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Mass drug administration campaigns for scabies and impetigo: protocol for a systematic review and meta-analysis

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ABSTRACT

Introduction Scabies is recognised as a neglected tropical disease, disproportionately affecting the most vulnerable populations around the world. Impetigo often occurs secondarily to scabies. Several studies have explored mass drug administration (MDA) programmes, with some showing positive outcomes—but a systematic evaluation of such studies is yet to be reported. The main aim of this systematic review is to generate comprehensive evidence on the effect and feasibility of MDA programmes in reducing the burden of scabies and impetigo.

Methods and analysis A systematic review and meta-analysis will be conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-analysis statement. Electronic databases to be searched will include CINAHL EBSCOhost, Medline Ovid, ProQuest, Science Direct, PubMed and SCOPUS. In addition, grey literature will be explored via the Australian Institute of Health and Welfare, Australian Indigenous HealthInfoNet, Informit, Oalster database and WHO. No language restrictions will be applied. All treatment studies following an MDA protocol, including randomised/quasi-controlled trials, and prospective before–after interventional studies, will be considered. The main outcome is the change in prevalence of scabies and impetigo The Cochrane collaboration risk of bias assessment tool will be used for assessing the methodological quality of studies. A random-effect restricted maximum likelihood meta-analysis will be performed to generate pooled effect (OR) using STATA V.16. Appropriate statistical tests will be carried out to quantify heterogeneity between studies and publication bias.

Ethics and dissemination Ethical approval is not required since data will be extracted from published works. The findings will be communicated to the scientific community through a peer-reviewed journal publication. This systematic review will present an evidence on the effect of MDA interventions on scabies and impetigo, which is instrumental to obtain a clear understanding of the treatments widely used in these programmes.

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What this study hope to add?

What is already known on this topic?

- Scabies outbreaks in the community can be extended and difficult to control.
- Mass drug administration (MDA) strategies appear promising in reducing the burden of various neglected tropical diseases and their associated complications.

What this study hopes to add?

- Although there are individual studies suggesting the feasibility and effectiveness of MDA, there has not been comprehensive systematic review of the literature evaluating this evidence.
- This review will provide evidence on the most effective drug, dose and dosage formulation, and frequency of treatment required in MDA programmes targeted at scabies and impetigo.

BACKGROUND

Scabies and impetigo present significant health challenges in resource-limited settings and remote communities, compared with urban settings.[1] Globally, around 200 million children are estimated to be affected by scabies and about 162 million children suffer from impetigo at any given time.[2 3] If left untreated these skin conditions can lead to serious complications, including sepsis, renal disease and rheumatic heart disease.[1]

Mass drug administration

Mass drug administration (MDA) is a treatment and containment approach where all individuals in a particular community are subjected to treatment without any individual diagnosis.[4] MDA dates back to the 1960s, when schools in the USA showed positive results following MDA of anthelminthic drugs; this resulted in a decrease in the prevalence of worm infections and increase in school enrolment and attendance after the drug treatment.[5] MDA is a well-established strategy for some of the highly prevalent neglected tropical diseases (NTDs; eg, trachoma, soil-transmitted helminthiasis, schistosomiasis,

lymphatic filariasis) and is a part of the integrated approach to NTDs in various settings.[6] The World Health Organisation recognises MDA as a useful strategy for controlling scabies in resource-constrained communities, where the condition is hyperendemic, based on evidence from individual studies.[4] As the intervention is often population based, it reduces the burden of the disease and it integrates cost-reduction strategies, which is a major hurdle in these areas.[7] In various endemic populations of the Pacific region, MDA has shown positive results in reducing the burden of scabies and impetigo, especially in indigenous communities.[8] MDA has shown potential for both social and economic benefits.[5]

Scabies and impetigo—common paediatric infections in resource-limited settings

Scabies is a skin disease that is caused by the acarine itch mite *Sarcoptes scabiei*.[9] The mite can live inside the host for up to 60 days and have a 17-day life cycle.[10] They can easily spread from person to person via direct or sexual contact and can also spread through non-living objects such as bedding, clothes and even furniture.[11] The global burden of the disease is estimated to be around 200 million, most of which are children living in resource-limited societies.[12] Scabies is a highly infectious and extremely itchy condition that can lead to loss of sleep and reduced quality of life.[11 13] A more severe form of scabies is known as 'crusted scabies' (also called Norwegian scabies), characterised by thick crusts on the patient's skin, which harbour up to several million scabies mites; they are highly infectious and such cases should receive quick and aggressive medical treatment.[14] This is mostly seen in immunocompromised patients suffering from AIDS or cancer.[10 14] Despite the efficacy of the individual targeted therapies for treating scabies, it is difficult to contain scabies and its associated complications.[15] Current treatments for scabies, include the first-line topical permethrin, the second-line topical benzyl benzoate and the third-line oral ivermectin.[16] These treatments have been generally effective when the course has been completed properly; however, there remain a number of challenges associated with current treatments. These include poor adherence to treatments, high costs for resource-poor communities, single-drug modality and increasing treatment failure.[17–19] The possibility of reinfestation remains high when close contacts are not treated, or the disease is endemic in a population. Also, no currently available treatments possess the combined ability to kill eggs, or have a combined antibacterial and anti-inflammatory/anti-itch properties. They are all ineffective at preventing treatment relapse arising from newly hatched mites, and evidence indicates that the mites are becoming increasingly resistant to existing treatments.[20 21]

Scabies is associated with a serious itching that often leads to scratching and thereby leading to secondary skin infections. Impetigo is the most common bacterial skin infection—often occur secondary to scabies—typically caused by *Staphylococcus aureus* or *Streptococcus pyogenes* and it predominantly affects young children.[22] Further, complement inhibitors produced by the scabies mite create a conducive environment for the growth and survival of *S pyogenes*, putting patients at increased risk of complications like septicaemia, acute post-streptococcal glomerulonephritis (APSGN) and acute rheumatic fever.[13 23 24] About 50% of cases of APSGN in tropical settings (around 470 000 cases/year worldwide) result from bacterial skin infections.[25] APSGN has also been identified as a strong risk factor for chronic kidney disease later in life.[25] *S. pyogenes* (group A streptococci) remains a significant causative agent for the vast majority of cases of acute rheumatic fever and rheumatic heart disease, particularly in low-resource settings.[12]

People living in the so-called endemic communities where scabies and impetigo are very common (eg, Aboriginal communities in remote Australia and other tropical regions, refugee camps and other places with crowded living arrangements) are at substantial risk of serious complications, including post-streptococcal sequelae, premature disability, and mortality.[26] There is a clear imperative for a large-scale coordinated and evidence-based approach for the treatment and prevention of these conditions in endemic regions. Due to the co-existence of scabies and impetigo and the need for streamlined and novel strategies for the management of these common infectious skin conditions in resource-limited settings, the feasibility and effectiveness of MDA programmes have been evaluated in different parts of the globe. However, the lack of conclusive data on the impact of MDA programmes (eg, ivermectin based) on scabies reduction after nearly three decades is a major deficit, evidenced by signs of emerging resistance and challenges associated with its administration in community settings, especially in endemic settings. A systematic review of the existing literature on the feasibility and effectiveness of MDAs will create an evidence base required for its future applicability. This systematic review aims to synthesise and quantitatively analyse the evidence in relation to the effect of MDA in reducing the burden of scabies and associated impetigo.

METHODS

This study protocol is prepared in compliance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols (PRISMA-P)[27] and has been registered with the International Prospective Register of Systematic Reviews (PROSPERO; CRD42020169544).

Search strategy, keywords

Preliminary searches of the literature will be done to identify the keywords, which will be integrated and listed to undertake a more extensive search. These will be combined with Boolean operators and various medical subject headings to formulate a refined search method. To identify the keywords regarding scabies MDA, the keywords 'scabies', 'crusted scabies', 'Norwegian scabies',

'skin sores', 'impetigo', 'school sores', 'interventions', 'skin disease', 'permethrin', 'ivermectin', 'azithromycin', 'pyoderma', 'resistance', 'benzyl benzoate', 'lindane', 'crotamiton', 'malathion', 'mass drug administration', 'disease management', 'therapeutics', OR anti-infective agents' OR 'anti-bacterial agents' OR 'antibiotic' OR 'antibiotic prophylaxis' OR 'prevention and control' OR 'drug therapy' OR clinical OR routine OR 'pharmaceutical preparations' OR 'treatment' OR 'intervention' OR 'therapy' OR 'medicine' OR ' management' OR 'mass administration' or 'mass treatment' OR 'mass distribution' OR 'preventative chemotherapy' will be used. All searches will be performed from database inception until May 2021 and all languages will be included, and the search strategy will be developed based on the instructions in the Cochrane handbook for systematic reviews of interventions[28] and will be specific for each database. A detailed search strategy has been listed in online supplemental appendix 1. The results will be presented in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) flow chart (online supplemental appendix 2, p16–17).[29 30]

Information databases

Electronic databases, including CINAHL (EBSCOhost), Medline (Ovid), ProQuest, Science Direct, PubMed and SCOPUS, will be searched for studies, along with the ANZ Clinical Trials Registry, ClinicalTrials.gov, and WHO International Clinical Trials Registry. In addition, grey literature will be explored via the Australian Institute of Health and Welfare, Australian Indigenous HealthInfoNet, Informit, OaIster database and WHO. Further, the references of the included articles will also be thoroughly screened for relevant articles potentially missed during the main search.

Types of studies to be included

All treatment studies following MDA protocol, including randomised/quasi-controlled trials, cross-sectional studies, cohort studies and case-control studies, will be considered.

Participants/Settings

The review will consider studies that include participants of any age, gender, or country of origin. Studies that aimed to evaluate the effectiveness of individual drug treatments for people with diagnosis of scabies and/or impetigo outside MDA will not be considered.

Intervention, exposure

The review will examine any MDA treatment campaigns involving scabicides that aimed to reduce the burden of scabies and associated impetigo. Treatment interventions may include any antiparasitic drug which is known to have therapeutic activity against scabies infestation, including ivermectin, permethrin, benzyl benzoate, lindane, crotamiton, or malathion.

Comparator/control

Studies with any type of comparator will be included, which may include the intervention population prior to intervention, a population from the same setting as the intervention but not exposed to the intervention, or a population exposed to a different scabies control intervention.

Outcomes

The main outcome is the change in prevalence of scabies and impetigo from baseline to follow-up after MDA intervention. Additional outcomes include relief of symptoms, recurrence rate, adherence to treatment or management regimen, patient acceptability of treatment/s, and adverse effects.

Selection of studies

The citations found from the search will be transferred to Covidence[31] for screening, data extraction and risk-of-bias assessment purpose. Full texts of potentially relevant studies that passed the initial screening will be examined for eligibility. Where possible, we will attempt to contact the primary authors via email when eligibility for inclusion is not clear. Two independent reviewers will perform eligibility assessment, and data extraction. Any disagreements that arise between the reviewers regarding the studies for final inclusion will be resolved by third member of the study steering group. Reasons for excluding any trial will be recorded.

Data extraction and management

Two review authors will extract the data and check for discrepancies at each level (title, abstract and full text) using the inclusion and exclusion criteria. We will specifically extract the following data:

- *General information*: author, journal, year(s) the study took place, year of publication, country, sample size, sociodemographic characteristics of study participants.
- *Study methodology*: study design, inclusion/exclusion criteria, sample size.
- *Details of intervention* included in the MDA campaign: dose, formulation, frequency, duration, administration requirements (if any) and combination with other medicines.
- *Comparators*: details for placebo or no treatment, control intervention of non-pharmacological nature or other medicine.
- *Outcomes*: Scabies and impetigo prevalence before MDA and following MDA, secondary outcomes, and results (including effect size estimates).
- *Study limitations*.
- Discussion re possible *factors contributing to the success (or lack of success) of the MDA campaign*.

Risk-of bias assessment

Two reviewers will independently assess the risk of bias of included studies. The Cochrane risk of bias assessment

(V.2.0)[32] tool will be employed for assessing the methodological quality of randomised trials. The studies will be assessed on domains, such as selection bias, performance bias, detection bias, attrition bias, reporting bias and other sources of bias including an assessment for confounding for non-RCTs. Each domain will be judged as 'low risk', 'some concerns' and 'high risk', which are collectively used to decide on the overall risk of bias in a study. For non-randomised studies, The Johanna Briggs Institute Critical Appraisal tool will be used.[33]

Strategy for data synthesis

The extracted data will be narratively synthesised and be presented in tabulated form in the results section, in accordance with PRISMA statement.[29] A flow diagram will be presented to summarise the number of articles retained at each screening stage and provide the reasons for exclusion.

Strategies for meta-analysis

For studies reporting proportions in each of the comparator groups, 2×2 contingency tables will be derived for calculation of OR and the corresponding 95% CI. Random effects restricted maximum likelihood meta-analysis model will be fitted, given its variance estimation method is more robust in small sample studies,[34] and forest plot with the respective OR and 95% CI for each study and pooled data will be generated. The Z-statistic will be used in testing overall effect with statistical significance set at $\alpha \leq 0.05$. Subgroup analyses will be performed based on the type of pharmacological treatments used—oral or topical treatment. This will allow us to compare the relative effectiveness of these drug formulations in MDA campaigns for scabies and impetigo.

Heterogeneity between studies will be assessed by calculating the I^2 statistic. The Begg's funnel plot and Egger test for small-study effects[35] will be carried out to assess risk of bias across studies. The funnel plot will be created by plotting the log-odds ratio of each study against the SE and the symmetry of the funnel plot visually assessed. We will also attempt a sensitivity analysis by fitting a fixed-effect Mantel-Haenszel model to assess if estimates with the random effect model differ. Meta-analysis will be conducted in STATA V.16 (StataCorp LLC).

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