%, in which one round of azithromycin mass treatment (MDA) had previously been administered by the health ministry, achieving mean MDA coverage of ~80% (69.5–83.9). These districts implemented the full "SAFE" strategy (Surgery, Antibiotics, Facial Cleanliness and Environmental improvement) as part of the National Trachoma Program. The F&E components involved a health education promotion package, and a behavior change component (facial cleanliness, appropriate disposal of solid human waste and encouraging communities to be open defecation free).

A series of cross sectional studies were conducted to re-estimate the prevalence of TF, with each survey occurring at least 6 months after the single round of MDA.

In 18 EUs, a total of 432 clusters were selected, as per protocol: in other words, 24 clusters per EU, and 30 households per cluster, were visited. In total, from the 12,960 households, 28,095 children aged 1-9 years were enrolled, among which 26,158 (93%) were examined. Consent for examination was refused for 120 children; 1,810 children were absent at the time of the survey team's visit; and 7 children were ill and not examined. All EUs had a TF prevalence in 1–9 years old of <5.0 % (below the WHO-defined threshold for elimination of active trachoma), with the lowest having a prevalence of 0% and the highest 2.9%. The upper bound of the 95% confidence interval for each TF prevalence estimate was <5.0%.

Overall, the results suggest that one round of MDA, applied to low endemic districts, was enough. The moderate-to-high MDA coverage achieved in the 8 Malawi districts here, coupled with the F&E strategy that was implemented as part of the program, was associated with post-MDA prevalences of TF of <5% in each of the districts' 18 constituent EUs, and can therefore be considered, in hindsight, to have been adequate. If the low TF prevalences observed at impact survey are sustained in the absence of antibiotic pressure over the subsequent two years of

surveillance, it may be reasonable to believe that one round of well-conducted, relatively high-coverage antibiotic MDA may be sufficient to eliminate active trachoma in districts that are hypoendemic at baseline.

These findings are likely to be weighed up in future reviews of global guidelines, as the human, financial, and pharmaceutical (azithromycin) resources required for one MDA round are much less than those needed for several rounds. Combatting "trachoma" should, however, involve implementation of all aspects of the A, F and E components of the "SAFE" strategy, not just the use of antibiotics.

8. **A Longitudinal Analysis of Chlamydial Infection and Trachomatous Inflammation Following Mass Azithromycin Distribution**

Ophthalmic Epidemiol. 2018 Aug 28:1-8. doi: 10.1080/09286586.2018.1512635.
Morberg DP, Alemayehu W, Melese M, Lakew T, Sisay A, Zhou Z, Cevallos V, Oldenburg CE, Porco TC, Lietman TM, Keenan JD

Trachoma is caused by ocular chlamydia infection. The elimination strategy supported by the World Health Organization (WHO) centers around mass distributions of azithromycin to reduce the community burden of infection. Mass azithromycin distributions are effective for clearing ocular chlamydia. But in areas with highly prevalent trachoma, infection frequently returns even after many years of repeated mass azithromycin distributions. Mass azithromycin distributions have been found to have several unintended benefits, including preventing childhood mortality, but they also present the potential harm of antibiotic resistance. Targeting antibiotics to those children most likely to become re-infected would reduce the overall amount of antibiotics distributed in the community and hence reduce the potential for antimicrobial resistance, but the optimal population for targeting antibiotics is not clear.

We performed a secondary analysis of a cluster-randomized trial conducted in a trachoma-hyperendemic region of Ethiopia in 2003. In the trial, 21 villages were treated with a single mass azithromycin distribution. All children 5 years and younger were invited for a conjunctival swab and eye examination before treatment and at 2 and 6 months following treatment. The swab was processed for chlamydia with a polymerase chain reaction (PCR) assay and the examination was performed according to the WHO's simplified grading system in order to assess for trachomatous inflammation—follicular (TF) and trachomatous inflammation—intense (TI).

1102 children aged 1-5 years were swabbed at all three time points and were included in the analysis. At baseline, 617 (56.0%) of these children were infected with ocular chlamydia. All 21 villages were subsequently treated with a mass azithromycin distribution, with an estimated azithromycin treatment coverage of 88.7% (95% confidence interval [CI] 85.7 to 91.8%). At the 2-month visit, a total of 1005 children (91.2%) tested negative for ocular chlamydia, of whom 41 became infected by 6 months (1.0 incident chlamydia infections per 100 person-months,

95%CI 0.7 to 1.4). Children with TI at baseline were significantly more likely to have incident infection at 6 months (incidence rate ratio [IRR] 1.91, 95%CI 1.03-3.55). Children with an infected sibling at baseline were also more likely to become re-infected by 6 months, although this was not statistically significant (IRR 2.37, 95%CI 0.73-7.73). These results suggest that targeting antibiotic treatments to children with TI may be one potential treatment strategy for trachoma. Moreover, if targeted treatments were pursued, these results support the idea of treating all siblings in a household.

As has been shown before, the clinical signs of trachoma had generally poor agreement with ocular chlamydia infection. Before treatment, children with TF were infected 61% of the time and children with TI 77% of the time. Six months after treatment, children with TF were infected 15% of the time and children with TI 25% of the time. Thus, while neither grade correlated well with infection after mass azithromycin treatments, TI was more indicative of infection, suggesting this grade might be used to target treatments.

Ocular chlamydia infections clustered more within households than communities, with an intraclass correlation coefficient (ICC) of 0.01 (95%CI 0.002-0.06) for communities and 0.29 (95%CI 0.19-0.41) for households six months post-treatment. The ICC can be interpreted as the chance that any two household members have the same infection status; thus higher numbers indicate more clustering. These results reinforce the idea of targeting treatments to entire households if pursuing a strategy of targeted treatments.

We assessed for risk factors for persistent clinically active trachoma, defined as having TF and/or TI at both months 2 and 6. Persistent clinically active trachoma was more common in younger children (odds ratio [OR] 1.20 per year of younger age, 95%CI 1.05 to 1.37) and in children infected at baseline (OR 2.04, 95%CI 1.39 to 3.00). Since persistent conjunctival inflammation is ultimately the basis of future trachomatous scarring, trichiasis, and blindness, this suggests that targeting treatments to the youngest children may be a potential strategy. Chlamydial testing would also provide a potential mechanism for targeting treatments, as would examinations for TI given the association between TI and ocular chlamydia infection.

In summary, this study suggests that potential populations for targeted antibiotic strategies include young children, children with TI, and households with children who were infected before the azithromycin distribution.

9. **Longer-term assessment of azithromycin for reducing childhood mortality in Africa**

N Engl J Med. 2019 Jun 6;380(23):2207-2214. doi: 10.1056/NEJMoa1817213.

Keenan JD, Arzika AM, Maliki R, Boubacar N, Elh Adamou S, Moussa Ali M, Cook C, Lebas E, Lin Y, Ray KJ, O'Brien KS, Doan T, Oldenburg CE, Callahan EK, Emerson PM, Porco TC, Lietman TM.

Summary of MORDOR I. The MORDOR (Macrolides Oraux pour Réduire les Décés avec un Oeil sur la Résistance) trial was a cluster-randomized trial conducted in Malawi, Niger, and Tanzania in which communities were randomized to mass distributions of either azithromycin or placebo targeted to children 1-59 months of age. MORDOR found an overall 14% (95%CI 7 to 20%) reduction in mortality among 1-59 month-old children over the two-year study period, with a 6% (95%CI -10 to 20%) reduction in Malawi, 18% (95%CI 10 to 26%) reduction in Niger, and 3% (95%CI -21 to 23%) reduction in Tanzania.

Rationale for MORDOR II. Repeated mass azithromycin distributions have been shown to select for antibiotic resistance when given for trachoma. Emerging antimicrobial resistance could have negative health impacts on the community, potentially negating any mortality benefits of mass azithromycin. Thus, longer term follow-up of the intervention was necessary to determine whether the mortality benefit waned or even reversed over time.
Study Design. MORDOR II was a continuation trial of MORDOR I at the Niger study site, with a similar study design and procedures. In MORDOR I, a population census was performed every 6 months over a two-year period. Children aged 1-59 months were offered a dose of study drug during each census visit (20mg/kg azithromycin suspension approximated by height-based dosing for children who could stand, or an analogous dose of identical-appearing placebo suspension). The child's vital status was assessed at the subsequent biannual census, with children who were alive at the initial census and absent due to death at the subsequent census being counted as a mortality outcome. The same procedures were followed in MORDOR II for two additional six-month study periods, except that all children received open-label azithromycin. Thus, MORDOR II was a comparison of communities receiving their third year of mass azithromycin (i.e., the communities originally randomized to azithromycin in MORDOR I) versus those receiving their first year of mass azithromycin (i.e., those originally randomized to placebo in MORDOR I).

Results. All 594 communities from the Niger site of MORDOR I were included in MORDOR II. All communities received mass azithromycin, with a mean (±SD) antibiotic coverage of 92.0±6.6%. The mortality rate among 1-59 month-old children during the 12-month MORDOR II study period was 24 per 1000 person-years in communities receiving their first year of azithromycin, compared with 23.3 per 1000 person-years in those receiving their third year of azithromycin (*P*=0.55). In a secondary, observational analysis, the mortality rate during MORDOR I was compared with that of MORDOR II within each treatment arm. In this analysis, the mortality rate during MORDOR II was 13% lower (95%CI 6 to 20%) for communities receiving placebo for the preceding two years, and 3.6% higher (95%CI -12 to 5%) for communities receiving azithromycin for the preceding two years.

Discussion. MORDOR II found no evidence to suggest a waning or reversal of the effectiveness of mass azithromycin distributions for preventing childhood mortality. For communities that received placebo during MORDOR I and azithromycin during MORDOR II, mass azithromycin distributions were associated with a similar reduction in mortality as was observed during MORDOR I, providing more evidence of the effectiveness of this intervention for preventing childhood mortality. Even longer follow-up will be important to monitor for emergent antimicrobial resistance.

10. Antimicrobial resistance following mass azithromycin distribution for trachoma: a systematic review

Kieran S O'Brien [1], Paul Emerson [2], P J Hooper [2], Arthur L Reingold [3], Elena G Dennis [4], Jeremy D Keenan [5], Thomas M Lietman [6], Catherine E Oldenburg [7]

The mass drug administration (MDA) of azithromycin is an essential component of trachoma control programs and may contribute to reducing the burden of other childhood infectious diseases and mortality in some settings. Use of azithromycin has the potential to select for macrolide resistance, however, which could reduce the effectiveness of azithromycin against *Chlamydia trachomatis* over time. Moreover, the increased antibiotic pressure from MDA may select for resistance in other pathogenic organisms.
In this systematic review, we aimed to summarize evidence on the prevalence of antimicrobial resistance after azithromycin MDA. We searched electronic databases, conference abstracts, and grey literature for relevant reports up to June 14, 2018. We included studies on MDA of oral azithromycin for trachoma that assessed macrolide resistance in any organism, excluding reports of mathematical modelling, surveillance, and review articles. We contacted authors of included studies to request unpublished data. Two independent team members screened all identified reports for eligibility, reviewed full texts, and extracted data from the included reports. A third team member adjudicated discrepancies.
Overall, 213 studies were identified from all searches, 19 of which met criteria for inclusion. Given the heterogeneity in study design, frequency and duration of azithromycin distribution, and follow-up time points for resistance assessment, we decided to forgo formal meta-analysis and focused on a qualitative synthesis of study results. Of the final included studies, 12 assessed resistance in *Streptococcus pneumoniae,* three assessed resistance in *C trachomatis,* three assessed resistance in *Escherichia coli,* two assessed resistance in *Staphylococcus aureus,* and one assessed resistance in *Plasmodium falciparum.*
The studies examining *S pneumoniae* were conducted in Nepal, Ethiopia, Tanzania, Australia, the Gambia, and Niger. Baseline prevalence of macrolide resistance in *S pneumoniae* was assessed in 6 of these studies and ranged from 0.0% to 35.8%. Nine studies looked at resistance 6 months after the final treatment, at which point the prevalence of resistance in isolated *S pneumoniae* ranged from 0.0% to 89.1%. Six studies examined resistance at more than two time points. Three of these studies showed increases in prevalence of resistance immediately after MDA with subsequent declines in resistance to near baseline levels over time following cessation, two found no or very low resistance at all time points, and one study with a high baseline prevalence found increases in resistance at all time points. Only one study with

multiple time points followed subjects for longer than 6 months after the final MDA; this study found that resistance decreased over time.

Few studies examined the other organisms. No clinically significant resistance was identified in any of the three studies examining *C trachomatis*, and none was found in the study that assessed resistance in *P falciparum.* Each of the studies on *E coli* and *S aureus* identified moderate levels of resistance after azithromycin MDA. The studies on *E coli* and *S aureus* that included multiple time points found evidence of increases in resistance after MDA with decreases after MDA was stopped.

Overall, evidence of macrolide resistance has been identified in three of the five organisms studied. The lack of evidence of resistance in *C trachomatis* is encouraging for trachoma control programs, as is the suggestion of there being only a transient effect in other organisms. Given the limited available evidence and wide range of study type and quality, continued, longer-term surveillance will help to further elucidate the effects of azithromycin MDA on selection for antimicrobial resistance in target and non-target organisms.