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Effectiveness and efficacy of implementing the "SAFE" strategy for the elimination of trachoma and other related blindness in African communities: A Systematic Review and a meta-analysis

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Abstract

Implementation of the 'SAFE' strategy remains critical in the prevention of chlamydial trachomatis infection and other trachoma-related blindness among children and adults in Africa. Trachoma is the commonest blindness-causing infectious disease and the World Health Organization (WHO) has recognizedthe 'SAFE' strategy for its elimination. The elimination strategy is summarized by the acronym "SAFE", which means Surgery for advanced disease, Antibiotics to clear Chlamydia trachomatis infection, Facial cleanliness, and Environmental improvement, to reduce trachoma transmission. This review aim to establish the extent of evidence, for the 'SAFE' strategy in eliminating chlamydial trachomatis infections, and preventing trachoma-related blindness among children and adults in Africa. A systematic review and a meta-analysiswas conducted from six electronic databases to retrieve

randomized controlled trial studies that evaluated the effectiveness,and efficacyof either mass administration of antibiotics, surgery, facial cleanness, and environmental improvement intervention towards trachoma prevention and elimination.Pooled odds ratio (POR) with 95% confidence intervals were generated using random effect models. We conducted a subgroup analysis and sensitivity analysis within a stratum, and meta-analysis regression to assess the effect of the individual study intervention. ARevMan review manager 5.3, and STATA version 15 (Stata-Corp, College Station, TX) were used for analysis. The summary effect measured from the 38eligible studies included inthe meta-analysis were categorized as mass administration of antibiotics, facial cleanness, or environmental improvement, and their pooled effect measures were (OR=0.62, 95% CI [0.33, 1.15], p=0.13), and (OR=0.67, 95% CI [0.39, 1.16], p=0.15) respectively, and these findings suggest non-significant interventions towards Trachoma preventionand elimination effort. Surgery for advanced Trachomatous trichiasis had increased odds of (OR=3.10, 95% CI [1.36, 7.08], p=0.0007), favoring communities without trichiasis surgery interventions. The pooled overall summary effect measure of 'SAFE' strategy program component suggests a statistically non-significant probability of (OR=0.86, 95% CI [0.55, 1.36], p=0.52), I^2= 99%, p=0.001,to eliminate chlamydial trachomatis infections andits related blindness in Africa. This review found no statistical difference between communities and individuals who received the SAFE strategy intervention and those in the control group. These results indicate that there is no significant evidence that the implementation of the 'SAFE' strategy program componentseliminate chlamydial trachomatis infections,nor reduce the prevalenceof trachoma-related blindness among children and adults in Africa.

Keywords: *'SAFE' strategy, effectiveness, efficacy, chlamydial Trachomatis elimination effort.*

Introduction

Trachoma is an eye disease caused by an intraocular bacterium infection called *Chlamydial trachomatis* (Diab, Allen, Gawdat, & Saif, 2018) and the leading cause of preventable blindness worldwide (Organization, 2019). Countries in low-resource settings, like African contriesare at a greater risk to have exponentiated prevalence of active trachoma and trachoma-related blindness (WoldeKidan, Daka, Legesse, Laelago, & Betebo, 2019a). In Africa, the risk of trachomatis infection is predominately found in individuals aged between 1-18 years and those between 30-40years (WHO, 2020). Trachoma is commonly seen in rural, economically deprived, underdeveloped regions withpoor living conditions: overcrowdedness, lack of clean water supplies, and basic sanitation facilities (WHO, 2018). *Chlamydial trachomatis Infection* spreads through personal contact, via hands, and by flies that have been in contact with discharge from the eyes or nose of an infected person (WHO, 2018).

Trachoma is responsible for the blindness and visual impairment of about 1.9 million people, and has resulted in about 1.4% of all blindness globally (WHO, 2019). Overall, Africa remains the most affected region with a high prevalence of trachoma, and it is estimated that 137 million people are infected with trachoma disease (mondiale de la Santé & Organization, 2020; WHO, 2019) to date. The World Health Organization (WHO) significantly recognizesthe "SAFE" as an effective strategy to eliminate trachoma and prevent trachoma-related blindness (Robin Bailey & Lietman, 2001; M. Reacher, M. Huber, R. Canagaratnam, & A. Alghassany, 1990). The elimination strategy is summarized by the acronym "SAFE", Surgery for advanced disease, Antibiotics to clear Chlamydia, trachomatis infection, Facial cleanliness, and Environmental improvement to reduce transmission (WHO, 2020). Currently, a combination of these intervention approaches were proved to be effective to prevent and eliminate trachoma among children and adults (Robin Bailey & Lietman, 2001; Lavett, Lansingh, Carter, Eckert, & Silva, 2013). Previous studies have empirically examined the effectiveness and efficacy of the 'SAFE' strategy, For

example, mass administration of antibiotics 'Azithromycin' was found to be effective in eliminating active trachoma infection and reducing trachoma-related blindness in both adults and children in Africa (Amza et al., 2017; Emerson, Burton, Solomon, Bailey, & Mabey, 2006; Organization, 2017; Heathcote R Wright, Keeffe, & Taylor, 2010). Unfortunately, some studies found that mass administration of Azithromycin was hazardous to health in children aged between 1 -12 years (Catherine E Oldenburg et al., 2019; C. E. Oldenburg et al., 2018). Also, Azithromycin was found to be ineffective in eliminating *ChlamydialTrachomatis infection* (Campbell, Mkocha, Munoz, & West, 2009; Keenan et al., 2018; Liu et al., 2014; Wilson et al., 2019). Furthermore, Surgery for trachomatous trichiasis was found to be effective inimproving visual acuityand reducing the prevalence of trachomatous trichiasis infection (Alemayehu et al., 2004; Rajak et al., 2011; M. H. Reacher, M. J. Huber, R. Canagaratnam, & A. Alghassany, 1990; E. S. West et al., 2005; Wolle et al., 2011; T. A. Woreta, B. E. Munoz, E. W. Gower, W. Alemayehu, & S. K. West, 2009). Similarly, the same was found in facial cleanness promotion (Gebre et al., 2011; S. West et al., 1995; H. R. Wright, Keeffe, & Taylor, 2006), and environmental improvement promotion effort (Paul M Emerson et al., 2004; Emerson et al., 2002; Emerson et al., 1999; Lee et al., 2007; Munoz, West, Emerson, McHiwa, & Mabey, 2005; S. K. West et al., 2006). In contrast however, other studies found that the trichiasis surgery program does notimprove visual acuity (Habtamu et al., 2016; Rajak et al., 2010), neither doesmass administration of antibiotics 'Azithromycin' (M. J. Burton, F. Kinteh, et al., 2005; Keenan et al., 2018; Wilson et al., 2019), environmental improvement (Sheila K West et al., 2006), facial cleanness and latrine promotion programme (Gebre et al., 2011).

Although existing literature shows that individual components of the 'SAFE' strategy eliminate *Chlamydial Trachomatis infection* and prevent trachoma-related blindness among children and adults in Africa, evidence on efficacy, effectiveness, and safety of the 'SAFE' strategy program as a wholeis limited (Keenan et al., 2018; Liu et al., 2014).

Aims: This review aimsto collate and assess the sum of evidence of the effect of the 'SAFE' strategy program for trachoma elimination among children and adults in Africa. We further seek to address sources of heterogeneity of effects of the relationship between the individual components of the SAFE strategy.

We hope that findings from this review will inform policymakers, program implementers, and other concerned bodies on the need for improvement or restructuring of the available strategies to successfully eliminate trachoma and prevent future trachoma-related blindness among children and adults in Africa.

Methods

Study inclusion criteria

In this review, we included only randomized controlled trials published in the English language and studied the components of the 'SAFE' strategy. Studies involves communities and individuals aged between 1-18 years and those between 30-40 years receiving one of the "SAFE" strategy components": surgery for trichiasis, mass administration of antibiotics, facial cleanness, and environmental improvement campaign, and comparing them to communities and individuals receivingthe standard of care.

Study exclusion criteria

The review was carried out independently, and data was extracted blindly after assessment of the abstracts and the full texts of the literature. Articles with incomplete data, inaccessible full articles, and those with unclear information on methodology, participants, intervention, and outcome were excluded from the review.

Study population
Individuals are aged between 1-18 years and those between 30-40 years who received “SAFE” strategy intervention programs to prevent and eliminate trachoma.

Study area: We reviewed and synthesized studies conductedin low-resource setting countries in Africa.

Types of interventions
The “SAFE” strategy intervention. This is the combination of various program component known by the acronym "SAFE". The “SAFE” strategy isa community-based health intervention that eliminates and reduce the prevalence of active trachoma and related blindness among children and adults in Africa. The combination of this intervention was shown to be efficacious in randomized controlled trials to yield population benefits, once scaled-up in the community.

Comparator: “Communities and individuals who received the SAFE strategy intervention” Versus “No “SAFE” strategy intervention for trachoma elimination”.

Primary outcomes
(1) The proportion of individuals with active trachoma who recovered after receiving the “SAFE” strategy intervention. (2) The proportion of individuals who were protected from active trachoma during and after the implementation of the “SAFE” strategy in the communities from 1981 to 2020.

Secondary outcomes
The efficacy and effectiveness of the “SAFE” strategy in eliminating active trachoma and reducing the prevalence of trachoma related blindness in Africa.

Search methods for identification of studies
Electronic searches
This review was conducted to compile current and old evidences using published articles as well as grey literature documenting theefficacy and effectiveness of the Implementation of the “SAFE” strategy program in children and adults living in Africa. The electronic databases searched were PubMed, Google Scholar, Science Direct, EMBASE, Scopus, MEDLINE, and Cochrane library from 1981 to 2020. The search strategy included used both separation and combination of the Boolean operator like “OR” or “AND”. The search key terms were "Cluster randomized control trial" "Randomized controlled trial" "controlled clinical trial", “randomized”, “placebo”, “drug therapy”, "control arm", “intervention arm", “assessing”, “evaluating”, “investigating”, “efficacy”, “efficacious”, “efficiency”, “effectiveness”, “safety”, “hazards”, “risks”, “mortality”, “surgery”, “operation”, "trichiasis surgery", “lid surgery”, “BTR”, “Trabut”, “PLTR”, "distribution of antibiotic", “Azithromycin”, "facial cleanness", flies control", "environmental improvement", “SAFE strategy for trachoma elimination” “active trachoma”, “trachomatous trichiasis”, “ocular disease”, “elimination”, “reduction”, “control”, “Africa”. The Boolean operators were used differently in each set hypothesis to matchthe intervention. We hypothesized thatthe “SAFE” strategy is effective in reducing the prevalence of active trachoma, and eliminating trachoma related blindness among children and adults in Africa.

Searching other resources
Reference lists in other reviews and other related articles were searched and screened for additional studies (Figure 1). PRISM flow diagramillustrates the studies included and/or excluded from the review.

Data collection and analysis

Selection of studies

During the review process, databases were searched and eligible articles were imported into EndNote for reviewer access. We merged searched results using EndNote reference manager software and removed duplicate records. The selection of studies and the assessment of data quality were guided by the protocol of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Hutton et al., 2015). More than two authors scrutinized the included research articles by examining titles and abstracts to remove irrelevant reports. We retrieved the full text of the potentially relevant reports and a full review for a full-text was conducted to select and assess whether they met potential eligibility criteria for inclusion in the study. We linked together multiple reports of the same study. Disagreement on the selected and included studies between the two authors was resolved through discussion and consensus. The final decisions made on the included studies were guided by a formal calculation of the agreement scale using the kappa approach(Stock, 1994).

Data extraction and management

For data collection, Microsoft Access Google Form was developed. However, for consistency and accuracy on the data required, an intervention-RCT- only data collection form of Cochrane collaboration was adopted and modified to fit in the required sections. The data extracted from the studies included name of first author, year of publication, the country where the study was conducted, study design, type(s) of intervention, number of events, and total events in both interventionand control groups. The extracted data were entered directly into the Microsoft Excel database for cleaning and coding. For the studies that reported different effect measures other than odds ratio and events, and those that have two or more parallel active arm 'intervention-format', aRevMan review manager 5.4.1 calculator was used to convert the different measure of effect reported, to odds ratio and the sorted data were entered directly into RevMan review manager 5.4.1 for analysis.A random-effect model was used to calculate the odds ratio, and generate the forest plot and funnel plot in RevMan review manager 5.4.1. STATA version 15 (Stata-Corp, College Station, TX) was used to execute meta-analysis regression to test the effects of covariates in the estimates, and the findings were reported with a 95% confidence interval.

Quality assessment

Assessment of risk of bias in included studies

For the assessment of risk of bias in included studies, a CONSORT 2010 checklist for reporting a randomized trial was used (Group, 2010). The risk of bias was assessed as low, unclear, or high risk for each domain illustrated in Fig 2. Risk of bias graph for Cochrane Collaboration's tool for assessing the risk of bias was used (Higgins et al., 2011). Secondly, any discrepancies in the studies included in the review were settled through discussion and consensus between the two authors.

Measure of treatment effect

The study's dependent variableswere dichotomous types of data and were categorized as ***Effective / Not Effective,*** that 'SAFE' strategy eliminate and reduced the prevalence of active trachoma and trachoma related blindness among children and adults in Africa. Therefore, to estimate the effect measure, odds ratio (OR) was considered.

Unit of analysis and measure of treatment effect

In this review, we used the odds ratio (OR) to estimate the dichotomous data, "Yes for effectiveness, and No for ineffectiveness" of the "SAFE" strategy for trachoma elimination and reducing the prevalence of trachoma blindness in Africa, and all the findings were reported with 95% confidence intervals.

Dealing with missing data

Principally, we designed strategies for dealing with missing data from the selected studies. According to the Cochrane library review, the authors agreed to ignore the missing data. Lastly, we performed sensitivity analyses to investigate the possible impact of the selected outcome.

Assessment of heterogeneity

Heterogeneity between studies was checked by assessing the chi-squared statistic and its degree of freedom (df), and the I^2 index at a 95% confidence interval (Higgins & Thompson, 2002; Higgins, Thompson, Deeks, & Altman, 2003). The described I^2 percentage indicatesthe variability in effect estimates that is due to heterogeneity rather than sampling error (chance). For example, thresholds for the interpretation of I^2 were categorized as follows: 0-40% might not be important, 30-60% may represent moderate heterogeneity, 50-90% may represent substantial heterogeneity, and 75-100% represent considerable heterogeneity (Huedo-Medina, Sánchez-Meca, Marín-Martínez, & Botella, 2006). However, I^2 value can be misleading, since the importance of inconsistency depends on several factors, thus subgroup and sensitivity analysis were employed.

Assessment of reporting biases

The egger regression test was done via the funnel plot to assess the presence of publication bias in the studies included in the review. Figure 3, The funnel plot indicates symmetric dots of inverted funnel shape showing the absence of publication bias. In the RevMan review manager, studies evaluating the effectiveness of the "SAFE" strategy was categorized into three intervention traits (I) mass administration of antibiotics (ii) trichiasis surgery programs (iii) facial cleanness and environmental improvement campaign, and subgroup analysis was done to determine the random heterogeneity between the estimates ofprimary studies.

Data synthesis

Quantitative data were extracted from selected articles and entered into Microsoft excel by the first author for cleaning and coding. Before the data was entered into Revman software for synthesis and analysis, two more authors proofread and matched the entered data with Author's name and year of publication to avoid mismatch of data. RevMan calculator was used to convert, and deal with data reported in different measures of outcomes, to fit with the data inthe data set. A meta-analysis for dichotomous outcomes was used. RevMan review manager 5.4.1 was used to execute the random-effect model of Mantel-Haenszel inverse-variance statistical methods. To measure the primary outcome, a summary statistics effect odds ratio (OR) from a 2×2 table was calculated.

Subgroup analysis and investigation of heterogeneity

To investigate heterogeneity, the independent variables: antibiotics, surgery, and facial cleanness/ environmental improvement were grouped into subcategories.The subgroup analysis and sensitivity analysis was done (Figure 5), and independent variables for meta-regression were calculated.

We assessed the presence of statistical heterogeneity in the meta-analyses by visual inspection of the forest plot and Chi-squared test for heterogeneity at a threshold P-value of 0.05 was set to determine statistical significance. In the presence of heterogeneity, subgroup analysis was maintained. Statistical evidence for the presence of heterogeneity between subgroups was calculated. Heterogeneity was quantified as high (considerable), moderate, low with ranges of 75% or more, 50–75%, and 25% or less for I^2, respectively. With the presence of evidence, a sensitivity analysis was done. Secondly, considerable heterogeneity was ignored to minimize the loss of data quality. Several subgroups of studies of the same characteristics, measuring the same intervention and same outcomes were combined to form a categorical group within the Revman review manager and the results were interpreted. Here we grouped studies,

evaluated the efficacy and safety of Group 1 (Surgery for trichiasis), Group 2 (Administration and distribution of Antibiotics' Azithromycin), andGroup 3 (Studies looking at Facial cleanness and Environmental Improvement effort for trachoma elimination).Sensitivity analysisbetween groupswas done to determine whether conclusions are sufficiently robust to make decisions during the review process, such as inclusion/exclusion of particular studies from a meta-analysis, imputing missing data or choice of an analysis method. If evidence is found of heterogeneity in the effect of treatment between studies, then meta-regression was used to analyze associations between treatment effect and study characteristics.

Results

Description, selection, and characteristics of included studies

Full-text studies included in the review were 38 RCTs. The summary characteristics of these studies are described in **Table 1.** All the studies included in the meta-analysis were onlyrandomized controlled trials conducted in Africa; from the inceptionof the "SAFE" strategy in Africa in 1981 to 2020. The study had a sample size of 163209 participants. Categorically, there was 25 RCTs-Mass administration of Antibiotics studies with a sample size of 147525 individuals aged between 1-18 years, and between 30-40 years where 64.7% (95471) individuals were randomized to receive mass administration of the antibiotic "Azithromycin", and 35.3% (52054) individuals were randomized to the conventional intervention (control arm). 8 RCT strichiasis surgery studieshad (N=8906) both children and adults, of which 53.2% (4741) were randomized to receive surgery intervention, and 46.8% (4165) were randomized to the control group. Another category was a 5 Facial cleanness/ environmental improvement promotion Clustered randomized controlled trials with a total population of (N=6778)) children and adults; 46.5% (3151) participants were randomized in the communities where intervention was implemented, and 53.5% (3627) were randomizedtothe control group. The Characteristics of included studies are described in Table 1. Author's name, year and country of publication, methods, Interventions, Outcomes, event, the total event for intervention, and control arm.

Table 1: The summary characteristics of the studies included in the review.

Results of Research

The process of study identification and selection is shown in Figure. 1. (The PRISMA flow diagram). The literature search yielded 4541 citations and 50 fromreferences. After a review of the title and abstract, 38 full-text articles were selected for critical review and inclusion. Table 1 describes the included studies in meta-analysis. We excluded 67 full-text articles with reasons. Articles with insufficient methodology information (N=8), Not reflecting randomization procedure (N=16), data not reflecting comparative arm (N=13), not reporting the outcome of interest (N=12), insufficient information on study subjects, sample size, and sample size of subjects allocated to each arm (N=18).

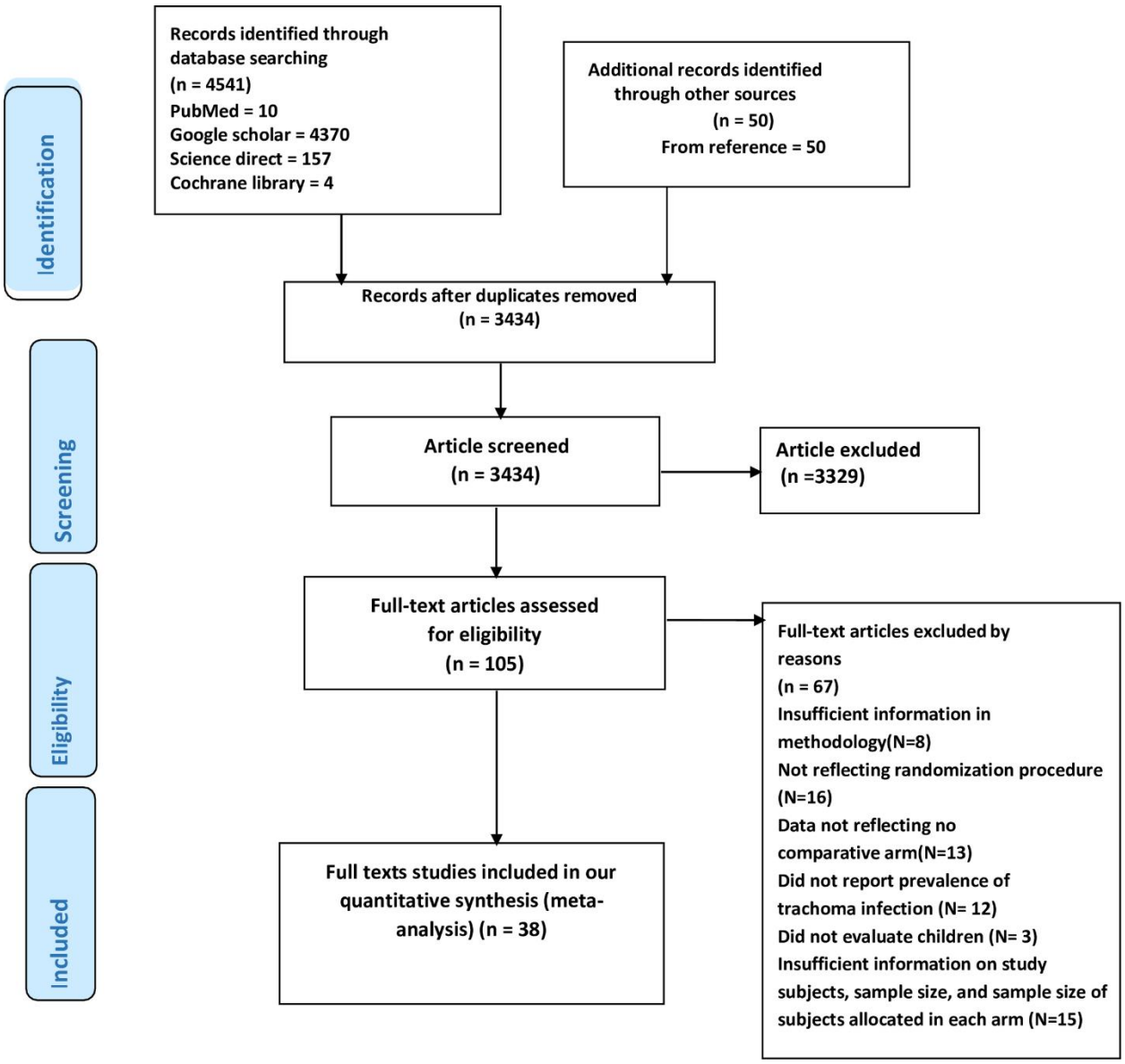

Figure 1: PRISMA Flow chart diagramdescribing selection of studies and references for meta-analysis, to synthesize the findings on efficacy and effectiveness of the "SAFE" strategy program for trachoma elimination in children and adults in low resource setting countries in Africa

Risk of Bias in Included Studies

The risk of bias of included studies summarized in the Risk of bias graph. Figure 2 indicates that all included studies had low risks of bias. i.e.there were low risks of bias during random sequence generation, allocation of study subjects, procedural concealment, blinding, and the incomplete outcome as described below.

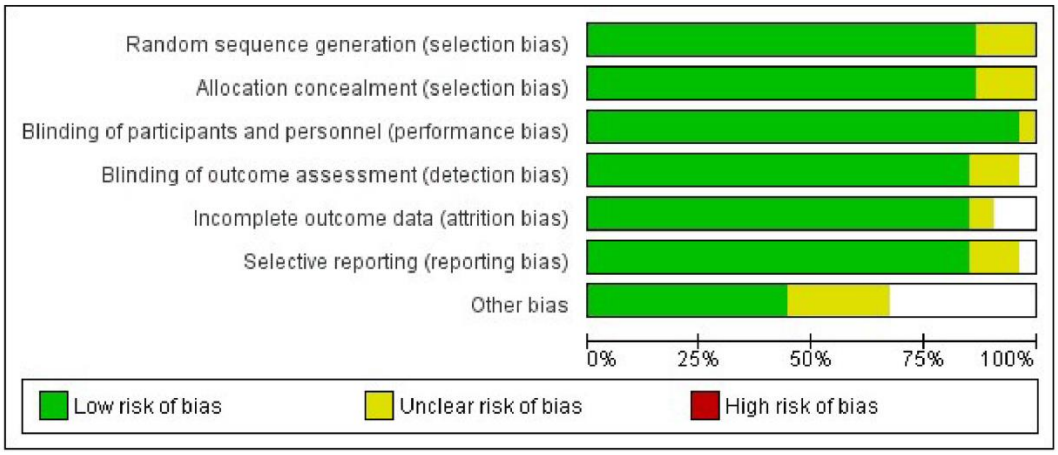

Figure 2: Risk of bias graph review authors' judgments about each risk of bias item presented as percentages across all included studies

Figure 3.The funnel plot with a symmetrical shape suggests the absence of publication bias.

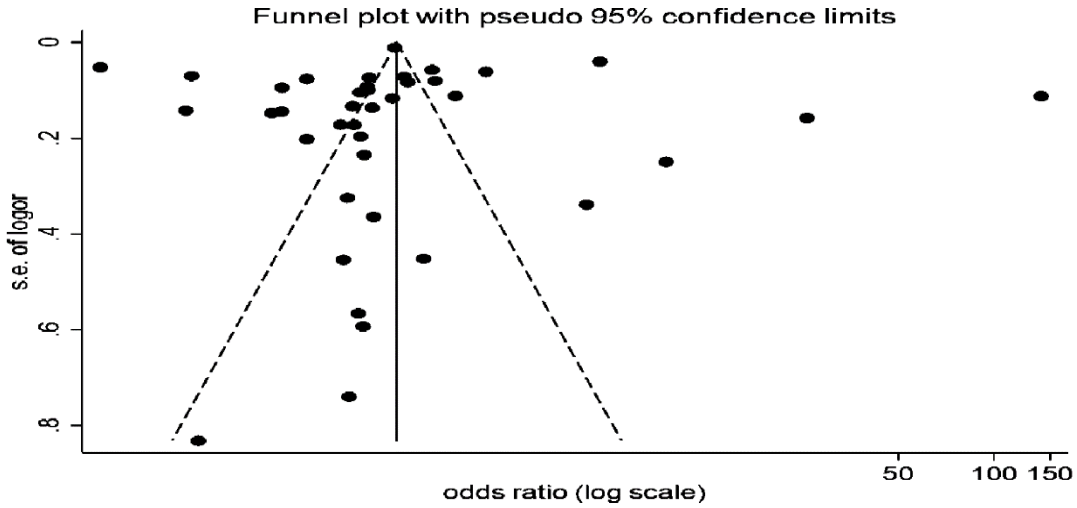

Figure 3: Funnel plot. The asymmetrical funnel plot which suggests no heterogeneity between studies included in the review

The efficacy and effectiveness of the "SAFE" strategy for trachoma elimination

Thirty-eight randomized controlled trials reported the efficacy and effectiveness of the 'SAFE' strategy for trachoma elimination as an outcome. The 38 RCTs reviewed indicated that the prevalence of active trachoma was 11.4% (11766) of 103363 participants randomized to receive the "SAFE" strategy compared with 19.9% (11947) of 59799 randomized in control group (OR =0.86, 95% [0.55, 1.37], p=0.53), I^2 =99%, P=0.00001 **Figure 4,.**

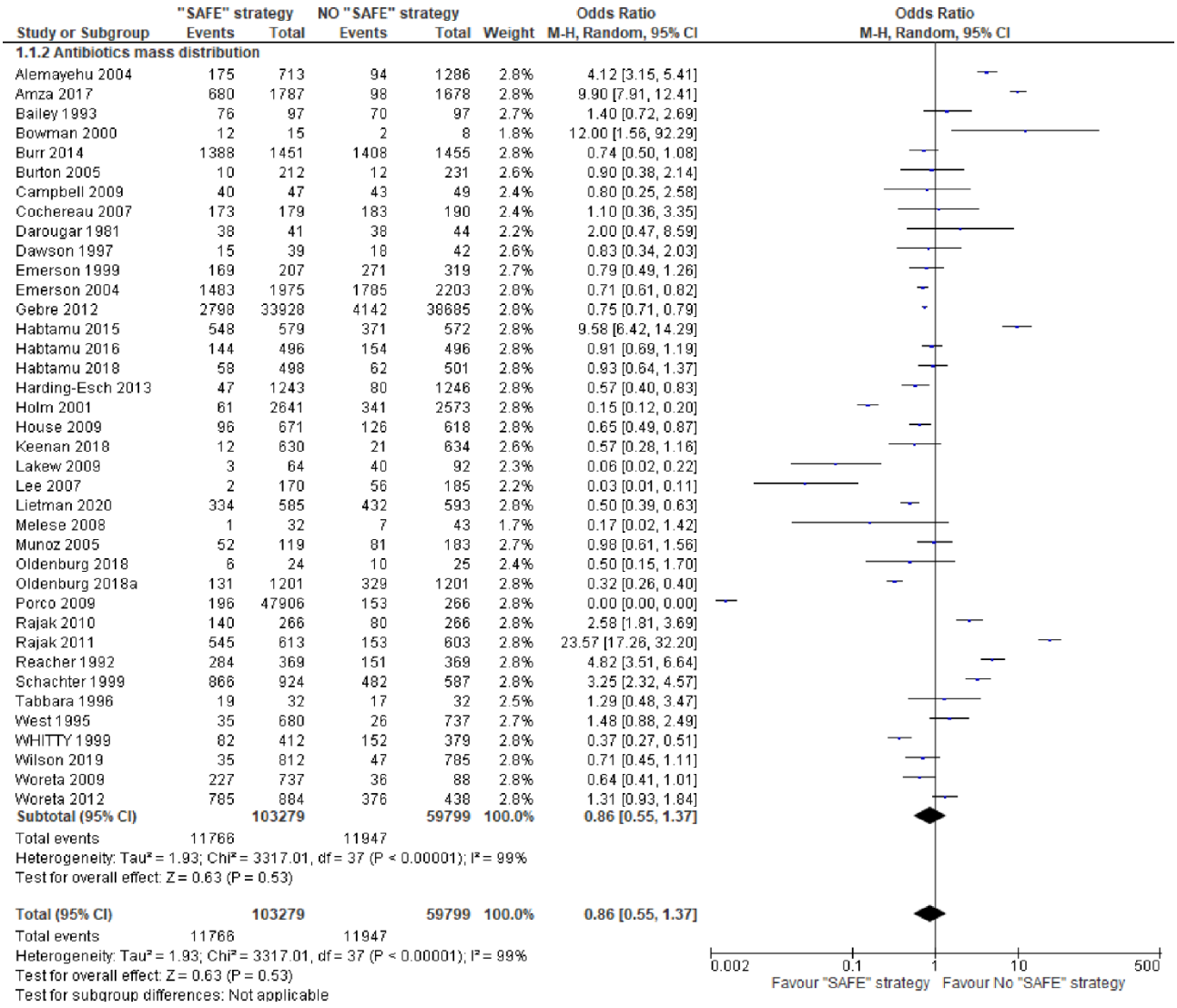

Figure 4: Forest plot of SAFE' strategy for trachoma elimination

Mass distribution of Antibiotics 'Azithromycin' to clear *Chlamydia trachomatis* infection

Twenty-five (25) RCTs studies reported the efficacy and effectiveness of mass administration of the antibiotics, Azithromycin among children and adults in Africa. The pooled overall summary effect measure is shown in Figure 5.A forest plot generated using a random effect model indicates that Azithromycin reduced active trachoma by 7.5% (7177) out of the 95471 individuals with active trachoma who were randomized to receive Azithromycin, and this rate was relatively lower among those in the control arm, which was a reduced rate of 15.9% (8323), with the odds of (OR=0.62, 95%, CI [0.33 1.15], p = 0.13), I^2 =99%. The pooled analysis showed no statistical difference in the rate of eliminating or reducingactive trachoma in those assigned to the Mass administration of the antibiotics, Azithromycin than those assigned to the control arm. The Heterogeneity between studies was statistically significant (Chi^2 = 2301.18, (P < 0.00001); I^2 = 99%.).

Trachomatous trichiasissurgery for advanced trachoma

Trichiasis surgery is the treatment for trachomatous trichiasis. **Figure 5.** The results of a pooled analysis from the 8 RCTs showed a statistically significant difference in the rate of improving visual acuity among individuals randomized to receive Trichiasis surgery compared to those in the control group (OR= 3.10, 95% CI [1.6, 7.80], p= 0.007). Such that among 4741 participants randomized to trichiasis surgery, 60.1% (2848) improved visual acuity compared to 33.9% (1415) of 4165 participants in the control group with a statistically significant Heterogeneity of (Chi^2 = 376.65, P < 0.00001, I^2 = 98%) between studies. However, the result shows that those in the control arm were significantly more likely to improve visual acuity by the odds of 3.10 times more, compared to those in the study intervention arm.

Environmental improvement and Facial cleanness campaign to reduce the transmission of *Chlamydial trachomatis infection*

Five cluster randomized controlled trials reported the prevalence of *Chlamydia trachomatis infections*as an outcome. The pooled overall effect measure showed no statistically significant difference in the rates of preventing the transmission of *Chlamydial trachomatis infection*between the two study groups (OR=0.67,95% CI [0.39, 1.16], p=0.15). The study indicated that of the 6778 subjects that participanted in the study, environmental improvement and facial cleanness intervention reduced the transmission rate of *Chlamydial trachomatis infection*by 55.3% (1741) of 3151 participants assigned to the study group compared withthe 61.2% (2219) of 3627 participants assigned to the control group with a higher statistically significant heterogeneity between studies [Chi^2 = 30.14, (P < 0.00001); I^2 = 87%] as illustrated in Figure 5.

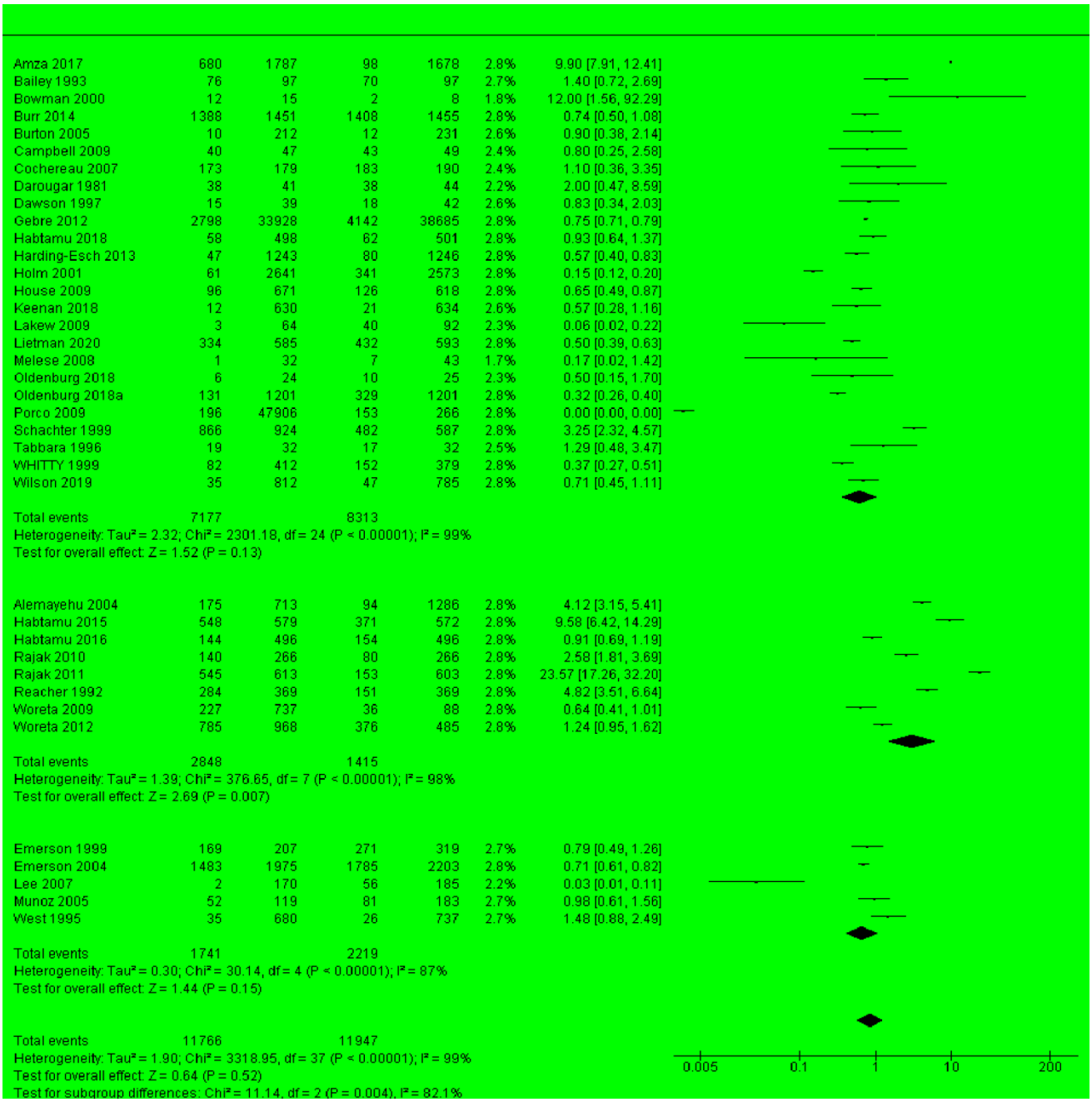

Figure 5: Forest plot of efficacy and effectiveness of the 'SAFE' strategy for trachoma elimination

Figure 5, The combined overall effect from the 38 RCTs indicated that active Trachoma elimination rate in the communities that received the 'SAFE' strategy intervention was 11.4% (11766) relatively lower than in the control group with a rate of 19.9% (11947), with a pooled odds ratio of (OR= 0.86, 95% [0.55, 1.36], p=0.52). The heterogeneity between studies was significantly high (Chi^2 = 3318.95, (P < 0.00001); I^2 = 99%). The difference between group was statistically significant (Chi^2 = 10.39, (P = 0.006), I^2 = 80.8%). The result of the pooled effect measure from the 38 randomized controlled trials showed no statistically significant difference in odds of eliminating or reducing the prevalence of active trachoma, and related blindness in the communities and individuals

randomized to intervention strategies than those randomized to the control group. We stratified the 'SAFE' strategy by intervention types, follow-up time, and study design to determine the effect of the study covariate hypothesized to be associated with the efficacy and effectiveness of the 'SAFE' strategy effect. After Meta-analysis regression of the three independent variables (study covariates), we found that the type of intervention had the regression coefficient of (-1.325, 95% CI [-4.28 1.64], p>0.381), study design had a regression coefficient of (-1.45, 95% CI [-2.87 5.77], p>0.511), and follow-up time(-1.32, 95% CI [-4.28 1.64], p>0.381). Findings demonstrated that the 'SAFE' strategy did not significantly vary by study covariates. By using egger test regression, we fitted a random effect model to Meta regress effect of publication bias. The pooled effect measure from the 38 studies was statistically significant (-11.96, 95% CI [-12.75 -11.17], p=001.

Discussion

The implementation of the 'SAFE' strategy program components is of considerable public health interest to eliminate trachoma disease and prevent trachoma-related blindness among children and adults in Africa. However, there is a concern that the implementation of the 'SAFE' strategy has yielded no potential benefit to the African communities towards the trachoma elimination effort, althoughprevious studies have demonstrated that mass Azithromycin distribution reduce the prevalence of ocular chlamydia infection, (Keenan et al., 2018; Liu et al., 2014), Facial cleaness and environment improvement prevent the transmission (Pinsent, Burton, & Gambhir, 2016), and Surgery provid a significant improvement in visual acuity (Tinsay A Woreta, Beatriz E Munoz, Emily W Gower, Wondu Alemayehu, & Sheila K West, 2009). This review intends to estimate the overall pooled effect measure of efficacy and effectiveness and safety of the 'SAFE' strategy components for trachoma elimination in children and adults in Africa. We used 38 relevant studies to perform a meta-analysis review to test our hypothesis that the 'SAFE' strategy program eliminates chlamydial trachomatis infection and reduces the prevalence of trachoma-related blindness in Africa. This review estimated that the efficacy and effectiveness of the 'SAFE' strategy for trachoma elimination rate was 11.4%, which is lower than the WHO target oftrachoma elimination rate of ≥80%. From 1981 to date, Africa continually implement the 'SAFE' strategy program components to eliminate trachoma disease and reduce the prevalence of trachoma-related blindness in Africa. Unfortunately, the prevalence of active trachoma and trachoma related blindness is still a public health burden in Africa (Alambo, Lake, Bitew Workie, & Wassie, 2020; Ndisabiye, Gahungu, Kayugi, & Waters, 2020; WoldeKidan, Daka, Legesse, Laelago, & Betebo, 2019b)

In this review, we found that the overall effect measure estimate of efficacy and effectiveness of the "SAFE" strategy was found to be the same among the communities and individuals who received the 'SAFE' strategy intervention compared with those in the control group. This similarity between these two groups suggestthat there is no statistically significant evidence of the 'SAFE' strategy's capability to eliminate *Chlamydial trachomatis infection*nor reduce the prevalence trachoma related blindness in Africa.

On stratification of intervention as described in figure 5, Mass administration of Antibiotics, and Facial cleanness/ Environmental improvement campaignwere statistically insignificant inpreventing and reducingactive trachoma infections among children and adults in Africa. Although surgery was significantly more likely to favor communities and individuals that received no trichiasis surgery intervention compared with those that received surgery, the explanation for this difference is unclear. Furthermore, this review indicatesa consistent trend across individual studies which indicateno difference between the two study groups.

The implication of these findings suggest that the effort and the resources spent implementing these combinations of trachoma elimination interventions (the 'SAFE'strategy) did not benefit the communities and individuals who received the interventions. The explanation forthe cause of this could be program implementation related challenges

like low levels of implementation fidelity of the 'SAFE' strategy, structural characteristics, patients' characteritics, limited resources, poor Implementation climate, knowledge and experience, beliefs about the intervention, and self-efficacy (Maritim et al., 2019).

The results from this review have important clinical and public health implications in the context of the WHO Alliance for the Global Elimination of blinding trachoma by 2020 target. The results also challenge the effort of program designers, the program implementers, and the entire 'SAFE' strategy implementation processes and planning. They alsoact as an impact indicator to inform policymakers, key stakeholders and funding agencies to understand the need for quality improvement, emphasize adherence to program protocol, monitoring, evaluation, and learning, and restructuring of available program implementation strategies to successfully eliminate trachoma and prevent future trachoma blindness among children and adults in Africa.

However, these findings are surprising,some 'SAFE' strategy intervention components like mass administration of Azithromycin was found to be more significantly likely to put children at risk. Previous studies reported more child death rates recorded in 3 year clustered randomized controlled trials conducted in sub-Saharan Africa (Catherine E Oldenburg et al., 2019). Other studies evaluated and found that Surgery (M. J. Burton, R. J. C. Bowman, et al., 2005), and facial cleanness/environmental improvement were protective (Pinsent et al., 2016). However, Gebrie 2019 (Gebrie, Alebel, Zegeye, Tesfaye, & Wagnew, 2019b), and other series of epidemiological studies reported an increased prevalence of active trachoma in the young population of Africa (Anteneh & Getu, 2016; Ferede, Dadi, Tariku, & Adane, 2017; Gebrie, Alebel, Zegeye, Tesfaye, & Wagnew, 2019a; Kassim et al., 2018, 2019; C. E. Oldenburg et al., 2018; See et al., 2015). Furthermore, our findingsshowsa consistent trend across the mass administration of Azithromycin intervention towards the reduction and elimination of active trachoma before and after adjusting for surgery and facial cleanness, and environmental improvement. Mass administration of Azithromycin drastically remained the best predictor for trachoma elimination effort. These findings radically explain the rationale of concentrating and putting much effort into mass administration of drug programs as it was significantly more likely to contribute to the decrease in the level of prevalence of trachoma disease in Africa, despite the risks associated with the intervention.

However, we cannot definitively conclude that antibiotics alone accounted for a tremendous reduction of active trachoma, other sister components of the 'SAFE' strategy program may be the necessary cause (Last et al., 2017; WoldeKidan, Daka, Legesse, Laelago, & Betebo, 2019c). Therefore, understanding unknown variables associated with the implementation of surgery and facial cleanness, and environmental improvement is crucial.

The strength of this study is that it considered RCT studies published in the English language only, and these studies were retrieved from a comprehensive search of several electronic databases to compile both current and old evidences using published articles as well as grey literature sources. The discrepancy of the data and disagreement was resolved by two independent authors, and lastly, the 38RCTs studies are quite enough to determine the true effect of the 'SAFE' strategy intervention. The challenge is that many of our studies were cluster randomized controlled trials that studied multiple active treatment arms and reported multiple outcomes, and their analysis was at a cluster unit, while other studies reported different effect measures. We assumed that by failing to put into account these differences, we may introduce the risks of bias in this review. Therefore, a RevMan package calculator was used to convert a directly entered measure to our desired effect measure. Secondly, sources of biases in RCTs studies were checked and the fitness level of our inclusion criterion was assessed using the RevMan bias assessing graph. Areas that were scrutinized for the presence of biases were methods, allocation, blinding, and analysis section. Any study that does not meetthe study criteria was excluded from the review. The limitations in this review were the exclusion of observational studies which may affect the overall pooled effect measure ofan estimate.

Conclusion

In summary, a combined overall summary effect measure from these reviews demonstrate that between communities and individual that received the 'SAFE' strategy intervention and those in the control group, there was no statistically significant difference in terms of trachoma elimination and reduction ofthe prevalence of trachoma blindness in Africa. This finding proves that the 'SAFE' strategy has no effect, or yielded no benefit towards the trachoma elimination efforts in Africa and this effect was influenced by the ineffectiveness of surgery, facialcleanliness, and environmental improvement promotion. Based on the available evidence therefore, this review proves that the 'SAFE' strategy program intervention provides no benefits to African communities in trachoma elimination effort as set by WHO Alliance for the Global Elimination of blinding trachoma by 2020 target. However, further research may be needed to further examine the implementation fidelity of the 'SAFE' strategy component, in particular, those not studied yet. For example; Mass administration of Antibiotics 'Azithromycin', environmental improvement, and facial cleanness in African communities.

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Abbreviations

PRISMA: Preferred Reporting Items of Systematic Reviews and Meta-Analysis; WHO: World Health Organization, SAFE; Sugery, Antibiotics, Facial cleanness, Enviroment improvement, RCT; Randomized Controlled Trial.

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Table 1: The summary characteristics of the studies included in the review

Table 1. The summary characteristics of these studies are described

Patients or population: Children and adults living in trachoma endemic areas.

Intervention: SAFE strategy (surgery for trichiasis, Antibiotics for active Trachoma, Facial cleanness, and Environmental Improvement) program

Context (settings): Low-resource setting countries in Africa

Outcome: Elimination of active Trachoma infection and reversible related blindness

				SAFE Intervention arm		Intervention Control arm				Odds Ratio	
Id	Author s' Name	year	Country	Total recovery	total treated	Total recovery	Total treated	Study design	Intervention	M-H Random, 95% CI.	Intervention outcome
1	Woreta 2012(Woreta, Munoz, Gower, Alemayehu, & West, 2012)	2012	Ethiopia	785	884	376	438	Cluster RCT	Surgery	0.64 [0.41, 1.01]	Prevent trachoma
2	Wilson 2019(Wilson et al., 2019)	2019	Ethiopia	35	812	47	785	Cluster RCT	antibiotics	0.71 [0.45, 1.11]	Prevent trachoma
3	WHITTY 1999(WHITTY, GLASGOW, SADIQ, MABEY, & BAILEY, 1999)	1999	Gambia	82	412	152	379	Cluster RCT	antibiotics	0.37 [0.27, 0.51]	Treat trichiasis
4	Tabbara 1996(Tabbara, Abu El-Asrar, Al-Omar, Choudhury, & Al-Faisal, 1996)	1995	Saudi	19	32	17	32	Cluster RCT	antibiotics	1.29 [0.48, 3.47]	Prevent trachoma
5	Schachter 1999(Schachter et al., 1999)	1999	Egypt	866	924	482	587	Cluster RCT	antibiotics	3.25 [2.32, 4.57]	Prevent trachoma
6	Porco 2009(Porco et al., 2009)	2009	Ethiopia	196	47906	153	266	RCT	antibiotics	0.00 [0.00, 0.00]	Prevention of trachoma
7	Oldenburg 2018(C. E. Oldenburg et al., 2018)	2018	Niger	131	1201	329	1201	cluster RCT	antibiotics	0.32 [0.26, 0.40]	Safety of azithromycin

10	Lietman 2020(Lietman et al., 2020)	2020	Ethiopia	334	585	432	593	cluster RCT	antibiotics	0.50 [0.39, 0.63]	Reduce trachoma
12	Keenan 2018(Keenan et al., 2018)	2018	Ethiopia	12	630	21	634	RCT	antibiotics	0.57 [0.28, 1.16]	Elimination of trachoma
13	House 2009(House et al., 2009)	2009	Ethiopia	96	671	126	618	Cluster RCT	antibiotics	0.65 [0.49, 0.87]	Reduce prevalence TF and TI
14	Holm 2001(Holm et al., 2001)	2001	Nepal	61	2641	341	2573	RCT	antibiotics	0.15 [0.12, 0.20]	Reduce trachoma
15	Harding-Esch 2013(Harding-Esch et al., 2013)	2013	Gambia	47	1243	80	1246	RCT	antibiotics	0.57 [0.40, 0.83]	Reduce trachoma prevalence
16	Habtamu 2018(Habtamu et al., 2018)	2018	Ethiopia	58	498	62	501	RCT	antibiotics	0.93 [0.64, 1.37]	Prevention of trachoma
17	Gebre 2012(Gower et al., 2013)	2012	Ethiopia	2798	33928	4142	38685	RCT	antibiotics	0.75 [0.71, 0.79]	Elimination of TT recurrence
18	Dawson 1997(Dawson et al., 1997)	1997	Egypt	15	39	18	42	RCT	antibiotics	0.83 [0.34, 2.03]	Prevention trachomatis
19	Darougar 1981	1981	Nigeria	38	41	38	44	RCT	antibiotics	2.00 [0.47, 8.59]	Treatment of trachoma
20	Cochereau 2007(Cochereau et al., 2007)	2009	Guinea	173	179	183	190	RCT	antibiotics	1.10 [0.36, 3.35]	Efficacy and safety
21	Campbell 2009(Campbell et al., 2009)	2009	Tanzania	40	47	43	49	RCT	antibiotics	0.80 [0.25, 2.58]	Safety and reduce trachoma
22	Burton 2005(M. Burton et al., 2005)	2005	Gambia	10	212	12	231	RCT	antibiotics	0.90 [0.38, 2.14]	trichiasis surgery outcome
23	Burr 2014(Burr et al., 2014)	2014	Gambia	1388	1451	1408	1455	RCT	antibiotics	0.74 [0.50, 1.08]	Treat trichiasis infection
25	Bailey 1993(RL Bailey, Arullendran, Mabey, & Whittle, 1993)	1993	Gambia	76	97	70	97	RCT	antibiotics	1.40 [0.72, 2.69]	Reduce trachoma
26	Amza 2017(Amza et al., 2017)	2017	Niger	680	1787	98	1678	RCT	antibiotics	9.90 [7.91, 12.41]	Prevention of trachoma

27	Woreta 2009(T. A. Woreta et al., 2009)	2009	Ethiopia	227	737	36	88	RCT	Surgery	0.64 [0.41, 1.01]	Cure rate of trachomatous trichiasis
28	Reacher 1992(Reacher et al., 1992)	1992	Oman	284	369	151	369	RCT	Surgery	4.82 [3.51, 6.64]	Reduce the prevalence of trachoma
29	Rajak 2011(Rajak et al., 2011)	2011	Ethiopia	545	613	153	603	RCT	Surgery	23.57 [17.26, 32.20]	Cure of trachomatous trichiasis
30	Rajak 2010(Rajak et al., 2010)	2010	Ethiopia	140	266	80	266	RCT	Surgery	2.58 [1.81, 3.69]	Treatment of trachomatous trichiasis
31	Habtamu 2016(Habtamu et al., 2016)	2016	Ethiopia	144	496	154	496	RCT	Surgery	0.91 [0.69, 1.19]	Treatment of trachomatous trichiasis
32	Habtamu 2015(Habtamu et al., 2015)	2015	Ethiopia	548	579	371	572	RCT	Epilation	9.58 [6.42, 14.29]	Prevention of trachomatous trichiasis
33	Alemayehu 2004(Alemayehu et al., 2004)	2004	Ethiopia	175	713	94	1286	RCT	Surgery	4.12 [3.15, 5.41]	Prevention of trachomatous trichiasis
34	West 1995(S. West et al., 1995)	1995	Tanzania	35	680	26	737	Cluster RCT	facial & environmental	1.48 [0.88, 2.49]	Prevention of trachoma infection
35	Munoz 2005(Munoz et al., 2005)	2005	Tanzania	52	119	81	183	Cluster RCT	facial & environmental	0.98 [0.61, 1.56]	Prevention of trachoma infection
36	Lee 2007(Lee et al., 2007)	2007	Ethiopia	2	170	56	185	RCT	facial & environmental	0.03 [0.01, 0.11]	Prevention of trachoma infection
37	Emerson 2004(Paul M. Emerson et al., 2004)	2004	Gambia	1483	1975	1785	2203	Cluster RCT	facial & environmental	0.71 [0.61, 0.82]	Prevention of trachoma infection
38	Emerson 1999(Emerson et al., 1999)	1999	Gambia	169	207	271	319	Cluster RCT	Fly control	0.79 [0.49, 1.26]	Prevention of trachoma infection