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A Review of Scabies: An Infestation More than Skin Deep

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Abstract
Human scabies, a common infestation, has a worldwide distribution with a variable impact and presentation depending on the clinical situation. In developed, high-income settings, health institution and residential home outbreaks challenge health and social care services. In resource-poor settings, it is the downstream sequelae of staphylococcal and streptococcal bacteraemia, induced by scratching, which have a significant impact on the long-term health of communities. Over the past decade scabies has been recognised as a "neglected tropical disease" (NTD) by the World Health Organisation, has an accepted practical system of global diagnostic criteria and is being adopted into integrated programmes of mass drug administration for NTDs in field settings. This review seeks to summarise the recent advances in the understanding of scabies and highlight the advocacy and research headlines with their implication for diagnosis and management of outbreaks and individuals. In addition, it will indicate the priorities and questions that remain.

Introduction

Scabies is a parasitic infestation of the skin caused by the mite *Sarcoptes scabiei*. In developed countries, scabies outbreaks are common in residential and nursing care homes where they cause significant morbidity and distress [1–4]. Diagnosis is challenging and often delayed, and management of outbreaks is costly. Globally, more than 200 million people are affected, with a particularly high prevalence in resource-poor tropical regions [3]. This review describes recent advances in the understanding, diagnosis and treatment of scabies focusing on the global implications of the infestation across both resource-poor and -rich settings.

The Scabies Mite

The life cycle of the scabies mite (*S. scabiei* var. *hominis*) begins with the pregnant female burrowing into the human epidermis and laying 2–3 eggs per day. Larvae emerge after 48–72 h and form new burrows. The larvae reach adulthood in 10–14 days, mate, and the cycle is repeated. Transmission is by direct skin-to-skin contact. Human scabies mites are capable of surviving in the en-

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vironment, outside of the human body, for 24–36 h in normal room conditions (21 °C and 40–80% relative humidity); during this time, they remain capable of infestation [5]. Indirect transmission (via clothing, bedding and other fomites) has been proposed; however, this has been difficult to prove experimentally [6]. Early experiments conducted by Mellanby [7] showed that indirect transmission is unlikely to play a significant role, except perhaps in cases of crusted scabies where the host is heavily infected. In these experiments, volunteers slept in bedding that had been used less than 24 h before by persons with scabies [7]. When the patients had parasite rates of 20–50, only 1.3% of volunteers (4 out of 300) became infested. When the patients had parasite rates of 200 or more, 30% of volunteers (3 out of 10) became infested.

Clinical Presentation

Infestation with the scabies mite results in an intensely itchy skin eruption consisting of papules, nodules and vesicles. Mostly this is the result of host hypersensitivity although the direct effect of mite invasion contributes. For this reason, the incubation period before symptoms occur is 3–6 weeks in cases of primary infestation, but as little as 1–2 days in cases of reinfestation [7, 8]. Sensitisation to mite antigens has been demonstrated up to 1 month after primary infestation [9], and indeed it can take up to 6 weeks for signs and symptoms of hypersensitivity to resolve. Symptoms that persist beyond this should be reinvestigated. Burrows are formed as the adult female mites consume [10, 11] their way through the epidermis; detection of even one burrow is pathognomonic; however, they are often unidentifiable due to scratching, crusting or secondary infection, and may be observed only in a minority of cases [4].

The typical distribution of signs of infestation includes areas between the fingers, the wrists, axillae, groins, buttocks, genitals, and the breasts in women. In infants and young children, the palms, soles and head (face, neck and scalp) are more commonly involved [12]. Mites seem to avoid areas with a high density of pilosebaceous follicles [13]. Although effective treatments exist, people living in regions where the pathogen is endemic are susceptible to reinfestation. This can occur rapidly even when household contacts are treated [14]. With chronic infestation, severe eczematous skin changes occur and so-called "scabies nodules" may be observed particularly on the male genitalia and breasts. The predominant symptom of scabies infection is severe, persistent pruritus which can be highly debilitating and stigmatising. Patients typically describe pruritus as being most intense at night, and this is associated with sleep disturbance and a reduced ability to concentrate.

In a small number of cases, hyperinfestation can occur leading to crusted scabies, where the host may be colonised with many millions of mites. This is in contrast to classical scabies in which the host will harbour on average 10–15 mites. Crusted scabies occurs often, although not exclusively, in the setting of immunosuppression, for example in those with advanced HIV infection or malignancy, and in the elderly. Pathogen factors, such as virulence of the scabies mite, are not thought to play a role. Clinically crusted scabies presents as a hyperkeratotic dermatosis, typically involving the palms and soles, often with deep skin fissures. Generalised lymphadenopathy, peripheral blood eosinophilia [15, 16] and raised serum IgE levels [17] are frequently observed, and secondary bacterial infection is common and associated with a significant mortality [18].

Davis et al. [19] developed a clinical grading scale for crusted scabies, which is useful for assessing disease severity and guiding treatment. The score is based on the clinical assessment of four domains: distribution and extent of disease (body surface area), severity/depth of skin crusting, the number of previous episodes (hospitalisations) for crusted scabies, and the degree of skin cracking and pyoderma. Each domain is scored between 1 (mild) and 3 (severe) and combined to produce an overall score: grade 1 (score 4–6), grade 2 (7–9), grade 3 (10–12).

Diagnosis

The diagnosis of scabies is made largely on clinical grounds. The description of an intensely itchy rash, often worse at night, is supportive and a history of contact with known cases is often present. Examination may reveal skin lesions in a typical distribution (see above), and characteristic serpiginous burrows may be visible with the naked eye.

Closer examination with a handheld dermatoscope allows better visualisation of the curvilinear scaly burrow, and the mite itself may be seen at the end of the burrow as a dark triangular structure, corresponding to the pigmented head and anterior legs of the scabies mite. This picture is often referred to as a "jet with contrail." Additionally, eggs may be seen as small ovoid structures within the burrow. Less commonly observed is the "mini triangle sign" which refers to scabies eggs that show the head

of the maturing mite within the egg [20]. Emerging larvae escape through the roof of the burrow, moving closer to the skin surface, where they burrow out small pockets and moult to the next developmental stage [13]. Other non-invasive imaging techniques have been used, including videodermatoscopy [21, 22] and reflectance confocal microscopy [23], which provide a more detailed inspection of the mite. Parasitological confirmation can be obtained with gentle skin scraping to remove the mite which can then be placed on a glass slide and seen under low-power microscopy. However, the sensitivity and reliability of this method in practice is limited, requiring expertise. Additionally, skin scraping may be poorly tolerated, particularly by young patients.

A recent Delphi study involving international experts established consensus criteria for the diagnosis of scabies with a very high level of agreement (>89%) [24]. This study introduces three categories of diagnosis – "confirmed scabies," "clinical scabies" or "suspected scabies" – each with its own set of criteria corresponding to the level of diagnostic certainty. The diagnosis of "confirmed scabies" requires direct visualisation of the mite or mite products (eggs, faeces) by at least one method, e.g. microscopy, dermoscopy or videodermoscopy. The diagnosis of "clinical scabies" and "suspected scabies" relies on the detection of typical skin lesions in a characteristic distribution, supported by key features in the history. These criteria are summarised in Table 1. The use of these criteria will support health workers in making a diagnosis of scabies in field settings. They will also be vitally important for scabies research to provide a standardised diagnostic language that will facilitate consistency and comparison between studies.

Table 1. Summary of 2018 IACS criteria for the diagnosis of scabies [13]

A	Confirmed scabies	At least one of:
	A1	Mites, eggs or faeces on light microscopy of skin samples
	A2	Mites, eggs or faeces visualised on individual using high-powered imaging device
	A3	Mite visualised on individual using dermoscopy
B	Clinical scabies	At least one of:
	B1	Scabies burrows
	B2	Typical lesions affecting male genitalia
	B3	Typical lesions in a typical distribution and two history features
C	Suspected scabies	One of:
	C1	Typical lesions in a typical distribution and one history feature
	C2	Atypical lesions or atypical distribution and two history features
		History features:
	H1	Itch
	H2	Close contact with an individual who has itch or typical lesions in a typical distribution

These criteria should be used in conjunction with the full explanatory notes and definitions (in preparation). Diagnosis can be made at one of the three levels (A, B or C). A diagnosis of clinical and suspected scabies should only be made if other differential diagnoses are considered less likely than scabies. Reproduced from Engelman et al. [13].

There are no standardised laboratory tests available for the diagnosis of scabies. A number of candidate antigen and antibody immunoassays have been evaluated but the performance of these tests has been suboptimal, and none have been widely adopted. A sensitive and specific rapid diagnostic test for scabies would be of great value in the field; modern molecular techniques may offer solutions, and this area should be prioritised in the scabies research agenda. Conventional PCR targeting the mitochondrial cytochrome c oxidase subunit 1 (cox1) gene of *S. scabiei* has previously been used to diagnose scabies infestation; however, the positive diagnosis rate was too low to produce satisfactory results [25]. In a recent study by Hahm et al. [26], the use of a nested PCR assay based on the cox1 gene offered improved sensitivity for diagnosing scabies infestation. In this study all microscopically proven cases tested positive using the nested PCR assay; in addition, 26% of the microscopy-negative cases tested positive, which is improvement over the 14% detection rate reported by Wong et al. [25] using conventional PCR. Employing novel molecular techniques such as this for the diagnosis of scabies could offer great benefit in a variety of clinical research settings.

Complications of Scabies

Scabies has a number of important sequelae. The resultant scratching of the skin is an important cause of impetigo. Disruption of the skin barrier allows secondary bacterial infection, most often due to *Streptococcus pyogenes* (group A streptococcus, GAS) and *Staphylococcus aureus*. These bacteria have been isolated from skin burrows and mite products (faecal pellets) suggesting that mites could contribute directly to the spread of bacteria. Additionally, it has been shown that complement inhibi-

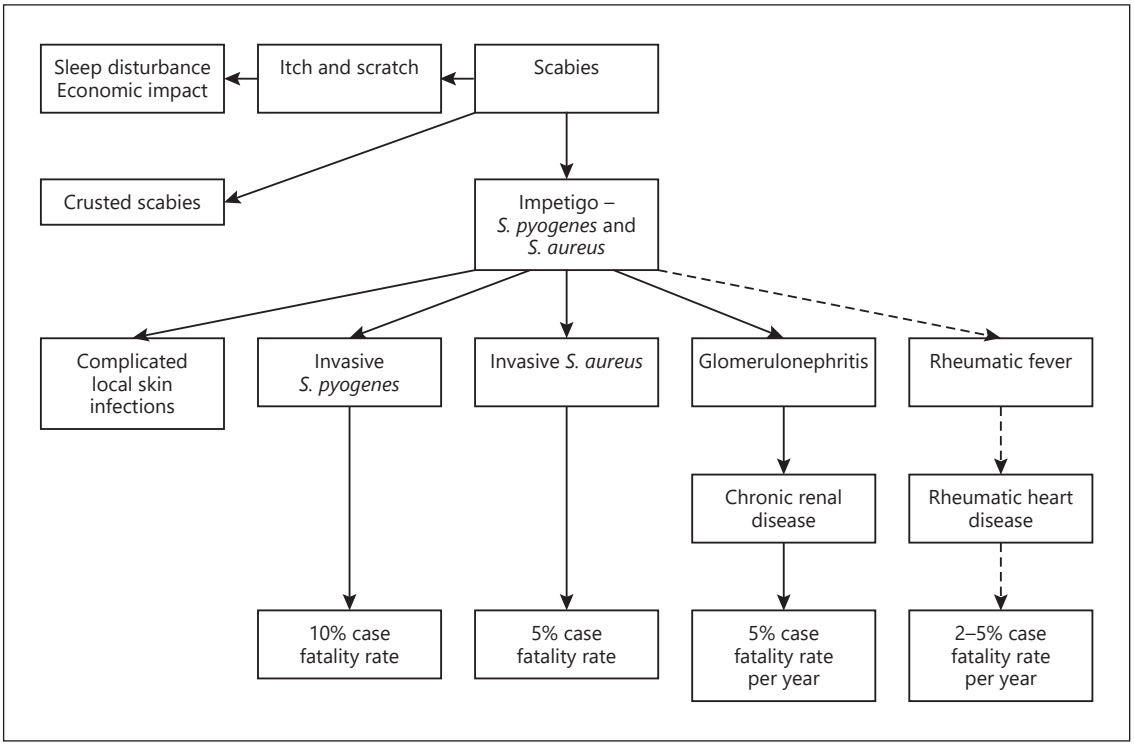

Fig. 1. Complications of scabies infestation. Reproduced from Engelman et al. [92].

tors produced by the scabies mite promote the growth and survival of *S. pyogenes* in vitro, with the suggestion that this may also apply to mite-infested skin in vivo [27]. The presence of scabies is associated with an increased risk of impetigo. Data from the SHIFT trial, conducted in Fiji, show that the attributable risk of scabies infestation on impetigo was 94% [28].

Impetigo due to *S. pyogenes* acts as a precursor to a diverse range of clinical manifestations. These include invasive GAS infections, toxin-mediated diseases including scarlet fever and streptococcal toxic shock syndrome, and the autoimmune complications of rheumatic fever and glomerulonephritis.

Invasive GAS infections are serious and potentially fatal, and include infection of skin, soft tissue (including necrotising fasciitis), joints and lower respiratory tract in addition to bacteraemia without an obvious focus of infection. The burden of invasive GAS diseases globally is high, with more than 663,000 new cases and 163,000 deaths each year, in addition to more than 111 million prevalent cases of GAS pyoderma [29]. There is likely also to be a significant morbidity and mortality associated with staphylococcal infection (Fig. 1).

Acute post-streptococcal glomerulonephritis can occur after throat or skin infection. In tropical regions, skin infection accounts for at least 50% of acute post-streptococcal glomerulonephritis [30], which acts as a strong risk factor for developing chronic kidney disease in later life [31]. In contrast, it has been accepted for many years that acute rheumatic fever occurs only following GAS pharyngitis; however, this is unlikely to be the case in tropical settings [32]. The greatest prevalence of rheumatic heart disease is found among the indigenous populations of Australia and the Pacific Island nations, where there is a high burden of GAS impetigo [33]. In these populations GAS pharyngitis is rare, and cases of GAS impetigo outnumber throat carriage or infection ninefold [34]. It is also known that there is greater diversity of GAS in tropical regions with a predominance of skin-associated strains [34, 35]. There is evidence to support the exchange of GAS between the skin and pharynx, and this could explain the involvement of skin strains in rheumatic fever and rheumatic heart disease; however, this area is poorly understood and requires further investigation.

The Impact of Scabies

Scabies accounts for a significant global health burden, with implications for both resource-poor and developed regions.

Using data from the Global Burden of Disease Study 2015, Karimkhani et al. [3] provided for the first time a robust estimate of the global burden of scabies. They used prevalence estimates, weighted for disability, to calculate disability-adjusted life-years (DALYs), assuming a zero mortality for scabies. The greatest burden from scabies was demonstrated in east and south-east Asia, Oceania and tropical Latin America. In these and other resource-poor tropical regions, the DALY burden is highest in younger age groups and particularly in children aged 1–4 years. In contrast, regions with low overall scabies burden such as North America and western Europe show a more even distribution of scabies prevalence across all age groups. Of the 246 conditions included in the Global Burden of Disease 2015 Study, scabies ranked 101 in age-standardised global DALYs, just ahead of atrial fibrillation or flutter (102) and acute lymphoid leukaemia (103). It is important to note that this study focused specifically on the direct effect of the skin infestation; it did not include in its estimates the significant contribution to overall disease burden of bacterial superinfection and subsequent complications. In resource-poor regions, scabies-related impetigo is the principal cause of post-streptococcal glomerulonephritis, of which there are almost half a million new cases per year [29], as well as rheumatic fever and rheumatic heart disease, which account for at least 300,000 deaths worldwide every year [36]. The mortality indirectly attributable to scabies has not been calculated yet but a theoretical algorithm has been developed (Fig. 1).

It is known that regional differences in scabies burden exist within countries. Australian aboriginal communities for example have a much higher prevalence of scabies and impetigo than the non-indigenous population [37]. Factors that might contribute to high levels of endemic scabies within these communities, and similar settings in other countries, include poverty (families with lower monthly income and those not owing their house) [38], overcrowding [39] and lack of access to medical facilities [40]. Crusted scabies is generally attributed to immunosuppression; however, it has been reported in indigenous Australians with no known immune deficiency. It might be the case that these individuals harbour a specific immune deficit, although the nature of this is currently unclear.

In developed countries in the western hemisphere, outbreaks of scabies are a particular problem in institutions, including care homes, schools, military camps and prisons. Within Europe, there is an increasing population of refugees seeking asylum, often those displaced from areas of Africa or the Middle East due to conflict. These are vulnerable populations, and individuals are at risk of contracting a number of important infectious diseases, in addition to scabies, which frequently coexist [41]. A recent observational study of scabies outbreaks, in residential and nursing care homes in south-east England, showed that the clinical presentation of scabies in this elderly population differs from the classic descriptions with which clinicians are familiar. Half of the patients in this study were asymptomatic, and 57% of patients had signs of scabies only on non-exposed areas of the body. The median time to diagnosis in this study was 22 days (IQR 7.5–186). Dementia was identified as a risk factor for scabies with an odds ratio of 2.37 (95% CI 1.38–4.07) highlighting the need for a high index of suspicion and thorough examination in this vulnerable group [4]. Significant economic costs are incurred by institutions in managing outbreaks of scabies, with direct costs ranging from USD 2,000 to 200,000 per outbreak [42, 43]. Costs relate predominantly to staffing (coping with absences and increased workload) and treatment (acaricide prescriptions).

Treatment

A range of effective treatments are available for scabies. However, clinical trials comparing the effectiveness of these treatments, in particular the available topical agents [44], are relatively few in number; as a result, prescribing practice varies widely between countries and is largely based on factors such as treatment availability and cost, and the preference of the physician.

Individual case management will be influenced by the level of diagnostic certainty, which may consider a broad differential diagnosis according to patient and geographic factors. The 2018 consensus criteria for the diagnosis of scabies [24] may help to guide case management by non-expert health workers, although they will be more relevant as a tool for use in research studies and mass treatment programmes, where the diagnostic hierarchy might be used to identify suitable or comparable populations. Individual cases of "suspected" scabies should be treated as such; in other words, treatment should not be restricted only to those with a diagnosis of "clinical" or "confirmed" scabies.

Treatment failure should not be diagnosed until at least 6 weeks after completion of treatment, as it can take this long for symptoms and signs of hypersensitivity to resolve. Most cases of treatment failure are likely to result from inadequate treatment or poor compliance with treatment; however, alternative diagnoses should be considered. In developed countries the differential diagnosis should include common pruritic dermatoses such as psoriasis, atopic eczema and lichen planus. If blistering is present, then bullous pemphigoid [45, 46] and dermatitis herpetiformis should be considered. Additionally, there appears to be an increased risk of developing psoriasis following scabies [47]. In infants and young children, the differential diagnosis might include Langerhans cell histiocytosis [48, 49], papular urticaria and infantile acropustulosis, and in tropical settings pyoderma without scabies is an important consideration. The differential diagnosis of crusted scabies includes hyperkeratotic disorders such as psoriasis [50, 51], seborrhoeic dermatitis, Darier's disease and palmoplantar keratoderma.

The risk of transmission or reinfestation via fomites is negligible in all but the severest forms of crusted scabies. Recommendations to treat clothes and bed linen (washing at 60 °C, freezing or keeping them in a sealed bag for at least 48–72 h) should therefore be restricted to these severe cases and not prescribed routinely. Evidence supporting this precautionary intervention is not yet available, so the advice remains somewhat controversial.

Two of the most commonly used treatments for scabies are topical permethrin (a synthetic pyrethroid insecticide) and oral ivermectin (a macrocyclic lactone antibiotic with broad-spectrum activity against nematodes and arthropods); both have comparable efficacy and are generally very well tolerated [52].

Permethrin 5% cream is the first-line topical therapy in the UK and the USA. Permethrin is adulticidal and ovicidal against the scabies mite and is therefore highly effective after a single application [53, 54]. However, in practice the prescribed regimen often involves two applications. Adverse effects occur infrequently and are limited to local cutaneous reactions including erythema, burning and pruritus [55, 56], although poor reporting is a major limitation. Many other topical treatments have been used to treat scabies. Sulphur compounds can be effective, with preparations of 5–10% sulphur in paraffin widely used throughout Africa and South America [57]; however, they are unpleasant to use and can cause skin irritation and are therefore poorly tolerated. Safety data are limited; however, both permethrin and sulphur preparations are considered safe for use in pregnant women and young children [58, 59]. Benzyl benzoate, an ester of benzoic acid and benzyl alcohol, has been used in 10–25% preparations in many countries, including in Europe and Australia. Benzyl benzoate is a very active antiscabietic agent with excellent cure rates if tolerated. It has been used effectively as an adjunct to ivermectin in the treatment of HIV-associated scabies [60] and in the control of an institutional outbreak of permethrin-resistant scabies [61]. However, its use is limited by severe skin irritation, which not uncommonly occurs within minutes of application, and the need for repeated applications. The low cost of sulphur and benzyl benzoate preparations means that they are often the first choice in developing countries. γ-Benzene hexachloride 1% (lindane) is an organic insecticide with potent antiscabietic effects. However, systemic absorption can occur, leading to neurotoxicity; this has occurred most commonly in paediatric and elderly populations [62], particularly where the drug was used in excessive quantities or applied to broken skin. Reported neurotoxic effects following topical application include nausea and vomiting, disorientation, restlessness, tremor, seizures and death [62–64]. The drug has therefore been withdrawn from sale in many countries. It is also contraindicated in pregnant and breastfeeding women. Crotamiton 10% (Eurax) has been favoured in children due to its low toxicity profile; however, it has limited efficacy, and multiple applications are usually required to achieve a satisfactory response.

Ivermectin is effective as an oral treatment for scabies. It is prescribed at a standard single dose of 200 μg/kg body weight. It lacks ovicidal activity, and a second dose is in theory required 14 days after the first dose to ensure that newly hatched mites are killed. Standard treatment, with 2 doses 2 weeks apart, results in a cure rate approaching 100%, comparable to that of topical 5% permethrin [52, 65]. Oral ivermectin has been available commercially for years; it was first approved for the treatment of scabies in France in 2001, where it is licensed for the treatment of outbreaks in residential homes [66]. In recent years it has gained approval in Australia, New Zealand, Japan, Germany and the Netherlands [52, 67]. Ivermectin is not licensed for treating scabies or any other condition in the UK; it can be prescribed off-label but is expensive and available only on a named-patient basis for the treatment of crusted scabies, from "special order" manufacturers or specialist importing companies. In countries such as India, oral ivermectin is easy to access and cheaper than permethrin, making it an attractive option [56]. Studies of mass drug administration (MDA) with ivermectin have demonstrated a very good safety profile [28]. Whilst

there is a lack of safety data concerning the use of ivermectin in pregnant women and children under 5 years of age, the drug has been used in these groups without reports of adverse outcomes emerging. Early studies of ivermectin for onchocerciasis suggested that it could be used safely in pregnancy; Pacqué et al. [68] observed no difference in birth defects or developmental status in 203 children born to women inadvertently treated with ivermectin during the first trimester of pregnancy, compared with the children of untreated mothers. More recent studies have explored the adverse outcomes associated with co-administration of ivermectin and albendazole, for the treatment of soil-transmitted helminths, failing to show any difference in the risk of congenital malformation or miscarriage due to treatment [69, 70].

In developing countries, ivermectin has been used for the control of scabies and many other neglected tropical diseases (NTDs) at the community level. The SHIFT trial, conducted in Fiji, showed that MDA with oral ivermectin (single dose, 200 μg/kg body weight) led to a significantly greater reduction in prevalence of both scabies and impetigo, compared with permethrin and standard approach to care [28]. In addition, it has been shown in the Solomon Islands that intensive scabies control using this strategy has long-lasting effects, with very low levels of scabies and associated bacterial skin infections maintained 15 years after cessation of control activities [71]. A higher dose of ivermectin (400 μg/kg) may offer improved efficacy over the standard dose (200 μg/kg), particularly for the treatment of crusted scabies, although this has not been confirmed.

Ivermectin is useful for combating a range of diseases and therefore offers many potential health benefits for the communities in which it is administered. It is particularly effective against human filarial diseases including onchocerciasis and lymphatic filariasis, for which hundreds of millions of treatments are donated free of charge each year as part of the Mectizan Donation Programme. Annual MDA of ivermectin as part of the lymphatic filariasis elimination programme in Unguja and Pemba Islands in Zanzibar was shown to significantly reduce the prevalence of scabies over a 6-year period [72]. This programme utilised social and religious networks to engage members of the community and achieve high coverage. In addition, it is thought that the successful treatment of scabies, which is highly symptomatic and often debilitating, increases clinic re-attendance, community engagement with the MDA and compliance with further treatment.

The management of crusted scabies is particularly challenging. Effective control requires prompt diagnosis, treatment and close monitoring; however, making the diagnosis is not always easy and may be missed. A pragmatic treatment approach has been developed by an Australian team which involves isolation of the patient and treatment with multiple doses of oral ivermectin (200 μg/kg/dose), according to disease severity [19, 73]. Grade 1 cases should receive 3 doses of ivermectin over a period of 1 week and can be treated in the community in consultation with an infectious diseases physician. It is recommended that grade 2 and 3 cases are admitted to hospital and treated with a combination of oral and topical treatments. Grade 2 cases should receive 5 doses of ivermectin over 2 weeks, and grade 3 cases should receive 7 doses over 4 weeks. Topical treatments, such as urea-based emollients, are given for scabies and hyperkeratosis. Treatment may also be required for secondary bacterial and fungal skin infection. Treatment of all household and close contacts, and treatment of the homes of patients with crusted scabies, are considered important aspects of effective management. Education of patients and all staff within an institution is key to maximising the effectiveness of treatment and control measures, in order to prevent further spread. Robust evidence supporting the above intervention is not yet available.

The most effective community control strategies have incorporated ongoing post-treatment surveillance [74, 75]. This is particularly important for patients with crusted scabies, who are "core infectors" of other community members [76]. The "Healthy Skin Program" in Northern Territory, Australia, suggests that a "chronic care plan" should be instituted to provide regular skin checks and ongoing preventive topical treatments, as part of the management of crusted scabies in remote aboriginal communities [73]. Regular follow-up of these patients and household contacts offer additional opportunities for community education and engagement, which are thought to be key factors contributing to the success of such programmes [74]. This process could be implemented by non-expert health workers from a range of backgrounds providing they are appropriately trained and supervised. It is unclear to what extent these ongoing surveillance activities are required; fortnightly or monthly skin checks (depending on the level of infectivity and risk of recurrence) have been suggested [77], although uncertainty exists regarding the optimal frequency and duration of monitoring. Operational research is required to answer these questions and deliver cost-effective solutions. There are numerous opportunities for integration of surveillance activities for scabies with other NTDs.

Scabies outbreaks are difficult to control and constitute a significant public health problem in developed countries. Heavily infested patients with crusted scabies are highly infectious and often the source of outbreaks in institutions and vulnerable communities; these patients should be isolated and measures taken to prevent transmission, including the use of protective clothing by anyone coming into close contact with them. In nursing and residential care homes management of outbreaks is complicated by the high prevalence of dementia (68% of the study population) [4] and the atypical clinical presentation of scabies. Treatment using topical agents in this population is logistically difficult and distressing for patients. Oral ivermectin is at least as effective as topical permethrin, and easier to administer in this population. Mass treatment with ivermectin was also shown to be effective in controlling outbreaks of scabies in refugees and asylum seekers in the Netherlands [78].

Emerging resistance to currently available agents, permethrin and ivermectin, has stimulated interest in understanding the underlying mechanisms and exploring the possibilities for novel therapeutic agents or even a scabies vaccine. Moxidectin is a newer agent that offers promise; it has better retention in the skin and a much longer half-life (more than 20 days, compared with 14 h for ivermectin) meaning that a single dose may be enough to eliminate infestation [79, 80]. It also appears to prevent reinfestation for a longer period of time after treatment, compared with ivermectin. A scabies vaccine could be effective, although currently more work is needed to better understand the interaction between the host immune system and the scabies mite, and it is likely to take many years for a vaccine to become available. Additional approaches to treatment of scabies include the use of insect growth regulators, such as Fluazuron, and natural products, including essential oils and novel plant products [81]. Fluazuron blocks the synthesis of chitin, a major component of the exoskeleton of arthropods including the scabies mite. It prevents the growth of new larvae within the eggs but has no activity against adult mites. The use of fluazuron in pigs with *S. scabiei* var. *suis* infestation resulted in a reduced number of early stage mites, and clinical improvement [82]. Using this in combination with traditional acaricides could offer improved efficacy and might for example eliminate the need for a second dose of ivermectin. Fluralaner is an isoxazoline ectoparasiticide that inhibits the arthropod nervous system. Administration of a single dose of fluralaner is an effective treatment for naturally acquired *S. scabiei* var. *canis* infestation in dogs [83], and recent data show that a single dose of oral fluralaner is as effective as a single dose of oral ivermectin for the treatment of human scabies, with cure rates of 86 and 83% 4 weeks after treatment, respectively [Goldust, unpubl.; 84]. Afoxolaner, a related molecule also belonging to the antiparasitic isoxazolines, has shown promise in a porcine model of human scabies infestation [85]. Tea tree oil is used by indigenous tribes in Australia, and in secondary care settings as a therapeutic adjunct; it has known antimicrobial properties and reduces the survival time of the scabies mite compared with permethrin and ivermectin [86]. Other botanical products used with varying results include clove, *Lippia* and neem oils, and turmeric [87, 88].

Strategy for Scabies Control

The control of scabies requires a coordinated effort with input from a range of sectors. The recent addition of scabies to the World Health Organisation list of NTDs is a positive action and one that should allow scabies to feature on the global health agenda and gain recognition in relevant health policy in both low- and high-income settings. Funding will be required to support an increase in scabies research; priority areas include the development of robust diagnostic tests for scabies, and improved treatment and control strategies, particularly in view of the emerging threat of drug resistance. In the USA, funding for scabies research was shown to be under-represented in relation to the associated disease burden, and this gap needs to be addressed [89]. In the UK research and policy efforts should address the management of scabies outbreaks in institutions, with particular focus on the use of oral treatments, such as ivermectin or moxidectin, and increasing the availability of these drugs.

Integration of activities that control NTDs affecting the skin, many of which coexist, could be a cost-effective and beneficial approach [90]. Opportunities for integration range from diagnosis and surveillance to mass drug administration and morbidity management. These activities have already been successfully combined with existing programmes for trachoma and yaws in the Solomon Islands for the purpose of coordinating mass treatment studies [91]. Initiatives to support the provision of oral ivermectin for scabies are needed in low-resource settings, in the way that the Mectizan Donation Program provides for onchocerciasis and lymphatic filariasis. The International Alliance for the Control of Scabies (IACS) consists of a group of experts from various disciplines who are committed to overcoming these challenges and improving the health of affected communities worldwide [92].

Definitive strategies for the control of scabies, including management in endemic settings and outbreak response plans, are under development. Targets for the control or elimination of scabies have not been agreed. At this stage it is worth noting the experience of our colleagues in efforts to control other NTDs. Lockwood et al. [93] draw attention to some of the hazards of setting targets for elimination, from their experience with leprosy. They highlight the need to have clear and realistic control targets that are based on an understanding of disease biology and the effectiveness of available treatment options. Targets and progress should be monitored transparently and adjusted if needed.

Conclusion

Human scabies, a condition amendable to treatment, continues to be widespread and to cause intense suffering. Developments of accurate diagnostic tests, increasing the convenience and acceptability of treatment, improving the understanding of epidemic outbreaks and control remain key priorities in achieving the number one priority for the IACS: to advance the establishment of global control measures for reducing the impact of scabies on human populations.

Key Message

Scabies, a neglected tropical disease, continues to have a global impact and long-term health sequelae.

Disclosure Statement

Dr. L.C. Fuller is a member of the steering committee of the IACS. The authors declare no financial conflicts of interest.

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