



CLEAN FACES, STRONG EYES!

Trachoma



Antibiotic Treatments of Trachoma: A Systematic Review



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Melbourne School of Population Health University of Melbourne

Harold Mitchell Foundation

Ian Potter Foundation

Cybec Foundation

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ISBN 978-0-7340-4195-1

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Executive Summary

BACKGROUND

Trachoma is the leading infectious cause of blindness worldwide. The aim of this analysis was to systematically assess the effectiveness of azithromycin treatment on the prevalence of active trachoma and conjunctival infections with *Chlamydia trachomatis* in endemic communities.

METHODS

Following the PRISMA statement, we searched The Cochrane Library, MEDLINE, EMBASE, CINAHL as well as local databases using the following MeSH and free-text words: trachoma, azithromycin, and SAFE strategy. Studies were included if they met the following criteria: people with, or at risk of, trachoma who were receiving one of the following interventions – azithromycin or azithromycin combined with the F and/or E components of the SAFE strategy – in trachoma endemic areas. Following qualitative analysis, studies were further refined by the requirement to report at least one year of follow-up data and to have implemented family or community-wide distribution of antibiotics. A meta-regression was then performed to further investigate the importance of including infants in mass-antibiotic treatment programs in the community-wide eradication of active trachoma.

RESULTS

A total of 44 studies which met our inclusion criteria for analysis were identified, however only 11 studies provided appropriate data for analysis. Collectively these 11 cohorts demonstrated a significant reduction of active disease could be attained through specific delivery and administration of azithromycin. Baseline clinical trachoma and detectable infection prevalence was 21.5% and 29.5% respectively. At 12 months, this was 14.2% and 4.2%. The relative prevalence reduction for clinical trachoma was 33.9% (95%CI 20.6% -47.2; $p=0.049$) and 85.8% (95% CI 3.9- 38.4) to 51.5 (95%CI 34.2 -68.7) when infants aged less than one year were included in mass distribution programmes ($p=0.049$). In a meta-analysis no additional impact could be confirmed by increasing coverage beyond 80%.

CONCLUSION

Overall there is substantial evidence supporting the use of azithromycin therapy in the control of trachoma. Other studies support the concept of the independent protective effect of the other components of the SAFE strategy including health educational programs, facial cleanliness and the establishment of pit latrines. Pooled analyses of studies including infants less than one year in mass-antibiotic treatment programs showed a relative prevalence reduction in clinical trachoma.



PROJECT OVERVIEW

Overcoming Indigenous Disadvantage, or 'closing the gap' in health, education, housing and other key areas has been identified as a priority by the Australian Government, particularly in the last decade (Australian Government Productivity Commission 2009).

The Australian National Indigenous Eye Health Survey reveals substantial challenges in closing the gap in Indigenous Eye Health. Although vision loss is five times lower in Indigenous children than mainstream children, the rate of blindness in Indigenous adults is six times higher than in the mainstream (Taylor 2009).

Optimal prevention and treatment of Indigenous eye disease requires that practitioners and policy-makers have ready access to up-to-date research evidence. Therefore, systematic reviews in two priority topics in Indigenous Health were undertaken:

1. The effectiveness of oral azithromycin in the management of Trachoma
2. The effectiveness of various methods of screening for Diabetic Retinopathy

The systematic review process involved:

1. Conducting a comprehensive search of literature addressing each question
2. Developing a taxonomy identifying key contextual features that may influence the application of this evidence to the Australian Indigenous setting
3. Building an evidence map that classified the retrieved studies according to key screening method and context characteristics identified in the taxonomy
4. Extracting, summarising and analysing the results of the identified studies
5. Describing the relevance of this information to Indigenous eye disease services and outlining the need for further research relevant to the priority questions.

This report contains the results of the systematic review and meta-regression on the effectiveness of azithromycin treatment on the prevalence of trachoma and the need for including infants in mass treatment programs.

Introduction

TRACHOMA

Trachoma is the leading infectious cause of blindness worldwide (Wright 2008). Repeated and prolonged infections with *Chlamydia trachomatis* cause a chronic follicular conjunctivitis which leads to conjunctival scarring, entropion formation, trichiasis, and ultimately blinding corneal opacification. With active disease affecting an estimated 45 million people worldwide, trachoma remains an important public health problem (Mariotti 2009).

Data on the global distribution of trachoma suggests that this disease primarily affects impoverished regions (Polack 2005); however, community-wide elimination can be achieved. The World Health Organization (WHO) has developed and supported the implementation of the 'SAFE' strategy for the global elimination of trachoma. This program promotes surgery (S) for entropion and trichiasis, antibiotics (A) for infectious disease, facial cleanliness (F) and environmental improvements (E) to reduce transmission. The prospect for global elimination of trachoma has been facilitated by the availability of azithromycin for communities partaking in the SAFE scheme. Interestingly, azithromycin is often not recommended for children less than one year of age although it is registered in many countries for use in children aged six months and above and is also recommended for specific purposes in newborn children. It has recently been postulated that untreated infants act as a nidus for re-infection in their family, and in turn community, re-infection (Taylor 2009).

The aim of this analysis was to systematically assess the effectiveness of azithromycin treatment on reducing the prevalence of clinically active trachoma and conjunctival infections with *C. trachomatis* in endemic communities. In particular, we investigated the impact of oral azithromycin alone or in combination with the F and E components of the SAFE strategy. A meta-regression was then performed to further investigate the importance of including infants in mass-antibiotic treatment programs.

SEARCH DESCRIPTION AND METHODOLOGY

The method used for this review was derived from the methodology outlined in the PRISMA statement (Moher 2009). We searched The Cochrane Library Issue 3 2008, MEDLINE (1950 to September 2009), EMBASE (1980 to September 2009), CINAHL (1982 to September 2009) as well as local databases such as RURAL and Indigenous Australia (up to September 2009) using the following Medical Subject Headings (MeSH) and free-text words: trachoma, azithromycin, and SAFE strategy (see Appendix 1). The reference lists of retrieved articles were also hand-searched to identify other studies that may have qualified for inclusion in the review.

STUDY SELECTION

Studies were included if they met the following criteria: people with, or at risk of, trachoma who were receiving one of the following interventions – azithromycin or azithromycin combined with the F and/or E components of the SAFE strategy – in trachoma endemic areas. In particular, we examined oral azithromycin at any dose or frequency compared with other oral or topical antibiotic regimes. Studies focusing specifically on dose regimens or principally on surgery for trichiasis were excluded. We included all study designs in which the evaluation of the intervention at the individual or community level was the primary focus. However, editorials, commentaries, other reviews, feasibility studies and theoretical analyses or clinical overviews were excluded.

The primary outcome for this study was the change in prevalence of active trachoma. The number of participants with clinically defined active trachoma, as characterised by follicular inflammation (TF) or trachoma intense inflammation (TI) and defined according to various grading systems (Thylefors 1987) at any reported follow-up period was retrieved. Outcome measures were recoded for all major intervals which had been reported. Twelve months was selected to represent the period in which recurrence or relapse of infection occurs. The secondary outcome measure was a positive molecular test for *C. trachomatis* using nucleic acid amplification tests. Adverse events were recorded when reported in the primary studies.

DATA EXTRACTION & SYNTHESIS

Studies retrieved by the initial search were scanned by two authors to exclude obviously irrelevant studies, and then identified studies were individually reviewed again ensuring that they did not meet the inclusion criteria. Full-text articles were retrieved and reviewed for the purpose of applying the inclusion criteria independently. Data from the studies were extracted independently using a standardised database. Variables included: study characteristics (design, sample size); participant demographics (age, gender, country and regional location); interventions and type of outcome measures. We recorded outcomes in terms of clinical efficacy and adverse events when reported. Due to the heterogeneity of retrieved studies in terms of outcomes and various interventions, quantitative pooling of data from all studies meeting our general inclusion was not possible; thus, the results were initially synthesized as a narrative review. For ease of interpretation studies, the studies were grouped according to the aspect of active trachoma management they address. In particular, we examined:

1. Azithromycin versus topical agents
2. Mass azithromycin distribution
3. Mass azithromycin therapy versus targeted azithromycin therapy
4. Azithromycin versus various components of the SAFE strategy

Methods

DATA ANALYSIS: EFFECTS OF TREATING INFANTS IN MASS DISTRIBUTION PROGRAMS

Inclusion for this analysis was further refined by the requirement for studies to report at least one year of follow-up data and to have implemented family or community-wide distribution of antibiotics. Reports of case-only antibiotic distribution were excluded. Outcome measures included both the prevalence of clinically active disease and evidence of infection. Given the variation in molecular techniques used to detect the presence of *C. trachomatis* and the likely heterogeneity of results obtained from different methods, studies used in analysis were required to have used the Amplicor (Roche Molecular Systems) polymerase chain reaction (PCR) assay.

Prevalence data were extracted from the individual studies and cohorts within studies. The denominator for this prevalence was the number of individuals assessed. However, due to intra-village clustering of trachoma (Katz 1988; West 1991), the effective sample size for the prevalence estimates was less than the number of individuals actually assessed, with the reduction dependent on the size of the intra-village correlation of trachoma, the number of villages studied, and the number of individuals studied within each village. This proportionate reduction was termed the “design effect”. Such design effects at baseline and 12 month assessments were estimated by calculating intra-village correlations from the data provided within each cohort within study where available, or by using intra-village correlations (ICC) obtained from published studies in a similar location.

The effect of the intervention in each cohort was measured by the absolute and relative reduction in prevalence from baseline to 12 months follow up. These were estimated using the observed prevalence's and the effective sample size as described above and reported together with 95% confidence intervals (95% CI) in forest plots. To account for multiple cohorts being reported within each study and for heterogeneity of prevalence's between studies, a three-level random-intercepts logistic regression model using 20 numerical quadrature points was employed to produce summary estimates (procedure `xtmelogit` in Stata v10.1). This model assumed that conditional upon the random effects at study and cohort-within-study level that the number of positive trachoma assessments was independently binomially distributed, and a further assumption was employed that the individuals presenting for baseline and 12 month assessment were distinct.

This latter assumption was necessary as the included studies did not provide sufficient information with which to assess within-individual correlation across assessments. The analyses reported here therefore assume a repeated cross-sectional design rather than a pre-post cohort design. The random effects model that was employed accommodated for heterogeneity in the prevalence (on the logit scale) between studies, and also between cohorts within the same study. It produces pooled (combined) odds ratios and confidence intervals on the logit scale and both the estimates and 95% CI endpoints were back-transformed to the probability scale for presentation as relative prevalence reductions.

The pooled absolute and relative prevalence reductions for subgroups of cohorts (e.g. treated children <1 year old versus no treatment), and the comparison thereof, were obtained by adding the relevant subgroup variable to the logistic regression models, together with the interaction of the subgroup variable with the “occasion” indicator variable. Due to the small number of studies and cohorts within studies, all models assumed that each subgroup has a common level of heterogeneity across studies and cohorts-within-studies.

Assessment of the effect of quantitative factors such as coverage rates on prevalence reduction was performed by linear regression using change in relative prevalence as the outcome variable with weighting by its inverse variance using the effective sample size, and accommodating multiple cohorts within studies using a jack-knife standard error correction. This was accomplished in the “metareg” procedure of Stata.

SEARCH AND SELECTION

A total of 645 references were identified. These were screened and the full text of 161 potentially relevant articles were retrieved and examined and assessed in full text. Of these, 117 were excluded from the review and the remaining 44 studies met the inclusion criteria for this qualitative review. Further details can be found in Figure 1.

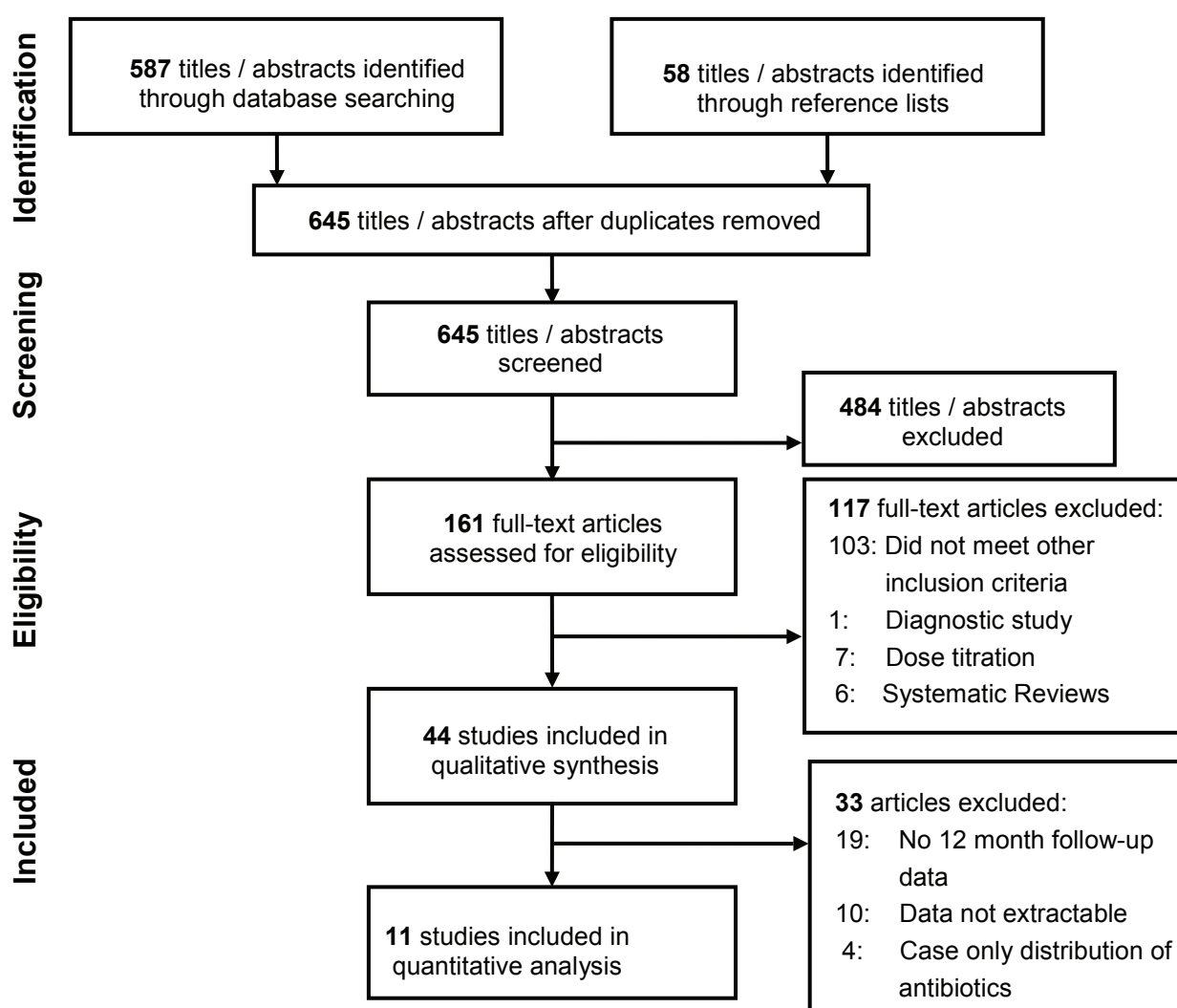


Figure 1: Study Search and Selection (based upon PRISMA Flow Diagram, Moher 2009)

Results

EVIDENCE MAP OF SCREENING METHODS AND STUDY DESIGN

Table 1 categorises the eligible studies in terms of intervention and study design. Close to half of the included studies (n=20) investigated pm mass azithromycin therapy. Eleven studies investigated on azithromycin versus various components of the SAFE strategy, five on azithromycin versus topical agents, and five on mass therapy versus targeted azithromycin.

The predominant study design was RCTs and interrupted time series (ITS) with a control group (n=11 each), with seven each of cross-sectional and case series studies, four clustered RCTs, two ITS without a control group, and one each of pseudo-RCT and case control design.

Table 1 : Interventions and study design of the evidence map

Intervention	n	RCT	RCT (pseudo)	RCT (cluster)	Case-control	ITS (with control)	ITS (without control)	Cross-sectional	Case series
Mass therapy versus targeted azithromycin therapy	5	1		1			1		2
Azithromycin versus various components of the SAFE strategy	11	1		1			1	5	2
TOTAL	44	11	1	4	1	2	11	7	7

Key: ITS: interrupted time series; RCT: randomised controlled trial

Results

DESCRIPTION OF STUDIES

Study Characteristics

The retrieved studies were conducted in 16 countries between 1997 and 2009. Countries of studies were recruited from:

- Ethiopia: Melese 2008; Gill 2008; Edwards 2008; Chidambaram 2006; Saidel 2005; Melese 2004; Chidambaram 2004; House 2009; Lakew 2009; Cumberland 2008; Broman 2006; Solomon 2008; West 2007; West 2005a; West 2005b; Desmond 2005; Lynch 2003; West 2006; Solomon 2004
- Gambia: Whitty 1999; Bowman 2000; Fraser-Hurt 2001; Bailey 1993; Burton 2005
- Nepal: Jha 2002; Fry 2002; Chern 1999; Osaki-Holm 2001; Frick 2001
- Australia: Laming 2000; Wallace 1997; Ewald 2003
- Sudan: Ngondi 2006; Ngondi 2008
- Multiple countries: Schachter 1999; Kuper 2005
- Vietnam: Atik 2006
- Kenya: Karimurio 2007
- Pakistan: Cochereau 2007
- Turkey: Guzey 2000
- Mali: Schemann 2007
- Egypt: Dawson 1997
- Saudi Arabia: Tabbara 1996
- Zambia: Astle 2006

The prevalence of active trachoma varied considerably among the studies due to different settings, patient populations, various antibiotic treatment regimes including specific programs designed for different subgroups within trachoma endemic areas, and community-based interventions, in which all residents of the community received treatment irrespective of the disease status.

Study Participants

All the studies recruited participants from trachoma endemic communities. The participants were normally resident in those communities, though many studies noted the transient-nature of their study population. The reported demographic data is contained in Table 2-5.

Types of Interventions

The treatment schedules of trials comparing azithromycin at any dose or frequency compared with other oral or topical antibiotic regimes given over a period of time, or single dose azithromycin given were examined alongside single and targeted mass regimes. In most instances, oral azithromycin at 20mg per kilogram (kg) of body weight was dispensed, and comparisons were made to topical tetracycline.

Table 2: Demographic details for studies investigating the role of azithromycin therapy compared to topical agents

Author (year)	Study Design	Country	Region	Target Population	Method of Trachoma Classification Method	Other Clinical Features Assessed	Methods to prevent specimen contamination documented	Negative Controls for Swabs Taken
Tabbara (1996)	RCT	Saudi Arabia	Eastern Province	Individual	Simplified WHO	Conjunctiva swab (taken at baseline and 24 weeks after treatment)	No	No
Bailey (1993)	RCT	Gambia	Jali (Kiang West) and Berending (Kombo South)	Individual	WHO grading system	1) Conjunctival swab (ELISA) 2) Nasopharyngeal swabs	No	No
Dawson (1997)	RCT	Egypt	N/A	Individual	Simplified WHO	Conjunctival swab (fluorescent antibody staining)	No	No
Whitty (1999)	RCT	Gambia	Sanjal Region	Mixed	Simplified WHO	None	No	N/A
Bowman (2000)	RCT	Gambia	Western Division	Individual	Simplified WHO	None	No	N/A
Cochereau (2007)	RCT	Pakistan	Kankan area of Guinea Conakry and Rawalpindi and Attock Districts	Individual	Simplified WHO	Conjunctival swab(PCR) (taken on days 0, 30, and 60)	Yes	No
Guzey (2000)	Pseudo RCT	Turkey	Sanliurfa	Individual	Simplified WHO	1) Conjunctival swab (taken at 3 and 6 months after treatment) 2) Complete blood count, serum biochemistry (Baseline, 2 and 4 weeks)	No	No
Fraser-Hurt (2001)	RCT	Gambia	Baddibu District	Community	Simplified WHO	None	No	N/A

Key: ELISA: Enzyme-linked immunosorbent assay; N/A: not applicable; PCR: polymerase chain reaction; RCT: randomised controlled trial; WHO: World Health Organization

Table 3: Demographic details for studies investigating the mass distribution of azithromycin

Author (year)	Study Design	Country	Region	Target Population	Method of Trachoma Classification Method	Other Clinical Features Assessed	Methods to prevent specimen contamination documented	Negative Controls for Swabs Taken
Broman (2006)	ITS w/o control	Tanzania	Kongwa	Community	Simplified WHO	Conjunctival swab (PCR)	Yes	No
Solomon (2008)	ITS w/o control	Tanzania	Kahe Mpya	Community	Simplified WHO	Conjunctival swab (PCR)	No	No
Melese (2008)	Cluster RCT	Ethiopia	Gurage Zone	Community	Simplified WHO	Conjunctival swab (pooled PCR) (with 5 negative controls)	Yes	Yes
Gill (2008)	Case series	Ethiopia	Gurage Zone	Community	None	Conjunctival swab (pooled PCR)	Yes	Yes
Edwards (2008)	ITS with control	Ethiopia	Gurage; Oromia; South Welo	Community	Simplified WHO	1) Conjunctival swab (PCR) 2) Presence of flies on eyes, 3) Cleanliness of hands & hair, 4) Discharge from the eyes & nose	Yes	Yes
West (2007)	ITS w/o control	Tanzania	Kongwa District	Community	Simplified WHO	Conjunctival swabs (RT-PCR (omp1))	Yes	No
Chidambaram (2006)	ITS with control	Ethiopia	Enemore/Ener District of the Gurage Zone	Family based	None	Conjunctival swab of right conjunctiva (pooled PCR)	Yes	Yes
West (2005a)	ITS w/o control	Tanzania	Kongwa	Community	Simplified WHO	Conjunctival swab (PCR)	No	No
West (2005b)	Case series	Tanzania	Kongwa	Community	Simplified WHO	Conjunctival swab (RT-PCR (omp1))	Yes	No
Saidel (2005)	Case series	Ethiopia	Gurage Zone	Individual	None	Conjunctival swab (PCR)	No	No

Author (year)	Study Design	Country	Region	Target Population	Method of Trachoma Classification Method	Other Clinical Features Assessed	Methods to prevent specimen contamination documented	Negative Controls for Swabs Taken
Burton (2005)	ITS w/o control	Gambia	Upper Saloum District	Community	Simplified WHO	1) Conjunctiva swab (PCR) 2) Nasopharyngeal swab (PCR)	No	No
Melese (2004)	ITS w/o control	Ethiopia	Gurage Zone	Community	None	Conjunctival swab (PCR)	Yes	Yes
Chidambaram (2004)	ITS w/o control	Ethiopia	Gurage Zone	Community	WHO grading system	Conjunctival swab (PCR)	Yes	Yes
Jha (2002)	ITS w/o control	Nepal	Kailali and Konchpur districts	Community	Simplified WHO	None	No	N/A
Fry (2002)	ITS w/o control	Nepal	Kailali and Kanchanpur in Seti and Mahakali Zones	Individual	WHO grading system	1) Skin examination (presence of impetigo) 2) Nasopharyngeal swab	No	No
Chern (1999)	RCT	Nepal	Lumbini Zone	Individual	WHO grading system	Conjunctival swab for bacterial cultures	No	No
Desmond (2005)	Cross sectional	Tanzania	Rombo	Community	None	Semi-structured/questionnaire regarding acceptance of treatment	N/A	N/A
Lynch (2003)	Case control	Tanzania	Kongwa District	Individual	Simplified WHO	None	No	N/A
House (2009)	Cluster RCT	Ethiopia	Goncha Seso woreda of the Amahara Region	Community	Simplified WHO	Conjunctival swab (PCR)	Yes	Yes
Lakew (2009)	Cross sectional	Ethiopia	Gurange Zone	Community	Simplified WHO	Conjunctival swab (PCR)	Yes	Yes

Key: N/A: not applicable; PCR: polymerase chain reaction; randomised controlled trial; WHO: World Health Organization; w/o: without

Table 4: Demographic details for studies investigating mass distribution of azithromycin therapy versus targeted azithromycin therapy

Author (year)	Study Design	Country	Region	Target Population	Method of Trachoma Classification Method	Other Clinical Features Assessed	Methods to prevent specimen contamination documented	Negative Controls for Swabs Taken
Schemann (2007)	ITS w/o control	Mali	Segou and Mopti	Other	Simplified WHO	1) Cleanliness of children's face 2) Education, environmental (including latrines) and socioeconomic conditions	No	N/A
Osaki-Holm (2001)	RCT	Nepal	Kailali District	Other	Simplified WHO	Conjunctival swab (LCR)	No	No
Frick (2001)	Case series	Nepal	NR	Other	Simplified WHO	None	No	N/A
Laming (2000)	Case series	Australia	Northern Territory	Individual	Simplified WHO	None	No	N/A
Schachter (1999)	Cluster RCT	Egypt, The Gambia, and Tanzania	NR	Community	WHO grading system	Conjunctival swab (LCR)	No	No

Key: N/A not applicable; NR: not reported; LCR: ligase chain reaction; PCR: polymerase chain reaction; RCT: randomised controlled trial; WHO: World Health Organization; w/o: without

Table 5: Demographic details for studies investigating azithromycin therapy versus various forms of the SAFE strategy

Author (year)	Study Design	Country	Region	Target Population	Method of Trachoma Classification Method	Other Clinical Features Assessed	Methods to prevent specimen contamination documented	Negative Controls for Swabs Taken
Cumberland (2008)	Cluster RCT	Ethiopia	Gurage and South Welo Zone	Family based	Simplified WHO	1) Conjunctival swab (PCR) 2) Knowledge and behaviour related to trachoma control	Yes	Yes
Atik (2006)	RCT	Vietnam	Thanh Hoa Province	Individual	Simplified WHO	Conjunctival swab (PCR)	No	No
West (2006)	RCT	Tanzania	Kongwa	Individual	Simplified WHO	Conjunctival swab (PCR)	No	No
Wallace (1997)	Case series	Australia	Northern Territory	Community	Five Sign System for Trachoma	None	No	N/A
Solomon (2004)	ITS w/o control	Tanzania	Kahe Mpya, Rombo	Community	Simplified WHO	Conjunctival swab (PCR)	No	No
Ngondi (2008)	Cross sectional	Sudan	Kiech Kuon, Padak, Katigiri and Tali	Family based	Simplified WHO	None	No	N/A
Ewald (2003)	Cross sectional	Australia	Central Australia	Community	Simplified WHO	None	No	N/A
Karimurio (2007)	Cross sectional	Kenya	Kajiado district, Rift Valley	Community	Simplified WHO	None	No	N/A
Ngondi (2006)	Cross sectional	Sudan	Kiech Kuon, Padak, Katigiri and Tali	Community	Simplified WHO	None	No	N/A
Astle (2006)	Case series	Zambia	Gwembe District	Community	Simplified WHO	None	No	N/A
Kuper (2005)	Cross sectional	Ethiopia, Ghana, Mali, Morocco, Nepal, Niger, Tanzania, Vietnam	NR	NR	Simplified WHO	None	No	N/A

Key: N/A: not applicable; NR: not reported; PCR: polymerase chain reaction; RCT: randomised controlled trial; WHO: World Health Organization; w/o: without

Results

AZITHROMYCIN VERSUS TOPICAL AGENTS

Treatment of active disease: oral azithromycin versus topical tetracycline (7 RCTs & 1 pseudo RCT)

There were seven RCTs comparing azithromycin with conventional topical tetracycline treatment for active trachoma (Whitty 1999; Bowman 2000; Fraser-Hurt 2001; Bailey 1993; Cochereau 2007; Guzey 2000; Dawson 1997; Tabbara 1996). These studies included children, aged three months to 14 years, with signs of active infection. Individuals were randomly allocated to receive oral azithromycin (20mg/kg body weight) as a single dose or topical tetracycline with one study (Bailey 1993) also using oral erythromycin as an adjunct to tetracycline for those with severe trachoma. The treatment schedules are outlined in Table 6. In these studies there was no regard for the presence of trachoma in family members, nor were family members treated. No other health promotion was conducted.

In the studies by Bailey (1993), Dawson (1997) and Tabbara (1996), the application of topical treatment in the control group was supervised by study research teams including trained field workers, whereas in Bowman (2000), the application of tetracycline ointment was initially undertaken by community nurses in front of the caregiver, with no ongoing supervision beyond the first dose. The primary outcome measure was signs of active trachoma (Bowman 2000; Bailey 1993; Dawson 1997; Tabbara 1996). Secondary outcome measures were conjunctival swabs for PCR testing taken at various time points (Dawson 1997; Tabbara 1996). Information regarding the precautions against contamination was not recorded, and none of these studies included negative control swabs.

Three RCTs (Bailey 1993; Dawson 1997; Tabbara 1996) showed no significant difference between the azithromycin and topical tetracycline group in the resolution of disease at three and six months. Although not statistically significant, Dawson (1997) suggested that azithromycin was superior to topical tetracycline. Adverse events were not reported by any of the studies. In the study by Bowman (2000), children allocated to azithromycin were significantly more likely to have resolved disease than those allocated to tetracycline, both at 10 weeks (azithromycin cure rate ratio, 1.31; 95% CI 1.08-1.59; $p<0.001$) and six months (azithromycin group cure rate ratio, 1.19; 95%CI 1.06-1.34; $p<0.001$). In addition, of those people identified with intense disease ($n=15$), 12 (80%) were found to be cured at six months in the azithromycin group, whereas only two (25%) of the eight patients were observed to have cleared disease in tetracycline group ($p=0.02$).

Treatment of active disease: oral azithromycin versus topical tetracycline (1 non-randomised study)

In the study by Guzey (2000), 96 children were randomly allocated to azithromycin (10mg/kg body weight) or topical oxytetracycline by room, in which all active cases within the room received the same treatment. At both three and six months, children allocated to azithromycin were significantly more likely to have resolved disease than those allocated to tetracycline, ($p=0.029$ and $p=0.012$, respectively). Symptoms of diarrhoea ($n=5$), vomiting ($n=3$) and abdominal pain ($n=10$) occurred seven days after azithromycin administration with no serious adverse events reported.

Treatment of active disease: topical azithromycin versus oral azithromycin (1 RCT)

In the study by Cochereau (2007), 670 children were randomly allocated to azithromycin 1.5% for two or three days or single oral azithromycin (20mg/kg body weight) dose. The primary end point was 'cure' at the end of the study, defined as a TF 0 grade for trachoma (i.e. <5 follicles with at least 0.5mm diameter in the upper tarsal conjunctiva) in the worse eye at the end of the study period. Over 95% of patients had cure in the worse eye at two months. Cure rates were 93%, 96.3% and 96.6% in the two-day, three-day and oral treatment groups, respectively. Only 4.2% of patients with cure at day 30 had re-emergence of trachoma in either eye at day 60: 4.9%, 4.0% and 3.6% in the two-day, three-day and oral treatment groups, respectively. Overall, the azithromycin 1.5% groups were not-inferior to oral azithromycin. Difficulty of instilling eye drops and crying during instillation were reported, but no treatment related adverse events were documented.

Table 6: Treatment regimens for studies investigating azithromycin therapy compared to topical agents

Author (year)	Intervention / Methodology	Infants Treated (<1yo)	Infants Treated (<6 months)	How infants were treated	Administering Personnel	Follow-up Period
Tabbara (1996)	Intervention: single dose AZR (20 mg/kg) Control: Topical tetracycline oc; BD both eyes for 5 days/week for 6/52	No	-	-	NR	4, 8, 12 & 24 weeks
Bailey (1993)	Intervention: single dose AZR (20 mg/kg) Control: tetracycline oc to each eye BD 6/52. In severe disease: oral erythromycin 250 mg QID for 2/52, adjusted per kg body weight	No	-	-	Study team	4, 8, 16 & 26 weeks
Dawson (1997)	1) Topical tetracycline oc daily for 5 consecutive days every 28 days for a total of six 5-day periods plus oral placebo suspension 2) Single dose AZR (20 mg/kg) 3) AZR (20 mg/kg) once weekly for 3 consecutive weeks 4) AZR (20 mg/kg) once every 28 days for a total of six treatments	No	-	-	Study team	2, 5, 8 & 12 months
Whitty (1999)	Intervention: single dose AZR (20 mg/kg) on days 1, 8 and 15 Control: Topical tetracycline oc daily for 42 days	Yes	Yes	AZR (20 mg/kg) or tetracycline oc	Field workers	Baseline, 7, 14, 21 & 28 days
Bowman (2000)	Intervention group: single dose AZR (20 mg/kg) Control group: Topical tetracycline oc; BD both eyes for 6 weeks	No	-	-	Nurse and caregivers	10 weeks & 6 months
Cochereau (2007)	1) AZR 1.5% for 3 days: One drop per eye BD for 3 days 2) AZR 1.5% for 2 days: One drop per eye BD for 2 days 3) Single dose, suspension 20mg/kg at day 0	No	-	-	Study team	Baseline, 2, 30 & 60 days
Guzey (2000)	Intervention: Single dose AZR (10mg/kg for 3/7) Control: Topical tetracycline oc; BD to each eye for 2/52	No	-	-	Trained observer	Baseline, 1, 2, 3 & 6 months
Fraser-Hurt (2001)	1) Single dose AZR (20 mg/kg) on days 1, 8 and 15 for 6/52; childbearing women: erythromycin (500 mg) BD 2/52; or amoxycillin (500 mg) TDS for 2/52 2) daily tetracycline oc	No	-	-	Ophthalmologists	Baseline, 2, 12 months
Schachter (1999)	1) Single dose AZR (20 mg/kg, up to 1g for adults); childbearing women: erythromycin (500 mg) 2) 1% oxytetracycline oc daily for 6 wks	Yes	Yes	AZR (20mg/kg)	Trained village assistants	Baseline, 2, 12 months

Key: AZR: azithromycin; BD: bis die (twice daily) ; NR: nor reported; PCR: polymerase chain reaction; yo: year old

Results

MASS AZITHROMYCIN THERAPY

Treatment of active disease: mass azithromycin therapy – oral azithromycin versus topical tetracycline (3 RCTs)

There were three RCTs comparing the efficacy of azithromycin with conventional tetracycline therapy for community-wide treatment and control of trachoma. These studies included children and adults in the endemic regions of Egypt, Tanzania and The Gambia (Whitty 1999; Fraser-Hurt 2001; Schachter 1999). In the multi-centre study by Schachter (1999), villages were identified and matched by prevalence of active disease in children and age; whilst villages were principally matched by size in the study by Fraser-Hurt (2001). The study by Whitty (1999), examined the effects of azithromycin given as mass treatment on common symptoms and formed part of the larger study undertaken by Schachter (1999).

Within each pair of, or within each village, individuals were randomly assigned to mass treatment with weekly oral azithromycin for three weeks (children: 20mg/kg up to a maximum dose of 1 gram; adult: 1 gram) or supervised application of 1% tetracycline ointment to both eyes, once daily for six weeks. Overall treatment supervision and village-wide compliance, as defined by one dose of azithromycin (or one week of erythromycin), or at least four weeks of tetracycline application, was slightly higher in the azithromycin treated than in the tetracycline-treated villages in both studies. Clinical examination and conjunctival swabs for *C. trachomatis* ligase chain reaction (LCR) were documented at baseline, three and 12 months by Schachter (1999).

In both studies, the results showed that individuals allocated to azithromycin were significantly more likely to have a reduction in the prevalence of active disease than those allocated to tetracycline, both at two, three and 12 months. Village-wide LCR positivity rates reported by Schachter (1999) were substantially lower than baseline with both treatment groups, although the decrease was greater with azithromycin than with tetracycline (93% versus 77% in Egypt, 78% versus 66% in The Gambia, 64% versus 55% in Tanzania). Whitty (1999) observed that fever and headache were the most common complaints with azithromycin administration. Interestingly people assigned to azithromycin had 20% fewer episodes of illness, fever and headache and 40% had fewer diarrhoea and vomiting episodes at follow-up than did the tetracycline group.

Treatment of active disease: mass azithromycin therapy – oral azithromycin versus oral azithromycin (delayed administration) (1 RCT)

There was one study comparing mass single dose azithromycin on the prevalence of active disease, species distribution and resistance of conjunctival bacterial flora. In the study by Chern (1999) 91 children were randomly allocated to azithromycin (20mg/kg) at baseline, and 31 children randomised to receive the same dose of azithromycin deferred until day 14 follow-up period. There was a statistically significant decline in the number of pathogenic bacteria before and after azithromycin treatment; however, those assigned delayed azithromycin administration showed no change in prevalence, distribution or resistance patterns.

Treatment of active disease: mass azithromycin therapy – oral azithromycin only (17 non-randomised studies)

There were 10 studies comparing the efficacy and adverse events of mass azithromycin for community-wide treatment and control of trachoma (Melese 2004; Chidambaram 2004; Broman 2006; Solomon 2008; West 2005a; West 2005b; West 2006; Bowman 2000; Burton 2005; Jha 2002). These studies involved random allocation of whole villages and high-risk groups to oral azithromycin (10-20mg/kg body weight) as a single dose or that of topical tetracycline or erythromycin if pregnant, less than 12 months of age or with signs of active trachoma. Only two studies (West 2007; Burton 2005) included children less than 12 months of age. The treatment schedules are outlined in Table 7.

The remaining seven studies included other interventions arms such as yearly mass treatment of the entire village versus treatment every two years (House 2009), intensive latrine construction or insecticide spraying (West 2007), specific recruitment strategies for azithromycin administration (Lynch 2003), observations surrounding patient antibiotic compliance (Desmond 2005) and combined antibiotic treatment regimes and health education programs (Edwards 2008; Saidel 2005; Broman 2006).

Three studies (Gill 2008; Chidambaram 2006; Burton 2005) showed that single mass azithromycin therapy reduced the prevalence of infection as measured by PCR over various time points. In Chidambaram (2006), children aged 1 to 5 years decreased their prevalence of infection from 43.5% at baseline to 5.1% after treatment. However, on average, infection returned gradually over 24 months in the absence of other interventions. In a similar study by Gill (2008), an overall reduction in trachoma prevalence was noted, although residual infection was identified at 30 months. In the study by Burton (2005), single dose azithromycin treatment in communities with a low baseline prevalence of active disease generally resulted in effective, long-lasting control of infection.

In the studies by Chidambaram (2004) and House (2009), the treatment of children decreased infection in untreated older children and adults who resided in villages, showing a form of “herd protection” from a mass antibiotic campaign. In particular, House (2009) noted that prevalence of clinically active trachoma in children was reduced from 48.4% to 3.6% after four mass treatments; and that the prevalence of ocular chlamydial infection in both studies, as measured by PCR, was progressively reduced with every treatment regime. Information regarding the prevention of contamination was only reported by Chidambaram (2004).

Jha (2002) noted a similar success with a 53% decrease in the prevalence of trachoma at six months and a 68% decrease 12 months after the administration of azithromycin. However, after accounting for seasonal variations and secular trends, the authors could only attribute an estimated 36% reduction to the direct effect of treatment six months previously. West (2007) showed that the rates of clinical trachoma did not differ significantly in the intervention and control villages at six months post-treatment (20% versus 33%, $p=0.07$), nor at 12 months (43% versus 44%, $p=0.90$). Infection with *C. trachomatis* did not differ between groups at six months post-treatment (9% versus 7%, $p=0.45$).

In five studies investigating the effect of azithromycin in trachoma hyper-endemic communities (Melese 2004; Solomon 2008; West 2007; West 2005a; Solomon 2004), a proportion of individuals in each of the studies had some success with eliminating infection at various time points. In Solomon (2004), the prevalence of infection fell from 9.5% before mass treatment to 2.1% at two months and with the six-monthly treatment of clinically active individuals with topical tetracycline the rate of infection fell to 0.1% at 24 months; and in a follow-up study 24 months after the initial study dose in 2004, Solomon (2008) showed that *C. trachomatis* was not detected in the conjunctiva of any of the sample population after further mass treatment.

A study by Melese (2004) noted the prevalence of infection was 56.3% pre-treatment and 11.0% at six months post-treatment in their study population. Four years later, Melese (2008) showed that in villages in which residents were treated annually, the prevalence of infection in preschool children was reduced from a mean of 42.6% to 6.8% at 24 months. In the villages in which residents were treated biannually, infection was reduced from 31.6% pre-treatment to 0.9% at 24 months.

West (2005a) showed generally similar findings with clinical trachoma falling from 57% pre-treatment to 12% 12 months after administration. In the study by West (2007), trachoma rates at five years after therapy remained lower than baseline, ranging from 45% in those aged 0 to three years to 8% in those aged 11 to 15 years (compared with 81% and 39% at baseline, respectively). Furthermore, *C. trachomatis* infection rates at baseline ranged from 71% to 57%, but were 27% to 17% at five years after two rounds of mass treatment. Similar findings were noted for West (2005a) who showed that treatment significantly decreased the proportion of individuals positive in the community and the *C. trachomatis* load in the community.

Table 7: Treatment regimens for studies investigating the importance of mass azithromycin therapy

Author (year)	Intervention / Methodology	Infants Treated (<1yo)	Infants Treated (<6 months)	How infants were treated	Administering Personnel	Follow-up Period
Broman (2006)	Single dose AZR (20 mg/kg, up to 1g for adults); topical tetracycline oc if pregnant or with clinical signs of trachoma	No	-	-	NR	Baseline, 18 months
Solomon (2008)	Single dose AZR (20 mg/kg, up to 1g for adults) at baseline, repeat treatment at 24 months. Topical tetracycline oc for those with active disease	No	-	-	Study team	Baseline, 24 months, 60 months
Melese (2008)	Biannual versus annual AZR administration (20 mg/kg, up to 1g for adults)	No	-	-	Fieldworkers	Baseline, 3, 6, 12, 18, 24 months
Gill (2008)	Biannual AZR for 2 years: single dose AZR (20 mg/kg, up to 1g for adults); topical tetracycline oc if pregnant	No	-	-	NR	Baseline, 12, 24 months
Edwards (2008)	3-year post-intervention follow-up survey	No	-	-	Ophthalmic nurse	Baseline, 36 months
West (2007)	Single dose AZR (20 mg/kg, up to 1g for adults); topical tetracycline oc if pregnant	Yes	No	AZR (20mg/kg) or tetracycline oc	Community based distribution	Baseline, 18 & 60 months
Chidambaram (2006)	Single dose AZR (20 mg/kg, up to 1g for adults)	No	-	-	Study team	Baseline, 2, 6, 12, 18, and 24 months
West (2005a)	Single dose AZR (20 mg/kg, up to 1g for adults); topical tetracycline oc if pregnant	No	-	-	NR	Baseline, 2,6,12 & 18 months
West (2005b)	Single dose AZR (20 mg/kg, up to 1g for adults); topical tetracycline oc if pregnant	No	-	-	NR	Baseline, 2 months
Saidel (2005)	Single dose AZR (10mg/kg for 3/7)	No	-	-	Study team	12 months
Burton (2005)	Single dose AZR (20 mg/kg, up to 1g for adults); topical tetracycline oc if younger than 6 months; childbearing women: erythromycin (500 mg) BD 2/52	Yes	Yes	AZR (20 mg/kg) or tetracycline oc BD for 2/52 if <6/12	Fieldworkers	2, 6, 12 & 17 months
Melese (2004)	Single dose AZR (20 mg/kg, up to 1g for adults); topical tetracycline oc if pregnant	No	-	-	Study team	Baseline, 6 months
Chidambaram (2004)	Intervention: AZR (dosage NR) Control: Delayed AZR (dosage NR)	No	-	-	Trained examiner	Baseline & 6 months

Author (year)	Intervention / Methodology	Infants Treated (<1yo)	Infants Treated (<6 months)	How infants were treated	Administering Personnel	Follow-up Period
Jha (2002)	Use of AZR (dosage NR) in high-risk groups Use of AZR (dosage NR) given to evaluate seasonal differences	No	-	-	Study team	6 months before treatment, baseline, 6 & 12 months
Fry (2002)	Single dose AZR (20 mg/kg, up to 1g for adults)	No	-	-	Project managers	Baseline, 10 & 180 days
Chern (1999)	Intervention: Single dose AZR (20 mg/kg, up to 1g for adults) Control: Single dose AZR (20 mg/kg, up to 1g for adults) deferred until day 14	No	-	-	Trained examiners	Baseline & 14 days
Desmond (2005)	Focus group discussions, individual interviews, questionnaires and direct observation to quantify, explore and contextualize reasons for acceptance or refusal of the drug.	No	-	-	NR	N/A
Lynch (2003)	Intervention: recruitment of village government (VG) or community volunteers (CV) Recruitment via door to door contact	No	-	-	Village leaders or selected volunteers	Baseline
House (2009)	1) Single dose AZR (20 mg/kg) four times per year/ for children <10yrs versus oral AZR (20 mg/kg) four times per year delayed until after 12 months 2) Yearly mass treatment of the entire community (intervention) with oral AZR versus mass treatment of the entire community every two years (control) 3) Intensive latrine construction over 24 months (intervention) versus no program specific latrine construction (control) In intervention (1), children younger than 1 year were offered 6 week course of topical tetracycline (applied BD to both eyes). In intervention (2), children younger than 1 year were offered topical tetracycline	Yes	Yes	tetracycline oc BD for 6/52	Trained health care professional	Baseline, 3, 6, 12 months
Lakew (2009)	Four biannual community-wide distributions. Single dose AZR (20 mg/kg, up to 1g for adults); topical tetracycline oc if pregnant	No	-	-	NR	Baseline, 6, 12, 18, 24, 30, 36 & 42 months

Key: AZR: azithromycin; BD: bis die (twice daily); N/A: not applicable; NR: not reported; PCR: polymerase chain reaction; yo: year old

Results

TARGETED AZITHROMYCIN THERAPIES

Treatment of active disease: targeted mass azithromycin therapy – oral azithromycin only (1 RCT)

One study compared mass treatment with targeted treatment of children aged 1–10 who were diagnosed with clinically active disease. In the study by Osaki-Holm (2003), both treatment strategies reduced the prevalence of clinically active disease in six months by approximately one-third. Individuals in the group for mass treatment of children were about 20% less likely to have clinically active trachoma at the follow up examination than those in the targeted household group, but this difference was not statistically significant ($p=0.33$). Although those in the group for mass treatment of children were less likely to be LCR positive six months after treatment, this result was also not clinically significant ($p=0.11$).

Treatment of active disease: targeted mass azithromycin therapy – oral azithromycin only (2 non-randomised studies)

There were two non-randomised studies that compared mass or mass and targeted treatment in a mixture of children and adult populations (Laming 2000; Schemann 2007). In the study by Schemann (2007), three groups - all age participants (group 1), children aged less than 11 years (group 2) and inhabitants of households where at least one child had clinically active trachoma (group 3) - were allocated to a single dose of azithromycin. At the same time, concurrent trachoma specific educational and health-promotion programs were also being conducted at each household. The outcome variable was clinically active trachoma at 12 months. Among children under 11 years of age, the active trachoma prevalence fell in each group from 23.7% to 6.4% in group 1, from 20.8% to 6.8% in group 2, and from 20.2% to 8.5% in group 3. In Laming (2000), all children and their contacts received single dose oral azithromycin suspension (20mg/kg to a maximum of 1gram) with the main outcome measure being prevalence of active trachoma. Targeted, single-dose azithromycin showed a reduction in active trachoma from 44% at baseline to 22% at 6-8 months ($p<0.0001$) and was 31% at 12 months ($p<0.05$).

AZITHROMYCIN VERSUS VARIOUS COMPONENTS OF THE SAFE STRATEGY

Role of azithromycin therapy in all facets of the SAFE program (1 RCT, 4 cross sectional studies, 1 case series)

Atik (2006) and colleagues undertook a RCT investigating the role of biannual azithromycin in conjunction with the full SAFE strategy or only surgical intervention. Interestingly they found that re-infection rates for second episodes were comparable between communes which had been exposed to the full SAFE program compared to those which had participated only in the surgical and antibiotic arms. Supporting these findings was Ngondi (2006) who found that there were often marked heterogeneity in both the uptake and effect of the SAFE strategy between different communities. From the work of Ngondi (2006) and Astle (2006), it was concluded that falls in active trachoma could occur in endemic areas where SAFE is implemented. In the more recent study by Ngondi (2008), it was found that the AFE components, or more specifically mass systemic azithromycin treatment, facial cleanliness, face washing, and use of pit latrines in the household, had independent protective effects against active trachoma.

The nation-wide implementation of the SAFE strategy has also been investigated. Kuper (2005) performed semi-structured interviews of programme stakeholders and found that the SAFE strategy was well established in only a few countries. Interestingly, it would appear that the full SAFE programme with azithromycin is only offered to a small proportion of endemic communities; however when in place, the mass distribution of antibiotics is generally undertaken well. Kuper (2005) also found that the number of surgeries for entropion or trichiasis performed annually was generally insufficient and that the quality of surgery was rarely monitored.

Combination of azithromycin therapy and Education arm alone (1 cluster RCT; 1 Case series)

The mass distribution of azithromycin coupled with different education programs was investigated by Cumberland (2008) in a cluster RCT. This work found that although antibiotic administration provided the most effective intervention, community-based health education programs could help reduce community prevalence of *C. trachomatis*. Interestingly, Cumberland (2008) concluded that receiving at least one dose of azithromycin was more critical than total number of doses received. Wallace (1997) reported that school-based health promotion and education programs, coupled with a single dose of azithromycin, could be implemented and offers an avenue for good coverage for up to six months.

Combination of azithromycin therapy and Environmental Modification alone: (1 RCT; 1 Cross-sectional study)

The role of fly reduction combined with azithromycin was directly investigated in a RCT by West (2006). Following an intensive insecticide spraying program and despite a significant reduction in the number of flies, no added benefit on trachoma reduction was found. In a cross-sectional study by Ewald (2003), the importance in improvements in housing and sewerage infrastructure were investigated. Similar to the study by west (2006), no major benefit environmental modification was observed. However, the cross-sectional study by Ewald (2003) was somewhat limited by a high attrition rate, with only approximately a third of residents appearing in all three censuses, and only a relatively modest increase in the proportion of houses with completely adequate facilities (increased from 0 to 16% over the study period). Ewald (2003) concluded that population mobility (both within and between communities), inadequate housing and continued crowding (despite improvements), as well as uncertainty about compliance with antibiotic treatment, are the most likely factors contributing to the lack of effective treatment.

Results

META-REGRESSION ANALYSIS

A total of 11 papers met the criteria for inclusion in the meta-regression (Melese 2008; Chidambaram 2006; House 2009; Lakew 2009; Broman 2006; West 2006; Solomon 2004; Fraser-Hurt 2001; Burton 2005; Schachter 1999; Atik 2006). Data regarding the change in prevalence of clinically active trachoma were available from seven studies (Broman 2006; West 2006; Solomon 2004; Fraser-Hurt 2001; Burton 2005; Schachter 1999; Atik 2006), of which four also contain data regarding the prevalence of *C. trachomatis* infection (Broman 2006; Solomon 2004; Burton 2005; Atik 2006). An additional four studies contained appropriate *C. trachomatis* infection data (Melese 2008; Chidambaram 2006; House 2009; Lakew 2009). Six studies contained more than one primary intervention cohort and thus were considered to have contributed two datasets for this analysis (Melese 2008; House 2009; West 2006; Fraser-Hurt 2001; Schachter 1999; Atik 2006). Design effects at baseline and 12 month assessments which were estimated as described in the methods section above, and are provided in Table 8. The design effects ranged from 1.0 to 81.2, with the latter being for one cohort where only one village was studied with 956 persons assessed (Solomon 2004).

Table 8: Effective sample size correction according to village clustering sampling designs

Study	Country	Design	N total	ICC	DEFF	Effective N
Atik (2006)	Vietnam	1 commune SAFE, 1 commune AE	523 to 1325	0.050*	27.2 to 67.3	19-20
Broman (2006)	Tanzania	1 village	269	0.084 (West 1991)	23.5	12
Burton (2005)	Gambia	14 villages, ~94/village	1319	0.016 (Fraser-Hurt 2001)	2.49	443
Chidambaram (2006)	Ethiopia	8 villages	515	Calculated as 0.053, 0.086 [0, 12mths]	4.3, 6.4	117, 80
Fraser-Hunt (2001)	Gambia	8 villages, 4 AZR, 4 TCN	422 to 947	Calculated: 0.016 AZR, 0 TC	4.9, 1	117 to 856
House (2009)	Ethiopia	12 villages children treated, 12 mass treated	598 to 763	Calculated for children treated only: 0.010, 0.037	1.5, 2.9	207 to 509
Lakew (2009)	Ethiopia	16 villages	689	Calculated: 0.072, 0.105	4.6, 6.1	150, 113
Melese (2008)	Ethiopia	16 villages: 8 with 2 treatment rounds, 8 with 4 treatment rounds	392 to 463	Calculated: 0.003 to 0.143	1.2 to 9.2	50 to 341
Schachter (1999)	Egypt, Gambia, Tanzania	1 village in each country for AZR and TCN	349 to 589	Egypt: 0.084; Tanzania 0.084 (West 1991); Gambia 0.016 (Fraser-Hurt 2001)	19.3, 14.4	66 to 77
Solomon (2004)	Tanzania	1 village	956	0.084 (West 1991)	81.2	12
West (2006)	Tanzania	1 village AZR, 1 village AE+fly	183, 119	0.084 (West 1991)	16.3, 10.9	11, 11

Key: DEFF = 1+(average village size-1)*ICC; *ICC=0.05 was approximate average ICC across all studies. Used here in absence of other information.

AZR: Azithromycin; DEFF: design effect; ICC: intraclass correlation coefficients; TCN: ocular tetracycline.

EFFECT OF TREATING INFANTS

An analysis was undertaken to see if there were a larger reduction in trachoma prevalence if young children, under the age of 12 months, were included in the distribution of treatment (see Table 9 and Figure 3-5). Five studies reported treating infants and six studies excluded them. When infants were included there was a marginally greater reduction in the relative prevalence of clinical trachoma, but paradoxically a significantly smaller reduction in the absolute prevalence of infection. However, it should be noted that the baseline prevalence of both clinical trachoma and infection was more than twice as high in those studies that did not treat infants and this may have significantly affected the respective outcomes. Because of the small sample size of these studies, formal meta-regression analyses were not conducted.

Table 9: The effect of including infants aged less than 1 year in mass distribution programmes on the reduction of clinical trachoma or detectable infection

	Baseline prevalence (pooled)	12 month prevalence (pooled)	Absolute prevalence reduction % (95%CI)	% Relative prevalence reduction (95% CI)	p*
CLINICAL TRACHOMA					
Overall	21.5	14.2	7.3 (1.4, 13.8)	33.9 (20.6, 47.2)	-
Infants <1 yo treated	13.0	6.3	6.7 (-1.5, 14.9)	51.5 (34.2, 68.7)	0.049
Infants <1 yo not treated	31.1	24.5	6.6 (-0.0, 13.2)	21.1 (3.9, 38.4)	
CHLAMYDIA INFECTION					
Overall	29.5	4.2	25.3 (12.6, 38.0)	85.8 (81.5, 90.1)	-
Infants <1 yo treated	17.5	3.0	14.5 (2.7, 27.6)	82.7 (76.9, 88.4)	0.001
Infants <1 yo not treated	42.4	4.1	38.3 (21.0, 55.6)	90.3 (85.3, 95.4)	

Key: Baseline and 12 month prevalence's are estimated from logistic regression models pooling data across cohorts (see methods)

*p-value for comparison of prevalence reduction between infants <1yo treated and untreated

CI: confidence interval; yo: year old

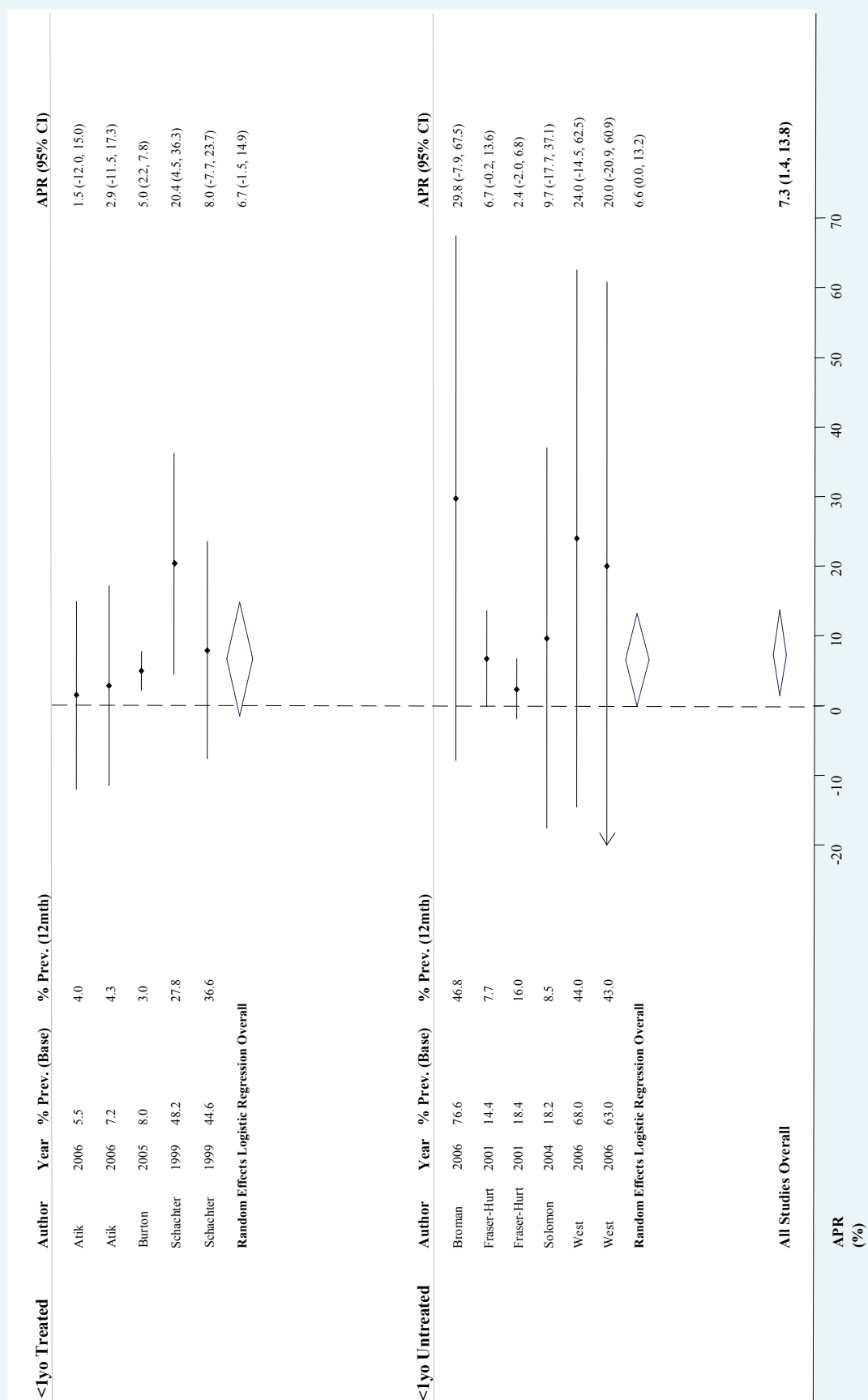


Figure 2: Absolute Prevalence Reduction (Clinical Trachoma) for <1yo Treated and Untreated Children
 mth= month(s); Prev= prevalence; APR= absolute prevalence reduction; yo= year old

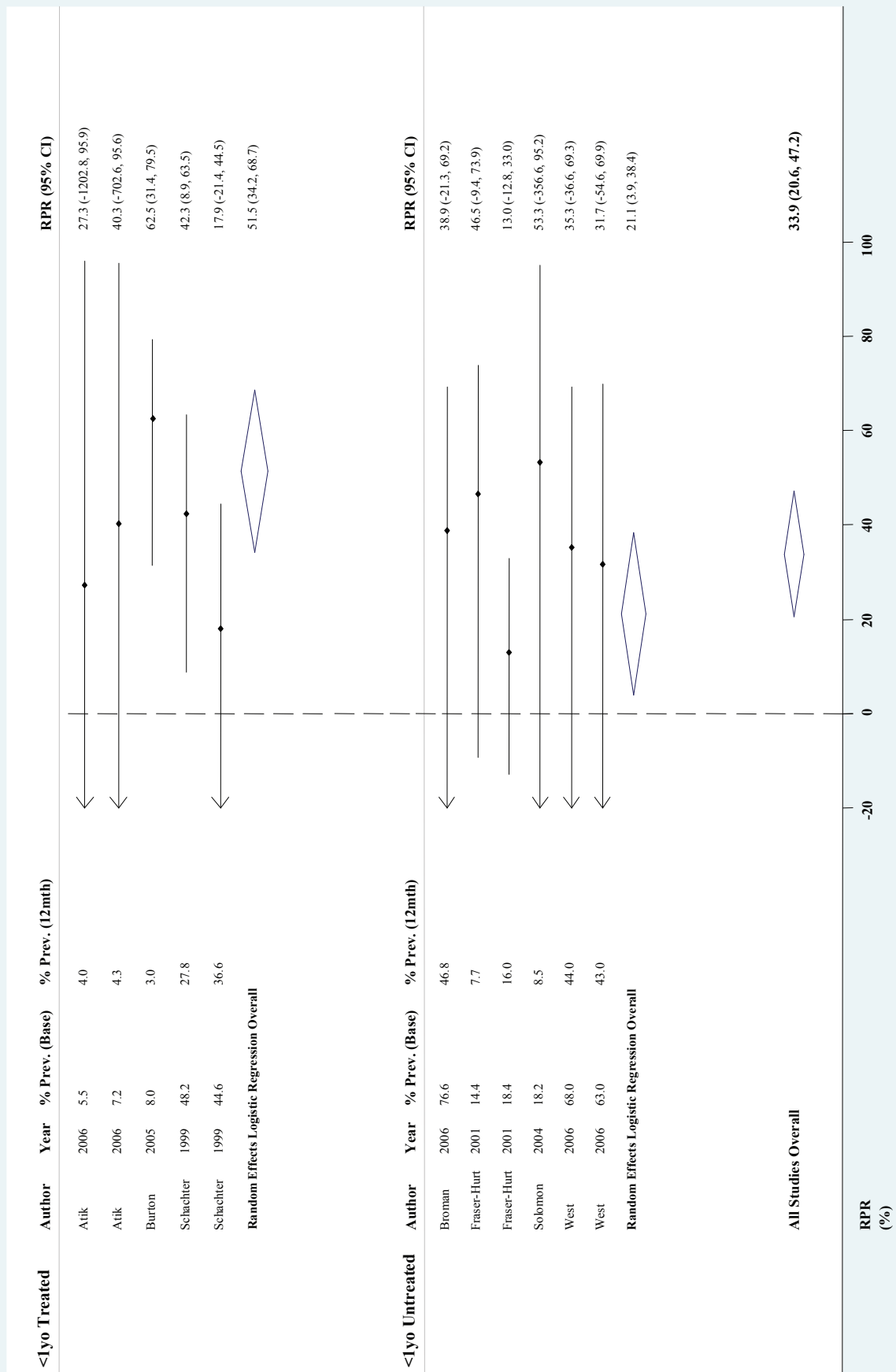


Figure 3: Relative Reduction (Clinical Trachoma) for <1yo Treated and Untreated Children
 mth= month(s); Prev= prevalence; RPR= relative prevalence reduction; yo= year old

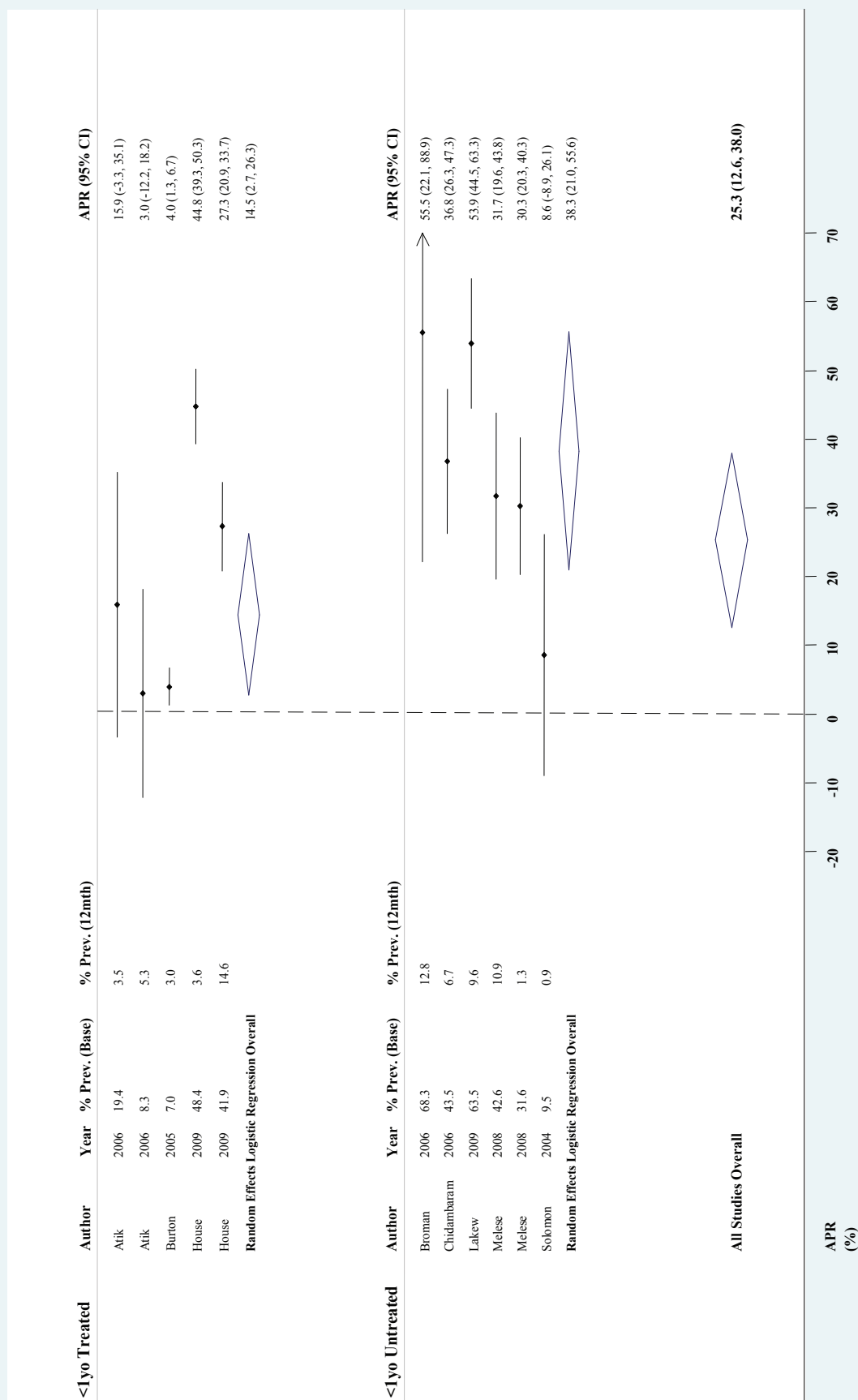


Figure 4: Absolute Prevalence Reduction (Chlamydial Infection) for <1yo Treated and Untreated Children
 mth= month(s); Prev= prevalence; APR= absolute prevalence reduction; yo= year old

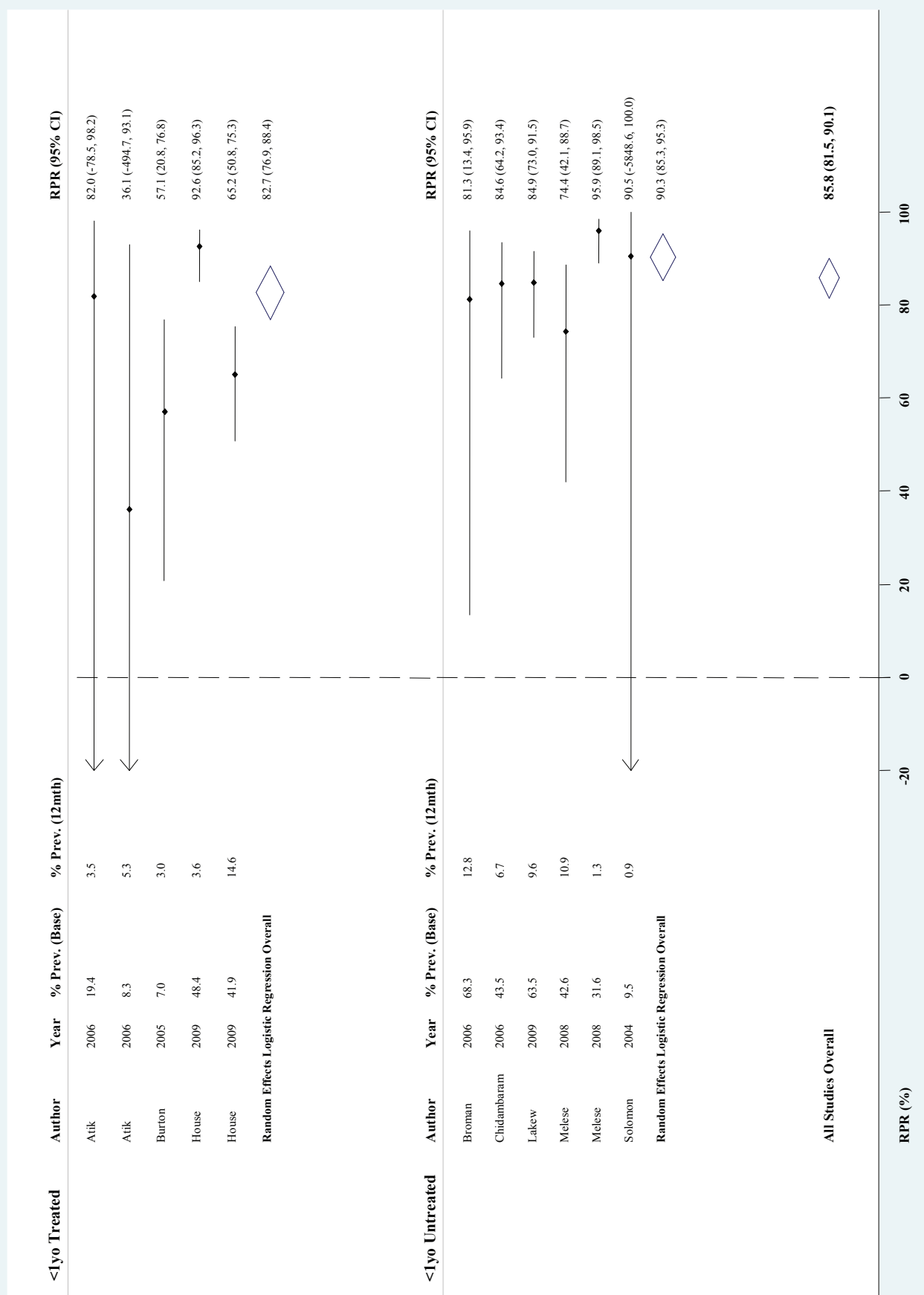


Figure 5: Relative Prevalence Reduction (Chlamydia Infection) for <1yo Treated and Untreated Children
 mth= month(s); Prev= prevalence; RPR= relative prevalence reduction; yo= year old

Results

EFFECT OF COVERAGE RATES

A meta-analysis was performed to examine the effect of increasing coverage rates of azithromycin distribution on the impact of treatment. Nine studies had data on the clinical outcome. The lowest reported coverage was already above 80% and no great impact was seen in the reduction of either the absolute or relative prevalence of clinical disease with increasing coverage (Figure 6-7).

Similarly 11 studies had data on the detection of infection and increasing coverage had no significant effect on either the absolute or relative reduction of prevalence (Figure 8-9).

These limited data suggest that the achievement of at least 80% coverage with azithromycin treatment may be sufficient.

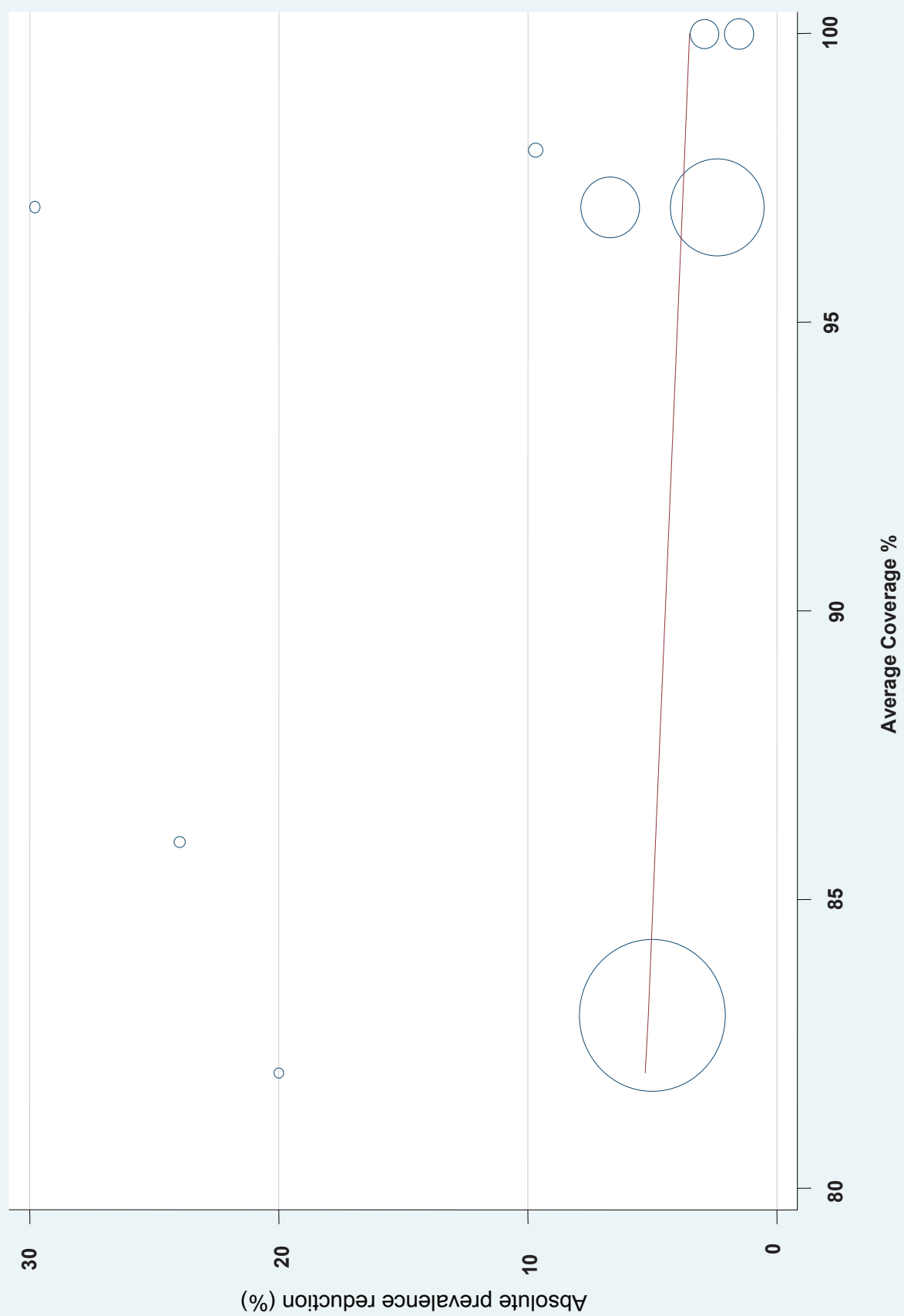


Figure 6: Absolute Prevalence Reduction and Average Coverage for Clinical Trachoma
 Slope= -0.1% 95% CI (-2.3- 2.1%), p=0.912

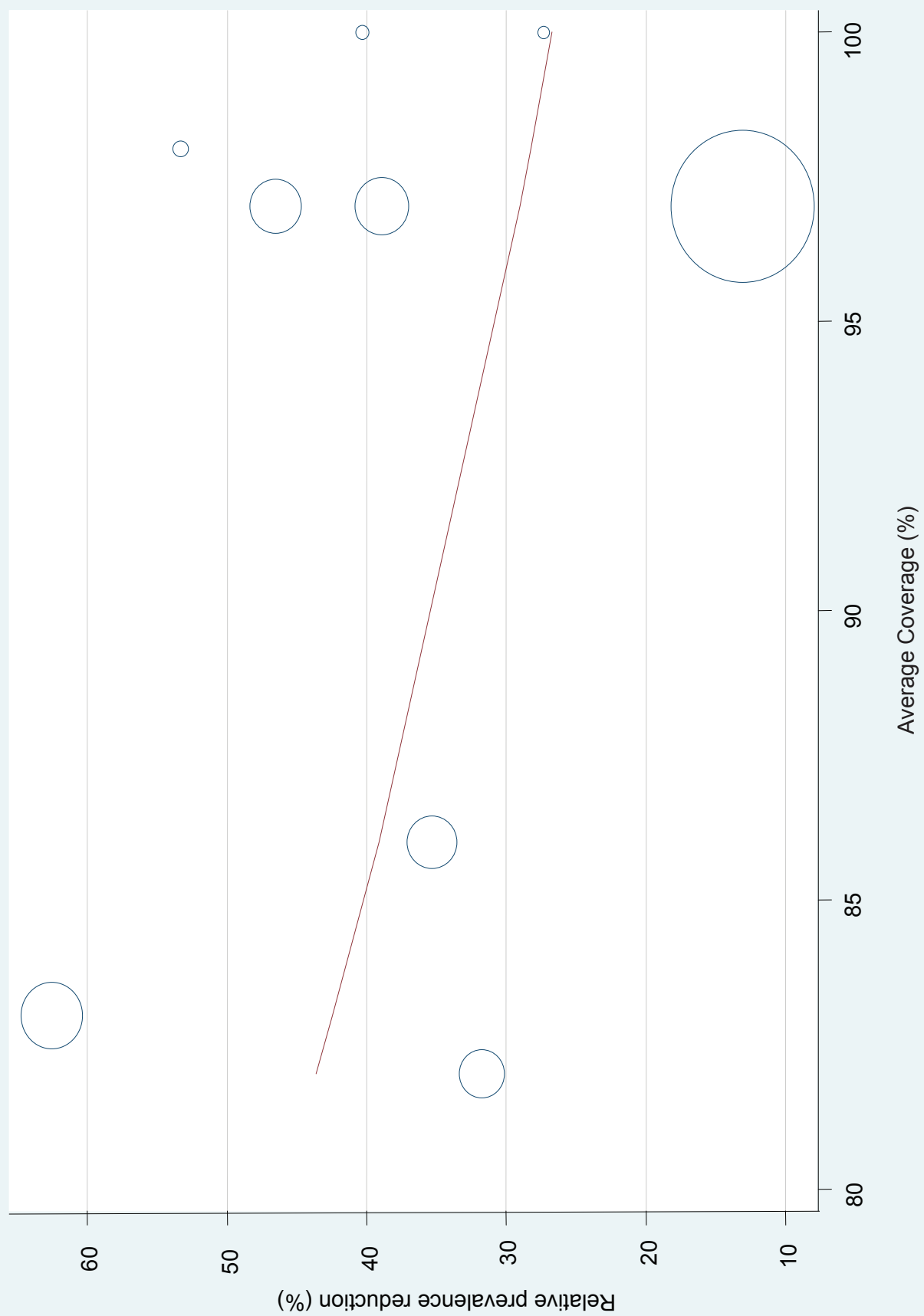


Figure 7: Relative Prevalence Reduction and Average Coverage for Clinical Trachoma
 Slope= -2.7%, p=0.418

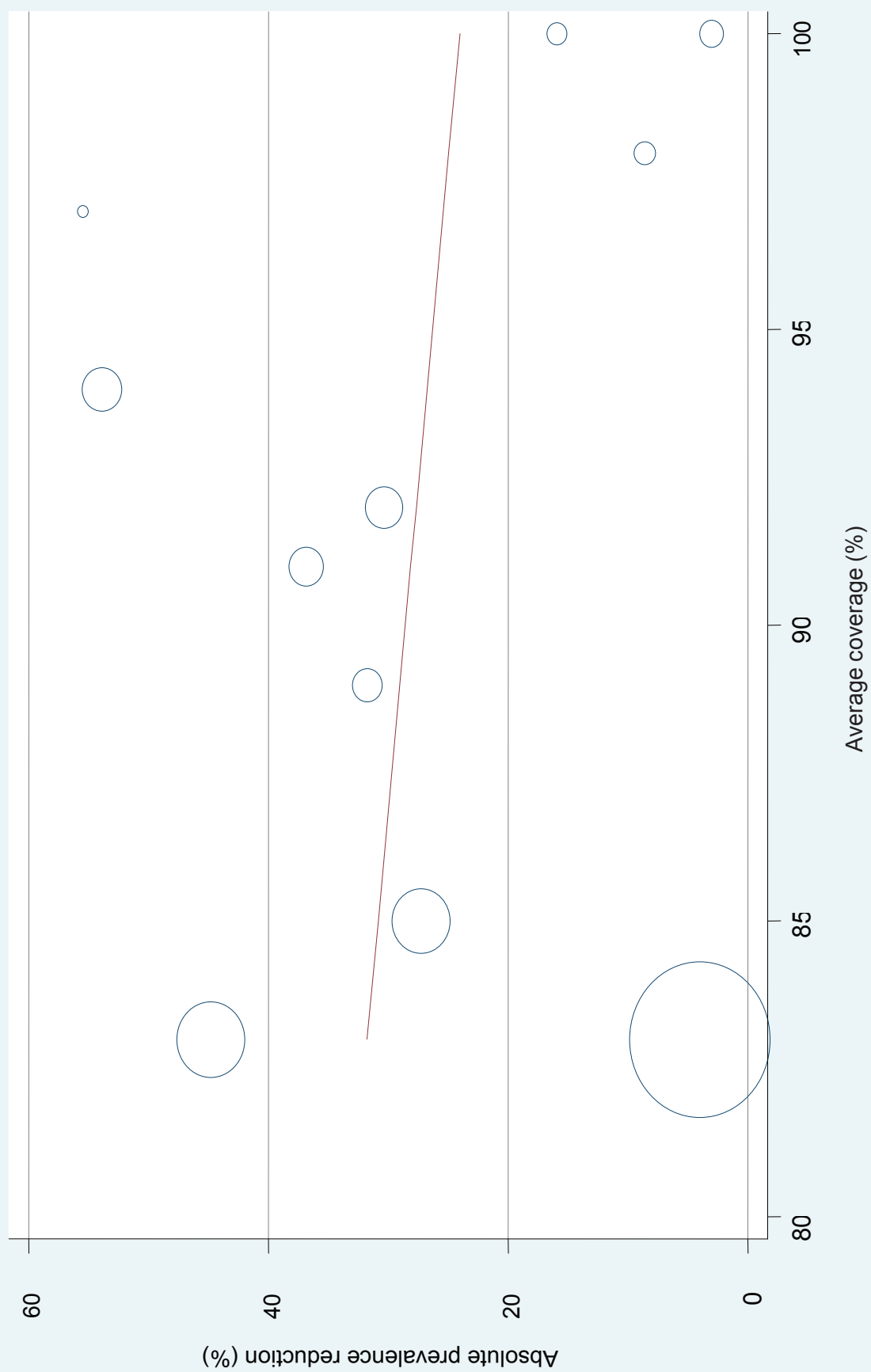


Figure 8: Absolute Prevalence Reduction and Average Coverage for Chlamydial Infection

Slope= -0.45, p= 0.768

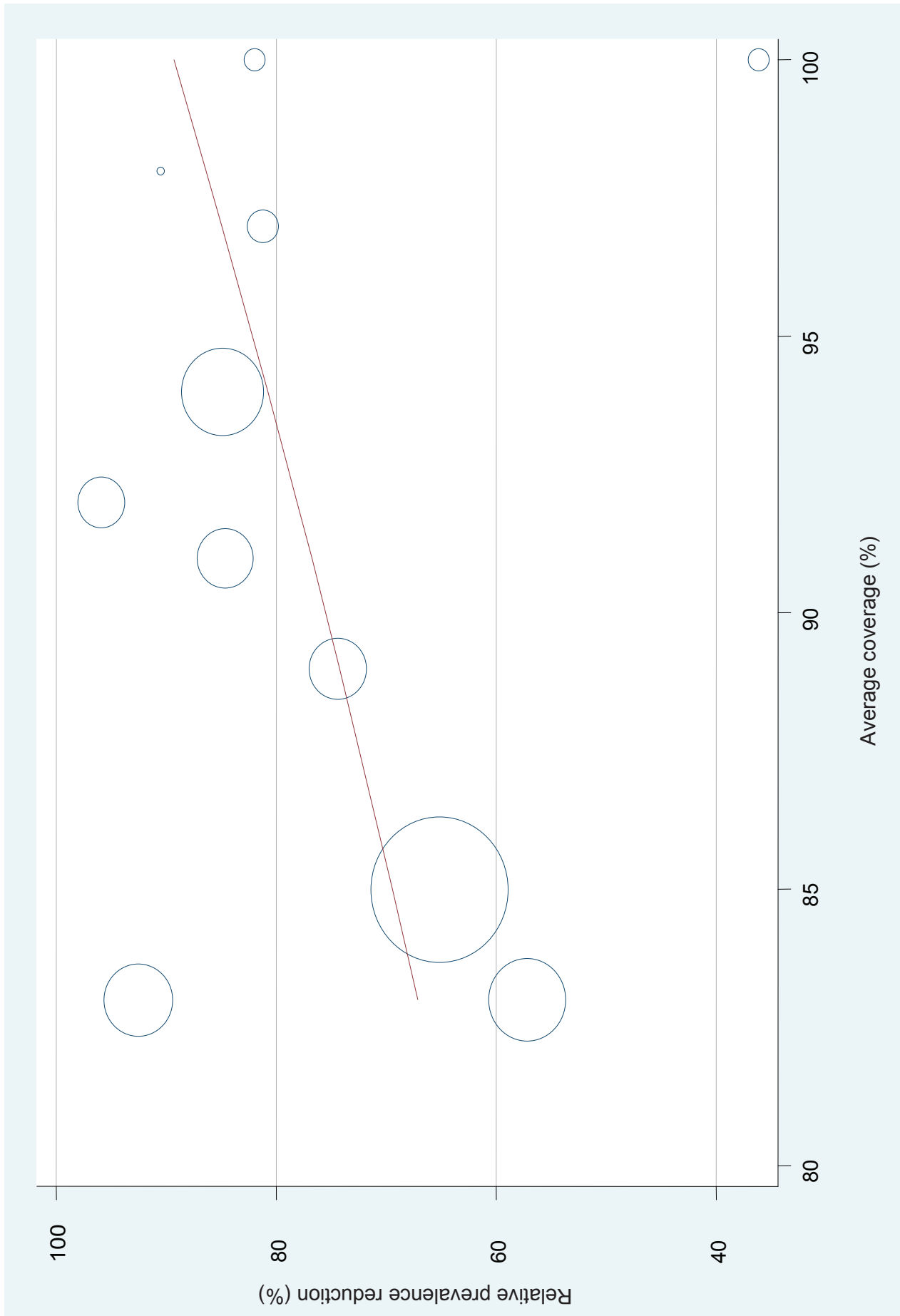


Figure 9: Relative Prevalence Reduction and Average Coverage for Chlamydial Infection
Slope= +1.7%, p= 0.229

The goal of this evidence-map was to systematically assess the effectiveness of azithromycin treatment on the prevalence of clinical active trachoma and conjunctival *C. trachomatis* infection in endemic communities. In particular, we qualitatively investigated the impact of oral azithromycin alone or in combination with other components of the SAFE strategy.

Despite the fact that azithromycin treatment protocols in the studies outlined to whom and how often treatment was given, there were significant variation in study designs that cause some disparity in levels of effectiveness. In particular, the course of treatment and subsequent retreatment schedules were highly variable with administration regimes that included single, multiple, and interrupted doses over time (e.g. weekly for three to 18 weeks). Individual doses also varied from single dose of 20mg/kg suspension, up to a maximum dose of 1g to 20mg/kg with no maximum doses. Topical azithromycin was also trialed in one study (Cochereau 2007), which showed to be as efficacious as the oral treatment; however, the twice daily dosage for three days coupled with difficulties of ocular administration would suggest that its use would be difficult to widely adopt although it might be a very useful alternative for very young children. The control arms of many studies used tetracycline ointment that required complex dosing regimes/applications (i.e. twice daily ocs for four to eight weeks). The treatment of the control arm was given under a variety of supervised or non-supervised conditions and therefore, it was likely that the degree of compliance achieved was variable but in some instances at least significantly higher than that normally achieved in non-supervised conditions (Burton 2005). Other comparators included oral erythromycin for those with severe disease.

Across the studies there was general consensus that azithromycin was either at least as effective as topical tetracycline (Schachter 1999) or more effective for cases of active trachoma (Bowman 2000). However, it is important to note that there were a number of studies which showed no significant differences between azithromycin and topical tetracycline or oxytetracycline polymyxin (Bailey 1993; Dawson 1997; Tabbara 1996). This observed equity of treatment efficacy could have been attributed to the sub-optimal compliance with the topical therapies or the lack of other SAFE subcomponents.

Secondly, the frequency of retreatment with azithromycin was highly variable with little consistency with the interval between doses. Annual retreatment is the normal standard recommended by WHO but often only a single dose was given. At other times treatment might be repeated every 6 months or every few years. The optimum frequency was dependent on the rate of re-emergence of disease following treatment, and the choice of most appropriate strategy for distribution needed to be determined at a community level after considering population-specific local and contextual factors (Lynch 2003). Of the 57 known trachoma endemic countries, the research identified was performed in less than a quarter of these countries (Mariotti 2009).

The duration of follow-up regarding disease-state varied from day 0 to 12 months; however, on average six months appeared to represent the period in which recurrence or relapse of infection occurred. The apparent failure of disease resolution may have been secondary to the rapid re-infection of successfully treated individuals rather than a primary failure of the treatment (Burton 2005). This was supported by a number of studies that demonstrated successful treatment could be followed by rapid re-infection. For example, in the study by West (2005b), almost a half of the children were PCR positive at baseline. At the end of the month-long course of topical tetracycline treatment only 4% of children were positive by PCR. However, one month after the completion of the treatment the infected rate had increased back to 20%.

Most re-infection occurs initially in the family household. Generally re-infection rates appeared to be dependent both on coverage rates (i.e. the overall burden of untreated infection within the community) and also on the degree of contact with members of other untreated communities. Infection with *C. trachomatis* can be asymptomatic and can occur without signs of active disease. Therefore, trachoma eradication programs which only targeted people with "active disease" may have been less successful at eradicating the infection from the community as a whole.

The widespread use of broad spectrum antibiotic use raised the question about the emergence of drug-resistant micro-organisms. Fry (2002) reported mild resistance of other bacteria in areas where azithromycin was widely used for trachoma control. Micro-organisms such as *S. pneumonia* have been colonised in children, although the

Discussion

numbers are small at day 180 post-intervention. Chern (1999) also reported a statistically significant drop in the prevalence of pathogenic conjunctival bacteria from 39% to 14%, but reported that three of seven *S. pneumonia* were found to be resistant to azithromycin. We identified no papers up to the systematic review search date investigating antibiotic resistance in the context of community-wide programs.

Few studies specifically examined the cost-effectiveness of azithromycin (Bowman 2000; Frick 2001; Schachter 1999). These studies took into account various costs such as personnel, travel, community time and antibiotic treatment. More so, it was important to note the inherent problems of inter-study cost-benefit analyses when alternate strategies are implemented in various ways in diverse settings and countries. Secondly, it was difficult to determine the true cost when different programs target different outcomes such as the prevention of blindness, decrease in the prevalence of infection rates or improvements in cure rates (Schemann 2007).

Adverse effects or events were rarely reported in the azithromycin literature. Minor adverse effects occurred less frequently than with other systematic antibiotics, such as erythromycin or doxycycline. In the work performed by Whitty (1999), it was found that people treated with azithromycin had less fever, headaches, diarrhoea, and vomiting compared to those treated with tetracycline.

The evidence base underlying the implementation of the full SAFE strategy was not as strong compared to that supporting the use of azithromycin specifically. Despite this relatively paucity of rigorously designed studies, some cross-sectional studies showed independent protective effects of educational programs endorsing facial cleanliness and latrines, against active trachoma (Ngondi 2008). However, the antibiotic arm of the SAFE strategy appeared to be the fundamental cornerstone in disease reduction in most reported studies (Ngondi 2006; Atik 2006). Nonetheless, despite results from a cluster RCT revealing that antibiotic administration provided the most effective intervention, Cumberland (2008) found the community-wide reduction in prevalence of *C. trachomatis* infection could be further improved with community-based health education programs. There was less evidence supporting other environmental interventions of the SAFE strategy. For example, current work suggests that fly eradication through intensive insecticide use has no additional role in reducing the burden of active trachoma (West 2006).

The effects of surgical intervention were difficult to study in a controlled manner. Additionally, given that the surgical arm of the SAFE strategy was aimed at managing a different stage of trachomatous disease (i.e. trichiasis and entropion) compared to the other arms, which are directed towards reducing active infection and clinical disease. Nonetheless, it was clearly important to ensure that the quality of any interventions is monitored. In particular, as Kuper (2005) found, the quality assurance of surgery for trichiasis or entropion are rarely monitored, and as such further work investigating this facet of the SAFE strategy is warranted (Kuper 2005). Finally, in considering the implementation of the full SAFE strategy, it is important to note that a large variation in the uptake of the full SAFE strategy has been observed between communities (Ngondi 2006). This finding underscored the importance of tailoring trachoma eradication programs to each individual community.

The cluster sampling design of the included studies resulted in the effective sample size for some cohorts being reduced markedly due to a large design effect (see Methods section for details and Table 8). This was particularly evident for studies of a large number of individuals conducted in a single village where a large design effect was assumed. For example, Solomon (2004) assessed 956 individuals in a single village yet the resulting effective sample size assuming an ICC of 0.084 was only 12 individuals. This would have been the same effective sample size had only 400 individuals been assessed, and moreover had 100 individuals been assessed the effective sample size would have been 11. Therefore single village studies provide little incremental sample size benefit for a possibly large assessment burden. In terms of statistical information, assessments of a small number of individuals in each of a moderate number of villages provides far greater information than the same total number of individuals assessed across a small number of villages.

Pooled analyses indicated large and significant benefits from mass distribution programmes on the reduction of both clinically active trachoma and infection irrespective of whether infants aged less than one were treated. Interestingly, the cohorts where infants aged less than one were treated displayed a greater relative reduction in clinical prevalence but a smaller relative reduction in the prevalence of infection. The relative prevalence reduction with untreated infants was 21.1% (95% CI 3.9-38.4) as compared to 51.5% (95% CI 34.2-68.7) when infants aged one year were included in mass distribution programmes ($p=0.049$).

However, the relative prevalence reduction of molecularly detectable *C.trachomatis* was 90.32% (95%CI 85.3-95.4) with untreated infants and 82.66% (95%CI 76.9-88.4) when infants were included in the treatment regimens ($p=0.0001$). Despite this latter statistical significance, it is important to appreciate the large relative prevalence reductions in both treated and untreated infants aged less than one. It is also important to note that although the pooled prevalence of infection reduction was clearly far greater than the pooled clinical reduction in the disease, a lot of care needs to be taken with any interpretation of this because they involve different sets of papers and cohorts. Importantly, there were only four papers which reported both clinical and molecular prevalence's (five cohorts). The pooled relative reduction in the prevalence of clinically active trachoma in these five cohorts was very close to that found for the reduction in infection (64.8%, 95%CI 45.0-84.5; versus 65.3%, 95%CI 45.5-85.1). Thus, the difference between the pooled clinical and molecular reductions across all studies appeared to be completely confounded by differences between studies that reported only one of these measures.

In summary, we identified 44 studies which demonstrated that a significant reduction in trachoma could be attained through the administration of azithromycin. There were also a smaller proportion of studies specifically focusing on implementation of the other components of the strategy. These studies support the concept of the independent protective effect of the other components of the SAFE strategy including health educational programs, facial cleanliness and the establishment of pit latrines, help in the reduction of trachoma. Pooled analyses of studies comparing the effects of including infants in mass-antibiotic treatment programs for the community-wide eradication of active trachoma displayed varying results between the relative prevalence reduction of clinically active trachoma infection. As such, the importance of untreated infants as a potential source for recurrent familial or community re-infection warrants further ongoing examination.

Appendices

APPENDIX 1: EXAMPLE OF SEARCH STRATEGY: MEDLINE DATABASE

1. Trachoma/
2. trichiasis.mp.
3. trachomatis.mp.
4. or/2-3
5. exp Eye/ or eye*.mp.
6. and/4-5
7. or/1,6
8. World Health Organization/
9. (safe adj2 strateg*).mp.
10. 8 and 9
11. and/7-8
12. or/10-11
13. Azithromycin/
14. (azithromycin or azithromicin).mp.
15. 7 and (13 or 14)
16. or/12,15

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