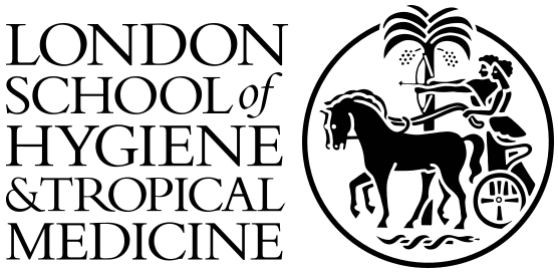

Title: The public health control of scabies: priorities for research and action

Short title: Research priorities for scabies control

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Summary

Scabies is a parasitic disease of the skin that disproportionately affects disadvantaged populations. Scabies causes considerable morbidity and leads to severe bacterial infection and immune-mediated disease. Recent scientific advances suggest that scabies is amenable to population-level control, particularly through mass drug administration. In recognition of these issues, WHO added scabies to the list of neglected tropical diseases (NTDs) in 2017. In order to develop a global control program, key operational research questions must now be addressed. Standardised approaches to diagnosis and methods for mapping are required to further understand the burden of disease. The safety of treatments for young children, including with ivermectin and moxidectin, should be investigated. Studies are needed to inform optimum implementation of mass treatment, including the threshold for intervention, target, dosing, and frequency. Frameworks for surveillance, monitoring and evaluation of control strategies are also necessary.

Introduction

In 2017, scabies was added to the World Health Organization (WHO) list of neglected tropical diseases (NTDs). Scabies was recommended to be included as a 'category A' NTD, defined as those conditions that fulfil all four specified criteria, and are recommended for large scale action in the portfolio of the NTD Department.[1] In reaching this recommendation, the WHO NTD Strategic and Technical Advisory Group noted the need for further research to inform control strategy as well as key issues for programmatic implementation, including ensuring affordable access to oral medications and developing guidelines for their public health use.[2] In March 2018, the WHO NTD Global Working Group on Monitoring and Evaluation discussed scabies for the first time. Key recommendations from that meeting included the need to better define the global burden; to integrate control efforts to capitalise on ivermectin-based programs for other NTDs; and to establish interim guidelines for public health interventions for scabies control.[3] In this rapidly evolving context, we review major recent advances in the science of control of human scabies, and identify key operational research questions that need to be addressed to develop a global scabies control program.

The burden of scabies

Scabies is caused by infestation with the microscopic ectoparasite *Sarcoptes scabiei* var. *hominis*, and leads to severe itch, skin lesions and more serious complications due to bacterial superinfection (Figure 1). Transmission requires skin-to-skin contact, and there is no non-human reservoir. Scabies occurs in all countries, but its distribution is not uniform. In high-income settings, most cases are sporadic, and the predominant public health issue is the management of outbreaks in institutions such as hospitals and residential aged care facilities. A far greater burden of disease is found in low- and middle-income countries, where access to effective treatment is limited and population crowding increases the opportunities for transmission. Areas with hot, humid climates have the highest reported prevalence, most prominently island communities in the Pacific region and Central America, and Indigenous communities of northern Australia.[4-6] In these settings, the community prevalence has been consistently estimated in the range of 20 – 30%, with a higher prevalence of up to 40 – 50% in children aged less than 18 years (Figure 2).[7-9]

In other resource-limited settings where baseline prevalence is lower, change in environmental or socio-political conditions can be associated with epidemics,[18] such as the

outbreak in the Amhara Region in Ethiopia that has been in progress since 2015 and has been estimated to affect more than one million people.[19,20] Circumstances with substantial population crowding frequently lead to high levels of transmission, and outbreaks are common within schools, prisons and camps for refugees and internally displaced persons.[21]

Scabies is one of the world's most common illnesses. The Global Burden of Disease (GBD) Study 2016 estimated the global point prevalence of scabies to be around 147 million, with 455 million annual incident cases.[22] Further GBD analyses estimated that scabies caused approximately 3.8 million disability-adjusted life years (DALYs), ranking scabies as one of the most important NTDs.[23] Scabies causes an age-adjusted morbidity burden similar to *Haemophilus influenzae* type B meningitis and acute lymphoid leukaemia.[24] These GBD analyses are modelled on the small number of published reports on the prevalence of scabies. Of note, the disability weighting only considers the skin changes and itch directly caused by infestation.[24] The estimated burden would be far greater if the morbidity and mortality caused by the complications of scabies were included (Figure 3). Scabies infestation causes a considerable proportion of bacterial skin infection (pyoderma) in many resource-limited settings, most commonly manifesting as infected sores (impetigo). [7,8,25,26] For example, Aboriginal children in Australia were 12 times more likely to develop impetigo when infected with the scabies mite,[26] and studies from Pacific island nations have estimated the attributable risk of scabies as a cause of impetigo to be 41% – 93%.[7,8,27] Scabetic lesions and traumatic scratching create breaches in the skin barrier that are a portal for bacterial entry. Scabies mite components such as serpins inhibit innate immune pathways including neutrophil function and directly promote the growth of *Staphylococcus aureus* and *Streptococcus pyogenes*.[28-31] Skin infection due to these bacteria can lead to severe soft tissue infections and invasive disease. Infection with *S. pyogenes* can also lead to immune-mediated complications including post-streptococcal glomerulonephritis and possibly acute rheumatic fever, which in turn contribute to chronic kidney disease and rheumatic heart disease (Figure 3).[32,33] Quantification of the proportion of the burden of these serious health consequences attributable to scabies will give a more accurate estimate of the global burden of scabies and the potential benefit of scabies control.

Diagnosis

Both the mapping of scabies and population-level control are hampered by the lack of a reliable, reproducible and standardised approach to diagnosis. Two systematic reviews of

diagnostic methods found a lack of consistency in the approach to scabies diagnosis.[34,35] Microscopy of skin scrapings to visualise mites and eggs is highly specific but insensitive and operator dependent, and therefore generally not useful for field settings. In order to address this gap, an international panel of experts, convened by the International Alliance for the Control of Scabies (IACS) recently used a Delphi consensus method to develop the 2018 IACS Criteria for Scabies Diagnosis in research and epidemiological settings.[36] These criteria enable diagnosis and reporting in three bands of diagnostic certainty - confirmed, clinical and suspected scabies. A diagnosis of confirmed scabies requires identification of the mite on microscopy or non-invasive visualisation techniques such as videomicrosopy and dermoscopy.[37] Clinical and suspected scabies categories rely on features of clinical history and examination. As such, the criteria can be adapted for use in a variety of settings, including field surveys, and may help to standardise reporting and the conduct of scabies research. Validation of these criteria in diverse environments is now required, followed by development of standardised training methods and materials.

Although the current focus should be on development of diagnostics for mapping and surveillance, in future, objective diagnostic tests may be needed, particularly if areas of low-endemicity transition to a target of disease elimination. A point-of care diagnostic test would be ideal for public health use. Direct skin-based testing for infestation using molecular techniques, including polymerase chain reaction[38,39] and loop mediated isothermal amplification,[40] have been proposed but none are currently ready for programmatic use. Development of ELISA-based tests to detect antibodies against scabies antigens[41] has been hindered by cross-reactivity between antigens from scabies and house dust mites.[42,43] If a specific antibody test for scabies was developed, in order for it to be diagnostic, further evaluation would need to ensure that measured antibody responses were directly associated with ongoing infestation and not a measure of previous exposure.

In addition to molecular diagnostics, non-invasive mite visualisation methods should be further evaluated. These high-magnification methods allow direct, in vivo visualisation of the mite (and with some methods, determination of mite survival or demise after treatment) without extraction of the mite by skin-scraping.[44,45] Although these devices are expensive and require specialised training, more simple and affordable videomicroscopes also permit accurate visualisation of the mite in vivo, and low cost dermatoscopes have been developed.[46,47] Further investigation and standardisation of outcome measures using these

methods would assist in assessing the efficacy of new treatments, and possibly validation of mapping and confirmation of outbreaks.[48]

Epidemiology and mapping

Despite an expansion of research on scabies in the last decade, the development of a global strategy has been constrained by a lack of prevalence data from most countries, including those suspected to be at-risk based on routinely reported clinical data or geographic or socioeconomic characteristics. For example, a worldwide systematic review of published scabies prevalence estimates found 48 studies, of variable quality, with over-representation of countries in the Pacific region and large areas of the world having no published prevalence data.[4] Experience from other NTDs suggests that the knowledge of disease burden gained through mapping is critical for stakeholder engagement, translational research and successful scale-up of control programs.[49]

Given the logistic challenge and cost of detailed mapping for NTDs,[50] a priority activity is the development of a simple, low-cost, rapid assessment tool to assist policy-makers in initially determining whether scabies is likely to be a public health problem in a given context. Standardised survey methods to map scabies prevalence would then be required for a more detailed estimate of disease burden and its variation within and between regions. Survey methods could utilise the 2018 IACS Diagnostic criteria,[36] if these criteria are found to be valid and reproducible. It may be possible to train non-expert examiners in a limited, brief skin examination, which could then be correlated with more detailed diagnostic methods.[51] A similar approach has been used for trachoma, where a rapid assessment may be followed by a standardised mapping survey.[52-55] Survey design will need to consider the most appropriate populations and settings in which to conduct mapping, including ease of access, spatial and age distributions of disease and community acceptability. For example, mapping of children attending school could be expected to provide a representation of the groups with the highest burden in a community. This may be efficient, practicable and amenable to integration with mapping for some other NTDs and other health and education programs.[56,57] Formal comparison of school versus community based sampling would help determine how well school prevalence correlates with community prevalence.[58,59]

Beyond national-level prevalence data, there is limited understanding of the epidemiology of specific high burden areas or populations within otherwise high-income or low-prevalence

settings. Recognized examples include disadvantaged Indigenous populations within Australia, New Zealand and Canada,[26,60-62] imprisoned [63,64] and homeless populations,[65] and among groups seeking asylum within Europe.[66-68] Scabies is a disease of poverty and inequity and it is likely that sub-populations with higher burdens would be found in many otherwise high-income settings.[69]

Institutional scabies outbreaks result in considerable morbidity, stigma and healthcare cost in high-income settings. These outbreaks are typically challenging to identify and manage, leading to lengthy delays in confirmation and control as well as substantial cost.[70-73] Changes in social demography, particularly aging, mean that these outbreaks may become more common, and the development of appropriate public health strategies is therefore warranted. A deeper appreciation of the features of institutional outbreaks in high-income settings could be leveraged for control of scabies elsewhere.

Transmission and complications

Despite scabies being an ancient disease, our understanding of the drivers of transmission remains limited. Understanding transmission dynamics is important for investigating the comparative effects of different control strategies, including through mathematical modelling.[74,75] The observed cycles of scabies prevalence in some temperate settings (leading to the misnomer "the seven-year itch") previously raised the possibility of herd immunity. However, in many tropical settings, recurrent infestations are common and present with more rapid onset of symptoms than in the initial infection.[43] Very high population prevalence is sustained in some of these settings, suggesting that variations across geographic regions and time are more likely explained by factors other than personal or herd immunity.[76,77]

Of particular importance to transmission is the role of individuals with the rare clinical variant of crusted scabies (previously known as Norwegian scabies), usually in association with immunosuppression (disease or drug-related) or neurological illness. People with crusted scabies may carry thousands to millions of mites and are highly infectious, thereby acting as core transmitters within some communities.[78] Failure to identify and manage these individuals may undermine the success of control programs.[79] There is an incomplete understanding of why there are many individuals in northern Australia with crusted scabies in the absence of identifiable causes of immunosuppression, but relatively few such cases have been described in other high-prevalence settings.[7,78,80,81]

The pathogenic links between scabies, impetigo, the infectious complications of *S. aureus* and *S. pyogenes* and the immune-mediated complications of *S. pyogenes* need further investigation. If these high morbidity and mortality conditions can be more definitively linked with scabies, and can be shown to be effectively prevented through scabies control, the rationale to invest in scabies control will be more compelling for governments, potential donors and other stakeholders. The relevant associations have been considered most thoroughly in the Pacific region,[61,82-84] where impetigo is very common, but the limited data from other regions suggest endemic scabies occurs in those environments with lower prevalence of impetigo.[4] This pattern needs to be properly quantified and the reasons for any variation, if genuinely present, further explored. Impetigo caused by *S. pyogenes* is a major cause of acute glomerulonephritis,[85] which in turn contributes to the high burden of chronic kidney disease in low-income settings.[86] Scabies has been associated with chronic kidney disease in both epidemiological studies and case reports.[87-89] Rheumatic heart disease is estimated to cause over 300,000 deaths per year, with a global distribution that overlaps with areas highly-endemic for scabies.[90] A global resolution on rheumatic fever and rheumatic heart disease was adopted by the World Health Assembly in 2018.[91] Primary prevention of streptococcal skin infection through scabies control could potentially be an important component of preventing these diseases.[61]

Social and economic issues

As a disease that affects the skin, scabies is a potent cause of stigma and reduced quality of life.[11,92,93] Increasingly, the chronic disfigurement caused by scabies and other NTDs is understood to adversely affect mental health,[56,94] although this aspect has not been factored into current GBD estimates of DALYs. Understanding the conception of scabies, itch and impetigo within various cultures will help define what 'scabies as a public health problem' means to the most affected communities. This research will also assist in building partnerships with communities to develop control intervention, and to maximise participation in them. Scabies is often incorrectly attributed to 'poor hygiene,' which may lead to stigma, shame and reduced health-seeking. However, hygiene and handwashing do not affect the mite or transmission,[95] and highly effective control has been demonstrated without any measures addressing hygiene or environment (see below),[96] suggesting that associations with situations of poverty and disadvantage are likely due to poor access to healthcare and treatment, or the effects of overcrowding.[21,97] The economic burden of scabies in some areas is thought to be

substantial, particularly due to the infestation leading to absence from employment and education, as well as the direct costs of accessing healthcare and repeated treatments (Figure 3).[98] Economic studies of the costs of scabies infestation and complications are needed to define and advocate for the most cost-effective control strategies.

Treatment

Although there are a number of effective, topical preparations for treatment of individual cases, for multiple reasons these agents are poorly suited to population-level control interventions. Reasons include the prolonged duration of application required and local irritation, resulting in inadequate adherence.[99] Permethrin 5% cream is the most effective topical treatment,[100] but is expensive and unavailable in most countries.[21] Topical treatments that are available in some low- and middle-income countries include benzyl benzoate and sulphur ointments, but these are less well tolerated. Both options commonly cause skin irritation and stinging after application, and sulphur ointments are messy, malodourous and require repeat treatments.[21] The effectiveness and safety profile of novel topical agents, including tea tree oil, for individual case management should be further explored.[101-108]

Oral medicines have clear advantages for treatment of asymptomatic individuals, and particularly for treatment of whole populations through mass drug administration (MDA), where oral medications are more likely to be accepted and ingestion can be directly observed. Oral ivermectin is highly effective against scabies. Due to the lack of ovicidal action, a second treatment is usually recommended after 7-14 days for individual treatment, to kill newly hatched mites. A recent Cochrane review did not find any difference in efficacy when one dose was compared with two doses of ivermectin, or between oral ivermectin and topical permethrin.[109] Although the strength of the review conclusions was limited by the quality of included studies, available evidence suggests that a single dose of ivermectin has some efficacy, and that two doses are likely to be comparably effective to permethrin for individual treatment. There is extensive experience on the feasibility and safety of using ivermectin for MDA for other NTDs such as lymphatic filariasis and onchocerciasis.[110]

An oral agent with a longer duration of activity in the skin, that could persist for sufficient time to kill newly hatched mites, would obviate the need for a second dose and represent a major advance. Slow-release formulations of ivermectin have been developed, providing potential therapeutic effect for up to 6 months.[111] These warrant further investigation for

scabies, although if the dosage form is large, administration to children may be challenging. Moxidectin, a macrocyclic lactone anti-parasitic agent related to ivermectin, has a half-life of up to 43 days, with prolonged activity in the skin.[112,113] It is effective against *Sarcoptes* infestations in animals, and in a pre-clinical trial using a porcine-model of scabies, single dose moxidectin was superior to two doses of ivermectin based on the primary outcome measure of mite score.[114] Moxidectin has recently been approved by the United States Food and Drug Administration (FDA) for treatment of onchocerciasis in individuals aged 12 years and above.[115] Clinical trials of moxidectin for scabies have now commenced, with a plan to develop palatable products for children.[116]

Research into scabies treatments also needs to consider safety, including treatment of pregnant and breastfeeding women and small children, groups that carry a disproportionate burden of scabies and are responsible for much its transmission. Administration of topical treatment to these groups during ivermectin-based MDA is a major cost and logistic issue. Due to the inadequacy of existing safety data, use of ivermectin in MDA programs for other NTDs has been restricted to those weighing over 15 kg or measuring above 90 cm (or aged 5 years or older in some settings). It is worth noting, however, that several studies have reported no significant adverse outcomes from clinical and inadvertent public health use in young children.[117,118] Further investigation of the safety of ivermectin in young children, and prospective data on the safety of moxidectin, are priorities. Ivermectin is considered a pregnancy category C drug by the FDA, but this determination is based on animal studies that used doses far in excess of those recommended for people.[119] Studies comparing inadvertent treatment in pregnant women to controls have not demonstrated any concerning safety signal.[120-123] In other NTD programs, ivermectin is offered when the risk of disease is considered higher than the theoretical risk to the foetus.[124] In France, ivermectin is a recommended second-line treatment for scabies during pregnancy.[125] Ivermectin is excreted in very low concentrations in human milk, and is generally regarded as safe in lactating women after the infant is 7 days old. Ivermectin can cause serious adverse events in individuals with high blood counts of *Loa Loa* microfilariae, a parasite found in Central Africa. Development of new diagnostic technologies such as the Loascope may enable safe delivery of ivermectin MDA in these areas,[126] but further investigation of implementation is needed.[127]

In order to capitalise on existing MDA platforms for other NTDs, the safety of co-administration of ivermectin with other medications needs to be established. In addition to the long-standing practice of co-administration with albendazole, large-scale studies have now demonstrated the safety of co-administration with azithromycin, opening the possibility of integrating control of scabies with control of yaws and/or trachoma.[128-130] Similarly, early analysis of a multi-national safety cohort study of combination therapy of ivermectin, diethylcarbamazine and albendazole (IDA) for lymphatic filariasis did not reveal safety concerns and administration of this combination of agents has now been recommended for specific epidemiological contexts within WHO guidelines.[131-134]

Monitoring for development of resistance of mites to acaricides will also be important. There have been isolated case reports of resistance to ivermectin in patients with crusted scabies who received repeated and prolonged treatment.[135-137] Annual MDA may be less likely to promote the development of resistance than repeated individual treatments, but there is a lack of evidence on this subject.[138] The proposed use of ivermectin MDA for malaria control [119,139] could also promote resistance, particularly if a strategy of multiple doses each month is used.[140] However, the risk of resistance seems to be greater for intestinal helminths than ectoparasites, based on experiences in livestock, where resistance to ivermectin among intestinal parasites is now widespread.[141,142] Increasing use of topical treatments for other conditions in humans, such as permethrin for head lice and topical ivermectin for rosacea, may also promote resistance in scabies mites.[143]

Detailed treatment guidelines for scabies have been developed in several high-income countries and regions, but recommendations vary.[144-146] Standardised, evidence-based treatment guidelines for resource-limited settings, including individual case management and management of outbreaks in institutions or closed communities, would be valuable. Further investigation and development of guidelines for the appropriate treatment for individuals with crusted scabies in these settings, would also facilitate the success of control interventions.[81,147-149]

Population-level control

The strategy of individual case management has failed to appreciably reduce the transmission of scabies in high-prevalence settings.[6,150] Recent data from studies using MDA have led to renewed interest in the potential of MDA to contribute to sustained population-level

control.[151,152] Programs of mass treatment combined with additional screening and case management in Panama and Australia (using permethrin) [6,9,153] and the Solomon Islands (using ivermectin)[154] considerably reduced scabies prevalence. Indirect evidence from Zanzibar suggested a reduction in consultations and prescriptions for scabies following annual MDA of ivermectin and albendazole for lymphatic filariasis[155,156] but a study from a lower prevalence setting in mainland Tanzania did not show a sustained effect.[157] However, in lymphatic filariasis control programs, children under 5 years are not given ivermectin (or any other agent active against scabies), which may explain ongoing transmission in this context. The only controlled trial of community treatment published to date was conducted in small, relatively isolated island populations in Fiji, where a single round of ivermectin-based MDA reduced the prevalence of scabies by 94%, in comparison to the permethrin-based MDA (62% reduction) and screen-and-refer arms (49% reduction).[158] These effects have now been shown to be sustained up to 24 months post intervention.[159] The ivermectin-based MDA intervention also resulted in a reduction of impetigo of 67% without adjunctive mass antibiotic treatment. Further work in the Solomon Islands using ivermectin-based MDA in a much larger population reported reductions in scabies prevalence of around 90%, and in impetigo prevalence of around 75%. [14,130] Conversely, ivermectin-based MDA for scabies in northern Australia was not associated with a sustained reduction in prevalence.[79] The different results observed in the Australian study may have been due to increased interactions with surrounding untreated communities; lower baseline prevalence (4%, as compared to 32-42% in the Fiji study); and transmission from untreated individuals with crusted scabies.

These studies set the scene for further investigation of the role of programmatic MDA in scabies control. Priority future studies include investigation of whether a single dose of ivermectin (as opposed to two doses, 7 to 14 days apart) is sufficiently effective as MDA for scabies, and investigation of ivermectin-based MDA in other settings, including non-island populations where population mobility may be greater. While existing MDA data suggest effectiveness at high or very high population prevalence of 10 to 40%, the relative roles of MDA and case management at lower prevalence, for example, less than 10%, have not yet been adequately explored. Investigating the effect of MDA for scabies on complications such as skin and soft tissue infection, sepsis and autoimmune sequelae will be important, but require a large sample size and significant investment in infrastructure for active surveillance. Studies of moxidectin-based MDA should also be prioritised, if initial individually randomised clinical trials demonstrate efficacy.

Implementation research of integration of scabies control with other NTDs, particularly those affecting the skin, has the potential to demonstrate cost-efficient delivery of multiple health interventions.[56,160] Initial studies could focus on understanding the impact of ivermectin-based MDA for onchocerciasis and lymphatic filariasis on the prevalence of scabies in areas that are scaling up treatment, as well as the effect of cessation of MDA in areas that are scaling down treatment. There is concern that as ivermectin use for these programs is rolled back in some countries, there could be a resurgence of scabies infestation, which may be a major unintended consequence for communities. An additional research priority will be to investigate the feasibility and impact of adding topical scabies treatment of young children to existing ivermectin-based NTD programs. The possibility of developing a scabies vaccine has been considered, although this approach is still at an early stage of development.[43,161,162]

Developing a global strategy

Despite some deficiencies in the evidence for scabies control strategies, there is a need to develop preliminary recommendations that can be implemented by countries wishing to commence control measures, alongside pursuit of the research agenda described above. Initial guidance is required on the threshold of scabies prevalence above which MDA could be recommended, and other health system-related, geographic, socio-political or pragmatic factors that might affect this decision. In lower-prevalence settings, intensified case management strategies may be more appropriate. If MDA is to be utilised at large scale, then guidance will be required on the control target, number and frequency of MDA rounds, and monitoring and surveillance plan, including post-MDA surveillance, drawing on the lessons from other NTDs.[163] This initial guidance should draw on the existing evidence-base, and—acknowledging the limitations of current data—expert opinion and modelling work, with plans made for guidance to be refined as further evidence becomes available. If sustained control can be demonstrated, then it may be appropriate to consider the possibility of elimination (interruption of transmission) at a national or regional level.

Once a mapping strategy is developed as part of a global control strategy, it will be possible to estimate the at-risk population requiring ivermectin and permethrin within individual countries and, with less certainty, at regional and global levels. Individual countries would be able to develop control plans as part of broader NTD strategies, taking into consideration the relative burden of scabies and other health issues.

It will be essential to advocate for access to affordable, quality-assured medications. Ivermectin has been generously donated through the Mectizan Donation Program for onchocerciasis and lymphatic filariasis in Africa and Latin America. This donation has recently expanded for use in countries where onchocerciasis is not endemic, as part of the IDA treatment strategy for lymphatic filariasis elimination.[164] However, it is unclear if such a program could be extended to include scabies control as an indication. Although a donation program would maximise the likelihood of achieving control, low-cost, high-quality generic ivermectin may also be affordable in some settings. In addition to advocacy for donations, manufacturers of generic ivermectin could be supported to apply for WHO pre-qualification.[3] There is no precedent for a donation program for permethrin, and considerable amounts of it would be required for treatment of individuals for whom ivermectin is contraindicated. The licence holders of moxidectin, Medicines Development for Global Health, have committed to providing moxidectin at an affordable price for scabies control in low- and middle-income countries, if efficacy is demonstrated.[116]

Conclusions

Scabies is a common illness and major health issue affecting communities in many resource-limited settings, and warrants public health intervention. There is strong evidence that ivermectin-based MDA strategies can be highly effective in reducing the burden of scabies and impetigo in at least some settings. Future research priorities include further defining the burden of disease, developing standardised approaches to diagnosis and population burden estimation, novel diagnostics and treatments, and evaluating large-scale community control strategies. Interim guidance on scabies control is now required.

Contributors

D. Engelman and ACS conceived of the project. D. Engelman searched and reviewed the literature, wrote the first draft of the manuscript, made revisions and prepared Figure 3. D. Engelman, LR, MJW, JMK and ACS reviewed prevalence data for Figure 2. D. Engelman, PTC, MM, AWS, JMK and ACS contributed to further development of the structure and content. All authors reviewed drafts of the manuscript, provided comments and critical review, helped to revise the manuscript and agreed to the final version.

Declaration of Interests

Prof. Chosidow reports personal fees from Codexial and Zambon. All other authors declare they have no competing interests.

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Search strategy and selection criteria

References for this review were identified through searches of PubMed for articles published from January, 1990, to March, 2019, using the terms "scabies" and "*Sarcoptes scabiei.*" Reference lists of identified manuscripts were reviewed to identify additional relevant material. No language restrictions were imposed.

List of Acronyms

DALY, disability-adjusted life year

ELISA, enzyme-linked immunosorbent assay

GBD, Global Burden of Disease

IACS, International Alliance for the Control of Scabies

IDA, ivermectin, diethylcarbamazine and albendazole

LMIC, low- and middle-income countries

NTD, neglected tropical disease

MDA, mass drug administration

US FDA, United States Food and Drug Administration

WHO, World Health Organization

Panel 1. Key Research Questions

Diagnosis

- What is the accuracy and reproducibility of diagnosis using the 2018 IACS Criteria?
- Can a limited skin examination protocol by non-expert health workers provide acceptable accuracy for estimating prevalence?
- Can accurate skin-sample or blood tests be developed for scabies diagnosis?

Epidemiology and mapping

- What is the global burden of scabies? Which countries have the highest burdens of scabies?
- What is the at-risk population living in highly-endemic settings?
- Are there identifiable risk factors for areas of high prevalence?
- What is the correlation between prevalence in school-attending children and the community?

Transmission and complications

- What are the transmission dynamics of scabies?
- To what extent does crusted scabies drive transmission in highly endemic settings?
- What is the association between scabies and impetigo outside the Pacific region?

Social and economic

- What is the social burden of scabies as perceived and understood by affected communities?
- What is the acceptability of MDA for scabies to affected communities?
- What approaches can effectively engage communities to support scabies control initiatives?

Treatments

- Can ivermectin or other oral agents be safely administered to children of height < 90 cm, weight <15 kg or age <5 years?
- Are novel topical agents as effective, better tolerated or more affordable than permethrin?
- What is the effectiveness of moxidectin for individual treatment and MDA for scabies?

Mass drug administration for scabies

- What is the optimal dose and dosing strategy of ivermectin for MDA?
- What is the optimal interval between rounds of MDA?
- What is the impact of MDA for scabies on the burden of impetigo, severe bacterial soft-tissue and systemic infections, glomerulonephritis and rheumatic heart disease?
- Under what conditions would MDA for scabies be cost-effective?
- How can ivermectin-based MDA for scabies be safely and effectively integrated and/or co-administered with MDA for other NTDs?

Control strategy

- In what circumstances (threshold scabies prevalence or other factors) should MDA and intensified case management strategies be used?
- If MDA is not being used, how can intensified case management be implemented?

- What are the effects of ivermectin-based MDA programs for other NTDs on scabies? What happens to scabies prevalence when these programs cease?
- What is the feasibility and effect of adding permethrin treatment of young children to existing ivermectin-based MDA programs for other NTDs?
- What, if any, environmental measures should be recommended?

Panel 2. Key Programmatic Issues

Epidemiology

- Development of a protocol and training package for scabies mapping
- Mapping scabies prevalence using standardised methods, focusing on LMIC
- Integrated surveys with other NTD and health programs
- Surveillance strategies for potential outbreaks in high-risk settings
- Understanding high-burden groups within high-income settings

Population-level Control

- Interim guidance for public health control of scabies, including thresholds for starting and stopping MDA, number and frequency of rounds, drugs and doses.
- Interim guidance on control of scabies outbreaks in institutions and communities
- Monitoring and evaluation strategy for impact of interventions on scabies
- Monitoring and evaluation strategy for impact of interventions on scabies complications and other conditions.
- Monitoring for resistance

Strategy

- Define a global control strategy with targets
- Affordable and reliable access to oral and topical medications for treatment
- Ivermectin listing on WHO Essential Medicines List for scabies indication
- Integration with programs for other NTDs and other health programs
- Develop proposal for a future World Health Assembly resolution

FIGURE LEGEND

Figure 1: Child's feet with skin manifestations of scabies infestation and secondary pyoderma

Photo courtesy Millicent Osti

Figure 2: Prevalence of scabies in children and adolescents younger than 19 years

Prevalence is shown at the country level, using available data from Romani *et al.*, 2015[4] and updated with additional references.[8,10-17] Subnational variation exists but is not represented in the map.

Figure 3: Primary and secondary effects of scabies infestation