Literature Reviews

Development of Azithromycin Resistance in *Streptococcus pneumoniae* in the Setting of Trachoma Mass Drug Administration: A Systematic Review

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Abstract: Trachoma is a blinding eye disease caused by the bacterium *Chlamydia trachomatis*. The current global elimination of trachoma initiative includes the use of mass drug distribution of azithromycin in areas where the prevalence of follicular trachoma is >10% in children aged 1-9 years. This study aims to investigate the high quality evidence of whether mass drug administration for trachoma causes the development of azithromycin resistance in *S pneumoniae*. Secondary objectives include (1) changes in the overall *S pneumoniae* prevalence and (2) concomitant development of non-macrolide resistance. Six databases were searched for articles relevant to the study question. Studies were screened and findings recorded using the PRISMA flow diagram and the Cochrane data collection checklist. Studies were only included if they included both a control and experimental group. Two risk of bias tools were used for quality appraisal of each study. After reviewing all studies, four were included in the final analysis, including one randomized control trial, two cluster-randomized trials and one prospective cohort. Findings showed decreased *S pneumoniae* prevalence and increased azithromycin resistant isolates following mass drug administration. This review shows that mass drug administration for trachoma can lead to a transient rise in *S pneumoniae* azithromycin resistance with a possible reduction in overall *S pneumoniae* prevalence. There is also evidence of macrolide-induced tetracycline and clindamycin resistance. The clinical impact of these findings remains unclear and further studies need to be performed to establish the significance.

Keywords: Azithromycin, Drug-Resistance, Mass Drug Administration, *Streptococcus pneumonia*, Trachoma

Introduction

Trachoma, a blinding eye disease caused by the bacterium *Chlamydia trachomatis*, causes blindness or visual impairment in an estimated 1.9 million people and is commonly seen in developing areas (WHO, 2018; Trachoma, 2006). Infection by *C trachomatis* serotypes A, B, or C results in prolonged conjunctival inflammation causing mucopurulent keratoconjunctivitis (Mohammadpour *et al.*, 2016). The infection causes destruction of normal conjunctival epithelium resulting in replacement of subepithelial stroma with type IV and V collagen (Whittum-Hudson *et al.*, 1986). Recurrent infections over several years can lead to extensive eyelid scarring and subsequently trichiasis, or inversion of eyelashes, which can rub against the eyeball and cause corneal scarring. This can progress to irreversible opacities, visual impairment and blindness (WHO, 2018). This progression of the disease can be graded based on the World Health Organization's (WHO)

grading of clinical manifestations: Follicular Trachoma (TF), trachomatous intense, trachomatous scarring, trichiasis and corneal opacity.

Pre-school aged children are commonly affected by trachoma in endemic areas and visual impairment from recurrent infections over time is seen at the ages of 30 to 40 years (WHO, 2018). In 1993, the WHO initiated the SAFE strategy which promotes Surgery for trichiasis, Antibiotics for *C. trachomatis* infections, Facial cleanliness and Environmental improvements. In 1996, the WHO Alliance for the Global Elimination of Trachoma by 2020 (GET2020) was launched in an effort to implement SAFE and "the strengthening of national capacity through epidemiological surveys, monitoring, surveillance, project evaluation and resource mobilization" (WHO, 2018).

Through the SAFE strategy, the antibiotic of choice is azithromycin for the treatment of trachoma, though topical tetracycline can also be used when needed in populations where azithromycin is contraindicated. As part of the GET2020 elimination efforts, Mass Drug Administration (MDA) with azithromycin is advised. Children aged 1-9 years old are screened for follicular trachoma and areas found to have a TF prevalence > 10% undergo annual MDA for three years. Treatment is given to the entire district with a recommended coverage level of 80% of the eligible population. If TF prevalence is < 10%, then treatment is only implemented at the community level (WHO, 2006a; 2004). The threshold for discontinuing treatment is a TF prevalence < 5% in children aged 1-9 years.

Over the past several years, there have been concerns regarding the development of bacterial resistance to azithromycin in the setting of trachoma MDA. One particularly concerning pathogen is *Streptococcus pneumoniae*, which is one of the causative organisms in cases of pneumonia, meningitis, otitis media and other infections. According to the WHO, in 2017, 15% of mortality of children under the age of five years was due to pneumonia, with *S pneumoniae* being the most common bacterial cause (WHO, 2016b). The highest burden of this mortality is borne by low-middle income countries.

Several studies have documented *S pneumoniae* resistance to azithromycin in the setting of trachoma MDA. A systematic review by (Ho *et al.*, 2015) focused on studies of nasopharyngeal *S pneumoniae* and included some cohort studies which did not have a comparison control group. A review by (O'Brien *et al.*, 2019) also included studies that did not have a comparison group. This study aims to investigate the high quality evidence of whether mass drug administration for trachoma causes the development of azithromycin resistance in *S pneumoniae*. Secondary objectives of this study are to (1) determine the prevalence of *S pneumoniae* carriage following exposure to azithromycin and (2) determine whether there is development of non-macrolide antibiotic resistance along with macrolide resistance in *S pneumoniae* in the setting of trachoma azithromycin MDA.

Materials and Methods

Eligibility Criteria

Studies were selected for the review based on pre-specified eligibility criteria. They were included if they were quantitative, investigated azithromycin resistance in *S pneumoniae* only in the setting of trachoma MDA and were published following the initiation of the SAFE strategy in 1993. The population of interest were those living in a trachoma endemic area with no specific age cut-off. Studies also needed to have a comparison control group. Studies were excluded if they were cross-sectional, case reports, case-control, ecological, systematic reviews, ongoing or incomplete trials, opinion pieces, or letters. The language that the article was written in was not an exclusion criteria.

Search and Information Sources

Searches were performed independently by the author, Khan, using the electronic databases MEDLINE (Ovid), EMBASE (Ovid), Global Health, Africa-Wide Information, CINAHL Plus and Cochrane Library. The citation lists of key articles were also manually reviewed and relevant studies were searched. Search terms used for the databases included variations of: (azithromycin OR macrolide) AND resist* AND trachoma AND mass drug administration AND strep* pneumo*. No restrictions were placed in regards to language. Search timeframe was for all published studies until July 2018. Search terms were reviewed by second-reviewers Onen and Hilder.

Study Selection and Data Collection

Results obtained from the database search were screened for the inclusion criteria based on the title and abstract. Included studies were exported to the Mendeley platform and full text was subsequently reviewed for further inclusion and exclusion criteria. The Cochrane Effective Practice and Organisation of Care data collection template form (EPOC, 2002) was used to extract data from the included studies. All studies were reviewed for the inclusion/exclusion criteria by Khan, Onen and Hilder.

Risk of Bias Assessment

The validity of the eligible studies was completed independently by Khan to assess the reliability and adequacy of randomization, subject allocation, blinding, data collection and outcome assessment and reporting. Two quality appraisals were completed for

each study, including the Critical Appraisal Skills Program (CASP) checklist (CASP, 2013) (for either randomized clinical trials or cohorts, as appropriate), the Cochrane Risk of Bias Tool for the randomized studies (Higgins *et al.*, 2011) and the Risk of Bias in Non-Randomized Studies of Interventions (ROBINS-I) (Sterne *et al.*, 2016) for cohort or non-randomized trials. An independent quality appraisal was also conducted by second-reviewer Onen.

Synthesis of Data

Heterogeneity of studies was assessed using the Higgins and Thompson's I^2 statistic through Review Manger 5.3. Clinical heterogeneity among studies was also evaluated. Results of the prevalence of *S pneumoniae* and the number of resistant isolates from each study were converted to percentages to allow for comparability of trends, which were subsequently plotted on a line graph.

Results

Study Selection

In July 2018, database searches using MEDLINE (Ovid), EMBASE (Ovid), Global Health, Africa-Wide Information, CINAHL Plus and Cochrane Library, along with review of key paper references, identified a total of 160 articles after duplicates were removed. After reviewing the article titles and abstracts, 143 records were excluded, leaving 17 to be reviewed by full text. Of the 17 articles that were reviewed, 13 were excluded based on the pre-defined exclusion criteria. Supplemental Table 1 outlines a detailed review of the excluded articles and reason for exclusion. The main reasons for exclusion were for not meeting the criteria of study design. The excluded studies were either cross sectional, letter, systematic review, ongoing trial, case series, case report and studies with no control group. Four full-text articles were included and were reviewed

for study quality using the Cochrane Risk of Bias Tools and Critical Appraisal Skills Program checklist. Figure 1 illustrates the PRISMA flow diagram of the citation review process.

Characteristics of Included Studies

Table 1 summarizes the characteristics of the included articles. Of the four studies that were included, two were cluster-randomized control trials, one was a randomized control trial and one was a prospective cohort. There were significant variations across all four studies in the frequencies of azithromycin administration, duration and follow-up. Two studies had given subjects a single dose of azithromycin after which follow-up data was collected (Chern *et al.*, 1999; Coles *et al.*, 2013). However, the other two studies administered biannual azithromycin for three years or quarterly azithromycin for one year (Haug *et al.*, 2010; Skalet *et al.*, 2010). Frequency of follow up ranged from 14 days to two years from the last dose of azithromycin (Chern *et al.*, 1999; Haug *et al.*, 2010). The sample size varied significantly among the studies, ranging from 31 to 486. Only three studies were able to achieve the recommended azithromycin coverage target of greater than 80% (Chern *et al.*, 1999; Coles *et al.*, 2013; Haug *et al.*, 2010).

Risk of Bias

Two critical appraisal tools were used to assess each study. All studies addressed a clear question, had appropriate patient assignment and follow up. Blinding participants was not possible in all three randomized studies due to the nature of the study design (Chern *et al.*, 1999; Coles *et al.*, 2013; Haug *et al.*, 2010; Skalet *et al.*, 2010). The Cochrane tools, Risk of Bias Tool for randomized trials and the Risk of Bias in Non-Randomized Studies – of Intervention, were used for the respective studies. Overall, all studies had a moderate risk of bias. Tables 2 and 3 summarize the appraisal.

Table 1: Characteristics of the included studies

Source	Country	Study design	Treatment population	Treatment frequency	Follow-up	Test for resistance	Sample population	Initial sample size Treatment	Control	Treatment Coverage
Chern *et al.* (1999)	Nepal	Randomized control trial	Children aged 1-10 years	Single	Baseline 14 days	E-test	Children aged 1-10 years	91	31	100%
Coles *et al.* (2013)	Tanzania	Prospective cohort	Residents aged > 1 year	Single	Baseline 1 month 3 months 6 months	Kirby-Bauer disk diffusion E-test	Children < 5 years	486	468	90%
Haug *et al.* (2010)	Ethiopia	Cluster-randomized trial with repeated cross sections	Residents aged > 1 year	Biannual for 3 years	24 months[a] 36 months 42 months 54 months	Sensititre	Children 1-5 years	120	120	Baseline: 89.6% 6 months: 93.2% 12 months: 96% 18 months: 88.5% No data for 24 and 36 months
Skalet *et al.* (2010)	Ethiopia	Cluster-randomized control trial with repeated cross sections	Children aged 1-10 years	Quarterly for 1 year	Baseline[b] 12 months	E-test	Children ≤ 10 years	110	120	Baseline: 72.8% 3 months: 76.3% 6 months: 80.4% 9 months: 78.2%

a Specimen collected in control group only at 24 and 36 months; b No baseline specimens from control group

Table 2: Cochrane Risk of Bias assessment for randomized studies (Higgins *et al*., 2011) Summary of the quality appraisal of the three randomized studies

	Random sequence Generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Chern *et al*. (1999)	+	−	−	?	+	?	?
Haug *et al*. (2010)	?	−	−	+	?	?	− a
Skalet *et al*. (2010)	+	+	−	+	+	?	− b

a High risk of contamination; b High risk of cross over bias; + Low risk; ? Unclear risk; − High risk

Table 3: Risk of bias in non-randomized studies – intervention (Sterne *et al*., 2016)

Study	Risk of bias pre-intervention and at-intervention				Risk of bias post-intervention			Overall Assessment
	Bias due to confounding	Bias in selection of participants into the study	Bias in classification of interventions	Bias due to deviations from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported result	
Coles *et al*. (2013)	Serious	Low	Low	Low	Serious	Moderate	Low	Moderate

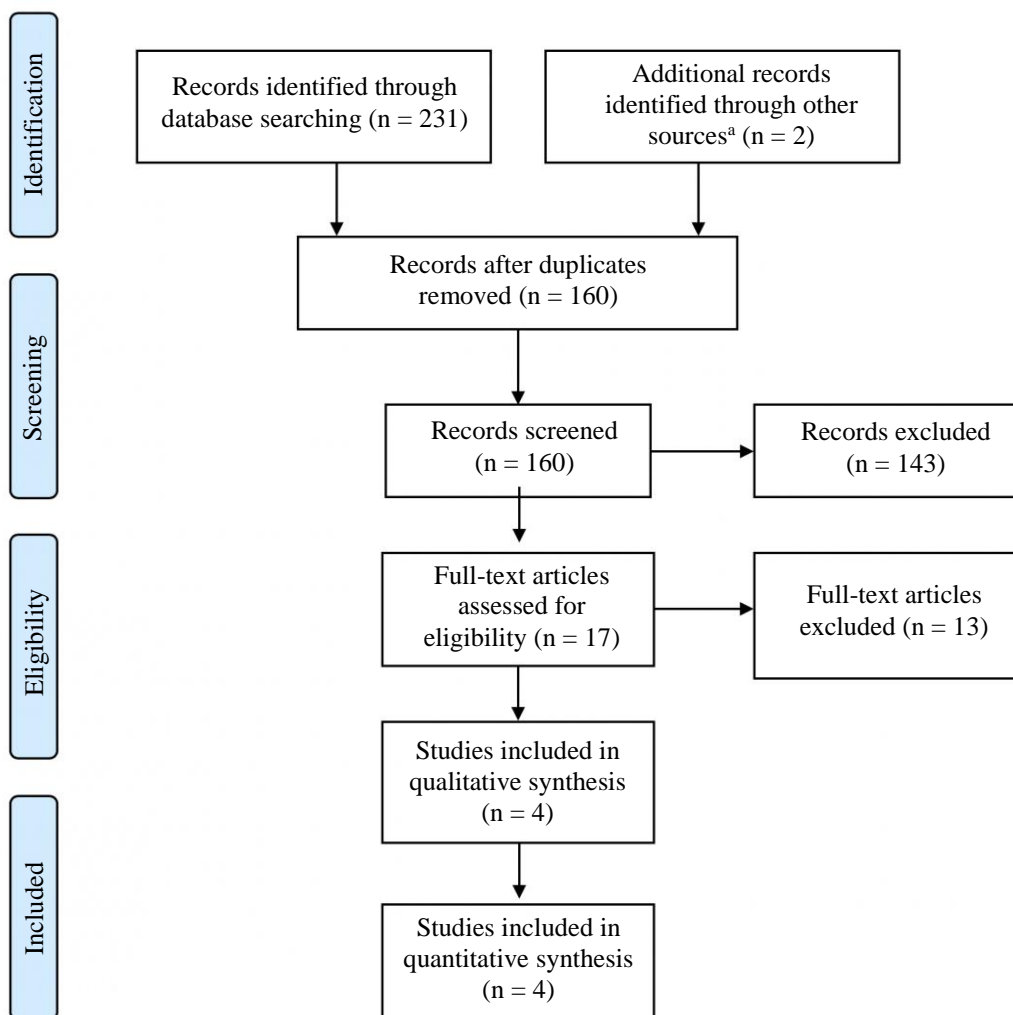Key: Low risk of bias; Moderate risk of bias; Serious risk of bias

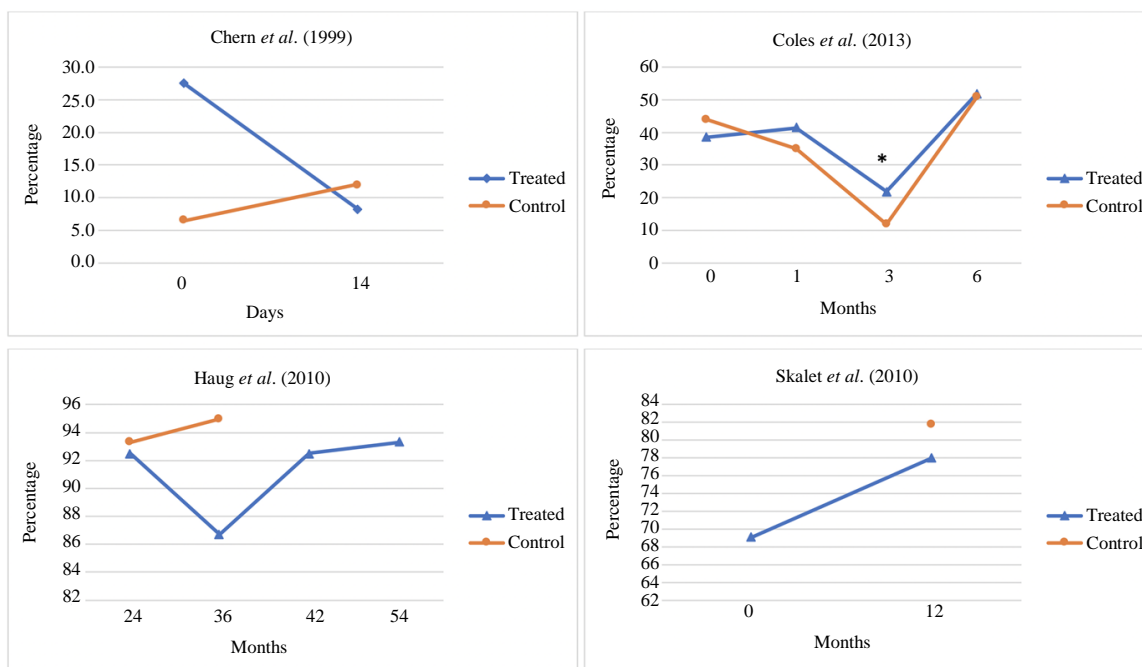**Fig. 1:** PRISMA flow diagram (Moher *et al*., 2009); a Review of references in key papers

Fig. 2: Prevalence of *S pneumoniae* carriage in the included studies; * p < 0.001
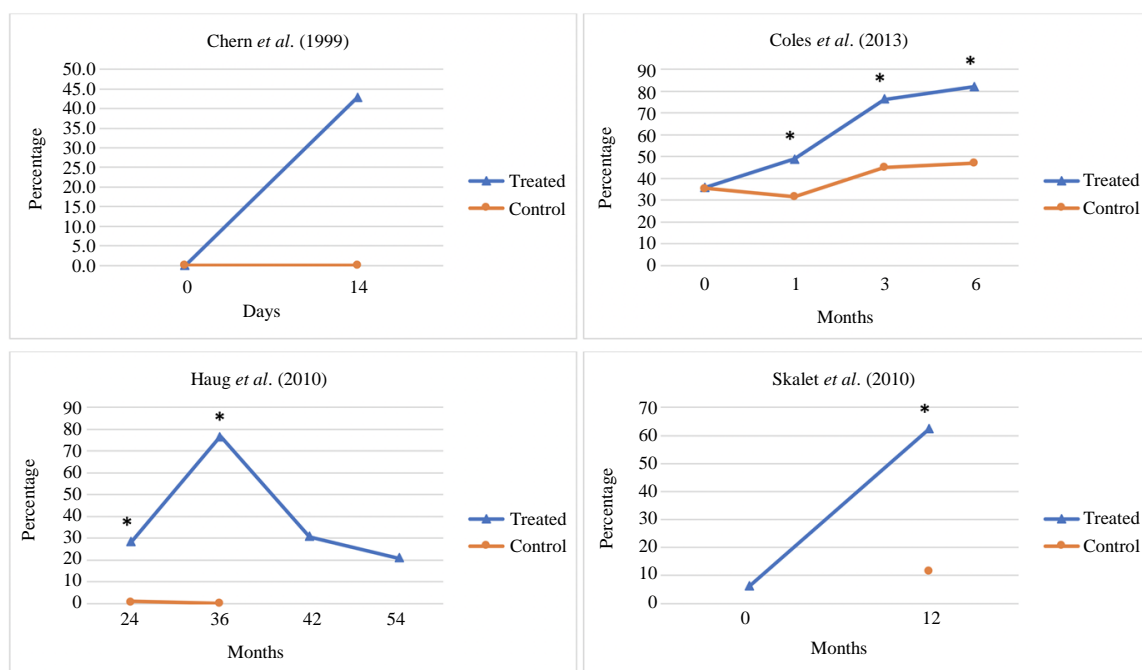

Fig. 3: Prevalence of azithromycin resistant *S pneumonia*; * p ≤ 0.001

Outcomes of Included Studies

S pneumoniae Prevalence

Figure 2 illustrates the prevalence of *S pneumoniae* across the four studies. In the prospective cohort by Coles *et al.* there was a statistically significant fall in prevalence in both control and treatment groups at three months where the treatment group had a higher prevalence (p < 0.001). Haug *et al.* showed the prevalence of *S pneumoniae* was lower in the treated group vs comparison; however, there was no significant difference between 24 and 36 months or 36 and 54 months as reported by the authors, which suggested a "constant rate of pneumococcal carriage".

S pneumoniae Azithromycin Resistance

Figure 3 summarizes the azithromycin resistance pattern observed in the four studies. In the study by Chern *et al.* on follow-up after treatment, 42.9% of isolates of the treated group were resistant to azithromycin compared to 0% in the control group. P values and confidence intervals were not provided for these findings. Coles *et al.* reported increasing azithromycin resistance in the MDA group as compared to the non-MDA group, which was significant. After multivariate analyses done by the authors to adjust for the head of household's education status and distance to fresh water source, the MDA-exposed group had a two-fold greater odds of resistance at one and three months and five-fold at six months. These findings were significant by the reported confidence intervals. Both Haug *et al.* and Skalet *et al.* also demonstrated a statistically significant higher prevalence of azithromycin resistance in the treatment group following azithromycin administration.

Resistance of S pneumoniae to Other Antimicrobials

The four included studies also assessed for the development of resistance to other antimicrobials in the setting of MDA. One study reported no development of penicillin resistance in either group at baseline or at follow up (Chern *et al.*, 1999). Another study reported rare penicillin resistance ranging from 0-1.9% without noting any consistent pattern (Coles *et al.*, 2013). Neither of the remaining studies noted any measurable change in penicillin resistance over the course of the study (Haug *et al.*, 2010; Skalet *et al.*, 2010).

One study tested for co-trimoxazole resistance and reported statistically significant, greater resistance in the non-MDA group at one month and six months of follow up (Coles *et al.*, 2013). There was also a reported rise in the number resistant to both azithromycin and co-trimoxazole over the six months in both groups, although reportedly more rapid development in the azithromycin-treated group. Another study did not note any significant change in the resistance pattern to trimethoprim-sulfamethoxazole (Haug *et al.*, 2010).

Tetracycline resistance was measured by two of the included studies. One study reported that the treatment group had greater resistance levels six months after the final three-year biannual azithromycin treatment than compared to the untreated group (p < 0.001) (Haug *et al.*, 2010). In this study, a rise in resistance was noted from 24 to 36 months, but this subsequently declined from 36 to 54 months. However, this finding was not significant. Another study also reported a significant increase in resistance to tetracycline from 15.2 to 35.5% in the treated group (p = 0.04), although this level was not significantly greater than the control group (Skalet *et al.*, 2010).

Clindamycin resistance was tested in one study and was significantly increased in the treatment group after mass azithromycin distribution (Skalet *et al.*, 2010). Resistance level increased from 1.5 to 16.9% at 12 months (p = 0.02). However, when compared to the control group, this did not reach statistical significance (Skalet *et al.*, 2010). Another study found that 34.5% of azithromycin resistant isolates were also resistant to clindamycin at six months after the final three-year biannual treatment (Haug *et al.*, 2010). This number increased to 60.0% at 54 months, although this change was not reported to be significant.

Synthesis of Results

For the purposes of this review, a meta-analysis and random-effects models were not completed due to the significant baseline variability in the eligible studies. All studies had different time points of follow-up. There were also different frequencies of azithromycin administration across studies. Furthermore, there were not enough studies to perform a combined analysis. The I^2 value that was attempted was > 50%, suggesting substantial heterogeneity.

Discussion

This review shows that even when only high quality studies are included, there is still evidence of *S pneumoniae* resistance to azithromycin in the setting of mass drug administration for trachoma. This pattern is seen in all the included studies despite the variations in the azithromycin dosing frequency and time between treatment and follow-up. Furthermore, this data may suggest the possibility that a greater number of azithromycin doses can lead to a greater prevalence of resistant *S pneumoniae*. The study with six azithromycin doses had a higher prevalence of resistant isolates than in the studies with only a single dose. However, it should be noted that comparability across the four studies is limited. In a longitudinal prospective cohort by (Hare *et al.*, 2013) a "cumulative dose response effect" was seen on *S pneumoniae* resistance.

The possibility of a short-lived rise in resistant *S pneumoniae* may also be considered from this study's findings. The longest period of follow-up was two years from the last dose of azithromycin, during which there was a decline in prevalence after one year. There was also a noted decline in the rate of resistance development at six months after a single dose. However, some of these findings lack significance and further longitudinal studies would need to be conducted to evaluate this trend.

Aside from the treatment of trachoma, there may be some beneficial secondary effects from azithromycin MDA. In this study, the data on carriage rates of *S pneumoniae* isolates, both susceptible and resistant, is variable. There is some suggestion for a decline in prevalence or a constant rate of carriage, though most of this data did not reach statistical significance. Pneumococcal colonization has been suggested to be a risk factor for developing pneumococcal disease (Bogaert *et al.*, 2004; Petraitiene *et al.*, 2015). In a 2015 study in Lithuania, preschool children with *S*

pneumoniae nasopharyngeal colonization were associated with longer duration of respiratory tract illness recovery and higher frequencies of pneumonia, sinusitis and acute otitis media (Petraitiene *et al.*, 2015). Given that azithromycin could possibly cause a reduction in *S pneumoniae* prevalence, there may be some benefit from mass drug administration. Consideration must be made that reduction of one bacteria can give way to the expansion and replacement of that niche with other bacterial colonizers such as *Staphylococcus aureus, Haemophilus influenzae* and *Neisseria meningitides* (Bogaert *et al.*, 2004; Veenhoven *et al.*, 2003).

There is limited data on whether colonized resistant *S pneumoniae* isolates lead to the development of antimicrobial resistant clinical disease. However, as noted above, *S pneumoniae* colonization is a risk factor for pneumococcal infection. In a study in Ohio of children in day care centers, carriers of multiply resistant *S pneumoniae* were more likely to have frequent otitis media infections and otitis media episodes that were not responsive to antimicrobials (Reichler *et al.*, 1992). However, these isolates were macrolide sensitive, but included resistances to beta-lactams. In a retrospective observational study by (Cilloniz *et al.*, 2015) subjects with macrolide resistant community-acquired pneumonia were not more severely ill nor had worse outcomes. In his review of macrolide-resistant *S pneumoniae*, (Niederman, 2015) also concludes that "even if macrolide-resistant pneumococci are common in [community acquired pneumonia], they do not affect the severity of illness on presentation".

Several studies have noted an association between increased macrolide consumption and increased macrolide and penicillin resistance (Barkai *et al.*, 2005; Bronzwaer *et al.*, 2002; García-Rey *et al.*, 2002). In this review, there was no significant associated resistance to penicillin or co-trimoxazole. There was however concurrent increased resistance noted to tetracycline and clindamycin. These findings can be due to the known macrolide resistance mechanisms of pneumococcus. The *tetM* gene, which encodes a protective protein for the ribosome, leads to tetracycline resistance (Cillóniz *et al.*, 2016). This gene is on the same transposon which encodes *erm*(B) and/or *mef*(E), which confer macrolide resistance (Cillóniz *et al.*, 2016). In regards to clindamycin, it has been noted previously that the *erm*(B) gene also allows for resistance to lincosamides due to its broad resistance activity (Schroeder and Stephens, 2016). Macrolide-induced multi-drug resistance may be concerning for the treatment of other illnesses. Further studies will need to be done to elucidate the clinical implications of these findings.

There are several limitations of this review. Firstly, there is an insufficient number of included studies, of which only three are randomized studies. Furthermore, the cluster-randomized design of two of the articles followed groups rather than individuals, making the applicability of data at the individual level difficult. Another limitation includes significant heterogeneity between the studies in duration, dosing frequency and frequency of follow-up. This limits the comparability of data across studies.

Conclusion

This review demonstrates that there is development of azithromycin resistance in *S pneumoniae* in areas that receive mass drug administration for trachoma, although this may only be short-lived. Several points should be considered in weighing the risks and benefits of macrolide treatment, especially in the light of new evidence that showed reduction in childhood mortality from azithromycin distribution (Keenan *et al.*, 2018). Further studies need to be performed to elucidate the clinical significance of macrolide-resistant *S pneumoniae* carriage. Studies or monitoring systems should be in place to research the effects of such isolates and whether they result in significant clinical disease.

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Authors Contributions

Nazia Khan: Database search, methodology, data collection, data analysis and interpretation of data, write-up of manuscript.

Barbara Lachana Onen: Review of search terms and included/excluded studies, independent quality appraisal, review of results and analysis, review of manuscript.

Robin Hilder: Review of search terms and included / excluded studies, review of results, review of manuscript.

Robin Bailey: Study concept and design, review of study analysis and data interpretation, review of manuscript.

Conflict of Interest

The authors declare that they have no conflict of interest.

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Supplemental Table 1: Excluded studies and reasons for exclusion

Study	Reason for exclusion
Abera B, Kibret M. Azithromycin, fluoroquinolone and chloramphenicol resistance of non-chlamydia conjunctival bacteria in rural community of Ethiopia. Indian J Ophthalmol. 2014; 62(2):236	Cross-sectional
Batt SL, Charalambous BM, Solomon AW, *et al*. Impact of azithromycin administration for trachoma control on the carriage of antibiotic-resistant Streptococcus pneumoniae. Antimicrob Agents Chemother. 2003;47(9):2765-2769.	Cross-sectional
Bloch EM, West SK, Mabula K, *et al*. Antibiotic resistance in young children in kilosa district, Tanzania 4 years after mass distribution of azithromycin for trachoma control. Am J Trop Med Hyg. 2017;97(3):815-818.	Cross-sectional
Burr SE, Milne S, Jafali J, *et al*. Mass administration of azithromycin and Streptococcus pneumoniae carriage: cross-sectional surveys in the Gambia. Bull World Health Organ. 2014;92(7):490-498.	Cross-sectional
Fry AM, Jha HC, Lietman TM, *et al*. Adverse and Beneficial Secondary Effects of Mass Treatment with Azithromycin to Eliminate Blindness Due to Trachoma in Nepal. Clin Infect Dis. 2002;35(4):395-402.	Surveillance study, no control
Gaynor BD, Holbrook KA, Whitcher JP, *et al*. Community treatment with azithromycin for trachoma is not associated with antibiotic resistance in Streptococcus pneumoniae at 1 year. Br J Ophthalmol. 2003;87(2):147-148.	Cross-sectional
Gaynor BD, Chidambaram JD, Cevallos V, *et al*. Topical ocular antibiotics induce bacterial resistance at extraocular sites. British Journal of Ophthalmology 2005:89(9):1097-1099.	Surveillance study with cross-sectional data
Ho DKH, Sawicki C, Grassly N. Antibiotic Resistance in Streptococcus pneumoniae after Azithromycin Distribution for Trachoma. Journal of Tropical Medicine. 2015;2015:1-9.	Systematic review
Keenan JD, Klugman KP, McGee L, *et al*. Evidence for clonal expansion after antibiotic selection pressure: Pneumococcal multilocus sequence types before and after mass azithromycin treatments. J Infect Dis. 2015;211(6):988-994.	Interrupted time series/cross sectional
Leach AJ, Shelby-James TM, Mayo M, *et al*. A prospective study of the impact of community-based azithromycin treatment of trachoma on carriage and resistance of Streptococcus pneumoniae. Clin Infect Dis. 1997;24(3):356-362.	Case series (cohort without a control group)
Lietman T, O'Brien KS, Emerson P. Tripartite International Research for the Elimination of Trachoma (TIRET) [Internet]. [cited 2018 Jul 13]. Available from: https://clinicaltrials.gov/ct2/show/NCT01202331	Currently ongoing trial (Group-randomized trial)
Peterson J, Treadway G. Impact of community-based azithromycin treatment of trachoma on carriage and resistance of Streptococcus pneumoniae. Clinical Infectious Diseases. 1998;26:248.	Letter
Smith-Vaughant HC, Marsh RL, Morris PS, *et al*. In vivo emergence of high-level macrolide resistance in Streptococcus pneumoniae following a single dose of azithromycin. Journal of Clinical Microbiology. 2007;45(12):4090-4091.	Case Report