Effectiveness of azithromycin mass drug administration on trachoma: a systematic review

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Backgrounds: Azithromycin mass drug administration (MDA) is a key part of the strategy for controlling trachoma. This systematic review aimed to comprehensively summarize the present studies of azithromycin MDA on trachoma; provide an overview of the impact of azithromycin MDA on trachoma in different districts; and explore the possible methods to enhance the effectiveness of azithromycin MDA in hyperendemic districts.

Methods: PubMed, Embase, the Cochrane Central Register of Controlled Trials, Web of Science, and ClinicalTrials.gov were searched up to February 2021 with no language restriction. Studies reporting the effect of azithromycin MDA on trachoma were included. Mathematical modeling studies, animal studies, case reports, and reviews were excluded. The trachomatous inflammation-follicular (TF) <5.0% was used to judge the effect of azithromycin MDA on eliminating trachoma as a public health problem. Two researchers independently conducted the selection process and risk of bias assessment.

Results: A total of 1543 studies were screened, of which 67 studies including 13 cluster-randomized controlled trials and 54 non-randomized studies were included. The effect of azithromycin MDA on trachoma was closely related to the baseline prevalence in districts. For the districts with baseline prevalence between 5.0% and 9.9%, a single round of MDA achieved a TF <5.0%. For the districts with baseline between 10.0% and 29.9%, annual MDA for 3 to 5 years reduced TF <5.0%. However, for the districts with high level of baseline prevalence (TF >30.0%), especially with baseline TF >50.0%, annual MDA was unable to achieve the TF <5.0% even after 5 to 7 years of treatment. Quarterly MDA is more effective in controlling trachoma in these hyperendemic districts.

Conclusions: Azithromycin MDA for controlling trachoma depends on the baseline prevalence. The recommendation by the World Health Organization that annual MDA for 3 to 5 years in the districts with TF baseline >10.0% is not appropriate for all eligible districts.

Keywords: Azithromycin; Mass drug administration; Trachoma; Strategy; Systematic review

Introduction

Infectious diseases, responsible for >25% of global diseases, are one of the leading causes of morbidity worldwide.[1] In tropical areas, endemic infectious diseases such as trachoma are very common and affect children's health. Trachoma is caused by *Chlamydia trachomatis (Ct)* infection, which is the major infectious cause of blindness and is commonly seen in young children.[2,3] In Africa, the prevalence of trachoma could reach >50.0%, especially in countries such as Ethiopia, Tanzania, and southern Sudan.[4] Controlling of tropical diseases including trachoma has been set as one of the millennium developmental goals.[5]

In 1996, the World Health Organization (WHO) recommended the Surgery, Antibiotic, Facial cleanliness and Environmental improvement (SAFE) strategy for globally eliminating trachoma as a public health problem

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by the year 2020. Azithromycin mass drug administration (MDA) is a crucial part of the SAFE program.[6] Three to five years of annual azithromycin MDA with ≥80.0% treatment coverage was recommended in districts with trachomatous inflammation-follicular (TF) ≥10.0% in children aged 1 to 9 years.[7] Furthermore, the azithromycin MDA cannot be stopped until the TF falls <5.0% in these districts.[7] Since azithromycin MDA started, >900 million doses of oral azithromycin have been distributed to control trachoma.[4] Although encouraging results in reducing trachoma prevalence have been achieved in many districts, progress has stalled in many hyperendemic districts despite years of efforts.[8-10] Trachoma was still endemic in >40 countries worldwide involving a total of 136 million people who required azithromycin MDA interventions.[4] The goal of eliminating trachoma as a public health problem by the year 2020 raised by WHO was not reached.

The effectiveness of azithromycin MDA on reducing trachoma is related to local epidemiology and the baseline TF prevalence. Additionally, the effects are also related to different methods of azithromycin MDA.[4] This study aims to summarize the present studies of azithromycin MDA on trachoma, and to overview the impact of azithromycin MDA on trachoma control in districts with different baseline TF prevalence.

Methods

This systematic review was conducted and reported according to the Preferred Reporting Items for Systematic Review and Meta-analyses statement guidelines. The protocol was registered at the International Prospective Register of Systematic Reviews (No. CRD42018114902) and published.[11] Full details of the search strategies, data extraction, and risk of bias assessment were available in the published protocol. In brief, the databases from PubMed, Embase, the Cochrane Central Register of Controlled Trials, Web of Science, and ClinicalTrials.gov were searched up to February 2021. The keywords "azithromycin," "Zithromax," "sumamed," "Vinzam," "AZT," "mass drug administration," "mass treatment," "mass distribution," "preventative chemotherapy," "MDA," and "SAFE" were searched for studies regarding azithromycin MDA. In addition, the reference lists of included studies were manually reviewed to add potential studies. Studies regarding azithromycin MDA or SAFE strategy on trachoma were included. Mathematical modeling studies, animal studies, case reports, and reviews were excluded. Information about study location, sample size, baseline prevalence, implemental coverage, frequency, duration, and follow-up prevalence were extracted.

Two researchers (TX and YY) independently conducted the selection process and assessed the trials for eligibility. Both researchers conducted data extraction and checked for discrepancies. Discrepancies were discussed with a third researcher (LQ). The level of evidence of individual study was rated using the Oxford Centre for Evidence-based Medicine's Levels of Evidence and Grades of Recommendation.[12] The risk of bias of included studies was independently assessed. The risk of bias assessment for randomized controlled trials (RCT) was used from the tools' rating scales of the criteria outlined in the Cochrane Handbook for Systematic Reviews of interventions.[13] In addition, the tool of the Risk of Bias in Non-randomized Studies of Interventions (ROBINS-I) was used to assess the bias for non-randomized studies.[14,15]

We conducted a qualitative analysis for the included studies. The prevalence of TF or Ct infection was used as main outcomes. Meta-analysis for the effectiveness of different MDA methods could not be conducted due to the wide variation in study designs, baseline prevalence, and reporting of outcomes. A systemic review was performed instead.

Results

Overall, 1543 studies were identified. After removing duplicates, the title and abstract of 889 studies were initially screened and the full texts of 167 studies were reviewed for eligibility. Finally, 67 studies were included [Supplementary Table 1, http://links.lww.com/CM9/A734],[2,4,8,9,16–78] consisting of 13 cluster-RCT,[18,31,35,64,65,67,72-78] and 54 non-randomized studies (23 longitudinal studies and 31 cross-sectional studies)[2,4,8,9,16,17,19-30,32-34,36-63,66,68-71] [Figure 1].

Quality of included studies

Risk of bias details were presented in Supplementary Table 2, http://links.lww.com/CM9/A734. For cluster-RCTs, the risks of bias were low or moderate from random sequence generation, masking of outcome assessors, incomplete outcome data, and selective reporting. The risks of bias were unclear or high from allocation concealment and masking of participants and personnel in most of the trials. For the non-randomized studies, the risk of bias from confounding were unclear in most of the studies, while 21 studies showed low to moderate risk and three represented high risk. The risk of bias from selection into study, incomplete outcome data, and selective reporting were low in most of the studies. Bias due to intervention classification and deviations from interventions were low or moderate in most of the studies, while a few studies lacked relevant information. Most studies did not report the information about masking of outcome assessors.

Study characteristics

The characteristics of the 67 included studies on trachoma were summarized in Supplementary Table 1, http://links.lww.com/CM9/A734. Half of the studies ($n = 39$) were from Tanzania and Ethiopia. The prevalence of TF was determined mainly among children aged <10 years. The baseline prevalence of TF varied among studies (5.0%–90.0%). The duration of azithromycin MDA ranged from a single distribution to >3 consecutive years of distribution. Most studies conducted annual treatment based on WHO recommendation, while several studies also determined the effectiveness of higher frequencies of treatment (biannual or quarterly). The coverage of azithromycin MDA reached 80% in most studies, and some studies had

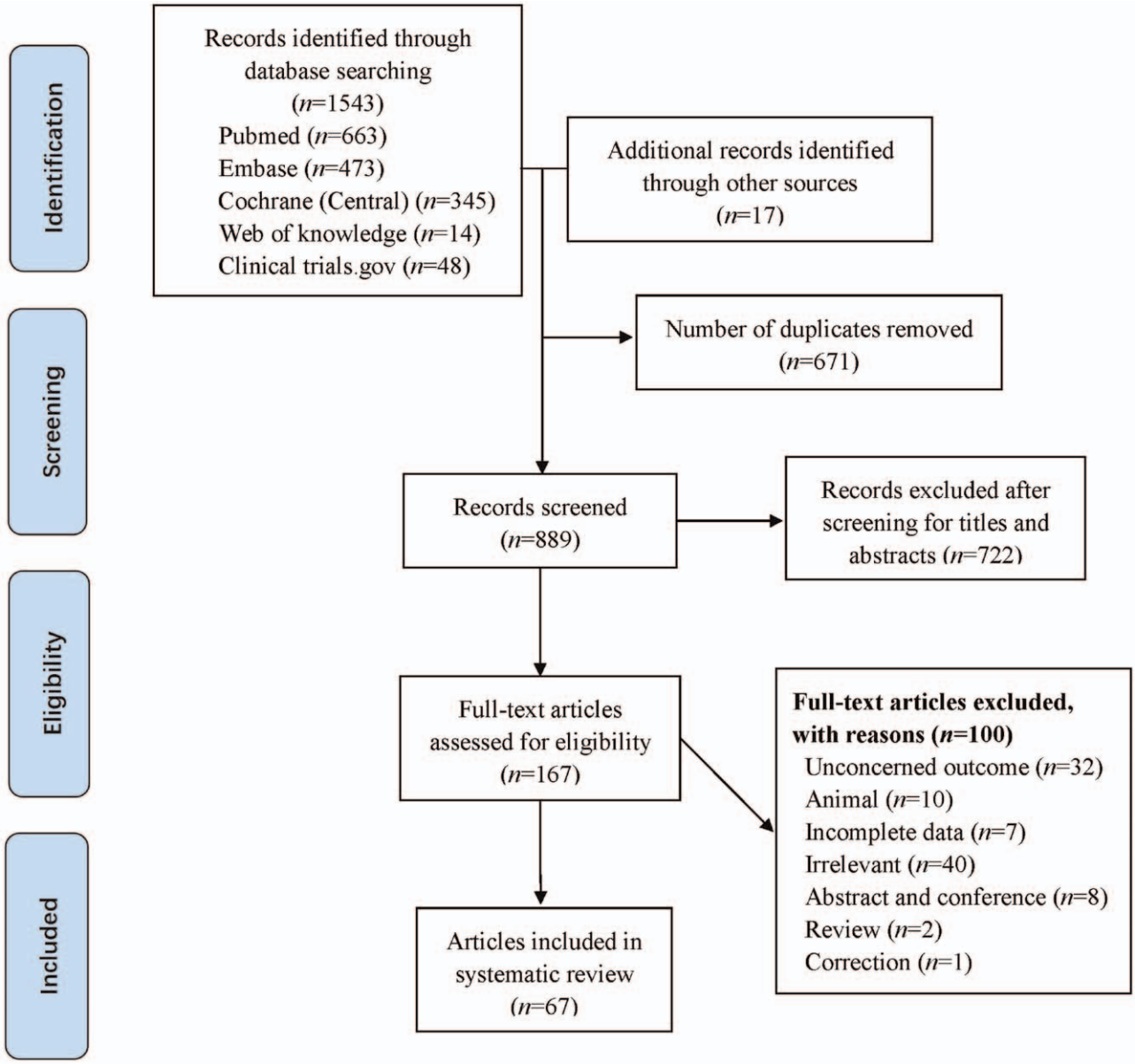

Figure 1: Flowchart of selection of studies for inclusion in the systematic review.

a higher coverage (>90%) or a lower coverage (<80%). The doses of azithromycin were similar among studies (20 mg/kg, up to a maximum dosage of 1 g). The rate of adverse events was not recorded in most studies except two of them that recorded no serious adverse events.[74,76]

Overview of azithromycin MDA on trachoma

Among the 67 studies, nine of them reported that the prevalence of TF was significantly decreased <5.0% (elimination threshold) at follow-up.[4,24,32-36,45,68] Seventeen studies reported close to elimination threshold (5.0%–10.0%).[9,27,28,31,37,44,51,56,61-67,72,78] These studies were mainly conducted in the areas of Malawi, Ghana, Gambia, Nigeria, Mali, Ghana, and Nepal where there was a low or moderate prevalence of TF. However, the remaining 41 studies showed that the prevalence of TF was still ≥10.0% after azithromycin MDA. They were mainly conducted in the districts with high prevalence of TF, including Amhara and Kongwa in Tanzania, Gurage in Ethiopia, and southern Sudan. All the 67 studies have reported that the prevalence of TF or *Ct* infection was decreased after azithromycin MDA in different extent.

Single dose of azithromycin MDA

The effects of single azithromycin MDA were investigated in 23 studies.[2,16-20,22-29,31-37,50,69] The baseline prevalence of TF ranged from 5.0% to 77.0%. Among the five studies with baseline prevalence of TF between 5.0% and 9.9%,[33-37] four of them showed that single MDA reduced TF prevalence <5.0%,[33-36] while one study reported that TF remained >5.0% at follow-up.[37] Among the eight studies with baseline prevalence of TF between 10.0%

and 29.9%,[24,26-29,31,32,50] two of them reported the TF prevalence <5.0%,[24,32] and three between 5.0% and 10.0% after azithromycin MDA.[27,28,31] However, the other three studies still had a TF prevalence >10.0% at follow-up survey.[26,29,30] Moreover, among the 10 studies with baseline prevalence of TF >30.0%, none of them reached TF prevalence <5.0% at follow up.[2,16-23,25]

Annual azithromycin MDA for 2 years

The effects of annual azithromycin MDA for 2 years were investigated in nine studies.[9,38-45] The baseline prevalence of TF ranged from 6.4% to 71.4% in the nine studies. Among them, one study with baseline TF prevalence of 6.4% reported that the prevalence was decreased to <5.0% after azithromycin MDA.[45] Additionally, two studies with baseline 5.9% to 17.4% showed that the prevalence of TF achieved or was close to the elimination threshold (0.4%–6.4%) after azithromycin MDA.[9,44] However, the other six studies which had baseline TF >20.0% showed a prevalence of TF >10.0% at follow-up.[38-43]

Annual azithromycin MDA for 3 to 5 years

The effects of annual azithromycin MDA for ≥3 years were investigated in 25 studies.[4,8,46-68] The baseline prevalence of TF in these 25 studies ranged from 10.0% to 69.0%. Three of them with baseline TF <40.0% showed that the TF prevalence was significantly decreased to a very low level (0.0%–1.6%).[4,57,68] Additionally, nine studies with baseline TF 12.0% to 50.5% reported that the prevalence of TF was close to elimination threshold (5.0%–10.0%).[51,56,61-67] However, the follow-up TF was still high (10.0%–43.5%) in 10 studies, which had a high baseline TF (30.0%–60.0%).[46-50,52-55,58] Moreover, three studies conducted trachoma surveys in multiple districts and assessed the number of districts that reached TF <5.0% after azithromycin MDA.[8,59,60] One study with baseline TF <30.0% showed that 53.0% of the districts reached elimination threshold after 3 to 5 years of azithromycin MDA.[60] However, one study with baseline TF >30.0% showed that only 6.0% districts reached the elimination threshold after 3 to 5 years of annual MDA.[59] Furthermore, the following study showed that this ratio only increased to 28.0% after receiving additional 4 years of MDA.[8]

Biannual azithromycin MDA for 2 to 3 years

The effects of biannual azithromycin MDA for 2 or 3 years were investigated in four studies. One of them with baseline prevalence of TF between 20.0% and 30.0% showed a reduction to 5.4% to 10.1%.[72] However, in the other three studies with baseline of TF between 40.0% and 91.6%, the prevalence of TF was still at a relatively high level at follow-up (17.0%–37.0%).[21,70,71]

Different frequencies of azithromycin MDA

Additionally, the effects of different frequencies of azithromycin MDA (annual, biannual, and quarterly) were investigated in six RCT studies.[73-78] One of them with baseline of TF between 20.0% and 30.0% was reduced to 7.8%–8.0% after 3 years of annual or biannual azithromycin MDA.[78] Out of the other five studies with baseline of TF between 52.0% and 84.0%, two of them found that the prevalence of TF was reduced but still remained at a relatively high level (25.4%–39.8%) even after 7 years of annual or biannual MDA.[73,74] The other three studies did not provide information about the prevalence of TF at follow-up, but a significant reduction of *Ct* infection to 0.9%–3.6% was reported with biannual (one study) or quarterly MDA (two studies).

Methods to enhancing the effectiveness of azithromycin MDA

Different frequencies of azithromycin MDA

Six cluster-RCTs compared the effectiveness of different frequencies on TF or *Ct* infection [Table 1].[73-78] Accordingly, we made line charts to visually compare the effects of TF and *Ct* infection after azithromycin MDA [Figure 2A and 2B].

One of the six cluster-RCTs compared the effectiveness of annual and biennial MDA and found that annual MDA was more effective in reducing *Ct* infection than biennial MDA.[77] Five cluster-RCTs compared the effectiveness between annual and biannual MDA.[73-75,77,78] Three of the five cluster-RCTs showed no difference for both TF and *Ct* infection between annual and biannual MDA at follow-up of 36 to 90 months [Figure 2A and 2B].[73,74,78] Two other studies indicated that biannual MDA significantly decreased the prevalence of *Ct* infection than that with annual MDA at 24 months without reporting the data of TF prevalence [Figure 2A and 2B].[75,77]

In addition, one study compared the effectiveness of quarterly with annual MDA, and found that quarterly MDA could significantly reduce *Ct* infection more than that with annual MDA at 12 months. However, the prevalence of TF was not reported [Figure 2A and 2B].[76,77]

Different coverage of azithromycin MDA

Four cluster-RCTs investigated the effectiveness of azithromycin MDA for different coverage including standard coverage (80%–90%) and enhanced coverage (>90%).[35,64,65,72] No difference was found in decreasing TF [Figure 3A] and *Ct* infection between these two coverages [Figure 3B].

Different target populations of azithromycin MDA

Two studies investigated the effectiveness of azithromycin MDA for different target populations.[27,31] One study compared azithromycin MDA for all children with the households of children with TF only.[31] It showed that both methods were effective in reducing TF prevalence without significant difference. The other study compared the effects of azithromycin MDA among all residents, children and women, and the households of children with TF.[27] All the three methods are effective in decreasing the prevalence of TF. Furthermore, the first two methods were significantly more effective than the third method.

Table 1: Summary of studies for different frequencies of azithromycin MDA.

Study	Follow-up time (months)	Outcome	Prevalence (%)	*P* value of difference
Annual *vs*. Biennial				
Lietman[77]	24	*Ct* infection	Mean difference: −11.1 (−14.9 to −7.2)	**$P = 0.008$**
Annual *vs*. Biannual				
Amza[78]	36	*Ct* infection	Biannual*: 3.8 (2.2–6.0) Annual: 5.8 (3.2–9.0)	Non-inferior
		TF	Biannual*: 7.8 (5.3–11.4) Annual: 8.0 (5.0–11.6)	$P = 0.670$
Gebre[73]	42	*Ct* infection	Annual: 1.9 (0.3–3.5) Biannual: 3.2 (0.0–6.5)	$P > 0.990$
		TF	Annual: 31.5 (21.6–41.3) Biannual: 35.0 (23.9–46.1)	$P = 0.120$
Keenan[74]	90	*Ct* infection	Annual: 9.9 (0–20.4) Biannual: 3.3 (0–7.5)	$P = 0.090$
		TF	Annual: 39.8 ± 16.4 Biannual: 25.4 ± 18.2	$P = 0.070$
Lietman[77]	24	*Ct* infection	Annual *vs*. biannual: Mean difference 3.3 (0.5 to 6.1)	$P < 0.050$
Melese[75]	24	*Ct* infection	Annual: 6.8 (1.2–12.4) Biannual: 0.9 (0.0–2.1)	$P = 0.030$
Annual *vs*. Quarterly†				
Lietman[77]	12	*Ct* infection	Mean difference: −11.4 (−19.5 to 3.3)	$P = 0.007$
House[76]	12	*Ct* infection	Annual: 14.6 (7.2–22.1) Quarterly: 3.6 (0.8–6.4)	$P = 0.001$

Prevalence is presented as percentage with 95% confidence interval or percentage ± standard deviation. *Biannual treatment targeted only to children aged 0 to 12 years. †Quarterly treatment targeted only to children aged 1 to 10 years. *Ct*: *Chlamydia trachomatis*; MDA: Mass drug administration; TF: Trachomatous inflammation-follicular.

Discussion

This systematic review provided an overview of the effectiveness of azithromycin MDA used for controlling trachoma. By including cohort and cross-sectional studies, a significantly greater amount of evidence was evaluated than the recent Cochrane review which only included randomized controlled clinical trials.[79] Additionally, the impact of different methods of azithromycin MDA on trachoma was assessed. These findings are helpful for choosing suitable method of azithromycin MDA in districts with different baseline prevalence of TF.

WHO has recommended a general method of 3 to 5 years of annual MDA to control trachoma in districts with TF ≥10.0%. However, based on the published studies, the effectiveness of azithromycin MDA on trachoma was highly dependent on the baseline prevalence in different districts. Therefore, in choosing azithromycin, MDA for trachoma needs to be adjusted according to the local baseline prevalence.

In low prevalence districts with TF between 5.0% and 9.9%, four of five studies showed that a single MDA reduced TF <5.0%.[33-36] Only one of them showed that the TF was 9.3% at follow up. The difference may due to its lower coverage of MDA (73%) in this study. Therefore, a single MDA with adequate coverage (>80%) is feasible to reduce TF <5.0% in districts with TF between 5.0% and 9.9%.

For districts with TF between 10.0% and 29.9%, the effectiveness of 3 to 5 years of annual MDA varied among districts. Although some districts could not achieve the elimination of trachoma as a public health problem threshold (TF <5.0%), the prevalence of TF could be brought down to a relatively low level (5.0%–10.0%). Therefore, these districts could still follow the strategy of 3 to 5 years of annual MDA, and receive resurveys to assess the prevalence of TF after MDA.

However, for districts with high level of TF (≥30.0%), it was quite difficult to reduce trachoma to <5.0% using 3 to 5 years of MDA. Only 28% districts in Amhara, Ethiopia (with baseline TF >50.0%) could achieve trachoma <5.0% even with 7 to 9 years of annual MDA.[59] It indicated a requirement of enhancing intensity of MDA in such hyperendemic districts.

Studies on different methods of azithromycin MDA are helpful to explore ways to enhance effectiveness of MDA in hyperendemic districts. In districts with TF between 20.0% and 30.0%, both annual and biannual MDA for 3 years could significantly reduce the prevalence of TF and *Ct* infection.[78] In districts with prevalence >50.0%, TF stuck at a high level (>25.0%) despite 7 years of annual or biannual MDA interventions,[73,74] which means even biannual MDA was not sufficient to control trachoma in such hyperendemic districts. Studies on higher frequency showed that quarterly MDA could significantly decrease

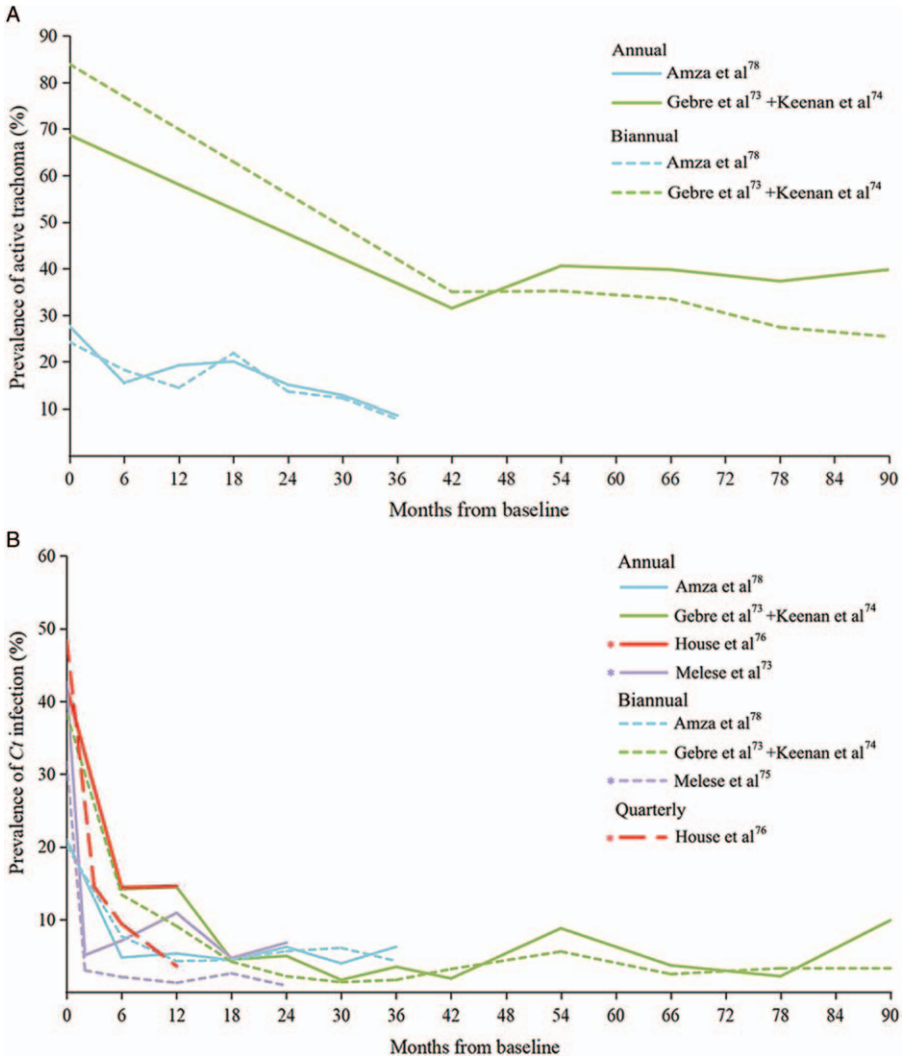

Figure 2: Prevalence of (A) TF and (B) *Ct* infection over time among groups treated with different frequencies. Arms of comparison were labeled with same color in one publication. Lines and dot lines represent different frequency of azithromycin MDA. Significant difference was marked with asterisks. No significant difference of (A) TF was observed between annual and biannual administration. Statistically significant difference of (B) *Ct* infection was found in House *et al*[76] and Melese *et al*[75] studies ($^{*}P < 0.05$). Non-significant difference was found in other three studies (Gebre *et al*[73] and Keenan *et al*[74] were from the same setting with different follow-up time. Green lines represent both studies). *Ct*: *Chlamydia trachomatis*; MDA: Mass drug administration; TF: Trachomatous inflammation-follicular.

Ct infection compared to annual or biannual MDA.[75-77] However, assessment based only on *Ct* infection without TF was insufficient since the prevalence of *Ct* infection could decrease drastically following MDA but might recrudesce several months after MDA. Therefore, different follow-up timepoints such as 12 months for annual MDA or 3 months for quarterly MDA might be a confounding factor when assessing the effectiveness of MDA. Therefore, quarterly MDA is a potential enhanced method for controlling trachoma in hyperendemic districts. Follow-up survey for TF to assess the effectiveness of quarterly MDA would be necessary in future studies.

Besides increasing the frequency of MDA, enhancing the coverage of MDA might be a potential method to enhance the effectiveness.[65] However, all the included cluster-RCTs showed no additional benefit while enhancing the coverage (>90%) compared with the standard coverage (80%–90%).

Conclusions

The effect of azithromycin MDA on trachoma was closely related to the baseline prevalence in the districts. A single round of MDA was feasible to achieve TF<5.0% for districts with TF between 5.0% and 9.9%. For districts with TF between 10.0% and 29.9%, 3 to 5 years of annual MDA was capable of reducing TF to <5.0%. For districts with TF >30.0% (especially >50.0%), it was difficult to achieve TF <5.0% using annual MDA. Quarterly MDA is expected as a method to enhance the effectiveness of azithromycin MDA in these hyperendemic districts.

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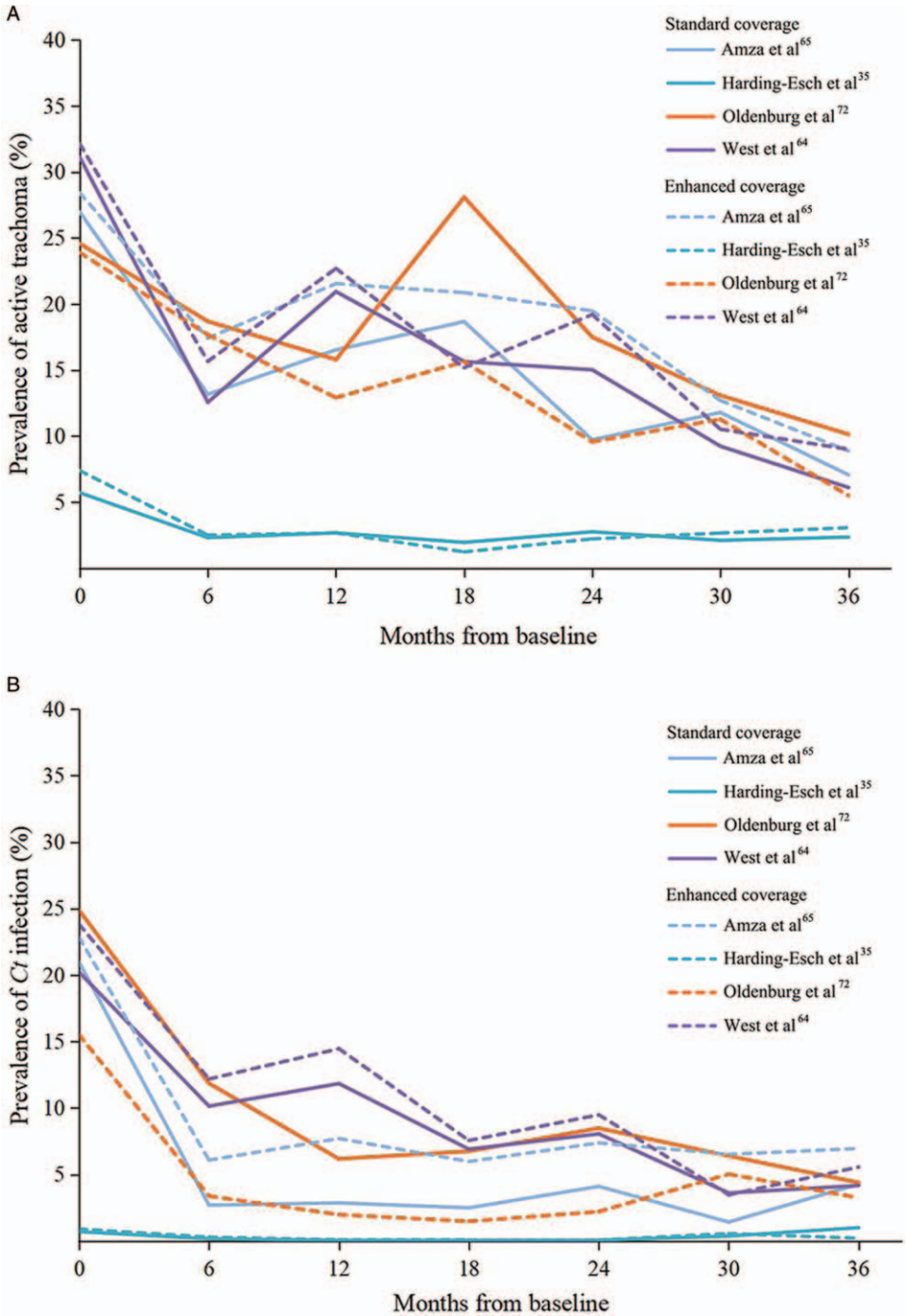

Figure 3: Prevalence of TF (A) and *Ct* infection (B) over time among groups treated with different coverages. Arms of comparison were labeled with same color in one publication. Lines and dot lines represent different coverage of azithromycin MDA. No significant difference was observed between standard coverage (80%–90%) and enhanced coverage (>90%). *Ct*: *Chlamydia trachomatis*; MDA: Mass drug administration; TF: Trachomatous inflammation-follicular.

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Conflicts of interest

None.

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