Endemic scabies as a neglected tropical disease: investigating prevalence and solutions for control

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Endemic Scabies as a Neglected Tropical Disease:

Investigating Prevalence and Solutions for Control

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Scabies is a neglected tropical disease (NTD) that contributes greatly to global morbidity and mortality. Caused by infestation with a microscopic mite, scabies is responsible for a wide range of infections including impetigo, abscesses and cellulitis that can lead to serious complications such as septicaemia, kidney disease and rheumatic heart disease. Despite the apparent burden of disease in many countries, the worldwide prevalence of scabies is uncertain. There have been few large-scale surveys of scabies prevalence or risk factors and control strategies have often proven to be ineffective, short-term solutions. This thesis aimed to provide new information on the occurrence and risk factors for scabies and impetigo and on control strategies aimed at eliminating scabies as a public health problem in resource-poor settings.

After an overall introduction to the topic, the thesis presents a systematic review of published studies on scabies and impetigo prevalence. The review found that scabies prevalence varied significantly between regions and communities with studies reporting data ranging from 0.2% to 70%. Most regions reported prevalence greater than 10% but overall scabies and impetigo prevalence were highest in the Pacific and particularly high in children. The next chapter reports on the world's first national population-based survey of scabies and impetigo to evaluate the magnitude of the problem and found that one in four adults and one in two children had scabies after surveying 10,000 people across Fiji.

Effective treatments are available for scabies but in populations where the disease is endemic reinfestation can occur rapidly even when contacts are treated. Mass drug administration (MDA) has proven to be successful for the control of other NTD. To strengthen the evidence-base for MDA for scabies control, a comparative trial was undertaken in Fiji and showed that MDA was safe and highly effective particularly with ivermectin as primary agent. These results demonstrated the potential role of MDA in addressing a serious cause of illness in many developing countries.

The baseline data from the trial were also analysed to identify risk factors for scabies. Scabies was strongly associated with overcrowding and age and was a major risk factor for impetigo. This burden of disease in resource-poor settings highlights the need to undertake research to investigate strategies for public health control of scabies and impetigo at population level.

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Romani L, Koroivueta J, Steer AC, et al. Scabies and impetigo prevalence and risk factors in Fiji: a national survey. **PLoS Negl Trop Dis** 2015;9:e0003452.

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Contents

Abstract

Scabies is a neglected tropical disease (NTD) that contributes greatly to global morbidity and mortality. Caused by infestation with a microscopic mite, scabies is responsible for a wide range of infections including impetigo, abscesses and cellulitis that can lead to serious complications such as septicaemia, kidney disease and rheumatic heart disease. Despite the apparent burden of disease in many countries, the worldwide prevalence of scabies is uncertain. There have been few large-scale surveys of scabies prevalence or risk factors and control strategies have often proven to be ineffective, short-term solutions. This thesis aimed to provide new information on the occurrence and risk factors for scabies and impetigo and on control strategies aimed at eliminating scabies as a public health problem in resource-poor settings.

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Effective treatments are available for scabies but in populations where the disease is endemic reinfestation can occur rapidly even when contacts are treated. Mass drug administration (MDA) has proven to be successful for the control of other NTD. To strengthen the evidence-base for MDA for scabies control, a comparative trial was undertaken in Fiji and showed that MDA was safe and highly effective particularly with

ivermectin as primary agent. These results demonstrated the potential role of MDA in addressing a serious cause of illness in many developing countries.

The baseline data from the trial were also analysed to identify risk factors for scabies. Scabies was strongly associated with overcrowding and age and was a major risk factor for impetigo. This burden of disease in resource-poor settings highlights the need to undertake research to investigate strategies for public health control of scabies and impetigo at population level.

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Abbreviations, prefixes and symbols

° C	Degrees Celcius
µ/kg	Micrograms per kilogram
APSGN	Acute post streptococcal glomerulonephritis
AIM	Azitromycin Ivermectin Mass drug administration
ARF	Acute rheumatic fever
CCDC	Centre for communicable disease control
CDC	Centers for disease control and prevention
DEC	Diethylcarbamzine
GAS	Group A streptococcus (streptococci)
GN	Glomerulonephritis
GrASP	Group A Streptococcal Project (Fiji)
HB	Haemoglobin
HDI	Human development index
HIV	Human immunodeficiency virus
ICT	Immunochromatographic card test
IMCI	Integrated management of childhood illness
LF	Lymphatic filariasis
MCRI	Murdoch Childrens Research Institute
MDA	Mass drug administration
MOH	Ministry of health
NGO	Non-governmental organisation
NSP	National Strategic Plan
NTD	Neglected tropical disease
RHD	Rheumatic heart disease
SHIFT	Skin health intervention: Fiji trial
SSTI	Skin soft tissue infection
STH	Soil transmitted helminths
TB	Tuberculosis
UNDP	United Nations Development Programme
UNSW	University of New South Wales
WHO	World Health Organization

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Thesis overview

Scabies is a neglected tropical disease (NTD) that is a substantial cause of ill health in a number of countries, particularly those of low and middle income. Despite the apparent burden of scabies and scabies-related disease in many countries, the information on scabies occurrence is generally scarce. There have been few large-scale surveys of scabies prevalence or risk factors and little systematic investigation of public health control strategies. The goal of this thesis was to provide new information on scabies occurrence and risk factors and on control strategies aimed at eliminating scabies as a public health problem in resource-poor settings. The studies included in this thesis involve the application of a range of research designs and analytical approaches.

Chapter 1 comprises literature review of the clinical, epidemiological and public health aspects of scabies and associated complications. It describes the treatment options available and recommendations for individual case management of simple and crusted scabies as well as the management of institutional outbreaks. In addition, this chapter investigates the socio-demographic risk factors for scabies and the broader public health aspects of scabies control. Finally, the concept of mass drug administration (MDA) is introduced and reviewed in the context of NTDs.

Chapter 2 is a published, systematic review of studies reporting on the prevalence of scabies and associated impetigo in population-based surveys. The chapter provides the most comprehensive overview available of the epidemiology of scabies worldwide. The majority of studies that met inclusion criteria were from low or middle income countries. In addition to describing the prevalence of scabies and impetigo in the general population, findings are presented with a focus on children, who have the highest reported prevalences. With the use of a map, the review illustrates the main geographical areas of high scabies, with the highest rates found in the Pacific region with most studies reporting prevalence at levels of 30% to 60% in children.

Chapter 3 is a published paper that reports on the world's first national population-based survey of scabies and impetigo. This was a survey conducted on more than 10,000 people in Fiji and based on household sampling methods. The study was conducted across all four geographical divisions, age group and ethnicities of Fiji, in both urban and rural settings and describes the demographics of the disease in the general population. Findings were compared to the distribution of demographic characteristics in the national census data. Overall 23.6% of the population had scabies and was highest in children aged 5 to 9 years (43.7%) and followed by children less than five (36.5%). This work represents the most comprehensive evidence of scabies prevalence in Fiji, and is still the only national survey reported from any country.

Chapter 4 is a published paper that describes the main finding of the Skin Health Intervention: Fiji Trial (SHIFT). SHIFT was the first comparative trial of MDA for scabies, and compared oral ivermectin, topical permethrin and standard care approaches. Effective treatments are available for scabies but in populations where the disease is endemic reinfestation can occur rapidly even when contacts are treated. MDA has proven to be successful for the control of other neglected tropical diseases. To strengthen the evidence-base for MDA for scabies control, this trial was undertaken in three isolated island communities of Fiji, and showed that MDA was safe and highly effective particularly with ivermectin as primary agent. In this group, the prevalence of scabies declined from 32.1% to 1.9% after one year, with a relative reduction in prevalence of 94%, compared to 67% and 49% in the permethrin and standard care groups respectively. The prevalence of impetigo also declined in all group, with the greatest reduction seen in the ivermectin group. These results demonstrated the potential role of MDA in addressing a serious cause of illness in many developing countries where the disease is endemic.

Chapter 5 analyses in more detail the baseline characteristics of participants in SHIFT. The data from the trial were analysed to identify risk factors for scabies. Prevalence of scabies was 36.4% overall and highest in children aged 5 to 9 years (55.6%). The presence of impetigo was strongly associated with a diagnosis of scabies and the association was significantly stronger in children under five years (PAR 71%). In SHIFT participants, the presence of scabies and impetigo were associated with age and overcrowding, defined as the number of individuals per household and the number of individuals per room.

Chapter 6 summarises the conclusions of this thesis. It explores the epidemiological and environmental health links between scabies and associated complications and their context within tropical developing countries. This chapter discusses limitations of current public health strategies, as well and research gaps and potential solutions for the elimination of scabies as a public health problem in underprivileged populations. It also includes a list of recommendations based on the findings of the included research studies.

Chapter 1

1.1. Scabies

1.1.1. What is scabies (*Sarcoptes scabiei*)?

History of scabies

Scabies is a common skin condition caused by the infestation of the microscopic mite *Sarcoptes scabiei*. The word scabies derives from the Latin word *scabere*, which means 'to scratch'. Humans are infested by the ectoparasite *Sarcoptes scabiei* variety *hominis*.

Scabies was first mentioned by Roman medical writer Aulus Cornelius Celsus in his text, *De medicina*, between 25 and 35AD.[1] In 1687 Italian physicians Giovan Cosimo Bonomo and Diacinto Cestoni described the causal relation between the scabies mite and the typical skin lesions seen after infestation, marking the first description of the parasitic theory of infectious disease.[1-3] Bonomo was also the first to provide a graphic representation of the parasite. In 1844, Austrian dermatologist Ferdinand Ritter von Hebra described the mite's life cycle as well as its stages of infection, proving that the mite was the only cause of scabies through a series of meticulously described experiments.[4] Later, during World War II, English zoologist Kenneth Mellanby demonstrated an immune response to the mite and described scabies transmission methods among soldiers in hospital. For this work, he was awarded the Order of the British Empire.

Since then, scabies has been commonly associated with war and times of conflict, probably due to overcrowding in unhygienic conditions. It was reported that in the British Army there were 6,000 new cases each month during the Second World War, and in Norway over 60,000 new cases in 1943.[1,5] Today, 100 million people worldwide are estimated to have the disease each year, the vast majority living in tropical developing countries.[6]

1.1.2. Anatomy, life cycle and transmission

Anatomy

The scabies mite is an eight-legged parasitic arthropod, barely visible to the naked eye (Figure1).[7] The size of the adult female mite ranges between 0.3 and 0.5 mm.[2,8] The female mite has an oval body that is flat on the under-surface and convex on the upper-surface, and has two pairs of anterior and posterior legs respectively. The anterior legs terminate in long, unjointed stalks referred to as 'suckers', whereas the posterior legs end in long bristles. The eggs are laid through the tocostome, a slit in the middle of the ventral surface of the female mite. Male mites are smaller in size and present an external genital apparatus.[5]

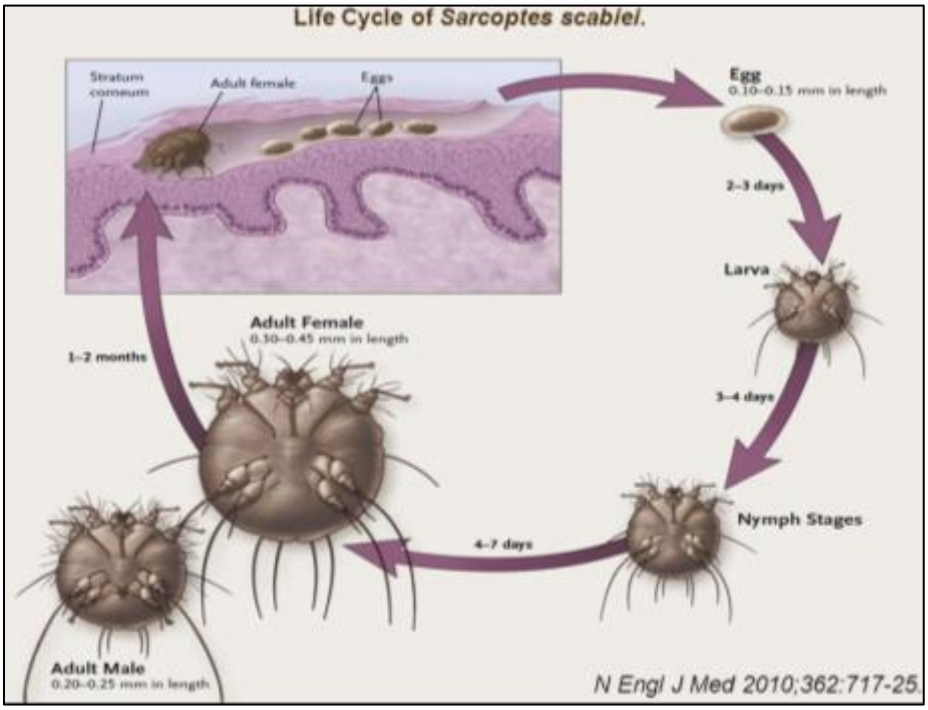
Figure 1: Adult gravid scabies mite

Source: Chosidow, New England Journal of Medicine [9]

Life cycle

A mite has three main development stages maturing from egg, to nymph and then larva.[9,10] Larvae hatch two to four days after the eggs have been laid, and the entire developmental life cycle from egg to adult mite takes approximately 15 days (Figure 2).[8,11]Adult female mites burrow into the epidermis of human skin using their front legs and mouth, with the process taking about 15 to 30 minutes to complete.[2,8] Adult females live for four to six weeks and produce a maximum of four eggs per day, which are deposited in the burrowed tunnel.[12] Due to considerable mortality in the development process, less than 10% of the eggs develop into adult mites.[5]

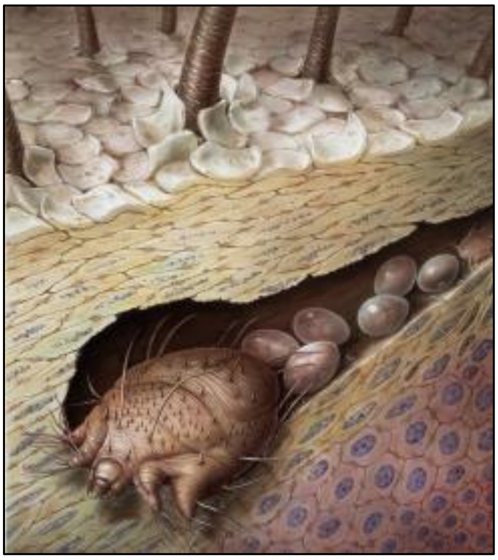
Figure 2: Life cycle of the scabies mite



Source: Currie et al., New England Journal of Medicine, 2010.[13]

A female spends most of her life in her burrow, extending it by 0.5 to 5 millimetres each day.[5,8] Within a few hours from initial infestation, the mite begins to deposit eggs and for the course of its life, the female advances in the burrow and eggs can be seen behind her body (Figure 3). Beside her eggs, she leaves behind empty shells as well as excretory and secretory products of the mites. When the larvae hatch from the eggs they briefly leave their burrow, reach the skin surface and enter hair follicles in search of food and shelter.

Figure 3: Female scabies mite laying eggs



Source: Open access images.

Experiments conducted to study the mite's reproduction, indicated that the highest numbers of mites in an infected host was retrieved between 80 to 115 days from infestation, with a peak parasite rate recorded between 50 and 380 mites.[12] However, considerable inconsistencies were found among patients and other experiments showed that mites reproduced for up to four weeks before an individual developed an immune response and the number of mites gradually decreased.[12] This is not the case for hosts infected with crusted scabies, who can be infested with thousands or even millions of mites at one time.[14]

Transmission

The main method of transmission is prolonged skin-to-skin contact with an infected individual. It takes about 15 to 20 minutes for a scabies mite to infect its host, therefore holding hands, sexual contact, breastfeeding and nursing babies become high risk activities if in contact with an infected person.[15] For these reasons, family members are generally the most common source of transmission.[15] Mites can survive and remain capable of infestation for 24–36 hours even when away from their hosts, particularly in humid environments,[8,9] but mites' infectivity decreases significantly the longer they are separated from their host.[8] Scabies mites use odour and body heat to find a new host.[2] For these stimuli to be intense enough, individuals must be in close skin contact, for example during sexual intercourse or while sharing a bed undressed.[15]

Sarcoptes scabiei (not of variety *hominis*) can affect several mammals other than humans, although in animals it has a shorter incubation period and infection may only last for three to four weeks.[10,16] Sarcoptic mange causes considerable morbidity in both domestic and wild animals, and can lead to large economic losses in livestock.[16] Scabies is generally thought to be a single species that has evolved to be capable of infecting various mammal hosts, with limited cross-infestation between different host species.[8,17-19] However, *Sarcoptes scabiei* from animals can occasionally infest humans. A small number of studies have shown that outbreaks caused by scabies mites from domesticated dogs and other animals can cause human infestation.[4,16,20,21] When scabies in humans is caused by infestation with animal scabies mites, compared with those from other humans, the distribution of the lesions appears to be limited to the areas that have been in contact with the animal and often resolves without treatment.[2,10,16,22]

Fomites and animals are often mentioned in the literature as sources of transmission, however only a few studies have documented the significant impact on humans. In patients with crusted scabies, transmission can occur through bed linen and clothes, although this is less common in people with classic scabies.[15] In 1940, British entomologist Kenneth Mellanby showed that transmission occurs primarily by prolonged body contact and that fomites are unlikely to facilitate infestation, in people with classic scabies.[11,23-25] In a classic experiment, 300 naked volunteers free of scabies occupied beds recently vacated by patients known to be infested with scabies.[11] Transmission of scabies to the scabies-free participants was low. Only four volunteers (1.3%) became infected when patients had fewer than 20 mites. However, this number rose to 15% when patients carried more than 50 infective mites, indicating that the number of scabies mites found in the initial patients played a role in the probability of participants becoming infected. In the case of patients with crusted (Norwegian) scabies, who can often carry thousands to millions of mites, transmission of the parasite is therefore more likely.[26,27] Overall these data suggest that transmission from bedclothes is uncommon, because the average number of mites living on a person with classic scabies is 10 to 15 mites.[11]

1.1.3. Clinical manifestations

The skin manifestations and symptoms of scabies are the result of an immune response that occurs due to hypersensitivity to the mite's saliva and excreta. The symptoms of infestations generally occur three to six weeks after initial infection, but even when infestation is eliminated, pruritic nodules can persist for several months.[28] When patients are infested for a second time, hypersensitivity can develop within days.[9] Parasite load is usually lower in second and subsequent episodes of infestation compared to first infestation, most likely due to protective immunity.[9,29] Several days after initial penetration of the adult female mite into the epidermis, burrows can be seen on the skin (Figure 4). In addition, the host inflammatory response leads to additional clinical signs and the first symptom of scabies which is severe itch, often worse at night.[9]

There are two main recognised forms of the disease: ordinary and crusted scabies. The different clinical manifestations are a result of the type and magnitude of the response to mite proteins.[7]

Ordinary scabies

In the case or ordinary scabies, inflammatory papules are small and erythematous and can vary in number. Over time papules can change into vesicles and bullae. The most affected body parts are the hands, fingers and wrists, as well as the feet, ankles, axillae, genital area and breasts. The face and neck, as well as palms and soles, are often affected in infants and children, but rarely in other age groups.[9,30-32] Scratch marks can be distributed in several body parts but are predominantly observed in the limbs. If scabies infestation is suspected, medical history of family members should also be evaluated.

Scratching of scabies lesions can often lead to secondary bacterial infections, resulting in a clinical picture similar to pyoderma, particularly in tropical countries. Papules and vesicles frequently develop into secondary scabies lesions such as excoriations, eczematisations, secondary infections, and crusts. Firm, red or brown nodules develop at sites such as the elbows, axillae, breast and genitalia. They can be visible in the skin for months and do not necessarily indicate active infestation.

Scabies can mimic a broad range of skin diseases. The clinical characteristics of classic scabies can often be misinterpreted and confused with other common skin conditions, such as urticaria, contact or atopic dermatitis, eczema, fungal infections and insect bites.

Figure 4: Clinical presentation of ordinary scabies and infected scabies

Source: Author’s photo library.

Crusted scabies

Crusted (or Norwegian) scabies is a hyperinfestation with thousands or millions of mites present in the host's skin, mostly as a result of impaired immunity in the affected person. When scabies mites infest an immunocompromised host, mites find no resistance and multiply, and the patient may not manifest the typical symptom of itch.[14,33] Crusted scabies has been described in patients with HIV and with oncologic diseases such as leukaemia especially following bone marrow transplant. Patients who are elderly, disabled or debilitated are also at risk, especially if living in institutions or within disadvantaged populations presumably due to increased transmission as a result of crowded living conditions. Rarely, crusted scabies has been documented in patients without any of these risk factors.[26,34]

Crusted scabies presents with scaly, crusted sores or plaques that may mimic those of psoriasis, eczema or fungal infections (Figure 5).[14,27,35] Persons with crusted scabies are highly infectious and are often the main transmitters of the disease in a community or an institutional outbreak.[26] These patients can have higher mortality rates due to more severe secondary bacterial infections and difficulty in treating the infestation.[26]

Figure 5: Clinical presentation of crusted (Norwegian) scabies

Source: Author's photo library.

1.1.4. Diagnosis

The diagnosis of scabies relies primarily on its clinical manifestations, based on the typical distribution and appearance of lesions. Presence of itch, usually more severe at night, is also common in a patient with scabies. Family history can help confirm the diagnosis of scabies. If another member of the household or a close contact presents similar lesions, a scabies diagnosis should be considered.[2,32]

If possible, the diagnosis of scabies should be confirmed by identifying the mite, mite eggs or faecal matter by removing the mite from its burrow usually with a needle or the back of a scalpel blade (as a scraping). However, this technique is often difficult and requires skilled medical personnel, and leaves a wide margin of diagnostic error.[7] When examined under a microscope the skin scraping can be examined for mites, eggs or excrement.[9] However, microscopy of skin scrapings has high specificity, but is technically difficult and has poor sensitivity, since only 10 to 15 mites are present on an infested person at the same time, and so mites are likely to be missed.[15] A study conducted in Nigeria looked at 210 hospital patients with a clinical diagnosis of scabies. Of those, 53% had a microscopic diagnosis of scabies. However, absence of microscopic confirmation may be due to factors such as distorted burrows, low mite load, poor sensitivity of the method and inefficient technique, which can be difficult even for experienced dermatologists.[36]

Occasionally, a visible burrow can be detected on the host's skin. Rubbing Indian ink into a lesion can draw the stain into the open end of the tunnel and reveal the mite's burrow as a contrast against the surrounding skin. Liquid tetracycline has been used in the same way as Indian ink, making the burrow appear a yellow-grey fluorescent colour when examined using a Wood's lamp.[28] However, detection of burrows using these techniques is difficult and time-consuming, and is rarely used in current practice, particularly in developing country settings where scabies is often endemic.[28]

A proposed method to enhance accuracy of diagnosis of scabies is to use dermatoscopy. Dermatoscopy is an examination of skin lesions with the use of a dermatoscope. This traditionally consists of a high quality magnifying lens and a lighting system, a transparent plate and a liquid medium between the instrument and the skin. This enables inspection of skin lesions unobstructed by skin surface reflections. Epiluminescence dermatoscopy and high-resolution videodermatoscopy, commonly used by practitioners and dermatologists in industrialised countries, are unsuited to developing country or remote Australian settings, and have not been shown to improve diagnostic accuracy in population settings.[37] In addition, the cost of the equipment used for these techniques makes it less accessible to resource poor communities.

In scabies endemic areas a clinical diagnosis has been demonstrated to be highly sensitive (100%) and specific (96.9%), compared to gold standard strategies such as dermatoscopy.[38] A published clinical diagnostic algorithm has proven to be practical, and highly accurate and is widely accepted for the diagnosis of scabies, particularly in developing country settings.[39]

Differential diagnosis

Several differential diagnoses should be considered for scabies. The most common skin conditions that can be mistaken for scabies are urticarial, psoriasis, eczema, fungal infections, atopic dermatitis, allergic reactions, lupus erythematosus and pyoderma.[35,40-43] In tropical countries where onchocerciasis is endemic, this differential diagnosis should also be evaluated[44] and age and local setting of the patient should be considered.

1.1.5. Scabies associated impetigo

The heavy burden of scabies in endemic countries has major health, economic, and social consequences, largely through its contribution to serious bacterial infection (Figure 6).[45] Scratching of scabies lesions causes breaks in the skin, creating an entry point for bacterial infections. Bacteria may be present under the fingernails, allowing direct access for bacteria with broken skin and with burrows.[46] Pyoderma, a localised purulent infection of the skin, is an umbrella term for nonbullous impetigo, bullous impetigo and folliculitis.[47] Nonbullous impetigo is the most common form of pyoderma and it is usually due to group A Streptococcal (GAS) infections, while bullous impetigo and folliculitis are frequently due to *Staphylococcus aureus*.

Nonbullous impetigo commonly presents as a small pimple which evolves to a purulent lesion covered by a honey-coloured crust. Lesions present mostly on the arms or legs, sites where scabies infestation also commonly occur.[48] Occasionally, bacterial lesions develop in the surrounding body areas. They may discharge pus, and as they heal the lesions become darker, flat and dry. Since the organism is highly infectious, patients may develop lesions elsewhere on their body, and multiple cases within the same household are common. Since impetigo is mostly seen among infants and children, it can easily spread within classrooms, and the term “school sores” is often used to describe the skin condition.[49]

The aetiology of impetigo varies between developing and industrialised countries. In tropical developing countries and resource poor settings, GAS is the major cause of impetigo, whereas in industrialised countries, *S. aureus* is the predominant pathogen impetigo.[48,50,51] Impetigo is estimated to affect approximately 162 million people worldwide and is endemic in many developing countries, where an estimated 10% of children suffer from the disease. However, the prevalence of impetigo is often as high as 50% in countries of the Pacific region and in Australian Aboriginal communities.[40,52-55] These estimates were confirmed by two systematic reviews published in 2015 describing the global epidemiology of impetigo, both reporting the highest burden of the disease in underprivileged children in marginalised communities, especially in the Oceania region.[52,54]

In tropical developing countries scabies is the most common cause of impetigo, through its link to infection of the skin with GAS and *S. aureus*. A survey of scabies and impetigo in Fiji found that one-fifth of the population is affected by impetigo at any one time and is particularly common in children where the prevalence in those aged 5-9 years was 34.2%.[30] In this study, scabies was identified as the major risk factor for impetigo, with a population attributable risk of between 40 and 60% depending upon age. In studies conducted in remote Aboriginal communities of Australia, scabies infestation was also identified as the underlying cause of bacterial infection.[50,55,56] A number of published intervention trials have shown that reductions in the community burden of scabies translates to a reduction in secondary bacterial skin infection.[31,57]

1.1.6. Other complications associated with scabies

Group A streptococcal infections are responsible for a large number and spectrum of clinical disease. Globally, the greatest burden of disease is found in tropical developing countries, and particularly in young children. The prevalence of disease caused by GAS is estimated to be over 18 million cases, with nearly two million new cases each year.[55] The global burden of severe GAS causes over 5000,000 deaths each year, the majority of them due to acute rheumatic fever, rheumatic heart disease, post-streptococcal glomerulonephritis and invasive infection.[55]

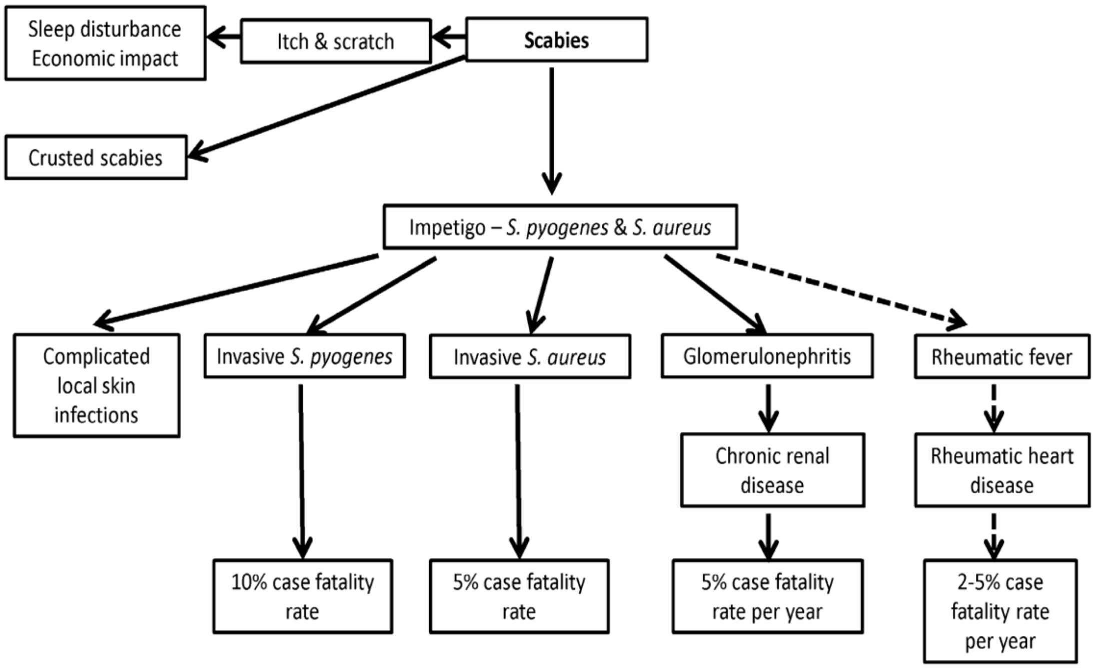
Skin and Soft Tissue Infections

In tropical settings impetigo frequently leads to more severe skin and soft tissue infections (SSTI), as the bacteria invade through the layers of the skin and underlying soft tissues. There are different clinical presentations and severity of SSTI, ranging from more mild infection as described above in the section on pyoderma, to serious life-threatening infections, including abscess, cellulitis and necrotising fasciitis.[58] Co-morbid conditions such as poorly controlled diabetes can easily transform a normally mild infection into a rapidly advancing threatening disease.[59,60]

Abscess is a swollen, purulent and painful inflammation of the skin tissue. The infection may spread locally or throughout the body may cause severe complications. Cellulitis is a deep skin tissue infection in a diffuse area of inflamed skin, which appears red and swollen and feels hot and tender. If left untreated it can rapidly become life-threatening. Necrotising fasciitis is a severe, rapidly spreading infection of muscle fascia, subcutaneous fat and epidermis that leads to necrosis of muscle fascia.[61] The evolution of necrotising fasciitis is rapid with progression to life-threatening disease usually occurring within 24 hours. The case fatality rate can be as high as 30% to 50% and more common in the elderly and in patients with underlying chronic illness.[62]

The epidemiology of SSTI has not been well documented, partly due to the wide range of clinical presentations. A review of hospitalised patients in North America, described the estimated prevalence of SSTI to be around 7%.[63,64] The estimated incidence rate of SSTI is the United States is 24.6 per 1000 person-years.[65]

Figure 6: Complications of scabies infestation



Source: Engelman et al. PLoS NTD, 2013.[66]

Invasive bacterial disease

Impetigo also provides a key portal of entry for GAS and *S. aureus* to cause invasive bacterial disease. Invasive bacterial infections occur when the bacteria evades the host immune system and enters into sterile body sites, most commonly the bloodstream.[67] Globally, there are, an estimated 670,000 incident cases of invasive disease caused by GAS, that lead to more than 160,000 deaths.[55] Global summary burden of disease data for community-acquired invasive *S. aureus* disease do not exist, but the disease burden is likely to be similar. The incidence of invasive disease due to both pathogens is highest in tropical low and middle income countries. The incidence in most developed countries, including North America, Europe and Australia is around 3 per 100,000 persons and the mortality rates varies between 7% and 20%.[55] These figures are much higher in developing countries.[68] For example, a study conducted in Kenya found an incidence of invasive GAS disease of 100 per 100,000 in infants, with a 25% mortality rate.[69] Studies conducted in Australian Aboriginal populations indicate that the all-ages incidence of invasive GAS is high in these groups including in one study in the Northern Territory (incidence 24 per 100,000) [70] and in another in northern Queensland (incidence 82.5 per 100,000).[71] The incidence of invasive GAS and *S. aureus* disease is high in Fiji. In studies conducted 2005-2007 in Fiji, the all-ages incidence of invasive GAS disease was 9.9 per 100,000 population and for *S. aureus* invasive disease was 50 per 100,000.[72,73] Invasive disease caused by GAS was most common in infants (45 per 100,000), with a high fatality rate of 32%.

Post-streptococcal glomerulonephritis

Glomerulonephritis refers to inflammation of the glomeruli within the kidney. When the disease follows acute inflammation with GAS skin or throat infection, it is known as acute post-streptococcal glomerulonephritis, a disease that occurs predominantly in children. The estimated annual 400,000 cases of post-streptococcal glomerulonephritis occurring each year in developing countries are overwhelmingly linked to impetigo rather than throat infection.[74] Since the 1970s substantial evidence indicates that scabies is an important risk factor for developing post-streptococcal glomerulonephritis.[75-77]

In Trinidad, the number of cases of post-streptococcal glomerulonephritis increased following an outbreak of scabies.[2,76] In a two year study of 132 children admitted to hospital in India with post-streptococcal glomerulonephritis, the over 50% of cases were noted to have concomitant scabies and/or impetigo infection.[78] A further study in the Solomon Islands showed that the number of cases of post-streptococcal glomerulonephritis decreased after an intensive scabies intervention program.[46]

Mortality due to acute post-streptococcal glomerulonephritis is estimated to be approximately 1%. However, post-streptococcal glomerulonephritis may not be as benign as once thought. Proteinuria, as a marker of risk of kidney damage, can persist for a long time in patients with post-streptococcal glomerulonephritis. In a study in Northern Australia, protenuria was detected in 13.4% of patients with a history of childhood post-streptococcal glomerulonephritis (median follow-up 16 years) compared to 4% of controls. [79,80] These data suggest that childhood post-streptococcal glomerulonephritis may contribute to the high rates of chronic renal failure observed among adults in indigenous populations of northern Australia.

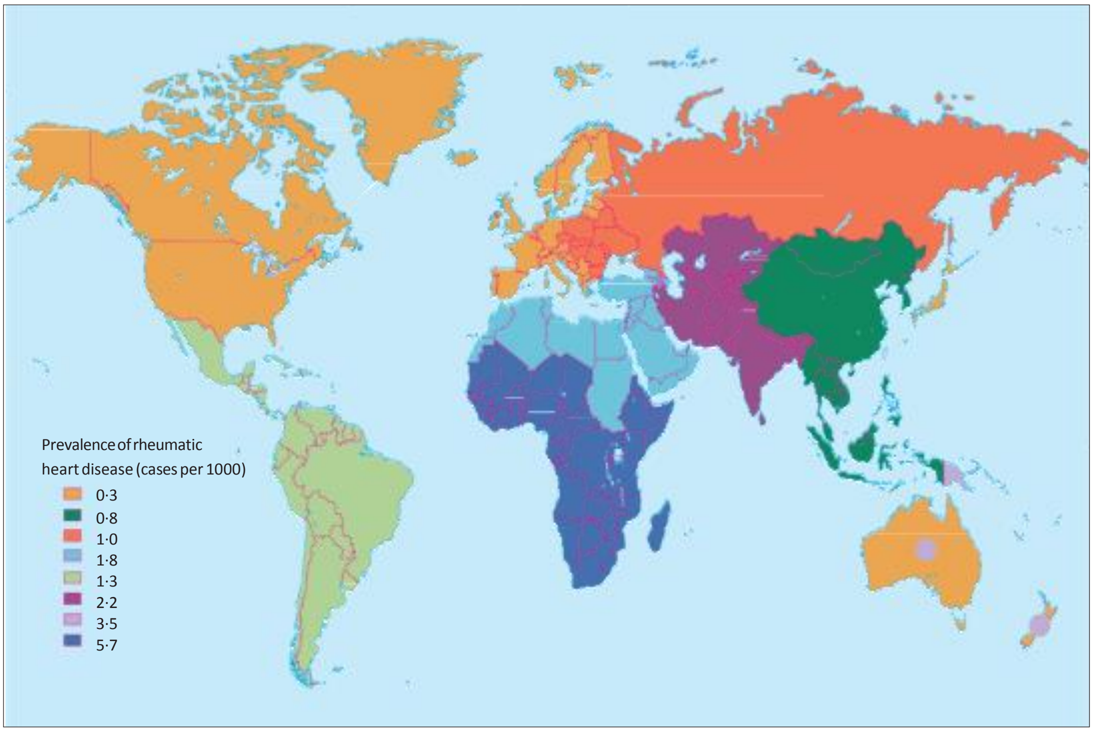
Acute rheumatic fever and rheumatic heart disease

Acute rheumatic fever (ARF) is an inflammatory disorder that follows infection with GAS. ARF is the precursor to rheumatic heart disease (RHD) a chronic disease of the cardiac valves. Repeated episodes of ARF lead to scarring of cardiac valves, most often the mitral valve, especially if the episodes are severe.[81-84]

More than 2.4 million children aged 5-14 years have RHD worldwide, nearly all found in developing countries (Figure 7).[47] This condition is responsible for some 350,000 deaths per year globally,[55] and occurs at the highest rates in Pacific countries as well as in Australian Aboriginal populations. In Fiji, ARF has an annual incidence of 25 cases per 100,000 children aged 5-14 years,[85,86] and RHD is the second most common cause of death in people aged 5 – 29 years.[87] Echocardiographic screening studies have found that up to 1% of all Fijian school children are affected by the disease.[88]

Figure 7: Prevalence of rheumatic heart disease in children aged 5–14 years.

The circles within Australia and New Zealand represent indigenous populations (and also Pacific Islanders in New Zealand).



Source: Carapetis, et al. Lancet Infectious Diseases, 2005.[55]

It is generally accepted that ARF follows infection with GAS pharyngitis, rather than skin related GAS, based on evidence from multiple studies of military recruits in the United States in the 1940s and 1950s.[83] However, there is emerging evidence that cutaneous infection with GAS may play a role in the pathogenesis of ARF.[47,84] The hypothesis was first proposed over five decades ago, but studies conducted in remote Australian Aboriginal communities over the last two decades, where a high burden of GAS impetigo but low burden of GAS pharyngitis has been consistently observed, has once again raised the question of whether GAS impetigo contributes to the very high rates of ARF in these communities.[84,89-91] Coincidentally, the prevalence of GAS pharyngitis in Australian indigenous populations and Pacific island countries is rare compared to that of impetigo.[92] The role of scabies in this context remains to be established, however the strong link between scabies and bacterial skin infections has been clearly documented, suggesting that scabies could be an important risk factor for RHD.

Table 1: Epidemiology of RHD, *S. pyogenes* impetigo and *S. pyogenes* pharingeal carriage in the United States and indigenous populations in the Pacific

Population	**RHD prevalence**	**S. pyogenes impetigo prevalence**	**S. pyogenes pharyngeal carriage**
United States	<1 per 1,000	<1%	15%
Indigenous Australian	9.6 per 1,000	69%	3.7%
Indigenous Fijians	8.4 per 1,000	33%	4.6%
Indigenous Samoans	77.8 per 1,000	44%	2.4%

Source: Parks et al. Current Opinion, 2012.[90]

Socio-economic complications of scabies

Apart from its many life-threatening complications, scabies itself has a direct and significant impact on quality of life. Itchiness, which can become very severe, is commonly worse at night and can cause sleep disturbance in up to 70% of cases and potentially contributes to delays in development and learning.[93]

Scabies also imposes a considerable economic cost on individuals, families and health services. Scabies and impetigo account for between 12% and 24% of primary health care centre presentations in tropical countries.[49] In countries of the Pacific region, over 50% of children attending health clinics present with impetigo, scabies or both.[39] In a study in Mexico, the average period of absence from school for scabies was eight days and for skin infection 15 days, with the average costs of treatment being US$24 and US$52 respectively,[94] a substantial imposition on poor communities, especially when incurred repeatedly. One study estimated that the cost of treating scabies in the United States would be approximately $95 per case, taking into account the cost of drugs and doctor visits.[95]

In many countries the term scabies, or its equivalent, is used as an insult which heightens its social stigma. Shame, restriction of leisure activities, and perceived social stigmatisation have been frequently reported.[96] In a study conducted in Brazil, 77% of adults and 47% of children identified shame as their main feeling when talking about scabies.[97] Other types of quality of life impairment described in this study were the need to dress differently, restriction of leisure activities, social exclusion and stigmatisation. Adults reported problems with sexual partners, while 26% of children mentioned teasing. Women and girls perceived more restrictions than men and boys. In this study, 14% of participants noticed a large effect on their life, while 65% considered their quality of life lightly or moderately reduced by scabies. Similar data were reported by researchers in China and Bangladesh.[98,99]

1.2. Treatment options for scabies

A variety of agents are available for the treatment of scabies. However, methods of application and dosage reported across several studies differ significantly and comparison between treatments is difficult as a result.[100] Currently there are a number of topical acaricides available for treatment. There is only one oral agent, ivermectin, available for treatment, but a second oral agent, moxidectin, is under development. The topical treatments include 5% permethrin, 8% - 10% sulphur, 10% - 25% benzyl benzoate, 10% crotamiton, 1% lindane and 0.5% malathion. Each agent has its own characteristics and the choice of treatment depends on local availability, severity of disease, healthcare practitioner's preference and cost rather than medical evidence.

1.2.1. Topical treatments

There is a paucity of controlled studies that has compared the effectiveness of topical compounds.[100] As a result, treatment recommendations and guidelines vary from one country to another. The main characteristics of each treatment are summarised below.

Permethrin

Permethrin was first used for the treatment of scabies in the 1980s. It is generally considered the gold standard for the treatment of common scabies and is used as first-line therapy in many countries. It is a synthetic pyrethoid, often effective after a single application due to its ability to kill both mites and eggs, although a second dose is frequently prescribed. Permethrin acts on the nerve cell membrane to disrupt the sodium channel current by which the polarization of the membrane is regulated. Delayed repolarization and paralysis of the pests are the consequences of this disturbance. Permethrin 5% is judged to have relatively low toxicity and few side effects.[13] It is expensive compared to other topical agents, however it is widespread in many developing countries. Adults are recommended to apply permethrin to the entire body from head to toes, and leave it on for eight to 14 hours before washing it off. It is advised to apply it before bedtime and wash it off in the morning. It is considered safe in younger children but infants less than two months are advised to leave the cream on for a shorter period of time, due to some potential neurological risks. In some countries, including the United States, permethrin is only approved for infants aged two months and over.

Benzyl benzoate

Benzyl benzoate cream or lotion, using a 10% or 25% solution, exerts toxic effects on the nervous system of the parasite, resulting in its death.[101] It is also toxic to mite ova, though its exact mechanism of action is unknown. In vitro, benzyl benzoate has been found to kill the Sarcoptes mite within minutes.[102]

It is commonly used as the first-line drug for scabies in many developing countries, due to its low cost. It became known in the 1930s after the successful treatment of thousands of patients with scabies in Denmark.[103] Benzyl benzoate should be applied to the entire body and left on for up to 24 hours. Different treatment regimens have been advocated, but generally it requires multiple applications and is recommended to apply it over two to three days with the process repeated after ten days.[7] Benzyl benzoate should be diluted to 12.5% in children and breastfeeding women, and 6.25% in infants to minimize irritation, but this can potentially decrease its efficacy.[7] The 25% solution is known to irritate the skin and can produce a burning sensation or contact dermatitis, making compliance harder to achieve. Antihistamines and analgesics can be used to reduce discomfort. Neurological complications are possible, but only when the agent is misused.[104] Benzyl benzoate requires extensive washing of the body and clothes after use which can be challenging, particularly for people living in underdeveloped areas with scarce or no water availability. Due to its side effects, it is no longer approved in some developing and industrialised countries including Fiji and the United States.

Lindane

Lindane is an organochloride insecticide that exerts its parasiticidal action by being directly absorbed through the parasite's exoskeleton and their ova. It cause paralysis, convulsions, and death of the mite. Lindane has very low ovicidal activity. For many years, lindane was the first-line medication for scabies. It has been in use since the 1940s, but reported toxic effects have prompted debate over its use since the 1970s. Lindane should be left on for up eight hours and avoided by infants, pregnant and lactating women. Adverse events have been reported particularly if ingested, possibly leading to nervous system damage and death.[105,106] Other side effects were reported when the label's instructions were not strictly followed, including using the agent more often than indicated or on broken skin.[106] Toxic effects are mainly neurotoxic symptoms such as numbness of skin, restlessness, anxiety, tremor and convulsions.[107] Cases of parasitic resistance and treatment failure have been frequently reported.[108] Due to its high toxicity and increasing resistance, Lindane 1% has been withdrawn as first-line of treatment from many countries, and is now a second-line treatment in some developed countries.[2]

Sulphur

Sulphur compounds have been used for centuries as a treatment for scabies and are still used in some resource-poor settings where they remain the only available option. In these populations, sulphur has been effective in the management of outbreaks. The mechanism of action on scabies is unknown, but its germicidal activity may be the result of its conversion to pentathionic acid by skin cells or by certain microorganisms. Unlike many other scabies drugs, sulphur (and permethrin) is safe for infants and pregnant women.[109] However, it is generally considered a messy, malodorous treatment that can cause skin irritation, hence compliance with this drug is often low.

Crotamiton

Crotamiton is an antiparasitic drug that is toxic to the scabies mite, although its mechanism of action is unkown. Crotamiton 10% cream has been in use since the 1970s although it is no longer commonly available. It is safe for use in children and infants as well as pregnant and breastfeeding women, although benzyl benzoate 10% is more commonly used in developing countries.

It should be applied from the neck down and left on for up to 24 hours before washing it off. The application should be repeated daily for five days. As a result of this requirement for multiple applications it is less practical than other treatments.

Malathion

Malathion is a nonsystemic, wide-spectrum organophosphate insecticide, causing toxicity in the nervous system of the parasite and ultimately death. Malathion 0.5% lotion has been in use since the 1970s. It is approved in many countries as a treatment for head lice. In the United Kingdom it is recommended for scabies and is available over the counter. It is generally known to have a good safety profile. Like most other antiscabeitics, malathion has to be applied from neck to toe and left on for 24 hours. Application needs to be repeated after seven days.

Herbal treatments

Herbal remedies have been used in many countries. Essential oils have shown encouraging results against scabies both in vitro and field studies. Tea tree oil (*Melaleuca alternifolia*) has shown effectiveness in vitro.[102,110] Non-randomised treatment studies have been conducted of a paste made from extracts of neem *(Azadirachta indica)* and turmeric (*Curcuma longa*) [111], as well as a bush tea (*Lippia multifl ora*) essential oil.[112] A randomised control study of a commercially available repellent containing coconut oil and jojoba was conducted in Brazil.[2] However, comparisons of herbal remedies with currently accepted treatments are lacking.[100]

1.2.2. Oral treatments

Ivermectin

Ivermectin is an oral semisynthetic macrocyclic lactone antibiotic agent. It’s derived from avermectins. Avermectins are isolated from the fermentation products of Streptomyces avermitilis and are highly active, broad-spectrum, antiparasitic agents, leading to paralysis and death of the parasite either directly or by starvation.[113] Ivermectin has been used since the 1980s as the main agent for mass treatment of onchocerciasis and lymphatic filariasis. Millions of individuals have been treated with the drug in Africa and South America as part of those two programmes. Ivermectin is approved for the treatment of ordinary scabies in France and Brazil. In Australia, ivermectin is approved for second-line treatment of ordinary scabies following failure of topical treatment, and it is also approved for first-line treatment of crusted scabies.[113]

Ivermectin has been used as treatment for scabies in institutional outbreaks, crusted scabies patients, immunocompromised patients or in cases in which infestation was recurrent and did not clear with topical agents.[114-117] In several developing countries, there is increasing interest in the use of ivermectin to reduce community prevalence of scabies and associated morbidity.[31,46,118,119] Compared to most other antiscabeitic treatments, ivermectin has the additional benefit of eliminating, simultaneously, a number of common parasitic diseases. This is a significant advantage for populations in many tropical developing countries, where intestinal nematodes and other ectoparasites are co-endemic.[120]

For scabies, ivermectin is recommended at a dose of 200 µ/kg to be taken with food. A single dose may be inadequate to eradicate the different stages of the parasite. A second dose is recommended after one to two weeks, because of its limited ovicidal activity, as ivermectin may not kill eggs that are unhatched at the time of initial treatment.[113]

The safety of ivermectin has been well studied through its usage in large-scale disease eradication programs. Over the past two decades, more than 1 billion doses of ivermectin tablets have been distributed for both onchocerciasis and filariasis, at doses of 100-200 µg/kg with excellent safety.[121-123] A review of women accidentally given ivermectin while pregnant showed no evidence of teratogenicity.[124] Although central nervous system toxicity due to ivermectin has been shown to occur in dogs, it does not cross the intact blood–brain barrier in humans.[125] As a result of the dog studies, ivermectin is currently not recommended for use in children under 15kg because of the theoretical possibility that it may potentially cross poorly-developed blood–brain barriers, leading to a risk of neurotoxicity. Although there are no data to support this restriction, and despite anecdotal reports of ivermectin being well tolerated without serious adverse effects in children aged less than five years when treated for scabies,[46] further data are needed to clearly establish safety in young children before authorities will allow its use in this age group.[125]

Previously, there had been some specific safety concerns raised by individual studies. Encephalopathy after treatment with ivermectin was seen in patients heavily infected with *Loa loa* microfilariae (only found in West Africa), and is now thought to occur as an immunologic response to the specific pathogen.[126] One report of excess mortality among elderly patients given ivermectin in a nursing home has never been confirmed.[127] Ivermectin is a substrate for the cytochrome P450 (CYP) 3A4 pathway and so caution should be exercised in people taking medications that induce or inhibit this pathway.

Resistance to oral ivermectin has been reported in few cases. In a study in Australia, two patients with chronic crusted scabies had received 30 and 58 doses of the drug respectively over four years, indicating that repetitive treatment could induce resitance.[37] There are other reports of patients with crusted scabies treated on multiple occasions. The repeat presence of scabies was considered to be due to re-infestaton after successful treatment, rather than resistance-related treatment failure.[128,129]

Ivermectin is a drug with a good safety profile. Adverse events are generally rare, of minor severity and transient. Three deaths were reported six months after treating elderly patients with ivermectin during an institutional outbreak of scabies.[127] However, whether the deaths were related to ivermectin was not established and the study was not replicated in other settings, hence the causation of the report was subsequently questioned.[130-132]

Moxidectin

Moxidectin is an emerging oral macrocylic lactone that has shown promising results in the treatment of veterinary parasitic infections, including sarcoptic mange. Its activity on scabies mites is currently being tested, with encouraging preliminary results.[133] A particular advantage of moxidectin is its long half-life, and it may be possible that only a single dose will be required for treatment of scabies. A study done in cattle with scabies has shown excellent efficacy as a single 200 µg/kg dose, with 100% cure after 14 days.[134] In another study in sheep with scabies, a single dose reduced the number of mites by 75% to 92%.[135,136] In this study 100% efficacy was achieved in a single dose when a higher dose of 1 mg/kg was used.[137,138]

Efficacy of interventions for treating scabies

There are a limited number of studies that compare various therapies for the treatment of scabies. Comparison is often impeded by low methodological quality of the studies, small sample sizes and a lack of standardised diagnostic criteria.

In a 2007 Cochrane review of interventions for treating scabies permethrin was identified as the most effective therapy when the studies were assessed using treatment failure as the outcome measure.[100] Permethrin was more effective than both lindane and crotamiton. In two trials, with some 200 participants enrolled, the treatment failure with permethrin was 0.24 when compared to that of crotamiton. In a study of 470 patients, a single application of 5% permethrin was as effective as lindane and was described as a good alternative for patients with resistance to lindane.[108,139] Treatment failures with permethrin have been described with the 1% formulation, which is appropriate for treatment of head lice, rather than scabies. Studies in Australia reported increasing resistance to permethrin following in vitro tests.[10,102] There were limited data to compare permethrin to benzoyl benzoate.

The review compared the effectiveness of oral ivermectin to topical treatments. Ivermectin was equivalent to, or better than lindane [100,140] and benzyl benzoate.[141,142] However, a randomised controlled trial conducted in Senegal and published after the Cochrane review was terminated due to the apparent superiority of benzyl benzoate, which obtained a 69% cure rate compared to the 25% cure rate of ivermectin.[143] However, the external validity of the study was criticised for several reasons. The main criticism was that ivermectin, was administered as a single dose, which is known to be inferior to two doses and not considered standard therapy.[144] When compared to permethrin cream in the Cochrane review, the efficacy of ivermectin was variable. One study showed that permethrin was superior to a single dose of ivermectin, but the two had similar efficacy when two doses of ivermectin were administered. This reflects the ovicidal and non-ovicidal activity of permethrin and ivermectin respectively. Ivermectin cured 70% of scabies cases with one dose and 95% of cases with two, while a single application of permethrin cured 98% of patients.[145]

There are no comparative trials showing data on the safety and efficacy of scabies agents for special populations, such as crusted scabies patients, infants and young children, immunosuppressed persons and the elderly. At present there are no studies comparing the efficacy of one versus two doses of ivermectin for scabies. Further research on dosage regimens, treatment in special groups, and standardised protocols for scabies diagnosis are required to reach a consensus on the best treatment strategies for the disease.

Mass drug administration for the management of community control of scabies has been used in developing country settings showing promising results. This concept is discussed further in chapter 1.3.3. and chapter 4.1.

1.2.3. Current treatment recommendations and contact management

Guidelines for the treatment of scabies differ due to a number of factors including geographical location, severity of the disease, level of endemicity and availability of treatment. However, recommendations from the Australian Government, Europe and the Centers for Disease Control and Prevention (CDC) are generally consistent.[146-149]

In most countries, case management recommendations include immediate treatment of the patient with an effective topical or oral treatment. The importance of treating close contacts, family members and sexual partners is emphasised whether or not they have symptoms of infestation. This is best practice to prevent the spread of the disease, since the interval between initial infestation and clinical manifestation of the symptoms can take as long as 10 weeks and some individuals may not be aware they are carrying the mite.[2,7,9]

Guidelines often include the counselling of patients and families in regards to exacerbation of itch. This could occur a few days following treatment due to the host's immune response to mite antigens, before the disappearance of symptoms. Antihistamines and analgesics can be prescribed to relieve discomfort. In the presence of infected scabies lesions, antibiotics are prescribed to treat the bacterial skin infection. In most cases, washing of bed linen and clothing in hot water is advised. Alternatively, items can be placed in sealed containers or plastic bags for at least three days.[13] There is no strong evidence base for this however as outlined above in 1.1.2.

In Australia, permethrin 5% cream is recommended as the first line of treatment for common scabies. In adults, the cream should be applied from the neck down, while young children and elderly people should apply it on the face, scalp and neck, making sure to avoid the area around the eyes. Particular attention should be paid to most affected areas, such as wrists and the interdigital spaces of hands and feet. The cream needs to be left on for at least eight hours and it is generally recommended to apply it before sleep and then wash it off in the morning. A second dose after one to two weeks is advised to guarantee successful elimination of mites and eggs. Ivermectin is approved for treatment of ordinary scabies if first-line topical treatment failures or if there is a contra-indication to topical treatment.

Many developing countries rely on guidelines outlined by the Integrated Management of Childhood Illness (IMCI) programs, which provide recommendations for treating skin diseases, including scabies and infected scabies, in infants and children below five years of age.[7,39]

Guidelines for the treatment of crusted scabies recommend a more intense regimen, since these patients carry a much higher load of scabies mites and because the hyper-keratotic crust can be difficult for both topical and oral treatments to penetrate.[14,26] In Australia, where crusted scabies has been well documented in remote indigenous populations, guidelines for healthcare workers have been designed to address both case and community management as well as chronic cases.[148] Once crusted scabies patients are identified and diagnosis confirmed by skin scraping, the disease is graded according to its severity, number of episodes and skin condition.[148] Hospital admission is recommended for more severe disease. The treatment regimen involves administration of oral ivermectin as a single dose at 200 μ/kg, on days 0, 1 and 7 with food, and often longer for those with more severe disease. Close contacts and family members are traced and advised to seek treatment. In addition to oral therapy, topical scabicides benzyl benzoate 25% or permethrin 5% are used every second day for a week, and urea cream is applied every second day to soften the skin where crusts or plaques are present. Environmental measures, such as washing of clothes and bed linen, are strongly encouraged to facilitate the elimination of mites and stop reinfestation. Ongoing case management is required after a full treatment for crusted scabies to ensure prevention of recurrence (Table 2).

Guidelines for the treatment of scabies and crusted scabies in care facilities and institutions such as nursing homes, prisons and hospitals typically involve the treatment of all residents, whether or not they have the disease. Often the outbreak management translates into a "small-scale" mass drug administration. This concept is discussed further in chapter 1.3.3.

Table 2: Management of chronic crusted scabies

Risk of recurrence and severity	How to grade	Frequency of skin checks	Preventative treatments
Low - Moderate	Low infectivity: Crusts isolated and discrete patches — less than 5% Total Body Surface Area (TBSA). Skin: Minimal shedding chronicity 0–3 prior hospitalisations for crusted scabies.	Monthly (examine skin including buttocks)	1. Encourage regular use of lactic acid/ urea and moisturiser on areas affected by past crusting. 2. Apply benzyl benzoate as needed if exposed to scabies. Consider supervision of benzyl benzoate.
High	High infectivity: Crusts lower legs, buttocks, trunk OR 10% or more of TBSA Skin: Current or past heavy shedding. AND chronicity : More than 3 prior hospitalisations for crusted scabies. And/ordepigmentation of legs/back or residual skin thickening/ scaly skin (ichthyosis).	Fortnightly (examine skin including buttocks)	1. Encourage regular use of lactic acid/ urea and moisturiser on areas affected by past crusting. 2. Apply benzyl benzoate from neck down fortnightly. 3. As needed apply benzyl benzoate immediately to any areas exposed to scabies (e.g. hands after visit of affected person).

Source: (Adapted from) One Disease. Managing crusted scabies in remote Aboriginal communities, 2015.[148]

1.3. Public health control of scabies

Despite a number of available therapies for the treatment of common scabies and its more severe forms, scabies is a major cause of morbidity in many developing countries. It leads to economic disadvantage, reduced quality of life and a substantially increased risk of serious complications due to secondary bacterial infection.

Scabies has until recently been a low priority for health programs and research, perhaps because its complications are diverse, under-recognised and spread across a broad range of medical disciplines including dermatology, infectious diseases and paediatrics. Endemic scabies is also primarily a disease of tropical developing countries where resources for new health initiatives are scarce. However, there is increasing recognition of scabies as a public health problem by ministries of health in a number of developing countries, including in Fiji and Ethiopia where both countries are developing national plans for scabies control.

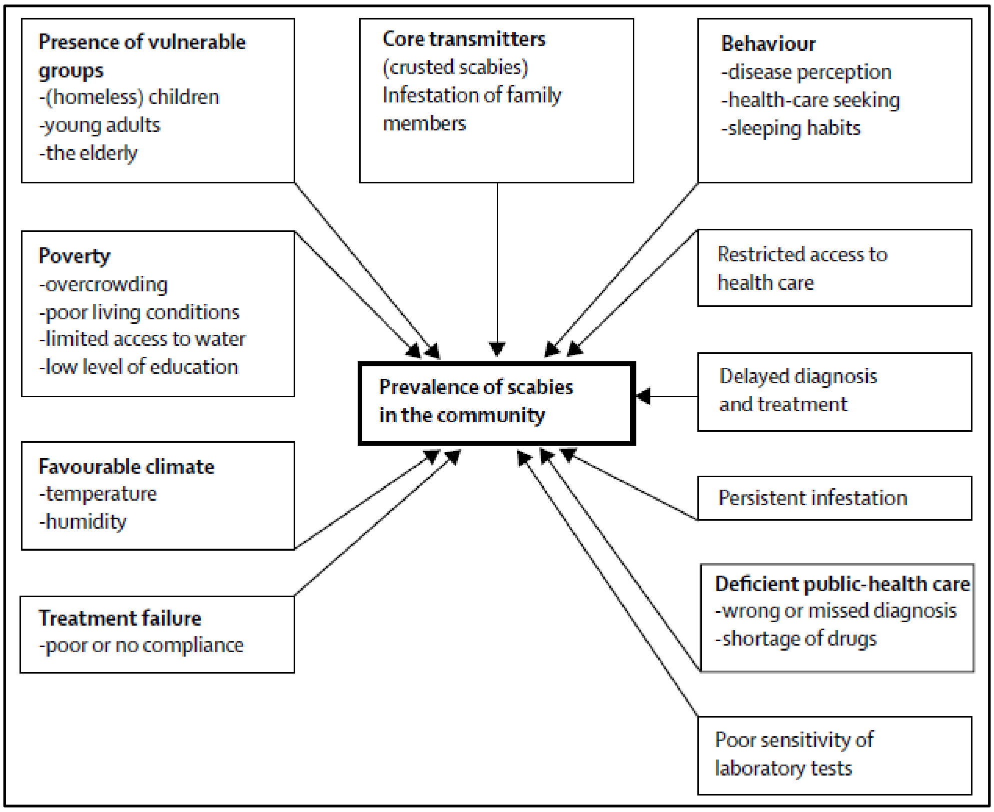
To achieve the goal of elimination of scabies as a public health problem, it is also important to have an understanding not only of strategies for the reduction of scabies prevalence, but also the risk factors associated with the disease to ensure that control measures are properly targeted.

1.3.1 Socio-demographic risk factors for scabies

There has been relatively little research on risk factors for scabies. However, a few studies conducted in developing countries describe what appears to be a strong relationship between high prevalence of scabies and poor socio-economic status that may be largely due to overcrowding of living conditions among others.

Factors that have been specifically investigated for their association with the prevalence of scabies and associated bacterial infections include low level of education, living conditions and proportion of children in communities. Some of these have been investigated by researchers in developing countries, including Heukelbach and colleagues who summarised the main risk factors of high scabies prevalence in a 2006 review (Figure 8).[2] Research evidence comes primarily from Brazil, Bangladesh, Pakistan, India and indigenous populations of northern Australia.[93,99,150-152]

Figure 8: Factors contributing to a high prevalence of scabies



Source: Heukelbach et al. The Lancet, 2006.[2]

In Australia, extensive scabies related research has been conducted in remote indigenous communities. A study published in 2010 conducted a multi-level analysis of association between carer report of common childhood illnesses and housing infrastructure, socio-economic, psychosocial and health related behaviours using baseline survey data from a housing intervention study.[152] Scabies was associated with age, overcrowding as well as the presence of rubbish and number of indoor smokers.

A study in Bangladesh described the socio-economic characteristics of living with scabies in a cohort of 492 children with scabies living in six randomly selected residential schools.[99] A correlation analysis showed a positive association between disease severity, re-infection, low household income and overcrowding. Compared to scabies-free children, those with scabies had a lower family income, washed their clothes and bathed less frequently, and were less likely to own a house and have electricity. The study also documented the limited access to treatment that disadvantaged populations may have. Nearly half of the children with scabies were not treated for up to 44 weeks after the development of scabies symptoms.[99]

In Pakistan, 200 patients with scabies and 200 controls were identified among male soldiers.[151] Poor hygiene, infrequent changing of clothes, low education, itching, and being away from the barracks were identified as significantly associated with scabies. Large family size, sharing of towels and hospitalisation were not. Similar finding confirmed by researchers in Brazil, who have documented characteristics associated with scabies in an impoverished rural community.[150] The most strongly linked were: young age, high number of children per household, illiteracy, low income and poor living conditions and hygiene.

A large multicentre study comparing the prevalence of scabies in Cambodia, Mali and Malawi collected information on more than 65,000 participants. Although overall scabies rates were substantially higher in Cambodia, all three populations reported higher prevalence in participants with lower socio-economic status.[153] Scabies was twice as common among those sharing their beds with other family members and three times more common in people who did not have a private water supply in the house. However, overcrowding was only reported in the Cambodian participants, possibly explaining the higher scabies prevalence in this population.

Although hygiene is often reported as a significant risk factor for scabies, no comparative studies have been able to provide a definitive answer. In 1977, 273 families were surveyed to investigate environmental factors in people with scabies in India. Overall, 1727 participants were surveyed. Authors found a significant association between overcrowding and sharing of clothing and towels. However, there was no difference between families with good, satisfactory of poor hygiene.[154]

Although such risk factors have been assessed in few countries, and methodological approaches have varied, consistent themes that appear are associations between scabies and poverty, young age and overcrowding are the most recurrent characteristics associated with high prevalence of scabies. The frequency of scabies and associated complications in tropical regions, also suggest that there may be a climatic factor likely to be linked to the disease. However its presence is by no means limited to these areas and can be found in all countries, again with an association with younger age, and crowded living conditions such as institutions.[7,155,156]

These findings add to other evidence that community control programs for scabies need to involve social and behavioural aspects for potential health gains to be fully achieved. Particularly in impoverished communities where scabies is endemic, public health strategies for disease control should address locally pertinent risk factors. These include, but are not limited to, factors such as level of education, housing conditions, number of children in the family and hygiene. Public health strategies alone cannot control the above factors and should be complemented by integrated country or regional policies looking towards long-term change.

1.3.2. Environmental and household strategies for scabies control

Environmental measures for the control and prevention of scabies are often encouraged by researchers and government guidelines, to complement individual based approaches to the therapeutic treatment of scabies.[147] However, a limited number of evidence-based data are available in the literature.

A Cochrane review reported in 2014 investigated interventions for preventing the spread of infestation in close contacts of people with scabies.[157] The aim of the review was to include randomised controlled trials in which people who had been in contact with people with scabies received medical treatment or advice about personal and environmental hygiene to prevent scabies infection from spreading. Authors sought to include studies designed so that treatment received (drug or hygiene advice) was randomly assigned. However, out of 29 studies considered, none met inclusion the criteria (16: no data for contacts; 11 not randomised; 2 case studies).[157] No literature review is currently available to evaluate the significance of environmental strategies for scabies.

Environmental guidelines for scabies control include washing and cleaning of clothing, bed linen and blankets, in hot water (above 60 C°) or tightly wrapped in plastic bags for at least three days to kill the mites and prevent re-infection.[147] However, in the case of uncomplicated scabies, clothing does not appear to be an important form of transmission and there is no evidence supporting the practice of washing or clothing disposal. In the case of a scabies infection picked up by bedding or other fomites, it is still unnecessary to disinfect these objects as the adequate medical treatment of scabies will have sufficient power to prevent further infestation.[5,12,154]

As mentioned in section 1.1.2, several experiments conducted in the 1940s showed that it is unlikely for scabies mites to infest a new host via inanimate objects, particularly in people with uncomplicated scabies.[11,12] In one of the studies 300 healthy volunteers occupied beds (without wearing clothes) vacated by scabies-infested patients within 24 hours.[12] Scabies patients had a parasite rate between 20 and 50 whereas only four volunteers (1.3%) developed scabies infestation. When the same experiment was conducted with patients carrying a very high number of mites (over 200, levels typically found infrequently in endemic settings), infection rates increased substantially, such that three out of 10 volunteers (30%) became infected. The study suggests that the number of scabies mites in index patients played a role in the probability of transmission via fomites.[12]

Another experiment by the same author supported this hypothesis. In an institute where 20 people with and without scabies lived together for two years, more than half residents had the infestation. All infected residents had a mild form of scabies, with less than 50 mites each. No contacts or visitors, all able to mix freely and share eating and sleeping space, became infected. However, when two volunteers with over 200 mites later attended the institute, two people without scabies became infected within a short period of time.[12]

These experiments suggest that only individuals carrying a very high number of mites are likely to transmit scabies via fomites and that the majority of infections are transmitted by prolonged body contact with an infected person.

1.3.3. Control of institutional outbreaks

In higher income countries, scabies occurs sporadically and is generally not perceived as a significant public health problem, although it does have an association with lower income communities. However, institutional outbreaks in places such as nursing homes, child care facilities and hospitals are not uncommon and have been reported on a regular basis.[158-161] Cultural and social changes, such as the increasing use of nursing homes and hospices for the elderly, as well as child care centres for young children are a possible explanation for this phenomenon. Overcrowding and mental or physical disabilities of these patients, as well as presence of immunocompromised and crusted scabies patients are also likely risk factors for the occurrence of outbreaks in these settings.[162]

Institutional outbreaks of scabies has been reported in many industrialized countries, including the Netherlands,[163] Norway,[160] Australia,[164] Switzerland,[165] and Korea.[166]

In Norway, 13 residents of a nursing home and six healthcare staff were diagnosed with scabies over a five month period. After repeated unsuccessful treatments with permethrin cream, patients were administered benzyl benzoate, which cleared the infestation. To stop re-infestation, a total of 370 people were treated, including patients, staff and relatives. Simultaneous washing of bedding and clothing as well as disinfection of the facility was performed.[160]

In Switzerland, an outbreak of scabies occurred in an intensive care unit of a university hospital and an affiliated rehabilitation centre.[165] An index patient with HIV and crusted scabies was identified. Scabies was diagnosed in 19 patients but all 1,640 exposed individuals, including healthcare workers and their household members, received preventative treatment. Therapy was initially with topical lindane or permethrin and was later changed to oral ivermectin as a result of the continuing progression of the outbreak.[165]

A review of nosocomial outbreaks of scabies, reported the epidemiological characteristics of 19 episodes.[162] There was a mean number of 18 scabies infected patients, range of 3 to 82 cases, while the mean number of affected healthcare personnel was 39 (range 6 to 278). The duration of infestation ranged from four weeks to a year, with a mean duration of 15 weeks. Authors noted an important association between scabies and prolonged hospitalisation, increase of workload for healthcare workers as well as a considerable economic burden for both patients and institutions.[162]

In lower income countries, alongside overcrowding, conditions of poverty may be considered to be potential factors in institutional outbreaks of scabies and skin infections. Institutional outbreaks of scabies have been reported in prisons,[114] orphanages,[167] schools,[99] and refugee camps.[168]

In a refugee camp in Sierra Leone 125 children were examined for scabies following an outbreak. Overall, 84 children (67%) aged one to 15 years were diagnosed with scabies. Scabies prevalence was 86% in those aged five to nine years and 77% in children under five.[168] Overcrowding and poverty were mentioned by the authors as the main factors associated with the outbreak.

An outbreak of scabies was investigated in a prison in Tanzania. To eradicate the infestation, 1153 prisoners were administered a single dose of ivermectin at 150 μ/kg. The cure rate after one week was 30%, and increased to 88% after four weeks and 95% after eight weeks. Sixteen inmates were diagnosed with crusted scabies and treated with 1% lindane lotion in addition to ivermectin. This regimen eliminated scabies from the prison for two years following infestation.[114]

Finally, a study in Thailand reported on outbreaks of scabies over a 12 month period in children living in two orphanages. Overall, 124 (87%) out of 142 children had the infestation at baseline and after all residents were treated with topical sulphur the prevalence of scabies dropped to less than 10% and was maintained for 12 months.[167]

In all institutional outbreaks, both in developing and industrialised countries, the procedures adopted to clear the infestation have relied on treatment with topical or oral agents of all residents as well as family members, staff and other close contacts. As evidenced by the examples above, in some cases the diagnosis of scabies in a dozen patients led to the preventative treatment of hundreds or thousands of potentially scabies-free contacts.[160,165]

The concept of treating everybody to eliminate endemic scabies in a closed confined institution is not dissimilar to the situation of some isolated communities, villages or small islands with endemic scabies. As mass drug administration this strategy offers an alternative to individual treatment for the population control of scabies and the possibility of eliminating the infestation as a public health problem in communities.

1.3.4. Neglected tropical diseases and mass drug administration

Management and control of scabies has primarily relied on individual-based treatment of symptomatic cases and their contacts.[13,39] Standard approaches to scabies control focus on people with symptoms, and their immediate household contacts with topical or oral treatments.[13,169,170]

The strategy of treating clinical cases of scabies and their contacts has been in effect for many years, and although it has undoubtedly provided relief for many individuals with scabies infestation, there are few longitudinal data to indicate success in reducing prevalence long-term. There are two main reasons why an individual-based approach has been ineffective in controlling scabies in endemic areas. First, adherence to treatment may be incomplete, both among presenting cases, but particularly among family members for whom treatment is prescribed based on the presence of an index case. As an example, less than 50% of household contacts of children with scabies were found to be adherent to treatment in a study in the Northern Territory of Australia.[171] Second, there is likely to be a substantial pool of infestation in households without symptomatic cases, which acts as a source of re-infestation when members of these untreated households come in contact with people who have been recently treated. Topical and oral treatments for scabies have high cure rates at an individual level, but in endemic settings reinfestation occurs rapidly. Accordingly, attention has shifted in recent years to the potential role of MDA.

MDA for neglected tropical diseases

The MDA strategy has been the centrepiece for ambitious global plans to eliminate several major NTDs over the past 30 years. For example, MDA is supported by WHO and multiple partners through large regional and global programmes such as the Global Lymphatic

Filariasis Elimination Programme and the Onchocerciasis Elimination Programmes in the Americas and Africa. These programmes aim at reducing prevalence to levels at which individual case management can be effectively applied.

There are five diseases that, where endemic, are controlled by MDA programs: soil transmitted helminths, trachoma, shistomaniasis, onchocerciasis and lymphatic filariasis. The five pharmaceutical agents prominent in MDA for NTDs are ivermectin, albendazole, azithromycin, diethylcarbamzine and praziquantel. Over 700 million people receive these medicines annually, with ivermectin the most frequently delivered drug. Over the last decade, more than 1 billion doses of ivermectin at 100-200 μg/kg have been given in MDA programmes for lymphatic filariasis [121] and onchocerciasis [172-174] with little or no safety signals beyond minor, reversible events.[121-123] In these programmes, pregnant women and young children have been excluded from taking ivermectin in the absence of formal safety studies,[175] but available observational evidence indicates that the drug is safe in both of these populations.[121] The 2015 Nobel Prize for Medicine was awarded to the discoverers of the drug in recognition of its contribution to global public health.

In the past, NTD initiatives have operated largely as stand-alone vertical programs, but recent experiences suggest that considerable savings in both financial and personnel costs can be achieved, along with enhanced program effectiveness, through the wider adoption of integration strategies. This is enhanced by the fact that all drugs used in MDA may also treat additional NTDs, as summarised in Figure 9.[176] Many countries of the Pacific, including Fiji, have high prevalence of scabies, filariasis and helminths and in recent years, the possibility of individual or integrated-based programs has been explored by the Ministry of Health and partner institutions.

Figure 9: The seven major NTDs targeted for integrated control and elimination

Seven Major NTDs Targeted by Rapid Impact	Major Drugs Used	Additional NTDs Targeted by Rapid Impact
Soil-transmitted helminth infections: ascariasis, trichuriasis, hookworm	Albendazole or mebendazole	Strongyloidiasis
Schistosomiasis	Praziquantel	Taeniasis Food-borne trematodiases
Lymphatic filariasis	Ivermectin or DEC + albendazole	Strongyloidiasis Scabies
Onchocerciasis	Ivermectin	Strongyloidiasis Scabies
Trachoma	Azithromycin	Other bacterial infections

Source: Hotez, et al. George Washington University and Sabin Vaccine Institute, 2011.[176]

MDA for population control of scabies

There has been some encouraging evidence of the potential impact of MDA as a strategy to control community prevalence of scabies in developing country settings.

The first indication of success came from the San Blas Islands of the Republic of Panama, where MDA of topical permethrin led to a fall in scabies prevalence from 33% to 1% which was sustained through regular follow up and retreatment over three years.[139] In a pilot study in Papua New Guinea, a small village of 60 people was given MDA with a single dose of ivermectin (400ug/kg) to control filariasis. The prevalence of scabies in the village was 87% prior to treatment and by five months had fallen to 26%, in comparison to a control village, where prevalence at baseline was 52% and 60% after one month.[177] In a fishing village in

Brazil, MDA with ivermectin (two doses of 200ug/kg, 10 days apart) was used to control parasitic skin disease and intestinal helminthiasis. [178] Scabies prevalence at baseline was 3.8%, and fell to 1% at one month. In the Solomon Islands, where populations on five small islands received a single or double dose of ivermectin (160-250ug/kg), [46] the prevalence of scabies dropped from 25% to less than 1% at three years, and impetigo prevalence fell from 40% to 22%. In a small study of ivermectin MDA (two doses) versus permethrin MDA (one dose) in 84 children in urban Delhi, only one re-infestation was observed in the children in MDA ivermectin group over a 6 month period versus 22 cases in the permethrin group.[179] In Fiji, a MDA trial of scabies was undertaken comparing benzyl benzoate and ivermectin in two rural villages.[180] At three weeks approximately half the skin lesions had disappeared in both villages, but the follow up time was very short. Finally, two studies were conducted in remote Indigenous communities of Australia. The first enrolled 2200 children under five years of age. Baseline prevalence of scabies, infected scabies and impetigo was 35%, 12% and 11% respectively. After one dose of topical permethrin to all children, and a second one to those diagnosed with scabies at baseline, the prevalence dropped to 3%, 1% and 4% respectively after six weeks and low prevalence was maintained for the duration of the study (7 months).[181] The second study was a before and after study of MDA for scabies in over 1000 people. One dose of ivermectin (200ug/kg), repeated if scabies was present at baseline, was given to all participants unless contraindicated. Scabies prevalence fell from 4% at baseline to 1% at six months Prevalence rose to 9% at month 12 amongst in association with an identified exposure to a crusted scabies case with a higher prevalence of 14% amongst new entries to the cohort. At month 18, scabies prevalence fell to 2%.[182] Although these studies collectively show that MDA may play an important role in scabies control, none of the studies directly compared MDA to a standard-of-care arm. Perhaps for this reason, they have had little or no impact on public health policy in developing countries.

To this date, there is no available information on the efficacy and feasibility of large-scale MDA programs for scabies community control. However, one study has provided information on the potential impact on scabies of a large and long-standing MDA programme. In Zanzibar, where ivermectin-based MDA for lymphatic filariasis was distributed to more than 1.3 million people over 5 years, clinical records were retrospectively reviewed for presentations with scabies.[29] There was a 68% reduction in recorded cases over this period suggesting that annual MDA with ivermectin can have a significant effect on community scabies burden. However, the study relied on clinic reports and did not use the gold standard for assessing scabies prevalence - community wide skin examination. Also, it was not able to determine the impact of MDA on the downstream complications that are a key motivation for scabies control.

1.4. Setting

1.4.1. The Pacific region

The Pacific region consists of 22 island countries and territories with a diverse range of geography, cultures, populations, politics and economics. Three different sub-regions are generally designated in the Pacific; Melanesia in the west, Polynesia in the southeast and Micronesia in the north (Figure 9), to indicate broad ethnic, linguistic and cultural characteristics, although there is very substantial diversity even within these sub-regions.

The Pacific covers 30 million square kilometres, of which 98% is ocean. There are 7500 islands but only around 500 are consistently inhabited.[183] Papua New Guinea is the largest, occupying 83% of the land area of the region, and the most populated, with seven million people. While some countries consist of just one island others number in the hundreds.

Despite regular interactions among the Pacific populations, both currently and historically, there are still many cultural differences, no doubt reinforced by isolation and lack of transport access. For example, with just 0.1% of the world's population the Pacific region is home to one-third of the world's languages, with 850 different languages spoken in Papua New Guinea alone.[184]

As proven by history, Pacific islanders are resilient people but due to the very nature of their islands they are especially vulnerable to natural disasters, particularly cyclones, tsunamis and flooding, and more recently climate change. Now they are also subject to the social and economic challenges that come with living as small populations in remote locations. These challenges affect the region's capacity to alleviate and prevent poverty, achieve sustainable development and help people realise their human rights and reach their potential. Some

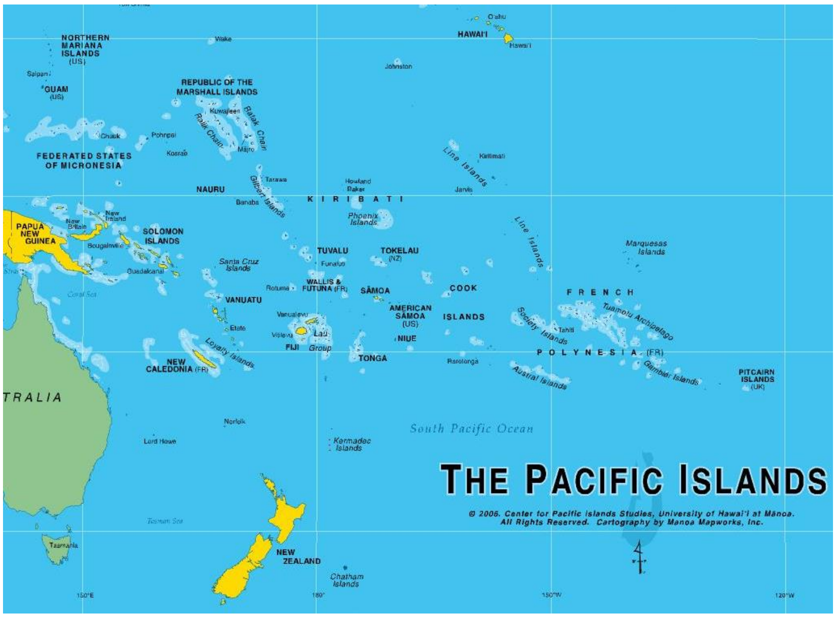
Pacific Island countries and territories experience among the highest average annual disaster losses, as a percentage of gross domestic product (GDP) in the world. Responses to these challenges require regional cooperation, political leadership and a deep understanding of context.

All 22 island nations are members of the Pacific Community (SPC), in addition to Australia, France, New Zealand and the United States of America. SPC was founded in 1947, and is the principal scientific and technical developmental organisation in the Pacific region. The region's activities focus on a broad range of areas such as climate change, disaster risk management, food security, gender equality, human rights, communicable and non-communicable diseases and youth employment. In addition, 16 of the 22 countries are members of the Pacific Islands Forum, a political grouping of independent states, founded in 1971 that is the principal political institution in the region. International organisation such as WHO also have a strong presence in the Pacific.

The health status of most people in the region is generally good by global standards, although several Pacific Island countries and territories did not meet the health-related Millennium Development Goals (MDGs) in 2015. Life expectancy has increased in many areas and infant mortality rates declined in all countries. However, gender inequity, income inequality and poverty, water and food insecurity, youth unemployment and shortages of skilled labour remain challenges. The high prevalence of non-communicable diseases (NCDs) also puts a strain on public health systems and finances. While NCDs have become the major cause of morbidity and mortality in most countries, some island states continue to have substantial burdens of infectious diseases such as malaria and tuberculosis attributable mainly to poor environmental conditions. There have been successes in reducing the incidence of infectious disease across the region, although many preventable diseases remain at high rates, especially for younger children.

Differences in economic growth and per capita GDP are evident among nations. The Cook Islands and Palau have by far the highest per capita GDP in the region. Both countries have small populations, are urbanised and have high rates of employment. At the other end of the scale are Papua New Guinea and the Solomon Islands, two countries with high-value exports but large village populations relatively unaffected by the country's economic transitions. Most Pacific Islanders live off agriculture and fishing or the monies gained from the export of these products.[185] The export of timber and fish (mainly tuna) is becoming increasingly important as a source of income and employment, primarily managed through foreign companies. Exports of traditional products, such as coconut and copra have declined in recent years. Fiji is the most successful example of the export potential of the region, with agricultural and mineral goods, ranging from sugar to gold, being exported annually. One of the most thriving sectors within Fiji's growing economy is manufacturing. This includes the manufacture of textiles, food processing, beverages and wood based industries.[185] Tourism is one of the key economic activities of the region. In Fiji the direct contribution of tourism to GDP was FJD 1.07 billion, 13.7% of total GDP.[186]

Figure 10: Map of Pacific Island countries



1.4.2. Fiji

Fiji is an independent island country in the South Pacific Ocean. It consists of more than 330 islands, 110 of which are permanently inhabited. It also contains more than 500 islets. The total land area amounts to 18,300 square kilometres (Figure 10).

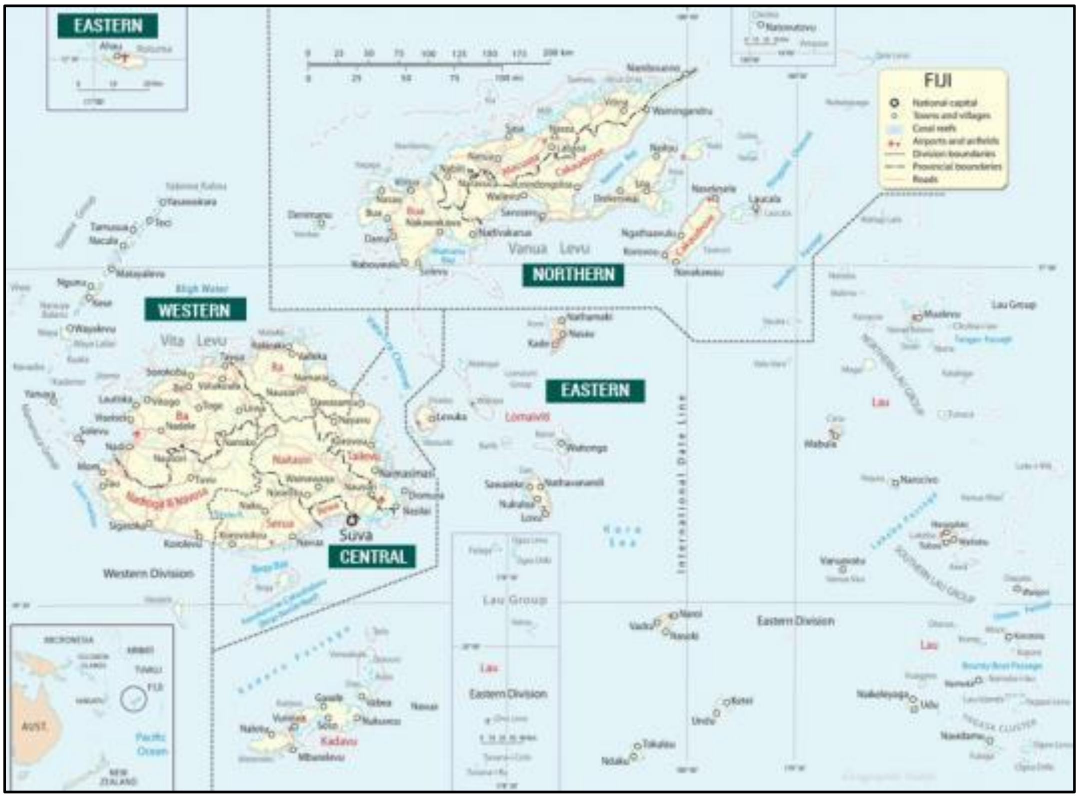
Fiji is the second most populated country in the region after Papua New Guinea. It has a population of approximately 909,400 (UN estimate, 2015) of which 87% reside on the two largest islands, Viti Levu and Vanua Levu. The nation's capital, Suva, is on Viti Levu and is the major centre for commerce in Fiji. Viti Levu has a sparsely populated interior and around 75% of the entire population of Fiji live on the coastline of the island, the majority in Suva. Other heavily populated areas include Nadi, hub of the tourism industry, and Lautoka, centre of the sugar industry.

Fijian is spoken by around 350,000 people as a first language. Another 200,000 use it as a second language. It is classed as an official language along with English and Hindustani, with English is the official language of government and the schools system. There are numerous different dialects of Fijian spoken around the islands, normally broken down into eastern and western dialects.

A national census of the population was conducted in 2007; further details are discussed in the third chapter of this thesis. The population of Fiji is considered to be made up of two main ethnicities, iTaukei (indigenous) Fijians (57%) and Indo-Fijians (38%) with the remaining 5% of the population comprised of people of other racial backgrounds including Chinese, European and people from Pacific Islands other than Fiji.[187] Christianity is the most prevalent religion among native Fijians while the majority of Indo-Fijians are Hindu or

Muslim. The relationship between the two main ethnic groups is complex and in the past has been an important factor in the island's politics.

Figure 11: Map of Fiji

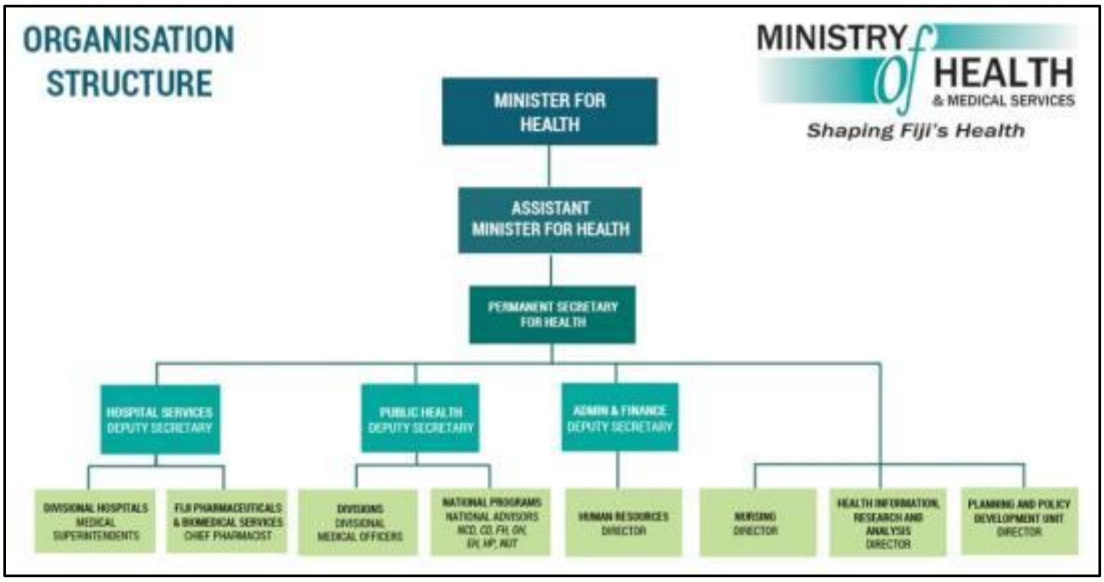


Fiji is ranked 90 out of 188 countries in the United Nations Human Development Index and has a gross domestic product of US dollars 4,532 per capita in 2014.[188,189] Indices of health are comparable for the two major ethnic groups. The average life expectancy for both groups is 67.5 years. It is estimated that 36% of the Indo-Fijian population live in poverty as compared to 34% of the iTaukei population.

Fiji's health system is headed by the Minister for Health, who is supported by an Assistant Minister and a Permanent Secretary for Health (Figure 10). Fiji's health system is administered by four divisions and twenty-one medical sub-divisions. Secondary and tertiary medical services are provided by three divisional hospitals two of which are considered as specialised national hospitals, one a dermatology, leprosy and tuberculosis hospital, the other a mental health institute. Primary care is provided at the village and district level, primarily by nurses. In 2014 there were 18 sub-divisional hospitals, more than 80 health centres and 99 nursing stations across the country.

Medical services are free of charge in Fiji but due to low number of doctors per capita long waiting times are common. Limited access to health facilities is however the biggest challenge. People from rural areas or remote islands often have to travel long distances to see a doctor or a nurse. As a result, doctors are only consulted for severe medical conditions, or those requiring long-term and expensive medication.

Figure 12: Fiji Ministry of Health's organisational structure



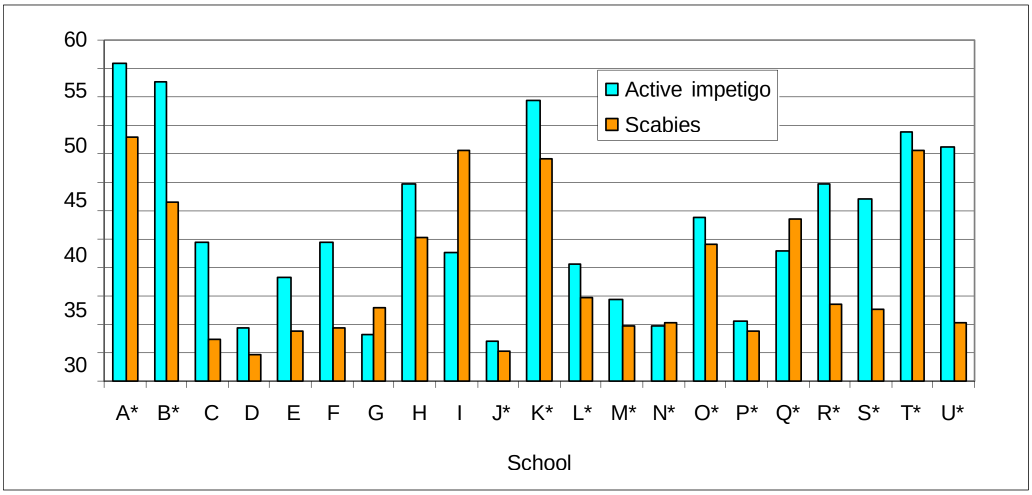
1.4.3. Scabies research and control in Fiji

Despite the growing interest in scabies and its complications in recent years, only a few observational and intervention studies had been conducted in Fiji to assess the prevalence of scabies and impetigo before the work presented in this thesis.

Three epidemiologic studies were conducted in 2006 and 2007 by Steer et al.[40]

The first was a large cross-sectional prevalence survey of scabies and impetigo in school children aged 5 to 15 years from 21 schools in the Central Division of Fiji. The study enrolled over 3400 primary school children.[40] After clinical skin examination was performed, 640 children were diagnosed with scabies (prevalence 18.5%, 95% CI 17.2 – 19.8). Of these, 191 (5.5%) children had evidence of secondary bacterial infection of scabies lesions and the prevalence of active impetigo was 25.6% (95% CI 24.1 – 27.1) (Figure 12). Children aged six years were at greatest risk of scabies and active impetigo with prevalence in this group of 26.6% and 33.9% respectively.[40] Participants with scabies or impetigo were referred to their local health clinic for treatment using local guidelines.[39]

Figure 13: Prevalence of impetigo and scabies at 21 primary schools in Fiji



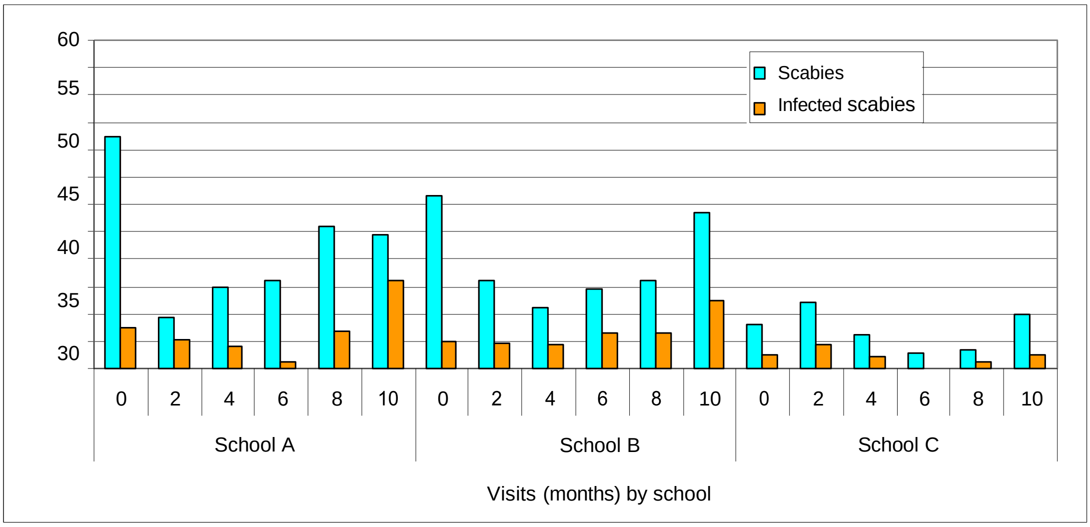
*Indicates rural school

Source: Steer et al. PLoS Neglected Tropical Diseases, 2009.[40]

The second was a prospective longitudinal study of scabies and impetigo in 457 Fijian school children over a period of ten months in 2006,[39] which documented for the first time the incidence of scabies, estimated at 51 cases per 100 child-years. This was a prospective cohort study performed in school children aged 5 – 15 years in three of the 21 schools included in the study described above. Two schools were Indigenous Fijian schools located in a rural area, while the third was a larger Indo-Fijian school located in Fiji's capital city, Suva. Each school was visited six times over a ten month period, at two monthly intervals. The examinations undertaken as part of the first larger study served as baseline visit in these three schools.

Of the 457 children seen, 23.0% had scabies and 40.9% had active impetigo at baseline but both varied across schools (Figure 13). The prevalence of scabies reduced by 57.8% at the second visit to a prevalence of 13.3% (95% CI 10.2 - 16.9, p<0.001), however this reduction was not maintained throughout the study period (prevalence at last visit 20.1%, 95% CI 16.3 – 24.4, p=0.3).[40]

Figure 14: Prevalence of scabies and infected scabies in three schools in Fiji

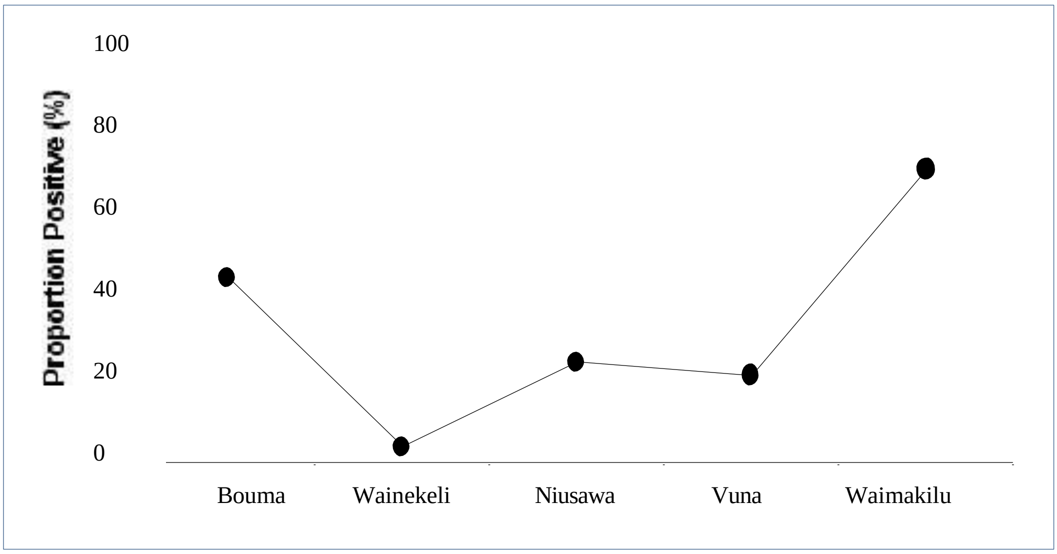


Source: Steer et al. PLoS Neglected Tropical Diseases, 2009.[40]

The third study by Steer et al. was a cross-sectional survey of 451 infants attending two maternal and child health care clinics, a rural and an urban one.[40] Participants had a median age of 20 weeks and were mostly (67%) of iTaukei ethnicity. Overall, 14% of infants received a scabies diagnosis while and 12% had evidence of impetigo. There were 36 participants (8%) with evidence of secondary bacterial infection of scabies lesions. Authors reported a clear association between GAS impetigo and scabies (OR 36.9, 95% CI 16.9 – 80.7).[40]

Thomas and colleagues conducted a study on the island of Taveuni, in the Northern Division of Fiji, to assess the prevalence of skin infections, soil-transmitted helminths and anaemia in school children.[190] After examining 258 children aged 5 to 15 years across five schools, 84 children were diagnosed with scabies, with an overall prevalence of 32%. Prevalence rates varied significantly across the five schools (Figure 14). Consistently with existing data in Fiji, the prevalence of scabies in children was high and no case of crusted scabies was found. However, in contrast with other studies, impetigo prevalence was low, with only 2% of children diagnosed with the disease.

Figure 15: Prevalence of scabies in children from five schools on Taveuni Islands, Fiji



Source: Thomas et al. The New Zealand Medical Journal, 2005.[190]

The only other intervention trial for scabies in Fiji, other than the one presented in this thesis, was conducted in 2004 by Haar and colleague (including the author).[118]

The study was a prospective trial comparing the efficacy and tolerability of two treatment strategies for scabies: benzyl benzoate and ivermectin. It was conducted in two villages of the Central Division of the main island of Viti Levu, Tailevu and Rewa. At the time of the study, benzyl benzoate was the standard treatment for scabies in Fiji, available at no cost through the clinics. A total of 750 participants were enrolled in the study: 435 in Tailevu and 325 in Rewa. In Tailevu those who consented in the study received 25% topical benzyl benzoate lotion, diluted to 12.5% for children aged 2 to 12 years, and 8.3% in those less than two years, according to local guidelines. In Rewa, participants were given a single dose of oral ivermectin at 200 μ/kg and permethrin cream 5% to children aged less than two years, pregnant and lactating women.

At baseline, scabies was high in both the benzyl benzoate and ivermectin groups: 38% and 24% respectively. The reduction in prevalence after the intervention was significant in both groups but slightly higher with benzyl benzoate (18% vs 14%). However, reported adverse events with topical treatment were also higher, with 9.5% complaining side effects compared to 2.4% of those who received ivermectin.[118] The main limitation of this study was the poor follow-up rates in both groups, particularly among adults, highlighting the importance of strategies to enhance community participation.

These studies documented the high burden of scabies and associated bacterial infections in Fiji and provide proof of principle that mass drug administration for scabies can reduce the prevalence of scabies at community level.

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Chapter 2

2.1. Prevalence of scabies and impetigo worldwide: a systematic review

Romani L, Steer AC, Whitfeld MJ, Kaldor JM. Prevalence of scabies and impetigo worldwide: a systematic review. **Lancet Infect Dis** 2015;15:960-7.

Prevalence of scabies and impetigo worldwide: a systematic review

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Scabies is a skin disease that, through secondary bacterial skin infection (impetigo), can lead to serious complications such as septicaemia, renal disease, and rheumatic heart disease. Yet the worldwide prevalence of scabies is uncertain. We undertook a systematic review, searching several databases and the grey literature, for population-based studies that reported on the prevalence of scabies and impetigo in a community setting. All included studies were assessed for quality. 2409 articles were identified and 48 studies were included. Data were available for all regions except North America. The prevalence of scabies ranged from 0·2% to 71·4%. All regions except for Europe and the Middle East included populations with a prevalence greater than 10%. Overall, scabies prevalence was highest in the Pacific and Latin American regions, and was substantially higher in children than in adolescents and adults. Impetigo was common, particularly in children, with the highest prevalence in Australian Aboriginal communities (49·0%). Comprehensive scabies control strategies are urgently needed, such as a community-based mass drug administration approach, along with a more systematic approach to the monitoring of disease burden.

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Introduction

Scabies is a skin disease caused by the mite *Sarcoptes scabiei*, which burrows under the skin and is transmitted through close personal contact.[1] Scabies and its complications are often regarded as disorders of resource-poor settings, and particularly affect young children.[1] The direct effect of scabies is debilitating itching, leading to scratching, which can result in complications due to bacterial infection of the skin (impetigo), predominantly by *Staphylococcus aureus* and *Streptococcus pyogenes*.[2] These complications range from local skin and soft tissue infections, including skin abscesses, cellulitis, and necrotising fasciitis, through to septicaemia, renal disease, and potentially rheumatic heart disease.[1,3] A more severe form of scabies called crusted or Norwegian scabies can occur in individuals who are immunosuppressed, including those with diabetes or HIV infection, and people who are malnourished, elderly people, or those living in institutions.[1] Scabies has several effective treatment options,[3] but population control is challenging because of the high levels of reinfestation that can occur through community and household contacts. The Global Burden of Disease Study 2010[4] estimated the worldwide prevalence of scabies to be 100 million. Countries of the Pacific region have been recognised as having a particularly high burden of scabies and its complications.[2,5–7]

Despite regular reports of its high prevalence, scabies has never been accorded priority in health programmes and research, perhaps because its disease complications are spread across a broad range of disciplines including dermatology, infectious diseases, and paediatrics. Endemic scabies and impetigo are also mainly diseases of tropical developing countries where resources for new health initiatives are scarce. Although scabies had previously been identified as a neglected disease,[3,8,9] it was only added to the WHO list of neglected tropical diseases in October, 2013.[10]

The only previous global assessment of scabies was focused on children and was published nearly a decade ago.[6] To better understand the extent of scabies and associated impetigo as health problems worldwide, we did a systematic review of prevalence studies of scabies, with the goal of guiding public health strategies for the control of the disease in endemic populations.

Methods

Search strategy and selection criteria

We searched for studies that reported on the epidemiology of scabies and impetigo, using a systematic review approach that followed the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines.[11] We searched Medline, Embase, and LILACS from January, 1985, to September, 2014, using the keywords "scabies", "*Sarcoptes scabiei*", "impetigo", "pyoderma", "skin disease", or "dermatology", combined with "incidence", "prevalence", "public health", "community", or "survey" (appendix). We did a search of the grey literature by seeking reports not published in peer-reviewed journals through a request via newsletter to the members of the International Alliance for the Control of Scabies, a search of the WHO website for reports on skin-related disease, a search of conference abstracts of meetings of the International Society of Dermatology, and a search of the Cochrane and Royal College of General Practitioners databases. No language restrictions were applied.

See Online for appendix

Study eligibility and quality assessment

We included population-based studies that reported on the prevalence of scabies in human populations in a community setting. All titles and abstracts of publications identified through the initial primary search, and information detected through a search of the grey literature, were reviewed for relevance by LR, with referral to ACS and JMK to resolve queries (figure 1). Full texts of papers were retrieved and checked for relevance by two authors (LR, ACS) independently of each other, with referral to JMK in the case of discordant opinions. Studies were excluded if they did not report the prevalence of scabies, or if they were deemed not to be population-based, including those reporting on outbreaks of scabies in institutions such as prisons, military barracks, or nursing homes, or a series of patients seen at specialty dermatology clinics, were excluded. When the same data were reported in two or more publications, we selected the most comprehensive paper. For studies with unclear methods we contacted authors to seek clarification. We presented data for impetigo prevalence rather than pyoderma, since pyoderma can include various bacterial skin infections such as folliculitis and ecthyma; however, when studies reported only prevalence of pyoderma without separating impetigo, we included it as a surrogate prevalence estimate for impetigo (appendix).

All included studies were assessed for quality on five criteria: definition of sampling frame, response rate, quality of scabies assessment, quality of impetigo assessment, and statistical analysis methods (appendix). All authors participated in assessment for quality, and all studies were independently reviewed by two authors, with disagreements resolved by referral to a third.

We established our own criteria for assessment of the quality of the included studies, modelled broadly on those used by the Cochrane collaboration for analytical studies[12] and on the STROBE guidelines for reporting observational studies.[13] The five criteria were assessed on a three-point numerical scale (0, 1, or 2) and involved assessment of selection bias through the quality of the sampling frame, attrition through assessment of non-response, detection bias through evaluation of the measurement criteria for the two key endpoints, and a form of reporting bias by showing how well the analysis had covered age and other key population descriptors. We also commented qualitatively on the overall representativeness of the body of published studies. We did not consider that such studies could be assessed against any criteria that corresponded to performance bias.

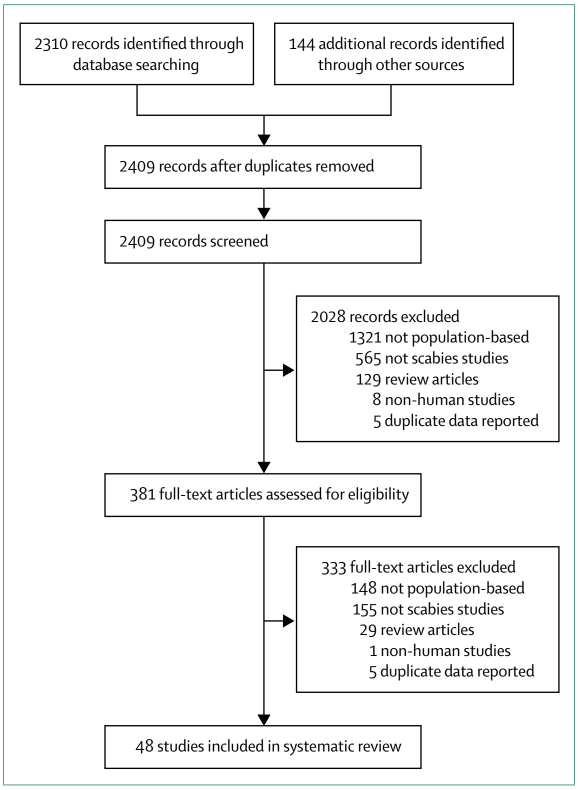

Figure 1: **Study profile**

Data extraction

Data were extracted by two authors (LR, ACS) with any disagreements referred to a third author (JMK) for resolution. Using Excel (version 14.4.4), we extracted the following variables from each study report: age range of participants, geographical region, sample size, sampling method, and study location including whether the setting was rural or urban. Each country was assigned a socioeconomic status, based on the UN Human Development Index (HDI)—a comparative measure of life expectancy, literacy, education, and standards of living which classifies countries from low to very high.[14] Regions, and subsequently countries, appear in alphabetical order (appendix). The association between scabies and impetigo prevalence was assessed visually by scatter plot.

Results

2182 records were identified through database searches and 272 additional datasets through other sources. After duplicates were removed, 2409 potentially relevant studies were first screened based on title and abstract, leaving 381 full manuscripts to be assessed for eligibility (figure 1). As a result of this assessment, 48 studies met the inclusion criteria (appendix).[2,7,15–60] Figure 2 shows the location of the studies reporting data in children (age <19 years).

Overall, the quality of the studies was poor (appendix). A common issue with quality was the scarce reporting of the criteria for diagnosis of scabies. Only four studies met minimum standards on all five criteria, 14 studies described sampling frames well, 21 studies gave response rates, 12 studies satisfactorily reported scabies assessment, and four satisfactorily reported on impetigo diagnosis. The sampling methods and sample size recorded varied substantially across studies. In some cases entire provinces or villages were selected, whereas in others the focus was on randomly selected schools or households. The largest studies were done in the Pacific region, including a study of around 18 000 people in Vanuatu and studies of roughly 10 000 people each in Fiji and the Solomon Islands.[55,57,60] Both the Vanuatu and Solomon Islands studies[57,60] recorded scabies prevalence data during a large-scale survey of yaws and leprosy, whereas the Fiji study[55] focused specifically on scabies

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prevalence, undertaken as a nationwide survey. The smallest sample size reported was 56 participants in Papua New Guinea.[56]

Most studies were in either medium or low HDI countries, or disadvantaged populations within high or very high HDI countries (appendix, figure 3). No population-based data were available from North America, most countries of Europe, or non-Aboriginal populations in Australia. The prevalence of scabies in European and Middle Eastern countries, where data were

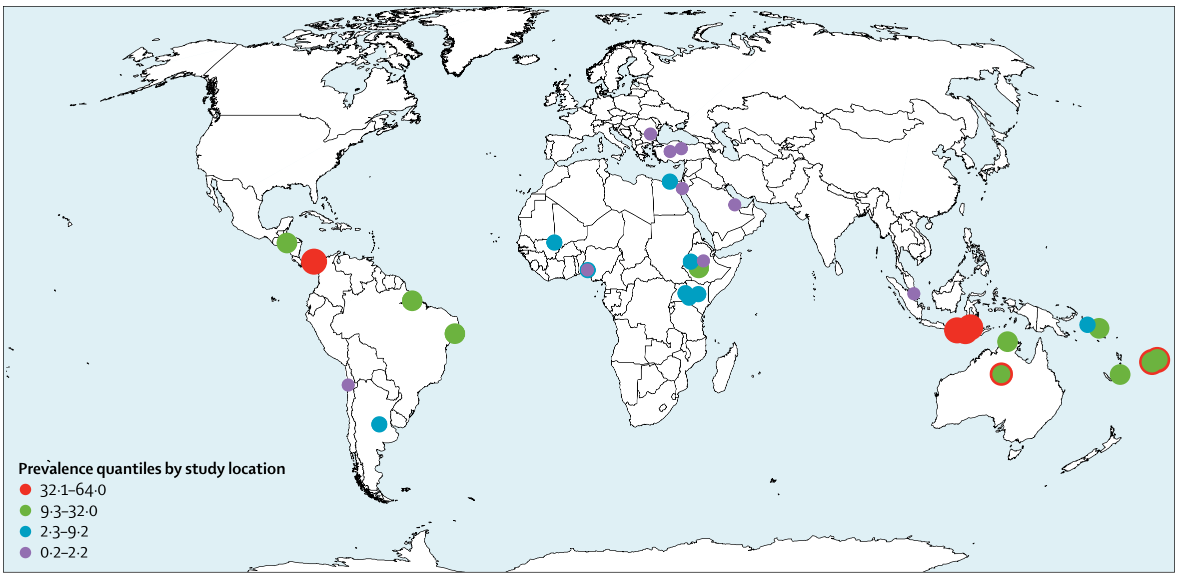

***Figure 2*: Map of scabies prevalence in children younger than 19 years**
This map shows the study sites for the 32 studies reporting data in children younger than 19 years (three studies were done at two sites).

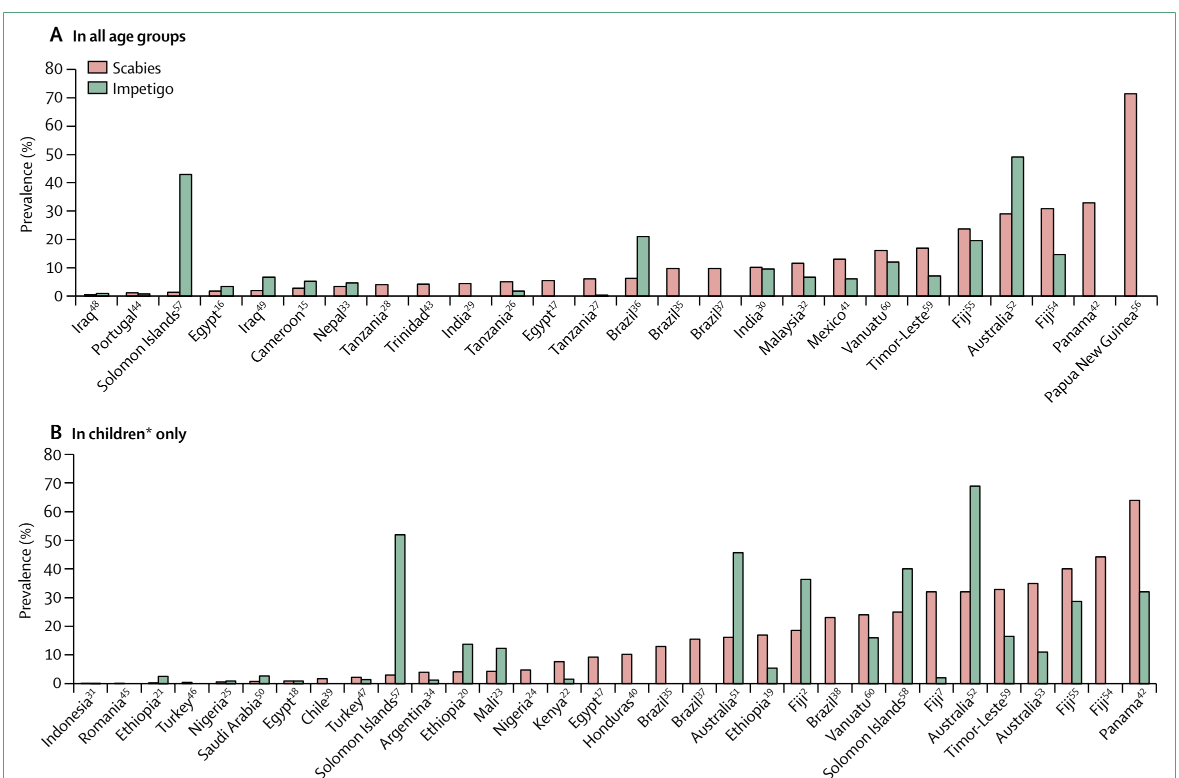

***Figure 3*: Scabies and impetigo prevalence by increasing scabies prevalence**
*Younger than 19 years.

available, was low (<2·2%). There was a broad range of prevalences noted in other regions, with consistently high prevalence in Pacific countries (figure 4).

Nearly half of the 48 included studies (n=21) were restricted to children. However, only nine studies reported on prevalence by age, with five of the paediatric studies further reporting data by age group. The prevalence of scabies was higher in children than in adults in all eight studies that reported on prevalence across several age groups (figure 5).[35,37,42,54,55,57,59,60] The highest prevalence of scabies reported in the general population was in Papua New Guinea (40 [71%] of 56) followed by Panama (245 [32%] of 756) and Fiji (242 [32%] of 760).[42,54,56] The highest scabies prevalence described in children was recorded in Panama, with scabies detected in 78% of children younger than 2 years and in 60% of those aged between 2 years and 6 years (participant numbers not reported).[42] In Fiji, prevalence of 44% (1053 of 2408) was reported in children aged 5–9 years[55] and scabies was present in 32% and 35% of children in two Australian Indigenous communities (numbers not reported).[52,53]

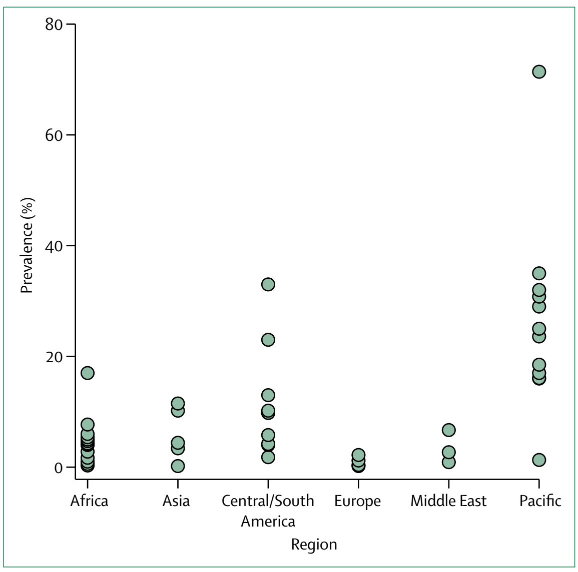

Figure 4: Scabies prevalence by geographical region

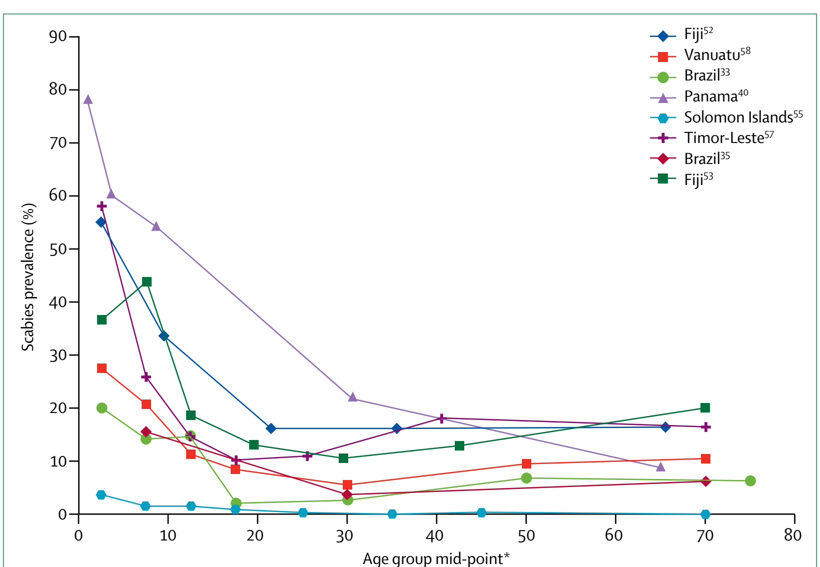

Figure 5: Scabies prevalence by age group in selected studies
*Age in the middle of each reported age group.

The prevalence of impetigo was recorded in 26 studies and was also generally high, particularly in two Aboriginal communities in northern Australia (49%)[52] and in the Solomon Islands (4370 [43%] of 10 224).[57] Like scabies, the prevalence of impetigo was generally higher in children than in adults, with 69% of children younger than 16 years in the Australian study affected.[52] High prevalence of impetigo in children was also fonotedund in Pacific countries, specifically the Solomon Islands (2678 [52%] of 5160), Fiji (1259 [36%] of 3462), and Vanuatu (16%; numbers not reported).[2,57,60] The prevalence of impetigo did not seem to strongly correlate with the prevalence of scabies across studies, both in the general population and in children (figure 6), although we did not formally assess this relation.

Discussion

This Review includes 48 studies done predominantly in countries with low or medium socioeconomic status, with the exception of Australia—where studies involved participants from remote Indigenous communities—and three countries in Europe. Although the methods and settings varied from one study to another, the papers included in this Review showed generally high prevalence of scabies and associated impetigo. The Global Burden of Disease Study 2010[4] provided an estimate of global prevalence but did not seem to base its estimate on a systematic review of the kind reported here. Scabies surveys were not selected on the basis of prevalence; however, they were mostly done in areas where scabies is perceived as a public health problem, and therefore likely to represent high-burden countries.

Island countries of the Pacific were the most affected populations, with scabies and impetigo particularly prevalent in children. Other areas where scabies prevalence was especially high included Panama, parts of Brazil, and Indigenous communities of northern Australia. Scabies and impetigo were particularly prevalent in tropical developing countries. The high prevalence in these countries might be due to low socioeconomic status, with resulting domestic crowding, but it might also be because scabies is inherently more suited to a tropical environment. Future studies should be undertaken to assess risk factors for scabies in more detail.

Although both skin disorders were more prevalent in children than in adults, they affected all age groups, and some studies showed a tendency for scabies to increase in prevalence in elderly people. Nearly half of the studies

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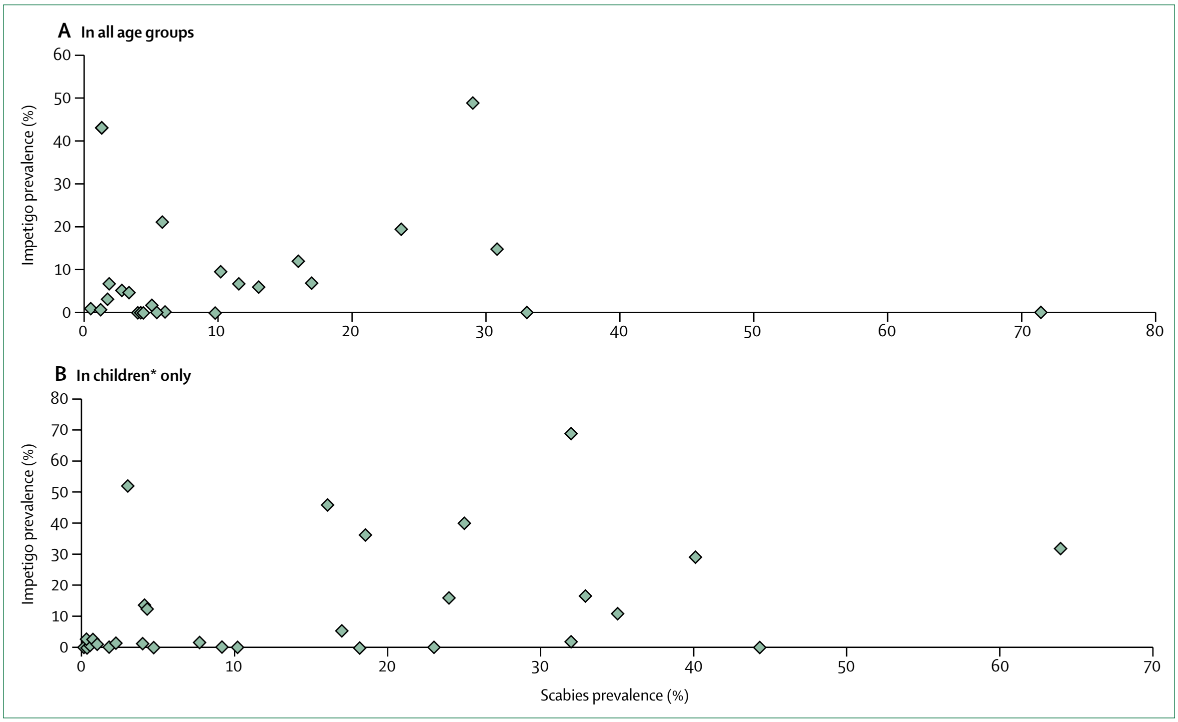

Figure 6: **Correlation of scabies and impetigo prevalence**
*Younger than 19 years.

included in this Review presented data sampled from all age groups, whereas the other half presented data for children only. Few papers presented a breakdown of scabies and impetigo prevalence by smaller age groups, making a reliable comparison of the disease distribution across age groups difficult between studies. A recommendation for future surveys is that age-specific prevalence be routinely provided, and that conventional 5-year age bands be the default for this information.

In view of the general understanding that scabies is one of the leading causes of impetigo, we were somewhat surprised that we did not note a stronger correlation across populations in the prevalence of the two conditions. Furthermore, some populations stood out for having either high rates of impetigo with relatively little scabies, or vice versa. Explanations for the first category could be an underdiagnosis of scabies, overestimation of impetigo prevalence for the reports for which we relied on pyoderma prevalence as a surrogate measure, or the presence of other important skin pathogens that are responsible for impetigo. In the second category, misdiagnosis is again a possible explanation. Resolution of this uncertainty will need more systematic and standardised surveys of scabies and impetigo, using consistent methods across populations, and further review of prevalence of impetigo and pyoderma worldwide is needed.

The main limitation of the available data was the heterogeneity of study design and methods. A key issue was the method of scabies diagnosis, which varied substantially across the included studies (appendix). No consensus criteria for the diagnosis of scabies exist. In some studies, recovery of live mites was needed for the diagnosis of scabies infestation,[23,42] whereas other studies used a clinical diagnosis, which was based on varying combinations of characteristic appearance (papules), characteristic distribution (such as the web spaces of fingers and toes), and the presence of itch, either in the individual or in family members.[2,36,58] The remaining 26 studies did not outline their diagnostic criteria in detail. Standardised and widely accepted diagnostic criteria and guidelines are clearly needed to guide future scabies and impetigo prevalence studies, so that comparison between studies and over time can be made more reliably. A process for the development of consensus and evidence-based diagnostic criteria for scabies is underway, led by the International Alliance for the Control of Scabies.[3] A further limitation was the targeted nature of the scabies surveys. Population-based studies are more likely to be done in settings where scabies is perceived as a clinical or public health issue, in regard to the selection of both the countries and the local areas within countries. Notably, no data from North

Search strategy and selection criteria

These are described in detail in the Methods section.

America and few from Europe were available. Publication bias could arise if scabies and impetigo data are not included in reports of skin surveys, on the grounds that they occurred rarely or were unimportant.

The sample sizes varied substantially in the included studies, ranging from fewer than 100 to more than 18000 participants. Only a few investigators clearly described the methods used to identify the sampling frame and the study sites selected. Our Review could have inadvertently included studies that were studies of outbreaks, rather than endemic disorders although we do not believe that to be the case. Finally, although we excluded non-population-based studies, data from these studies might have provided important information about scabies and impetigo epidemiology and risk factors worldwide.

The standard approach to scabies control is treatment of people with symptoms and their immediate household contacts. Although this strategy has provided relief for many individuals with scabies infestation, longitudinal data to suggest success in reducing long-term prevalence are scarce. Reinfestation is common in endemic settings, since people who have been effectively treated often come into contact with members of untreated households.[61] Further, in most settings the recommended treatment is a topical cream or lotion, such as permethrin or benzyl benzoate. Adherence to topical treatments is often low because they are laborious to apply, are often poorly tolerated because of itch, and are expensive.[62] An alternative to this strategy for endemic and hyperendemic regions is mass drug administration (MDA), which consists of the treatment of the entire community with topical medication, oral medication, or both. This approach has been successfully implemented in remote villages and islands, and in institutional outbreaks in schools, hospitals, prisons, and nursing homes.[42,58,63,64] The oral scabicide ivermectin is an attractive option for MDA. However, its widespread use has been hindered by a scarcity of safety data in young children and pregnant women, treatment cost, and an absence of trial data to support its use as an MDA agent.[3,65] A 2012 study in Zanzibar[66] assessed the effect that an annual ivermectin MDA programme for lymphatic filariasis had on scabies prevalence by retrospectively reviewing health clinic records for the number of patients treated for scabies.The authors reported a reduction of 68–98% in scabies cases over a 5-year period, suggesting that annual MDA with ivermectin might have had a substantial effect on the burden of scabies in the community. Future studies should assess whether such declines have been seen after ivermectin MDA programmes elsewhere, and establish the extent to which trends in clinic-based reports are matched by real declines in population prevalence. If trends in clinic reports are a valid surrogate for scabies prevalence, they could prove to be a more feasible method for impact assessment than prevalence surveys.[67] If MDA programmes are to be recommended more broadly for scabies control, further work consisting of mathematical modelling combined with empirical studies will be needed to define the threshold prevalence for taking this approach, as has been done for MDA in other disease areas such as lymphatic filariasis and onchocerciasis.[68]

The Integrated Management of Childhood Illness guidelines[5] are a comprehensive child health strategy developed by WHO and UNICEF for middle-income and low-income countries to identify (and treat) diseases in children younger than 5 years. In Fiji, these guidelines include the assessment of common skin diseases, such as scabies and impetigo, as part of the protocol to assess children's health.[5] We are not aware of such an expanded algorithm for the diagnosis and treatment of common childhood skin disorders being used in any other settings. Most of the studies of scabies prevalence in the Pacific region have been undertaken as international partnerships, allowing the cost, expertise, and time needed for such projects to be shared or obtained from competitive funding sources. The development of standardised algorithms for the diagnosis of scabies is likely to facilitate further scabies prevalence research.

We found that scabies and associated impetigo are common problems in many developing countries, affecting particularly children and communities in under-privileged areas and tropical countries, with a very high prevalence in the Pacific region. Despite methodological limitations affecting many of the published studies, scabies clearly remains a common and under-recognised health issue in many countries. In addition to the development and implementation of improved control strategies, more attention needs to be given to the conduct of comprehensive assessments of prevalence, based on repeatable and well documented methods, to identify the continuing need for and the effectiveness of control strategies as they are implemented.

Contributors

LR was the primary coordinator of data collection, analysis, and writing. ACS, MJW, and JMK supervised data collection, analysis, and writing. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Declaration of interests

We declare no competing interests.

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19 Figueroa JI, Fuller LC, Abraha A, Hay RJ. The prevalence of skin disease among school children in rural Ethiopia—a preliminary assessment of dermatologic needs. *Pediatr Dermatol* 1996; **13:** 378–81.
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2.2. Supplementary appendix

A. Search strategy

The following list shows steps in the key term strategy, using MEDLINE, resulting in the total number of abstracts screened.

# ▲	Searches	Results
1	Scabies/	2850
2	Sarcoptes scabiei/	578
3	Impetigo/	1100
4	Pyoderma/	2403
5	Skin Diseases/	48238
6	Dermatology/	13666
7	1 or 2 or 3 or 4 or 5 or 6	65501
8	Incidence/	181132
9	Prevalence/	197493
10	Epidemiology/	11652
11	Public Health/	61449
12	community.mp.	335996
13	Population/	27734
14	Survey.mp.	307666
15	8 or 9 or 10 or 11 or 12 or 13 or 14	1005365
16	7 and 15	2633
17	limit 16 to humans	2358
18	**limit 17 to yr="1985 -Current"**	**2182**

B. Bibliographic trail search results

The reference sections of all 381 studies which were retrieved in the primary search were reviewed for possible additional studies. Through these search, an additional three studies were included in the final analysis.

C. Quality assessment of included studies

The table summarises the quality assessment of all included reports using the following quality assessment framework.

Scoring matrix for 5 quality assessment elements:

A. Sampling frame defined

0. No information beyond overall population type (eg “schools” or “households”)
1. General information on sampling frame and procedures
2. Explicit details of procedures reported

B. Response rate

0. Not recorded/reported
1. Reported and under 65%
2. Reported and 65% or above

C. Quality of scabies assessment

0. No detail provided
1. General information on assessment methods
2. Detailed description on assessment methods and inclusion of diagnostic criteria

D. Quality of impetigo reporting and assessment

0. Not reported, or reported as pyoderma or other
1. Reported, but no diagnostic criteria
2. Reported, with diagnostic criteria

E. Statistical analysis

0. Only overall prevalence reported
1. Age-specific prevalence reported
2. Prevalence by age and other criteria (eg geographic, socio-demographic) reported

Citation	A. Sampling frame defined	B. Response rate	C. Quality of scabies assessment	D. Quality of impetigo assessment	E. Statistical analysis methods	Total quality score out of 10
[1] Al-Rubiay K, AL Rubaiy L. Dermatoepidemiology: A Household Survey Among Two Urban Areas In Basrah City, Iraq. *The Internet Journal of Dermatology* 2005; **4**(2).	2	2	0	1	0	5
[2] Abdel-Hafez K, Abdel-Aty MA, Hofny ERM. Prevalence of skin diseases in rural areas of Assiut Governorate, Upper Egypt. *International Journal of Dermatology* 2003; **42**(11): 887-92.	2	0	0	1	0	3
[3] Al Samarai AG. Prevalence of skin diseases in Iraq: a community based study. *Int J Dermatol* 2009; **48**(7): 734-9.	2	0	0	1	0	3
[4] Amin TT, Ali A, Kaliyadan F. Skin disorders among male primary school children in Al Hassa, Saudi Arabia: prevalence and socio-demographic correlates--a comparison of urban and rural populations. *Rural Remote Health* 2011; **11**(1): 1517.	2	2	0	1	0	6
[5] Andrews RM, Kearns T, Connors C, et al. A regional initiative to reduce skin infections amongst aboriginal children living in remote communities of the Northern Territory, Australia. *PLoS Negl Trop Dis* 2009; **3**(11): e554.	1	2	1	2	2	8
[6] Bissek AC, Tabah EN, Kouotou E, et al. The spectrum of skin diseases in a rural setting in Cameroon (sub-Saharan Africa). *BMC Dermatol* 2012; **12**: 7	1	2	1	1	1	6

[7] Bockarie MJ, Alexander ND, Kazura JW, Bockarie F, Griffin L, Alpers MP. Treatment with ivermectin reduces the high prevalence of scabies in a village in Papua New Guinea. *Acta Trop* 2000; **75**(1): 127-30.	0	0	1	0	0	1
[8] Carapetis JR, Connors C, Yarmirr D, Krause V, Currie BJ. Success of a scabies control program in an Australian aboriginal community. *Pediatr Infect Dis J* 1997; **16**(5): 494-9.	1	0	2	0	0	3
[9] Ciftci IH, Karaca S, Dogru O, Cetinkaya Z, Kulac M. Prevalence of pediculosis and scabies in preschool nursery children of Afyon, Turkey. *Korean J Parasitol* 2006; **44**(1): 95-8.	2	2	1	0	0	5
[10] Dos Santos MM, Amaral S, Harmen SP, Joseph HM, Fernandes JL, Counahan ML. The prevalence of common skin infections in four districts in Timor-Leste: a cross sectional survey. *BMC Infect Dis* 2010; **10**: 61.	1	1	0	0	1	3
[11] Eason RJ, Tasman-Jones T. Resurgent yaws and other skin diseases in the Western Province of the Solomon Islands. *Papua and New Guinea medical journal* 1985; **28**(4): 247-50.	1	2	0	0	1	4
[12] Estrada Castanon R, Andersson N, Hay R. Community dermatology and the management of skin diseases in developing countries. *Tropical Doctor* 1992; **22**(SUPPL. 1): 3-6.	1	0	0	0	0	1
[13] Feldmeier H, Jackson A, Ariza L, et al. The epidemiology of scabies in an impoverished community in rural Brazil: Presence and severity of disease are associated with poor living conditions and illiteracy. *Journal of the American Academy of Dermatology* 2009; **60**(3): 436-43	1	2	2	0	2	7

[14] Figueroa JI, Fuller LC, Abraha A, Hay RJ. The prevalence of skin disease among school children in rural Ethiopia - A preliminary assessment of dermatologic needs. *Pediatric Dermatology* 1996; **13**(5): 378-81.	0	0	1	0	1	2
[15] Figueroa JI, Hawranek T, Abraha A, Hay RJ. Prevalence of skin diseases in school children in rural and urban communities in the Illubabor province, south-western Ethiopia: A preliminary survey. *Journal of the European Academy of Dermatology and Venereology* 1997; **9**(2): 142-8.	0	0	0	1	2	3
[16] Gibbs S. Skin disease and socioeconomic conditions in rural Africa: Tanzania. *Int J Dermatol* 1996; **35**(9): 633-9	1	2	0	0	0	3
[17] Grills N, Grills C, Spelman T, et al. Prevalence survey of dermatological conditions in mountainous north India. *Int J Dermatol* 2012; **51**(5): 579-87.	2	2	1	0	0	5
[18] Haar K, Romani R, Filimone R, et al. Scabies community prevalence and mass drug administration (MDA) in two Fijian villages, 2013.	2	1	2	0	2	7
[19] Harris M, Nako D, Hopkins T, et al. Skin infections in Tanna, Vanuatu in 1989. *Papua New Guinea Medical Journal* 1992; **35**(2): 137-43.	1	2	0	1	2	6

[20] Hegazy AA, Darwish NM, Abdel-Hamid IA, Hammad SM. Epidemiology and control of scabies in an Egyptian village. *International Journal of Dermatology* 1999; **38**(4): 291-5.	0	0	2	0	2	4
[21] Henderson CA. Skin disease in rural Tanzania. *Int J Dermatol* 1996; **35**(9): 640-2	1	2	0	1	0	4
[22] Heukelbach J, Wilcke T, Winter B, Feldmeier H. Epidemiology and morbidity of scabies and pediculosis capitis in resource-poor communities in Brazil. *Br J Dermatol* 2005; **153**(1): 150-6	1	2	2	2	2	9
[23] Inanir I, Sahin MT, Gunduz K, Dinc G, Turel A, Ozturkcan S. Prevalence of skin conditions in primary school children in Turkey: differences based on socioeconomic factors. *Pediatr Dermatol* 2002; **19**(4): 307-11.	1	0	1	1	0	3
[24] Jackson A, Heukelbach J, Filho AF, Junior Ede B, Feldmeier H. Clinical features and associated morbidity of scabies in a rural community in Alagoas, Brazil. *Trop Med Int Health* 2007; **12**(4): 493-502.	2	2	2	0	2	8
[25] Kottenhahn RK, Heck JE. Prevalence of paediatric skin diseases in rural Honduras. *Trop Doct* 1994; **24**(2): 87-8.	0	0	0	1	1	2
[26] Lawrence G, Leafasia J, Sheridan J, et al. Control of scabies, skin sores and haematuria in children in the Solomon Islands: another role for ivermectin. *Bull World Health Organ* 2005; **83**(1): 34-42.	1	0	2	1	0	4
[27] Lee J, Koh D, Andijani M, et al. Effluents from a pulp and paper mill: a skin and health survey of children living in upstream and downstream villages. *Occup Environ Med* 2002; **59**(6): 373-9.	2	0	1	1	0	4

[28] Mahe A, Prual A, Konate M, Bobin P. Skin diseases of children in Mali: A public health problem. *Transactions of the Royal Society of Tropical Medicine and Hygiene* 1995; **89**(5): 467-70.	2	0	2	0	0	4
[29] Massa A, Alves R, Amado J, et al. [Prevalence of cutaneous lesions in Freixo de Espada a Cinta]. *Acta Med Port* 2000; **13**(5-6): 247-54.	0	1	0	1	0	2
[30] Meireles V, Barros C, Bacelar H. Incidence of scabies in students of public school in Belém-Pará. *Rev para med* 2001; **15**(4): 47-50.	1	0	0	0	0	1
[31] Murgia V, Bilcha KD, Shibeshi D. Community dermatology in Debre Markos: an attempt to define children's dermatological needs in a rural area of Ethiopia. *International Journal of Dermatology* 2010; **49**(6): 666-71.	1	0	0	0	0	1
[32] Norhayati binti Moktar M, Noor Hayati MI, Nor Fariza N, et al. Health status of Orang Asli (aborigine) community in Pos Piah, Sungai Siput, Perak, Malaysia. *Southeast Asian J Trop Med Public Health* 1998; **29**(1): 58-61.	0	0	0	1	1	2
[33] Ogunbiyi AO, Owoaje E, Ndahi A. Prevalence of skin disorders in school children in Ibadan, Nigeria. *Pediatr Dermatol* 2005; **22**(1): 6-10.	0	0	0	1	0	1

[34] Ogunbiyi AO, Omigbodun Y, Owoaje E. Prevalence of skin disorders in school children in southwest Nigeria. *Int J Adolesc Med Health* 2009; **21**(2): 235-41.	1	0	0	0	0	1
[35] Paldaof H, Dagatti M, Dalla Costa M, et al. Detection of school-age dermatoses: a study of 800 cildren in the Santa Fe province. *Arch Argent Dermatol* 1999; **49**(1): 37-40.	1	0	0	1	0	2
[36] Popescu R, Popescu CM, Williams HC, Forsea D. The prevalence of skin conditions in Romanian school children. *Br J Dermatol* 1999; **140**(5): 891-6.	1	2	0	0	0	3
[37] Rao GS, Kumar SS, Sandhya. Pattern of skin diseases in an Indian village. *Indian J Med Sci* 2003; **57**(3): 108-10.	0	0	0	1	0	1
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[41] Satimia FT, McBride SR, Leppard B. Prevalence of skin disease in rural Tanzania and factors influencing the choice of health care, modern or traditional. *Arch Dermatol* 1998; **134**(11): 1363-6.	2	0	0	0	0	2
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[47] Wong LC, Amega B, Barker R, et al. Factors supporting sustainability of a community-based scabies control program. *Australas J Dermatol* 2002; **43**(4): 274-7.	0	2	0	0	0	2
[48] Yamamah GA, Emam HM, Abdelhamid MF, et al. Epidemiologic study of dermatologic disorders among children in South Sinai, Egypt. *Int J Dermatol* 2012; **51**(10): 1180-5.	2	0	1	1	0	4

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D. Supplementary Table. Scabies and impetigo prevalence studies included in the review

REGION	COUNTRY	NATIONAL SOCIO ECONOMIC STATUS CLASSIFICATION	YEAR OF SURVEY	STUDY AREA	SAMPLING METHOD	AGE	SAMPLE SIZE	SCABIES PREVALENCE	IMPETIGO PREVALENCE	AUTHOR AND YEAR OF PUBLICATION
Africa	Cameroon	Low	2010	4 villages in 1 subdivision	Convenience sampling	9 to 51 yrs	400	2.8%	5.2%	Bissek 2012 [6]
	Egypt	Medium	1994	3 villages	Systematic random sample (all residents in every other house)	All	8008	1.7%	3.3%	Abdel Hafez 2003 [2]
	Egypt	Medium	1997	1 village	Convenience sampling	All	3147	5.4% <10y: 11.1, 10-19y: 7.3%	Not reported	Hegazy 1999 [20]
	Egypt	Medium	2009	4 areas in 1 city	Convenience sampling	< 18 yrs	2194	<1%	<1%	Yamamah 2012 [48]
	Ethiopia	Low	1992	1 School	Randomly selected children	5 to 16 yrs	112	17.0%	5.4% *	Figueroa 1996 [14]
	Ethiopia	Low	1995	3 schools in 1 province	Randomly selected children	5 to 15 yrs	212	4.1%	13.7%	Figueroa 1997 [15]
	Ethiopia	Low	Not specified	2 schools in 2 areas	Convenience sampling	7 to 19 yrs	1104	0.3%	2.6% *	Murgia 2010 [31]
	Kenya	Low	1999	13 schools in 4 villages	Randomly selected schools	3 to 17 yrs	4961	7.7%	1.6%	Schmeller 2001 [42]
	Mali	Low	1993	All schools in 1 region	Randomly selected children in 30 clusters.	< 13 yrs	1817	4.3%	12.3% *	Mahe 1995 [28]
	Nigeria	Low	Not specified	1 school	all children	4 to 15 yrs	1066	4.7%	0.0%	Ogunbiyi 2005 [33]
	Nigeria	Low	Not specified	15 schools, 1 state	Randomly selected children	10 to 20 yrs	1415	0.6%	1.0% *	Ogunbiyi 2009 [34]

	Tanzania	Low	1994	2 villages	Randomly selected households	All	1114	5.0%	1.7% *	Gibbs 1996 [16]
	Tanzania	Low	1991	1 village	One third randomly selected	All	936	6.0%	0.3%	Henderson 1996 [25]
	Tanzania	Low	Not specified	1 village	Randomly selected households	All	800	4.0%	Not reported	Satimia 1998 [41]
Asia	India	Medium	2010	8 villages in 1 state	All residents in randomnly selected villages	All	1250	4.4%	Not reported	Grills 2012 [17]
	India	Medium	Not specified	1 village	Convenience sampling	All	3673	10.2%	9.5%	Rao 2003 [37]
	Indonesia	Medium	1999	3 villages	Randomly selected households	< 12 yrs	433	0.2%	0.2%	Lee 2002 [27]
	Malaysia	High	1993	All 4 villages in 1 region	Convenience sampling	All	356	11.5%	6.7%	Norhayati 1998 [32]
	Nepal	Low	Not specified	5 villages in 1 distric	Randomly selected residents	All	878	3.4%	4.7%	Walker 2007 [46]
Central and South America	Argentina	Very High	1997	4 schools in 2 cities	All children	5 to 13 yrs	800	4.0%	1.3%	Paldaof 1999 [35]
	Brazil	High	2003	1 village	All households	All	1014	9.8% <4y: 20.1%, 5-9y: 14.4%, 10-14y: 14.9%, 15-19y: 2.1%	Not reported	Feldmeier 2009 [13]
	Brazil	High	2001	1 Urban slum and 1 Fishing village	representive population, all households	All	1733	5.8%	21.1%	Heukelbach 2005 [22]
	Brazil	High	2005	3 districts in 1 village	Convenience sampling	All	2003	9.8% <15y: 15.5%, 15-49y:3.7%, >50y: 6.1%	Not reported	Jackson 2007 [24]
	Brazil	High	Not specified	1 school, 1 city	All children	15 to 17 yrs	100	23.0%	Not reported	Meireles 2001 [30]

	Chile	Very High	1995	20 schools in 1 city	Convenience sampling	6 to 14 yrs	1122	1.8%	Not reported	Sagua 1997 [40]
	Honduras	Medium	1992	1 village	All children attending a temporary clinic	< 18 yrs	206	10.2%	20.9%	Kottenhanh 1994 [25]
	Mexico	High	Not specified	1 state	41 "sentinel sites", residents who underwent consultation	All	3812	13.0%	6.0% *	Estrada 1992 [12]
	Panama	High	1986	1 island	All residents	All	756	33.0% <2y: 78.0%, 2-6y: 60.0%, 6-10y: 54.0%	<10y: 32.0% *	Taplin 1991 [44]
	Trinidad	High	1988	1 village	All residents	All	313	4.2%	Not reported	Reid 1990 [38]
Europe	Portugal	Very High	1994	1 village	All residents	All	1037	1.2%	0.7%	Massa 2000 [29]
	Romania	High	1995	3 schools in 1 village	Randomly selected schools	6 to 12 yrs	1114	0.2%	Not reported	Popescu 1999 [36]
	Turkey	High	2005	43 pre-school nurseries in 1 city	All children	4 to 6 yrs	1134	0.4%	Not reported	Ciftci 2006 [9]
	Turkey	High	Not specified	2 schools in 1 city	Randomly selected children	6 to 14 yrs	785	2.2%	1.4%	Inanir 2002 [23]
Middle East	Iraq	Medium	Not specified	2 areas in 1 city	Randomly selected areas	All	6666	0.5%	0.9%	Al Rubiay 2005 [1]
	Iraq	Medium	Not specified	1545 households in 2 cities	Randonly selected househlds	All	8000	1.9%	6.7%	Al Samarai 2009 [3]
	Saudi Arabia	Very High	2009	16 schools in 1 province	Male children in randomly selected schools	6 to 13 yrs	1337	0.7%	2.7%	Amin 2011 [4]
Pacific	Australia	Very High	2004	5 remote Aboriginal communities in 1 region	All children	< 15 yrs	583	16.1%	45.7%	Andrews 2009 [5]
	Australia	Very High	1994	1 Aboriginal-inhabited island	All residents	All	125	29.0% 16y: 32.0%	49.0% * <16y: 69.0%	Carapetis 1997 [8]

Australia	Very High	2000	1 remote Aboriginal community	All resident children under 5	< 5 yrs	217	35.0%	11.0% *	Wong 2001 [47]
Fiji	Medium	2004	5 schools in villages on 1 island	all children	5 to 15 yrs	258	32.0%	2.0%	Thomas 2005 [45]
Fiji	Medium	2006	21 schools in 1 division	Randomly selected schools, all children	5 to 15 yrs	3462	18.5%	36.4%	Steer 2009 [43]
Fiji	Medium	2004	2 villages	All residents	All	760	30.8% <5y:55.0%, 5-14y: 33.7%, 15-29y:16.2%, >30y: 18.9%	14.7% #	Haar 2013 [18]
Fiji	Medium	2007	75 randomly selected villages, nationwide	All residents	All	10887	23.6% <5y: 36.5%, 5-9y: 43.7%	19.6% <5y: 23.1%, 5-9y: 34.2%	Romani 2009 [39]
Papua New Guinea	Low	1996	2 villages in 1 district	Lymphatic filariasis program participants	All	56	71.4%	Not reported	Bockarie 2000 [7]
Solomon Islands	Low	1984	1 Province	Yaws program participants	All	10224	1.3% <10y: 3.0%	43.0% * <15y: 52.0%	Eason 1985 [11]
Solomon Islands	Low	1997	2 islands	All children	< 12 yrs	267	25.0%	40.0%	Lawrence 2005 [26]
Timor Leste	Medium	2007	14 sites in 4 districts	Convenience sampling	All	1535	17.0% <5y:58.0%, 6-10y: 26.0%, 11-15y: 14.7%	7.0% * <5y:30.3%, 6-10y: 12.3%, 11-15y: 7.0%	Dos Santos 2010 [10]
Vanuatu	Medium	1989	1 island	Yaws program participants	All	18223	16.0% <10y: 24.0%	12.0% <10y: 16.0%	Harris 1992 [19]

* Data reported as "pyoderma"
\# Data reported as "skin sores"

Chapter 3

3.1 Scabies and impetigo prevalence and risk factors in Fiji: a national survey

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PLOS | NEGLECTED TROPICAL DISEASES

RESEARCH ARTICLE

Scabies and Impetigo Prevalence and Risk Factors in Fiji: A National Survey

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Abstract

Background

Scabies is recognised as a major public health problem in many countries, and is responsible for significant morbidity due to secondary bacterial infection of the skin causing impetigo, abscesses and cellulitis, that can in turn lead to serious systemic complications such as septicaemia, kidney disease and, potentially, rheumatic heart disease. Despite the apparent burden of disease in many countries, there have been few large-scale surveys of scabies prevalence or risk factors. We undertook a population-based survey in Fiji of scabies and impetigo to evaluate the magnitude of the problem and inform public health strategies.

Methodology/Principal Findings

A total of 75 communities, including villages and settlements in both urban and rural areas, were randomly selected from 305 communities across the four administrative divisions, and all residents in each location were invited to participate in skin examination by trained personnel. The study enrolled 10,887 participants. The prevalence of scabies was 23.6%, and when adjusted for age structure and geographic location based on census data, the estimated national prevalence was 18.5%. The prevalence was highest in children aged five to nine years (43.7%), followed by children aged less than five (36.5%), and there was also an indication of prevalence increasing again in older age. The prevalence of scabies was twice as high in iTaukei (indigenous) Fijians compared to Indo-Fijians. The prevalence of impetigo was 19.6%, with a peak in children aged five to nine years (34.2%). Scabies was very strongly associated with impetigo, with an estimated 93% population attributable risk.

Conclusions

As far as we are aware, this is the first national survey of scabies and impetigo ever conducted. We found that scabies occurs at high levels across all age groups, ethnicities, and geographical locations. Improved strategies are urgently needed to achieve control of scabies and its complications in endemic communities.

Competing Interests: The authors have declared that no competing interests exist.

Author Summary

Recently added to the World Health Organization list of neglected tropical diseases, scabies is an under-recognised cause of morbidity in many developing countries, due to secondary bacterial infection of the skin that can in turn lead to serious systemic complications such as kidney disease and, potentially, rheumatic heart disease. Despite the apparent burden of disease in many countries, there have been few large-scale surveys of scabies prevalence or risk factors. We undertook a population-based survey in Fiji of scabies and impetigo to evaluate the magnitude of the problem and inform public health strategies. We examined 10,887 people across 75 communities in all four geographical divisions of Fiji, covering both urban and rural areas. The national prevalence of scabies and impetigo was 23.6% and 19.6% respectively, and highest in children aged 5–9 years. We found that scabies was very strongly associated with impetigo. Scabies was twice as high in iTaukei (indigenous) Fijians compared to Indo-Fijians. Our study shows that scabies occurs at high levels across all age groups, ethnicities, and geographical locations. Improved strategies are urgently needed to achieve control of scabies and its complications in endemic communities.

Introduction

Scabies is a skin disease caused by infestation with a tiny mite (*Sarcoptes scabiei*) that burrows under the skin and is transmitted through close personal contact [1]. The direct effect of scabies is debilitating itching, leading to scratching, which is in turn followed by complications due to bacterial infection of the skin, ranging from impetigo, abscesses and cellulitis, through to septicaemia and even death [1]. Bacterial infections secondary to scabies can also lead to more serious sequelae associated with group A streptococcal infection such as rheumatic fever and glomerulonephritis [2–6].

Scabies and its complications are considered endemic in most Pacific Island countries and in many other tropical countries including in Africa largely on the basis of anecdotal reporting. Prevalence surveys of scabies have been conducted in localized areas of a limited number of countries [7–14]. These studies have generally confirmed high levels of scabies in these locations but none have been national that we are aware of, and have not been sufficiently broad-based to provide the basis for developing and informing national disease control strategies.

Scabies was recently added to the World Health Organization's list of Neglected Tropical Diseases, but has generally not been recognised as a public health priority in most developing countries, perhaps because of the absence of large scale surveys to fully define its extent and risk factors [3]. In order to provide comprehensive information on the prevalence of scabies and impetigo and the effect of demographic risk factors in a country believed to be highly endemic for these conditions, we undertook a national prevalence survey in Fiji.

Methods

Setting

Fiji is an island nation located in the South Pacific region. Its population, estimated at 851,744 in 2011 is located on an archipelago of more than 300 islands, and made up predominantly of iTaukei (indigenous) Fijians (57%) and Indo-Fijians (38%) [15].

Fiji is ranked 96 out of 187 countries in the United Nations Human Development Index, with a Gross Domestic Product (GDP) per capita of US dollars 4,728 in 2012 [16,17].

Fiji's national territory is divided into four administrative divisions and twenty medical subdivisions. Primary care is provided at the village and district level, primarily by nurses, and secondary and tertiary medical services are provided by three divisional hospitals of which two are considered as specialised national hospitals. The training component of the study was conducted at Tamavua Twomey Hospital, the national referral hospital for skin diseases, leprosy and tuberculosis, located in the capital Suva.

Study design

A cross-sectional survey of the national population was conducted to assess the prevalence of scabies and impetigo. The study, conducted in 2007, followed the sampling methodology of a survey previously undertaken as part of the Pacific Elimination of Lymphatic Filariasis programme (PacELF) in Fiji.

Study sampling

For the lymphatic filariasis survey, the Fiji population was divided into 23 strata designated by medical area within which there were 305 administrative units [18]. Under Fijian administrative designation, each unit was either a village or a settlement. Generally villages are rural and settlements urban or peri-urban, but there is some cross-over. The survey used a stratified cluster sampling method with stratification at the medical area level and administrative units designated as clusters. The target sample size was 17,250. After stratification 198 administrative units were randomly selected. For villages and settlements with a population above 200, a sample of 200 randomly chosen residents was invited to participate, whereas for those with less than 200 the entire population was invited.

Due to resource constraints, the scabies survey was not able to aim for a sample size as large as that of the lymphatic filariasis survey, so a member of the Fiji Ministry of Health randomly selected a subset (n = 77) of the PacELF survey sites. This number was chosen so that a minimum total sample size could be achieved within each of the four divisions. In contrast to the PacELF survey, all members of selected communities were invited to participate (rather than limiting to 200 in communities with populations above 200). Of the sites selected, two were excluded: one refused (see below) and the other was unable to participate in the study because of flooding.

Study procedures

For each community selected, approval of the chief was first sought. All residents were then sent a letter from the Fiji Ministry of Health describing the purpose and methods of the study. Eight Fijian senior nurses were selected and trained on the diagnosis and treatment of scabies and impetigo, as well as on research methodology, and divided into four survey teams, one per geographical division. Each team, made of two nurses and one village health worker, visited the study site and provided an overview of the project and invited residents to participate. The study coordinator attended several visits to assist the team, assess the quality of the survey procedures and take photos of scabies cases. Those who consented provided demographic details and underwent a complete skin examination by trained personnel. All exposed areas of the skin were examined and genitals and perimamillar regions were only examined if participants described symptomatic itching in these regions and consented for examination. All examinations were conducted in private areas using opaque screens. Participants were also invited to complete a brief clinical questionnaire regarding previous diagnosis and treatment of scabies and other skin conditions, and participants who were illiterate or with low vision were provided assistance to complete the questionnaire by the study staff Consent for children and adolescents under 18 years of age was provided by parents or guardians. All clinical results were made available to the local community care nurses, and study participants diagnosed with scabies or other skin conditions were referred for treatment to the local nursing station.

Case definitions

Scabies was diagnosed on the basis of characteristic clinical findings, defined as the presence of pruritic inflammatory papules with a typical acral distribution [19]. Impetigo was defined as papular, pustular or ulcerative lesions surrounded by erythema with or without the presence of crusts, frank pus or bullae. Impetigo lesions were counted and classified according to their number (1 to 4, 5–20 or more than 20 lesions) and graded as flat/dry (old, almost healed sores with no crust), crusted (yellow or red scab over a skin sore) or purulent (wet or moist sores with obvious presence of pus). If a mixture of impetigo types were seen, the dominant sore type was recorded.

Statistical analysis

Participant characteristics were summarised by demographic categories (age, sex, ethnicity, Fiji administrative division, urban/rural) and compared to the distribution of these characteristics in the 2007 national census data. Prevalence of scabies and skin sores were calculated for the whole population and by each of the demographic categories. Univariate and multivariate logistic regression models were used to identify factors independently associated with a high prevalence of scabies and impetigo. The age and division specific prevalences were used to calculate national estimates of scabies and impetigo prevalences, standardising against age and division specific national census figures. The population attributable risk was calculated to estimate the association between scabies and skin sore prevalence [20]. All statistical analyses were conducted using STATA 12.0 (College Station, TX, USA).

Ethical approvals

Ethical approval for this study was obtained from the Fiji National Research Ethics Review Committee and the Fiji National Health Research Committee and reviewed by the St Vincent's Hospital (Sydney) Research and Ethics Committee. Persons 18 years and over, willing to sign an informed consent form, and village members under 18 years old with a consent form signed by a parent/guardian were included in the study.

Results

A total of 75 sites were included in the survey, with a median proportion of 82% of the official resident population examined in each village, with an overall participation rate of 78.2%. In 72 of the villages the proportion examined was 60% or more. A total of 10,887 study participants were enrolled. As shown in Table 1, the demographic characteristics of the study sample were broadly comparable to that of the 2007 census population in regard to age and ethnicity, but there was substantial over-representation of younger age groups (54% of the sample was aged less than 15 years compared to 29% from census data), and of people from the Northern division of Fiji (40.0% of the sample vs. 16.2% from census data).

Scabies was observed in 2,564 participants (23.6%) of the population surveyed (Table 2). Prevalence was highest in children aged five to nine years (43.7%, adjusted odds ratio, OR, 3.7 when compared to those aged over 49 years, Fig. 1). Scabies was nearly twice as common in iTaukei Fijians (24.7%, adjusted OR 2.7 when compared to the Indo-Fijian population). Scabies was most prevalent in people living in the Northern division (28.5%), in people living in rural

Table 1. Demographic characteristics of the study sample compared to national census data.

Factor		Study (n = 10,887)		Census (n = 837,271)
		n	%	%
Gender	Female	5491	50.4	49.0
	Male	5396	49.6	51.0
Ethnicity	iTaukei	7580	69.6	56.8
	Indo-Fijian	3183	29.2	37.5
	Other	124	1.2	5.7
Age (years)*	<5	1023	9.4	9.9
	5–9	2408	22.1	9.3
	10–14	2448	22.5	9.8
	15–24	1587	14.6	19.1
	25–34	1256	11.5	16.4
	35–49	1131	10.4	19.5
	>49	951	8.7	16.0
Division	Western	3036	27.9	38.2
	Central	2955	27.2	40.9
	Eastern	538	4.9	4.7
	Northern	4358	40.0	16.2
Location	Rural	6304	57.9	50.7
	Urban/Peri Urban	4583	42.1	49.3

*data on 83 participants were not recorded

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areas (25.6%) and in females (24.8%). Taking into account the census distribution of age and geographical location by direct adjustment, the estimated national prevalence of scabies was 18.5% (95% CI 14.7–22.9). There were no cases of crusted scabies detected in this study.

The prevalence of impetigo was also high, with lesions observed in 19.6% of participants (Table 3). Impetigo followed a similar age distribution to scabies, being more common in children aged five to nine years (34.2%, adjusted OR 2.2). Similar to scabies, impetigo prevalence was twice as high in the iTaukei Fijians (22.8%, adjusted OR 2.4), in females (20.5%), in people living in rural areas (21.4%) and in the Northern division (23.7%). When taking into account the census distribution of age and geographical location the national prevalence of impetigo was 18.5% (95% CI 12.3–20.2). The majority of impetigo lesions were mild (53.5%) and flat/dry (54.8%), although severe cases were not uncommon (16.2%) and over a quarter of the sores were purulent (26.6%, Table 4).

The presence of impetigo was strongly associated with a diagnosis of scabies (relative risk, RR, 58.6, 95% CI 48.7–70.5). The population attributable risk of scabies as a cause of impetigo based on the national survey was 93.1%.

Study participants who reported a previous diagnosis of scabies (n = 2923, 26.9%) were more likely to have scabies infestation at the time of the survey (51.4%) compared to those who did not recall a prior scabies diagnosis (13.3%, RR 3.4, 95% CI 3.2–3.6). Similarly, participants reporting prior treatment (n = 1586, 14.6%) had a higher prevalence of scabies than those who did not (RR 2.7, 95% CI 2.6–2.9). Of those who reported prior treatment, the most common treatment was topical cream of an unspecified type (39.1%) followed by various local plant-based treatments (36.9%) and benzyl benzoate (12.8%). At the time of the survey, permethrin

Table 2. Prevalence of scabies in Fiji.

Factor		Sample	Participants with scabies			Adjusted OR† (95% CI)
		n	n	%	95% CI	
Total		10,887	2564	23.6	22.8–24.3	
Gender	Female	5491	1361	24.8	23.6–26.0	1.2 (1.1–1.3)
	Male	5396	1203	22.3	21.2–23.4	1
Ethnicity	iTaukei	7580	2077	27.4	26.4–28.4	2.7 (2.4–3.0)
	Indo-Fijian	3307	487	14.7	13.6–16.0	1
Age (years)*	<5	1023	373	36.5	33.5–39.5	2.5 (2.0–3.0)
	5–9	2408	1053	43.7	41.7–45.7	3.7 (3.0–4.4)
	10–14	2448	457	18.7	17.4–20.6	1.0 (0.8–1.2)
	15–24	1587	209	13.2	11.5–14.9	0.6 (0.5–0.8)
	25–34	1256	134	10.7	9.0–12.5	0.5 (0.4–0.6)
	35–49	1131	147	13.0	11.1–15.1	0.6 (0.5–0.8)
	>49	951	191	20.1	17.6–22.8	1
Division	Western	3036	644	21.2	19.8–22.7	1.0 (0.8–1.3)
	Central	2955	577	19.5	18.1–21.0	1.0 (0.8–1.3)
	Northern	4358	1240	28.5	27.1–29.8	1.3 (1.0–1.7)
	Eastern	538	103	19.1	15.9–22.7	1
Location	Rural	6304	1611	25.6	24.5–26.7	1.2 (1.1–1.4)
	Urban / Peri-urban	4583	953	20.8	19.6–22.0	1

*data on 83 participants were not recorded;
†adjusted odds ratio calculated by gender, ethnicity, age, division and location

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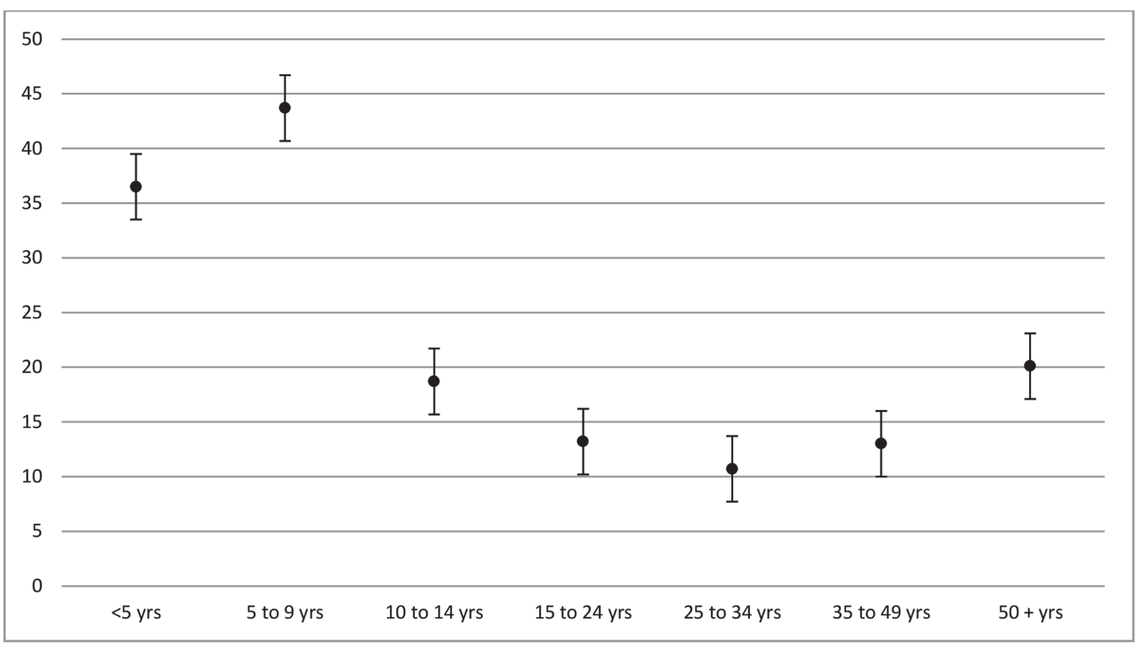

Fig 1. Distribution of scabies by age.

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Table 3. Prevalence of impetigo in Fiji.

		Sample	Participants with impetigo			Adjusted OR† (95% CI)
		n	n	%	95% CI	
Total		10,887	2133	19.6	18.9–20.4	
Gender	Female	5491	1127	20.5	19.5–21.6	1.2 (1.1–1.3)
	Male	5396	1006	18.6	17.6–19.7	1
Ethnicity	iTaukei	7579	1730	22.8	21.9–23.8	2.4 (2.2–2.8)
	Indo-Fijian	3308	371	11.2	10.2–12.3	1
Age (years)*	<5	1023	236	23.1	20.5–25.8	1.2 (1.0–1.5)
	5–9	2408	823	34.2	32.3–36.1	2.2 (1.9–2.7)
	10–14	2448	411	16.8	15.3–18.3	0.8 (0.7–1.0)
	15–24	1587	133	8.4	7.0–9.9	0.6 (0.5–0.8)
	25–34	1256	153	9.6	10.4–14.1	0.4 (0.3–0.5)
	35–49	1131	174	15.4	13.3–17.6	0.5 (0.4–0.6)
	>49	951	200	21.0	18.5–23.8	1
Division	Western	3036	553	18.2	16.9–19.6	1.2 (0.9–1.5)
	Central	2955	463	15.7	14.4–17.0	1.1 (0.8–1.4)
	Northern	4358	1035	23.7	22.5–25.0	1.4 (1.1–1.8)
	Eastern	538	82	15.2	12.3–18.6	1
Location	Rural	6304	1351	21.4	20.4–22.5	1.2 (1.1–1.3)
	Urban/Peri-urban	4583	782	17.1	16.0–18.1	1

*data on 83 participants were not recorded;

†adjusted odds ratio calculated by gender, ethnicity, age, division and location).

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cream was unavailable through the publicly funded clinics and could only be purchased through private pharmacies. Ivermectin, an oral treatment for scabies, is not available in Fiji.

Discussion

This study is the first national survey of scabies and impetigo prevalence conducted in any country and indeed the only one that we are aware of that is based on a rigorous sampling methodology and covers a substantial population and geographic area. Our survey confirms that scabies and impetigo are widespread problems in Fiji. While we observed that children are the most affected population group, no age group is free of scabies or impetigo, and there is an

Table 4. Association between scabies and impetigo.

		Total(n = 10,887)		Participants with scabies(n = 2564)*		Participants without scabies(n = 8323)	
		n	%	n	%	n	%
Impetigo		2133	19.6	2021	78.8	112	1.3
Number of lesions	<5	1142	53.5	1059	52.4	83	74.1
	5–20	646	30.3	622	30.8	24	21.4
	>20	345	16.2	340	16.8	5	4.5
Lesion type	Flat/Dry	1170	54.8	1116	55.2	54	48.2
	Crusted	396	18.6	371	18.4	25	22.3
	Purulent	567	26.6	534	26.4	33	29.5

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indication that prevalence increases after middle age. Scabies and impetigo are highly prevalent across all geographical divisions and both genders and in both the main ethnic groups.

High levels of scabies and related bacterial infections have previously been documented in tropical countries with low or medium socio-economic status and in disadvantaged populations, particularly in countries in the Pacific region [21]. However, all previous studies were conducted in smaller, localised areas, such as single provinces, schools or villages [21]. Prior reviews of the prevalence of scabies and impetigo have consistently documented high levels of both diseases in school-aged children [9,21]. Only a limited number of studies have described the tendency for scabies to reappear in older age groups, as we observed [7,14,22]. A possible explanation for this apparent phenomenon is that under the typical family structure in these countries, older community members frequently care for children, and are thereby exposed to a heightened risk of transmission of scabies from children. A further possible explanation is that repeated infestation in childhood leads to protective immunity in adulthood but this wanes in the elderly, although there are very few data to support this hypothesis. Consistent with our findings, previous studies in Fiji have documented that scabies and impetigo are most prevalent in the iTaukei Fijian population [8,14,21]. The reason for this is not clear but may be possibly linked to a higher number of children per family and the tendency to live in single-room houses. Other bacterial infections including pneumonia, invasive streptococcal and staphylococcal infections, and rheumatic heart disease have been observed to be more common in iTaukei Fijians [6,23–25].

Impetigo is common in Fiji. Over 15% of participants in this study had more than 20 impetigo lesions and over one quarter of participants had purulent lesions. This study clearly documents that scabies is the main driver of bacterial skin infection in Fiji with scabies contributing 93% of the risk of impetigo. This striking finding has considerable implications for public health efforts to control impetigo; that is, successful control measures directed at scabies would likely translate into significant reductions in the burden of impetigo.

The survey had a number of methodological limitations. Our sample had an over-representation of younger children and an under-representation of older people, possibly due to sampling of areas with primary or secondary schools in proximity of the selected sites, and the relative absence of adults due to regional work commitments. Further, there may have been weaknesses in the diagnosis of scabies and impetigo. Although diagnosis was entirely clinical, and did not use a microscope or scraping of scabies mites, we employed senior nurses, who received intensive training in relevant methods, and were paired to conduct the examination. However no further validation was conducted and we did not conduct any bacteriology tests to confirm the presence of bacterial infection of impetigo lesions.

The Fiji Ministry of Health received a preliminary report of this survey Romani [10], and has since undertaken a number of measures to increase community and health care worker awareness and knowledge of scabies. The Government's Integrated Management of Childhood Illness guidelines now include an assessment and treatment guide for skin health with a focus on scabies and bacterial skin infection [19]. Education about scabies has been conducted through the hospitals, clinics and health centres.

This large, nationwide survey of scabies and impetigo provides comprehensive data on the prevalence of these diseases in Fiji indicating that one-fifth of the population is affected at any one time, and that nearly 50% of school-aged children are affected. This tremendous burden of disease at a population level strongly supports the need for investment into research to investigate the best strategies for public health control of scabies in communities where resources are limited and scabies and it complications endemic. Our data suggest that an effective public health control measure for scabies will also likely lead to a considerable reduction in the burden of impetigo.

Supporting Information

S1 Checklist. STROBE Checklist.
(PDF)

Author Contributions

Conceived and designed the experiments: LR MJW JK MH MK. Performed the experiments: LR. Analyzed the data: LR HW. Contributed reagents/materials/analysis tools: MK. Wrote the paper: LR ACS MJW JMK. Designed the software used in analysis: LR AS.

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Chapter 4

4.1 Mass drug administration for scabies control in a population with endemic disease

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Mass Drug Administration for Scabies Control in a Population with Endemic Disease

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ABSTRACT

BACKGROUND

Scabies is an underrecognized cause of illness in many developing countries. It is associated with impetigo, which can lead to serious systemic complications. We conducted a trial of mass drug administration for scabies control in Fiji.

METHODS

We randomly assigned three island communities to one of three different interventions for scabies control: standard care involving the administration of permethrin to affected persons and their contacts (standard-care group), mass administration of permethrin (permethrin group), or mass administration of ivermectin (ivermectin group). The primary outcome was the change in the prevalence of scabies and of impetigo from baseline to 12 months.

RESULTS

A total of 2051 participants were enrolled; 803 were in the standard-care group, 532 in the permethrin group, and 716 in the ivermectin group. From baseline to 12 months, the prevalence of scabies declined significantly in all groups, with the greatest reduction seen in the ivermectin group. The prevalence declined from 36.6% to 18.8% in the standard-care group (relative reduction in prevalence, 49%; 95% confidence interval [CI], 37 to 60), from 41.7% to 15.8% in the permethrin group (relative reduction, 62%; 95% CI, 49 to 75), and from 32.1% to 1.9% in the ivermectin group (relative reduction, 94%; 95% CI, 83 to 100). The prevalence of impetigo also declined in all groups, with the greatest reduction seen in the ivermectin group. The prevalence declined from 21.4% to 14.6% in the standard-care group (relative reduction, 32%; 95% CI, 14 to 50), from 24.6% to 11.4% in the permethrin group (relative reduction, 54%; 95% CI, 35 to 73), and from 24.6% to 8.0% in the ivermectin group (relative reduction, 67%; 95% CI, 52 to 83). Adverse events were mild and were reported more frequently in the ivermectin group than in the permethrin group (15.6% vs. 6.8%).

CONCLUSIONS

Mass drug administration, particularly the administration of ivermectin, was efficacious for the control of scabies and impetigo. (Funded by the Australian National Health and Medical Research Council; Australian New Zealand Clinical Trials Registry number, ACTRN12613000474752.)

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A Quick Take is available at NEJM.org

Scabies, a skin condition that is recognized by the World Health Organization as a disease of public health importance,[1] is a substantial contributor to global morbidity and mortality. Scabies is caused by a microscopic mite (*Sarcoptes scabiei* var. *hominis*) and is transmitted primarily through person-to-person contact. Infestation can result in debilitating itchiness, with associated sleep disturbance, reduced ability to concentrate,[2] social stigmatization,[3] and ongoing health care expenses.[4,5]

In many developing countries, scabies-related scratching is an important cause of impetigo,[6-10] which is most often due to *Streptococcus pyogenes* or *Staphylococcus aureus* infection and can lead to septicemia, glomerulonephritis, and rheumatic heart disease.[11] An estimated 100 million persons have scabies worldwide; most live in tropical countries,[12] and those living in the Pacific Islands are particularly affected.[10,13-16]

Effective treatments, both topical and oral, are available for scabies. However, among persons who live in regions where the pathogen is endemic, reinfestation can occur rapidly, even when household contacts are also treated.[17] Mass drug administration, which generally involves repeat administration of single-dose therapeutic agents to whole communities, has become a central strategy for the control of several neglected tropical diseases.[1,18] Single-group studies of the mass administration of topical permethrin[6,8] and ivermectin (an oral agent that is the drug of choice for mass administration for onchocerciasis and lymphatic filariasis)[7,19-24] have shown promise. To strengthen the evidence base for mass drug administration for scabies control, we undertook a comparative trial called the Skin Health Intervention Fiji Trial (SHIFT).

METHODS

STUDY POPULATION

We conducted SHIFT in Fiji from September 2012 through September 2013. After consultation with health authorities, we identified three island communities as study groups (Fig. 1), on the basis of relative isolation, population size (small enough to be manageable but large enough to provide study power), and cultural similarities.[25] One community occupies a single island, the second occupies two neighboring islands, and the third occupies three islands. Each community has one nurse-staffed clinic.

STUDY PROCEDURES

The three island communities were randomly assigned, through the drawing of lots, to one of three different interventions for scabies control: standard care involving the administration of permethrin to affected persons and their contacts (standard-care group), mass administration of permethrin (permethrin group), or mass administration of ivermectin (ivermectin group). The study procedures were the same across communities and involved visits at baseline and at 12 months for all residents and a visit at 3 months for a random sample of 20% of each group. Each visit took place during a scheduled week.

All residents were eligible to participate. The residents were identified with the use of a 2012 population list provided by the study nurse; they were invited by letter to participate and then visited by the local district nurse if they were present in the community. When the study team arrived for the baseline visit, all residents who were present at the time were invited to enroll in the study. Those who provided consent to participate gave basic sociodemographic information and a brief medical history. When the study team returned for the 12-month visit, all residents who were present in the community were again approached by the study team. The residents who had enrolled in the study at baseline were reexamined and asked about any absences from the community since enrollment. The residents who were present but had not enrolled in the study at baseline were invited to enroll. At the baseline, 3-month, and 12-month visits, a skin examination of consenting participants was performed by the study nurse.

For the groups that underwent mass drug administration, data on adverse events were obtained through direct questioning of participants 7 to 14 days after the drug was administered. During the periods before and after the drug was administered, we used routinely collected health service data to record the number of patients who presented to community clinics with any skin condition and the number of clinic referrals to major health centers.

In accordance with the Integrated Management of Childhood Illness (IMCI) guidelines,[13] scabies was defined as the presence of pruritic inflammatory papules with a typical anatomical distribution (e.g., on the webs of the fingers, hands, wrists, or ankles).[26] Examination of the breasts and genitals was performed only when

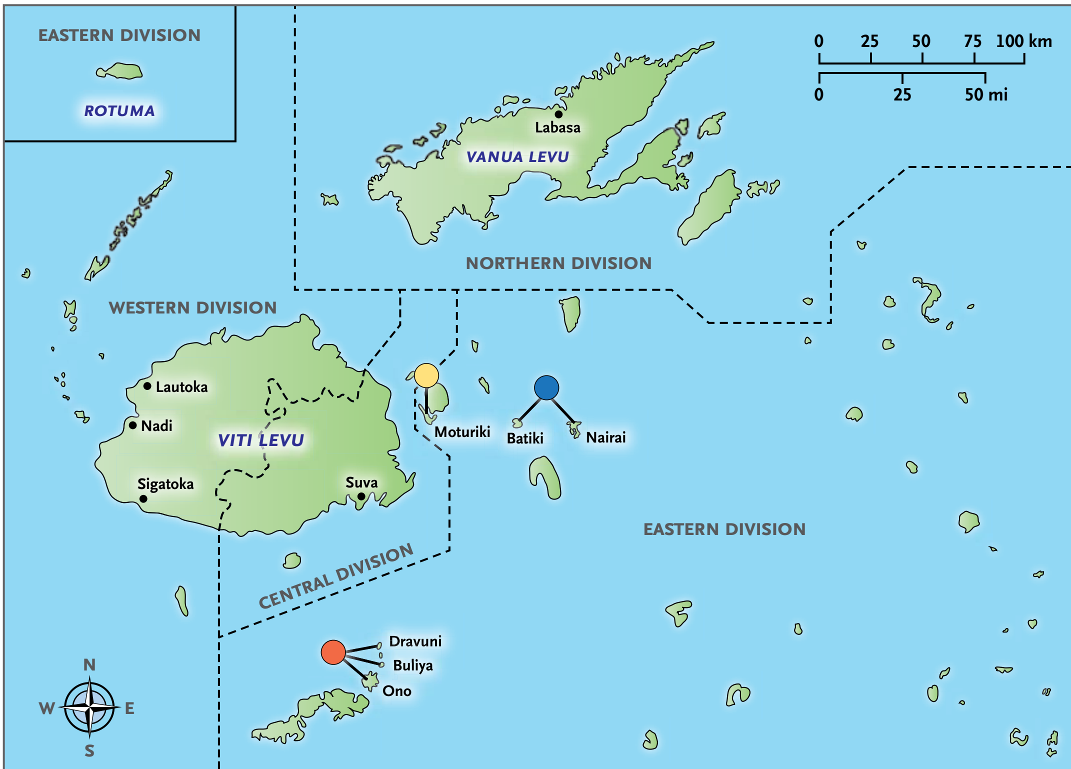

Figure 1. Study Sites in Fiji.

The figure shows the locations of the three island communities that were included in the study. The yellow pin indicates the site of the standard-care group, the red pin the sites of the permethrin group, and the blue pin the sites of the ivermectin group.

requested by participants and in a separate, private space. Determination of the severity of scabies was based on the number of lesions, in categories of mild (≤10), moderate (11 to 49), and severe (≥50). Infected scabies was defined as scabies plus the presence of pus-filled or crusted papules. If crusted ("Norwegian") scabies was suspected, a scraping of the skin was obtained for microscopic examination for mites, and a photograph was sent to the team's clinical advisors (the second and last authors). Impetigo was defined as the presence of a papular, pustular, or ulcerative lesion surrounded by erythema.

INTERVENTIONS

Standard-Care Group

Participants in the standard-care group who had scabies at baseline were referred to the local clinic for guideline-recommended treatment with one dose of topical permethrin cream, with a second dose provided after 14 days if symptoms persisted. The guidelines also recommended a single dose of permethrin for the patient's contacts.[13] We provided permethrin cream to the local clinics to ensure that the supply would be adequate.

Permethrin Group

All participants in the permethrin group were offered one dose of topical permethrin cream followed by a second dose 7 to 14 days later if scabies had been observed at baseline. For younger children, parents were asked to apply the cream under the direct observation of study staff. Older children and adults were encouraged to apply the cream in the clinic but could apply it at home. Participants were asked to apply the cream from neck to toes and to leave it on for 8 to 24 hours (or for 4 hours in the case of participants <2 months of age). In infants, the cream was also applied to the scalp.

Ivermectin Group

All participants in the ivermectin group were offered one dose of oral ivermectin (200 μg per kilogram of body weight), which was taken under the direct observation of study staff. Ivermectin was replaced with topical permethrin cream in the following participants: children who weighed less than 15 kg, women who were pregnant or breast-feeding,[27] persons with neurologic disease, and persons taking medications that are metabolized by the cytochrome P-450 pathway, including warfarin and some anticonvulsant agents. For participants who had scabies at baseline, a second dose of the medication that had been provided at baseline was distributed by study staff 7 to 14 days after the initial dose was administered.

Treatment for crusted scabies consisted of the administration of two doses of ivermectin 1 week apart and the administration of permethrin cream twice a week for 1 month, with follow-up at 1, 2, 3, and 12 months.[28] All participants with crusted or purulent impetigo lesions were referred to clinics in order to receive antibiotic agents, in accordance with Fiji IMCI guidelines.[13] Participants in all groups could present to their community clinic at any time and receive standard care with permethrin.

STUDY OUTCOMES

The primary outcome was the change in the prevalence of scabies and of impetigo from baseline to 12 months. Prevalence was calculated at baseline and 12 months with the use of data from the entire sample of participants at each time point.

Safety outcomes were based on adverse events, which were classified as serious if they were immediately life threatening, led to hospitalization, or resulted in persistent or substantial disability or death. We established an independent safety committee that consisted of academic physicians, including a Fijian representative. Adverse events were reviewed by the local study doctor, with subsequent referral to the safety committee.

STUDY OVERSIGHT

The trial was approved by the Fijian National Research Ethics Committee and the Royal Children's Hospital Human Research Ethics Committee. There was a delay in meeting registration deadlines for the study because the investigators initially were of the understanding that community-intervention studies of this kind, as opposed to individually randomized trials, do not require registration. Written informed consent was obtained from all participants. Merck Sharp and Dohme (Australia) provided the ivermectin but had no other role in the study. The Fiji Ministry of Health and Medical Services provided paid personnel. The study was designed by the authors. All the authors vouch for the integrity and completeness of the data and analyses and for the fidelity of the study to the protocol (available with the full text of this article at NEJM.org).

STATISTICAL ANALYSIS

We calculated the change in prevalence of scabies and of impetigo in each of the three study groups. We calculated both the absolute reduction (the difference between the prevalence at 12 months and the prevalence at baseline) and the relative reduction (the ratio of the prevalence at 12 months to the prevalence at baseline). Confidence intervals for the reductions were calculated with the use of the variance of the binomial distribution.[29] To compare the study groups, we calculated the ratio of the prevalence at 12 months to the prevalence at baseline in each group and then tested the null hypothesis that these ratios were equal.[30] All tests were two-sided. Among participants who were examined at both baseline and 12 months, we calculated the rates of the appearance of scabies (the proportion of persons without scabies at baseline who had scabies at 12 months) and the disappearance of scabies (the proportion of persons with scabies at baseline who did not have scabies at 12 months). Safety outcomes were summarized as proportions of participants in each group who had adverse events.

Study power and sample size were based on estimates from previous research conducted in Fiji. We estimated that the prevalence of scabies would be 23% at baseline and that the prevalence would fall to 5% in the groups that underwent mass drug administration[6-8] and to 10% in the standard-care group.[16,31] Assuming an 80% response rate in each group and a 20% loss to follow-up at 12 months, we estimated that a sample of 1920 participants would give the study more than 90% power to detect the estimated differences at a two-sided significance level of 0.05.

RESULTS

STUDY POPULATION

A total of 2051 persons consented to participate in the study (Table 1), representing more than 85% of the resident population of the three com-

Table 1. Characteristics of the Participants at Baseline and 12 Months.*

Characteristic	Ivermectin Group		Permethrin Group		Standard-Care Group		All Groups	
	Baseline (N=716)	12 Mo (N=587)	Baseline (N=532)	12 Mo (N=449)	Baseline (N=803)	12 Mo (N=746)	Baseline (N=2051)	12 Mo (N=1782)
Median age (IQR) — yr	24 (8–44)	24 (8–44)	25 (8–47)	26 (8–50)	22 (8–44)	25 (8–45)	24 (8–45)	25 (8–46)
Age — no. (%)								
<5 yr	86 (12.0)	71 (12.1)	70 (13.2)	56 (12.5)	101 (12.6)	97 (13.0)	257 (12.5)	224 (12.6)
5–9 yr	134 (18.7)	123 (21.0)	83 (15.6)	80 (17.8)	124 (15.4)	118 (15.8)	341 (16.6)	321 (18.0)
10–14 yr	96 (13.4)	73 (12.4)	60 (11.3)	50 (11.1)	121 (15.1)	88 (11.8)	277 (13.5)	211 (11.8)
15–24 yr	44 (6.1)	25 (4.3)	49 (9.2)	29 (6.5)	75 (9.3)	65 (8.7)	168 (8.2)	119 (6.7)
25–34 yr	106 (14.8)	81 (13.8)	69 (13.0)	56 (12.5)	105 (13.1)	100 (13.4)	280 (13.7)	237 (13.3)
≥35 yr	250 (34.9)	214 (36.4)	201 (37.8)	178 (39.6)	277 (34.5)	278 (37.3)	728 (35.5)	670 (37.6)
Sex — no. (%)								
Male	385 (53.8)	309 (52.6)	274 (51.5)	235 (52.3)	405 (50.4)	381 (51.1)	1064 (51.9)	925 (51.9)
Female	331 (46.2)	278 (47.4)	258 (48.5)	214 (47.7)	398 (49.6)	365 (48.9)	987 (48.1)	857 (48.1)
Persons in household — median (IQR)	5 (4–7)	NA	5 (4–6)	NA	5 (4–7)	NA	5 (4–7)	NA
≥1 Off-island trip in the previous 12 mo — no. of persons (%)	NA	158 (26.9)	NA	267 (59.5)	NA	232 (31.1)	NA	657 (36.9)

* IQR denotes interquartile range, and NA not applicable.

munities (for details about residents who did not participate in the study, see Table S1 in the Supplementary Appendix, available at NEJM.org). The distributions of age and sex were similar across the communities (Table 1); 99.7% of the residents in these communities were indigenous Fijians (iTaukei). Loss to follow-up at 12 months was higher in the standard-care group than in the permethrin and ivermectin groups (28.3% vs. 25.0% and 21.6%, respectively) (Fig. 2, and Table S2 in the Supplementary Appendix). At 12 months, an additional 246 participants were enrolled, with enrollment higher in the standard-care group than in the permethrin and ivermectin groups (170 persons vs. 50 and 26, respectively).

In the ivermectin group, 623 of the 716 participants received ivermectin under the direct observation of study staff, and 93 received permethrin, in accordance with the exceptions specified in the protocol. Of these 93 participants, 55 were younger than 5 years of age, 27 were lactating, 8 were pregnant, and 3 had other contraindications; the application of permethrin was directly observed in 61 of these participants, and thus therapy was administered to 96% of the ivermectin group under direct observation. The 230 participants in this group who had scabies at baseline received a second treatment; 200 received ivermectin and 30 received permethrin, and all the interventions were administered under direct observation.

In the permethrin group, 307 of the 532 participants (58%) received treatment under direct observation, and 181 of the 222 participants who had scabies at baseline (82%) received a second treatment. No data on the use of permethrin were collected for the standard-care group, since all treatment was administered in the community clinic.

PREVALENCE OF SCABIES AND IMPETIGO

At baseline, the prevalence of scabies was highest in the permethrin group, at 41.7% (Table 2). Among participants with scabies, the severity at baseline was similar across groups; 62% had fewer than 10 lesions, and 10% had 50 lesions or more. Scabies most commonly involved the hands (in 64%), arms (in 38%), feet (in 29%), and legs (in 26%). There was one diagnosis of crusted scabies in the entire study population, in the standard-care group.

At 12 months, the prevalence of scabies had declined in all study groups, with the greatest decline observed in the ivermectin group. The relative reduction in the prevalence of scabies was 94% (95% confidence interval [CI], 83 to

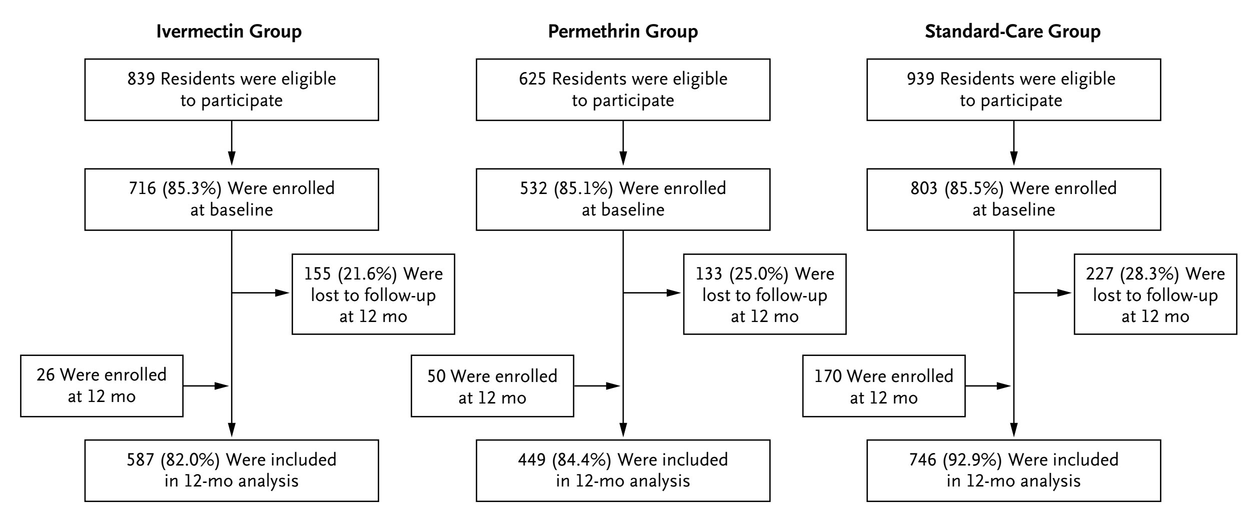

Figure 2. Enrollment and Follow-up.
The persons enrolled at 12 months were residents who were present at the 12-month visit but had not been present at baseline.

Table 2. Prevalence of Scabies and Impetigo at Baseline and 12 Months.*

Study Group	Prevalence at Baseline		Prevalence at 12 Mo		Absolute Reduction in Prevalence	Relative Reduction in Prevalence
	no./total no.	*% (95% CI)*	*no./total no.*	*% (95% CI)*	*percentage points (95% CI)*	*% (95% CI)*
Ivermectin						
Scabies	230/716	32.1 (28.8–35.6)	11/587	1.9 (0.9–3.3)	30.2 (26.6–33.9)	94 (83–100)
Impetigo	176/716	24.6 (21.6–27.9)	47/587	8.0 (6.1–10.5)	16.6 (12.7–20.4)	67 (52–83)
Permethrin						
Scabies	222/532	41.7 (37.6–46.0)	71/449	15.8 (12.6–19.5)	25.9 (20.4–31.2)	62 (49–75)
Impetigo	131/532	24.6 (21.2–28.5)	51/449	11.4 (8.8–14.6)	13.3 (8.5–17.9)	54 (35–73)
Standard care						
Scabies	294/803	36.6 (33.4–40.0)	140/746	18.8 (16.0–21.8)	17.8 (13.4–21.5)	49 (37–60)
Impetigo	172/803	21.4 (18.7–24.4)	109/746	14.6 (12.3–17.3)	6.8 (3.0–10.6)	32 (14–50)

* The absolute reduction is the difference between the prevalence at 12 months and the prevalence at baseline, and the relative reduction is the ratio of the prevalence at 12 months to the prevalence at baseline. CI denotes confidence interval.

100) in the ivermectin group, as compared with 62% (95% CI, 49 to 75) in the permethrin group (P<0.001) and 49% (95% CI, 37 to 60) in the standard-care group (P<0.001); the difference between the permethrin group and the standard-care group was not significant (P=0.09). The combined relative reduction in the two groups that underwent mass drug administration was 78% (95% CI, 69 to 87).

The reduction in the prevalence of scabies was similar when participants who were enrolled at 12 months were included in or excluded from the analysis (Table S3 in the Supplementary Appendix). In all groups, there was a reduction in the prevalence across all age groups and both sexes (Tables S4 and S5 in the Supplementary Appendix), as well as a reduction in the proportion of scabies cases that were categorized as severe (≥50 lesions) (Table S6 in the Supplementary Appendix).

Table 3. Rates of Disappearance and Appearance of Scabies among Participants Who Were Examined at Both Baseline and 12 Months.

Study Group	Disappearance of Scabies			Appearance of Scabies		
	Scabies Present at Baseline	Scabies Absent at 12 Mo	Rate of Disappearance	Scabies Absent at Baseline	Scabies Present at 12 Mo	Rate of Appearance
	no. of patients		*% (95% CI)*	*no. of patients*		*% (95% CI)*
Ivermectin	187	182	97.3 (93.9–99.1)	374	5	1.3 (0.4–3.1)
Permethrin	174	130	74.7 (67.6–81.0)	225	18	8.0 (4.8–12.3)
Standard care	218	161	73.9 (67.5–79.6)	358	55	15.4 (11.8–19.5)

At baseline, the prevalence of impetigo was 21.4% in the standard-care group and 24.6% in the combined groups that underwent mass drug administration (Table 2). At 12 months, the prevalence of impetigo had declined in all study groups, with the greatest decline observed in the ivermectin group. The relative reduction in the prevalence of impetigo was 67% (95% CI, 52 to 83) in the ivermectin group, as compared with 54% (95% CI, 35 to 73) in the permethrin group ($P=0.26$ for the comparison with the ivermectin group) and 32% (95% CI, 14 to 50) in the standard-care group ($P=0.05$ for the comparison with the ivermectin group); the difference between the permethrin group and the standard-care group was not significant ($P=0.17$). The combined relative reduction in the two groups that underwent mass drug administration was 62% (95% CI, 49 to 74).

At 12 months, the rate of the appearance of scabies was lowest in the ivermectin group (1.3%), and the rate of the disappearance of scabies was highest in this group (97.3%) (Table 3). The prevalence of scabies at 3 months was lower than the prevalence at baseline in all groups: 13.9% (95% CI, 9.2 to 20.5) in the ivermectin group, 22.2% (95% CI, 15.4 to 30.9) in the permethrin group, and 10.4% (95% CI, 6.7 to 16.1) in the standard-care group. The one participant with crusted scabies had been clinically cured by the time of the 3-month visit. In all the groups, the number of routine clinic consultations for skin disease was lower in the period after the intervention than in the period before the intervention, with 10.6 fewer consultations per 100 baseline population per year in the ivermectin group, 7.0 fewer in the permethrin group, and 13.7 fewer in the standard-care group (Table S7 in the Supplementary Appendix).

ADVERSE EVENTS

Adverse events were more common in the ivermectin group than in the permethrin group (with 15.6% having an event and 205 events in 112 participants vs. 6.8% having an event and 46 events in 36 participants) (Tables S8 and S9 in the Supplementary Appendix). No adverse event was serious or persisted for more than 7 days. Itching was the most common event (affecting 5.3% and 3.6% of participants in the ivermectin and permethrin groups, respectively), followed by headache (affecting 3.8% and 0.9%, respectively).

DISCUSSION

In this comparative trial, we found significant reductions in the prevalence of both scabies and impetigo from baseline to 1 year in all groups, with by far the largest reduction in the ivermectin group. Adverse events were more common in the ivermectin group, but all events were mild and resolved quickly.

Mass drug administration shows promise as an important control strategy in countries in which scabies is endemic. Previous single-group studies of the mass administration of permethrin and of ivermectin have shown reductions in disease prevalence[6-8,20,32] but have not determined whether this strategy is superior to an effective application of standard care.

In our study, the prevalence of scabies in the groups that underwent mass drug administration had declined by 3 months and declined further by 12 months; this finding was somewhat contrary to our expectation. A proportion of the scabies cases detected at 3 months may have represented postscabietic inflammatory nodules, which can persist after successful treatment.[26,33]

The relative reduction in the prevalence of scabies from baseline to 12 months was significantly greater in the ivermectin group than in the permethrin group (94% vs. 62%). During mass administration, any therapeutic advantage of permethrin[34] may be outweighed by poor adherence to the topical agent.[17] Administration of treatment was directly observed much more frequently in the ivermectin group than in the permethrin group (96% vs. 58%). The effect of adherence in the ivermectin group may have been enhanced by the second dose for participants with clinical scabies at baseline, since ivermectin is not effective against unhatched eggs.[35]

Adverse-event profiles were consistent with those in previous studies.[36] Itching was the most common event and was probably caused by an inflammatory response to dead mite antigens. The extensive mass administration of ivermectin in Africa and Latin America[24,37] has raised no safety concerns, except for a contraindication to the drug among persons at risk for *Loa loa* filariasis.[38] In the absence of data on safety in young children and pregnant women, caution dictates that the drug remain contraindicated in these two groups.

The considerable decline in the prevalence of scabies in the standard-care group may have occurred because the trial introduced a higher level of care than had been routinely available, including ensuring the availability of permethrin and generating greater awareness about treatment for contacts.

This study has several limitations. A true cluster-randomized trial would have required multiple communities to be included in each group, but this trial design was beyond the resources available to us. We targeted a very substantial level of effect to minimize the possibility that any finding would be interpreted as being a result of confounding. There were nevertheless differences among the three trial communities, with respect to population movement and isolation from the main island of Viti Levu (Fig. 1). The standard-care group had access to private boats to the main island, and the permethrin group had easier access to the mainland by ferry than did the ivermectin group. These differences were reflected in the reported movements of study participants and may have contributed to a greater potential for reinfestation in the standard-care and permethrin groups than in the ivermectin group. Finally, the high prevalences of scabies and impetigo at baseline were consistent with findings from earlier surveys in the Pacific Islands.[39] We used validated diagnostic criteria[13] but not dermatoscopy, since this type of examination was not practical to perform and has poor sensitivity.[40,41] The study nurse who performed all skin examinations had worked at the only dermatology hospital in Fiji for more than 20 years and had had particular experience in the detection of scabies and impetigo. We did not systematically examine breasts and genitals, which are regions with a predilection for infestation,[19,42] but any resulting underestimation is unlikely to have differed among the three groups.

These data support the mass administration of ivermectin for scabies control. Although scabies resistance has been reported very infrequently, it could occur.[43,44] We provided a second dose for participants who had scabies at baseline, but a simpler strategy for mass administration on a larger scale would be to provide two directly observed doses 7 to 14 days apart, regardless of whether clinical scabies is present. There is an opportunity to evaluate the effect of existing ivermectin-based programs for onchocerciasis and lymphatic filariasis on scabies and other ivermectin-susceptible parasites. In general, approaches to mass drug administration may yield better results if they are integrated across diseases in a way that is acceptable to individual persons and communities.

SHIFT fills an important gap in evidence for scabies control, but effectiveness must now be evaluated beyond island settings and in larger populations. Key issues will include the number of cycles needed; the model of delivery; the mechanism for evaluation of efficacy, cost effectiveness, and acceptability; and the effect of scabies and impetigo control on the severe downstream complications of these skin conditions.[45]

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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4.2 Supplementary Appendix

Mass drug administration to control scabies in a highly endemic population: The SHIFT trial

Romani L, Whitfeld M, Koroivueta J, Kama M, Wand H, Tikoduadua L, Tuicakau M, Koroi A, Andrews R, Kaldor J, Steer AC.

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Table S1. Reasons for non-enrolment at baseline in all three study arms

	Ivermectin arm	Permethrin arm	Standard care arm
Total population	839	625	939
Population enrolled	716	532	803
Non-enrolled and reason for non-enrolment:	123	93	136
Refusal to participate	2	4	6
Adult away from island	86	73	94
Child at school off island	21	14	24
Unable to leave work	12	2	9
Unwell	2	-	3

Table S2. Reasons for loss to follow-up at 12 months in all three study arms

	Ivermectin arm	Permethrin arm	Standard care arm
Total population	839	625	939
Population enrolled	716	532	803
Population seen at 12 months	587	449	746
Number and reason for loss to follow-up at 12 months:	155	133	227
Adult away from island	97	88	151
Child at school off island	26	23	31
Unable to leave work	18	14	32
Unwell	8	5	9
Deceased	6	3	4

Table S3. Prevalence of scabies at 12 months excluding new enrolees.

Study arm	Prevalence of scabies at 12 months including new enrolees (95% CI) n/N	Prevalence of scabies at 12 months excluding new enrolees (95% CI) n/N
Ivermectin arm	1.9% (0.9 – 3.3) (11/587)	1.8% (1.0 – 3.3) (10/561)
Permethrin arm	15.8% (12.6 – 19.5) (71/449)	15.8% (12.5 – 19.7) (63/399)
Standard care arm	18.8% (16.0 – 21.8) (140/746)	19.3% (16.3 - 22.7) (111/576)

Table S4. Prevalence of scabies by age group at baseline and 12 months in all three study arms

	Ivermectin arm		Permethrin arm		Standard care arm	
Age (years)	**Baseline N=230 n (%)***	**12 months N=11 n (%)**	**Baseline N=222 n (%)**	**12 months N=71 n (%)**	**Baseline N=294 n (%)**	**12 months N=140 n (%)**
< 5	33 (38.4)	3 (4.2)	42 (60.0)	14 (25.0)	47 (46.5)	31 (32.0)
5-9	61 (45.5)	6 (4.9)	57 (68.7)	28 (35.0)	72 (58.1)	38 (32.2)
10-14	35 (36.5)	2 (2.7)	34 (56.7)	13 (26.0)	63 (52.1)	24 (27.9)
15-24	12 (27.3)	0	18 (36.7)	1 (3.5)	22 (29.3)	3 (4.6)
25-34	19 (17.9)	0	17 (24.6)	1 (1.9)	31 (29.5)	9 (9.0)
≥35	70 (28.0)	0	54 (26.9)	14 (7.9)	59 (21.3)	35 (12.6)

*percentages refer to the prevalence of scabies within the specified age group

Table S5. Prevalence of scabies by gender at baseline and 12 months in all three study arms

	Ivermectin arm		Permethrin arm		Standard care arm	
Gender	**Baseline N=230 n (%)**	**12 months N=11 n (%)**	**Baseline N=222 n (%)**	**12 months N=71 n (%)**	**Baseline N=294 n (%)**	**12 months N=140 n (%)**
Male	117 (35.3)	5 (1.6)	106 (41.1)	44 (18.8)	164 (41.2)	54 (14.3)
Female	113 (29.4)	6 (2.2)	116 (42.3)	27 (12.7)	130 (32.1)	86 (23.6)

Table S6. Severity of scabies (measured by number of lesions) at baseline and 12 months in all three study arms

	Ivermectin arm		Permethrin arm		Standard care arm	
Number of scabies lesions	**Baseline N=230 n (%)***	**12 months N=11 n (%)**	**Baseline N=222 n (%)**	**12 months N=71 n (%)**	**Baseline N=294 n (%)**	**12 months N=140 n (%)**
Mild (≤10)	138 (60)	3 (27.3)	113 (50.9)	44 (62)	204 (69.4)	94 (67.1)
Moderate (11-49)	67 (29.1)	8 (72.7)	71 (32)	25 (35.2)	73 (24.8)	42 (30)
Severe (≥50)	25 (10.9)	0	38 (17.1)	2 (2.8)	17 (5.8)	4 (2.9)

*percentages refer to proportion of participants with scabies present whom had the specified category of severity

Table S7. Quarterly and annual routine clinic consultations for skin disease at local clinics in the three study arms

	Ivermectin arm (N=839)	Permethrin arm (N=625)	Standard care arm (N=939)
Pre-intervention			
Jan - Mar 2012	43	23	60
Apr - Jun 2012	31	16	44
Jul - Sep 2012	41	6	29
Total	115	45	133
Consultations per 100 baseline population per year*	18.3	10.0	18.9
Post-intervention			
Oct -Dec 2012†	27	4	15
Jan - Mar 2013	18	3	14
Apr - Jun 2013	13	6	7
Jul - Sep 2013	7	6	13
Total	65	19	49
Consultations per 100 baseline population per year	7.7	3.0	5.2

*adjusted from 9 months to 12 months rate
†does not include consultations in two weeks after baseline assessment (that is, those consultations that were expected to occur as part of the study protocol).

Table S8. Adverse event listing by arm

Event	Ivermectin arm N (%)	Permethrin arm N (%)	Total
Feel itchy	38 (5.3)	19 (3.6)	57 (4.6)
Headache	27 (3.8)	5 (0.9)	32 (2.6)
Abdominal pain	20 (2.8)	4 (0.7)	24 (1.9)
Joint pain	19 (2.6)	2 (0.4)	21 (1.7)
Dizziness	18 (2.5)	0 (0.00)	18 (1.4)
Cough	12 (1.7)	4 (0.7)	16 (1.3)
Weak / lacking energy	14 (1.8)	1 (0.2)	15 (1.2)
Fever	11 (1.5)	4 (0.70)	15 (1.2)
Nausea	14 (1.8)	0 (0.0)	14 (1.1)
Diarrhoea	12 (1.7)	0 (0.0)	12 (0.9)
Muscle pain	9 (1.3)	3 (0.6)	12 (0.9)
Sore throat	6 (0.8)	3 (0.6)	9 (0.7)
Ankle swelling	5 (1.0)	1 (0.2)	6 (0.5)
Total	**205 (28.6)**	**46 (8.6)**	**251 (20.1)**

Table S9. Adverse events distribution by individual

	Total number of adverse events	Number of adverse events among unique individuals	Average number of events (approximately)
Ivermectin arm	205	112	2 per person
Permethrin arm	46	36	1 per person

Table S10. CONSORT 2010 checklist of information to include when reporting a randomised trial

Section/Topic	Item No	Checklist item	Page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	3
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	4-5
	2b	Specific objectives or hypotheses	5, 9
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	5-10
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	NA
Participants	4a	Eligibility criteria for participants	6
	4b	Settings and locations where the data were collected	6
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	8-9
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	9
	6b	Any changes to trial outcomes after the trial commenced, with reasons	NA
Sample size	7a	How sample size was determined	10
	7b	When applicable, explanation of any interim analyses and stopping guidelines	NA
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	6
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	6
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	NA
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	NA
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers,	NA

		those assessing outcomes) and how	
	11b	If relevant, description of the similarity of interventions	NA
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	10
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	10
Results			
Participant flow - a diagram is strongly recommended	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	11, Fig2
	13b	For each group, losses and exclusions after randomisation, together with reasons	11, Fig2
Recruitment	14a	Dates defining the periods of recruitment and follow-up	Not includ ed
	14b	Why the trial ended or was stopped	NA
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	Table 1
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	12-13, Table 2
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	12-13, Table 2
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	12-13, Table 2
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	12-13, Table 3
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	13, Supp Tables
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	16-17
Generalisabili ty	21	Generalisability (external validity, applicability) of the trial findings	14
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	13-18
Other information			
Registration	23	Registration number and name of trial registry	11
Protocol	24	Where the full trial protocol can be accessed, if available	NA
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	20

Figure S1. Study timeline

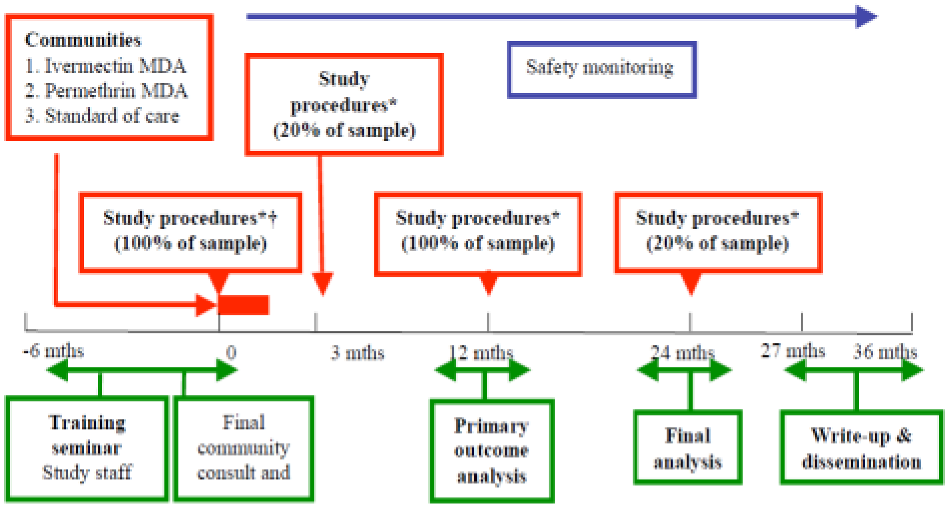
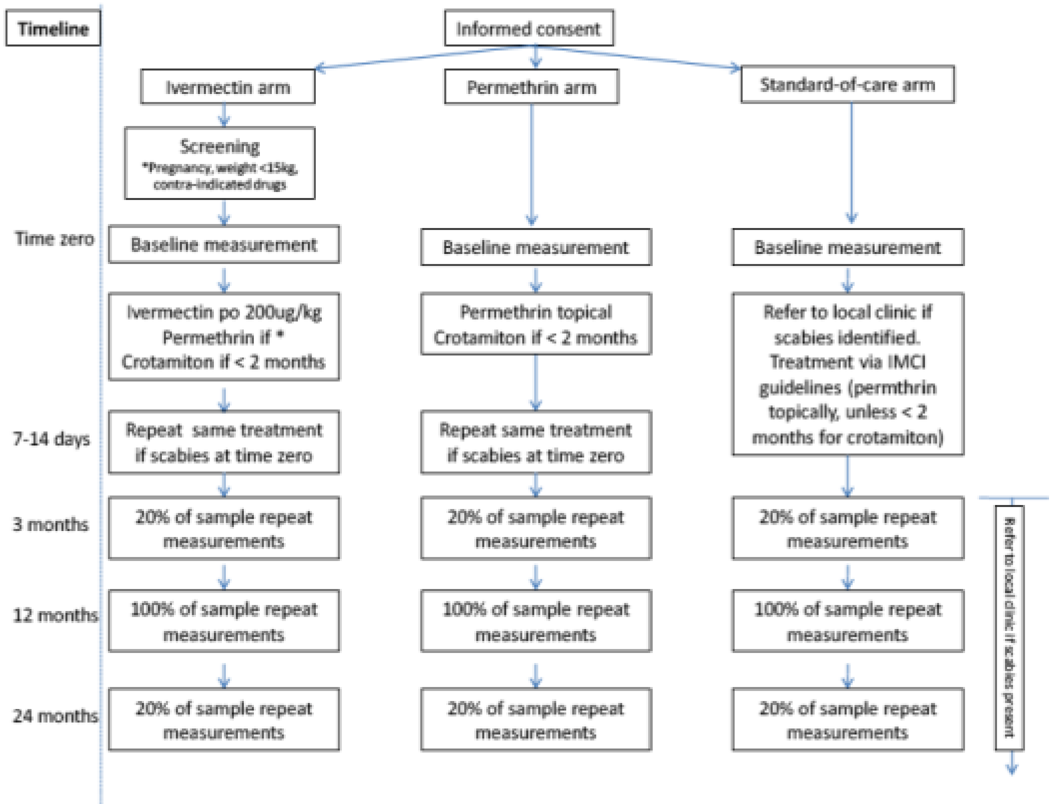


Figure S2: Study arm specific timeline



Chapter 5

5.1 The epidemiology of scabies and impetigo in relation to demographic and residential characteristics: baseline findings from the SHIFT trial

Draft ready for submission to a peer-reviewed journal.

Title: The epidemiology of scabies and impetigo in relation to demographic and residential characteristics: baseline findings from the SHIFT trial

Running title: Demographic and residential factors associated with scabies and impetigo

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ABSTRACT

Background: Scabies is a skin condition that is an under-recognised cause of morbidity in many developing countries. It is strongly associated with impetigo, which can in turn lead to systemic bacterial infections. To strengthen the evidence base for scabies control we undertook a trial of MDA for scabies. Here we report on the occurrence and predictors of scabies and impetigo in participants at baseline.

Methods: Participants were recruited in six island communities selected based on relative isolation, population size, and cultural similarities. They were examined for the presence of scabies and impetigo. In addition to descriptive analyses, logistic regression models were fit to assess the association between demographic variables and outcome of interest. Odd ratios and 95% confidence intervals were reported.

Results: The study enrolled 2051 participants. The prevalence of scabies was 36.4% overall, highest in children 5-9 years (55.7%). The prevalence of impetigo was 23.4%, highest in children aged 10 to 14 (39.0%). People with scabies were 2.8 times more likely to have impetigo. The population attributable risk of scabies as a cause of impetigo was 36.3%, and 71.0% in children aged less than five years. In the body site specific analysis, scabies in the torso and upper limbs were both attributed to approximately 50% of the impetigo cases, overall and in the youngest age-group. Households with four or more people sharing the same room were more likely to have scabies and impetigo (odds ratio 1.6 and 2.3 respectively) compared to households with rooms occupied by a single individual.

Conclusions: This study confirms the high burden of scabies and impetigo in Fiji and the strong association between these two conditions, particularly in young children. Overcrowding, young age and clinical distribution of lesion are important risk factors for scabies and impetigo. Further studies are needed to investigate the effect of scabies control

on serious secondary bacterial infections to determine whether the decline of endemic scabies would translate into a definite reduction of the burden of associated complications.

BACKGROUND

Scabies is a skin disease caused by infestation with a microscopic mite (*Sarcoptes scabiei* var *hominis*), which causes severe itchiness, sleep disturbance and social stigmatization.[1] An estimated 100 million people have scabies, most in tropical countries,[2] with the Pacific region particularly affected.[3-7] The disease is transmitted via close personal contact with an infected person and it is commonly spread within households and institutions.[8]

Impetigo, a common bacterial infection of the skin, often arises in people with scabies due to scratching of the lesions,[6,9-12] and can in turn lead to complications associated with group A streptococcal infection such as septicaemia, glomerulonephritis, and rheumatic heart disease, particularly in tropical settings.[4,7,13,14] Unlike industrialised countries, where scabies and impetigo are nuance diseases, in many resource-poor setting these diseases are endemic and reach prevalences as high as 25% in the general population and up to 50% in children.[5]

In countries where scabies is endemic, treatment that focusses on people with clinical scabies is often ineffective due to recurring reinfestation, even when extended to their household or family contacts. Mass drug administration (MDA), involving repeat administration of topical or oral treatments to whole communities, has been used for two decades to treat several neglected tropical diseases around the world and it is now emerging as a safe and effective strategy for the control of scabies.[3,9,10,15-17] The evidence base for MDA in scabies control was recently strengthened by a trial that we undertook in Fiji, called the Skin Health Intervention Fiji Trial (SHIFT).[3] The SHIFT trial also provided an opportunity to gain insight into the factors associated with scabies in endemic settings, and anatomical distribution of scabies and impetigo. Few studies conducted in developing countries including Brazil, Bangladesh, Cambodia and Pakistan investigated the complex relation between high prevalence of scabies and its socio-economic factors. Despite a growing number of data on scabies and impetigo prevalence in Fiji and internationally, limited information is available on risk factors associated with scabies, particularly in community and household settings. This paper reports on the clinical characteristics of SHIFT participants seen at baseline, with a particular focus on the occurrence of scabies and impetigo in relation anatomical sites and participants' living circumstances.

METHODS

Setting and study population

Fiji is located in the South Pacific region, with a population estimated at 909,389 in 2015 living on more than 300 islands, and made up of two main ethnicities, iTaukei (indigenous) Fijians (57%) and Indo-Fijians (38%).[18] It is the second most populous country in the Pacific region, after Papua New Guinea. Fiji is ranked 90 out of 188 countries in the United Nations Human Development Index, with a Gross Domestic Product (GDP) per capita of US dollars 4,532 in 2014.[19,20]

Participants of this study were recruited as part of the SHIFT trial, which took place during 2012-13 in Fiji.[3] After consultation with authorities, we identified six island communities in the Eastern Division of the country. All selected sites were rural coastline villages with approximately one third of the households having access to piped water. Nearly sixty per cent of residents live below the minimum wage of FJD 2.30 per hour and families' main income mostly comes from fishing and agriculture.[18] Typically, residents live in traditional huts made of wood and straw, or in houses made of cement or corrugated iron. Travels between villages are only possible by foot or boats; there are no vehicles or paved roads on any of the six islands. Residents of these islands typically dress in shorts, long skirts and sarongs, and tee-shirts or sleeveless tops. The majority of young children are either naked or wear only shorts. The average day-time temperatures in warmer months are between 30 and 32 degrees Celsius with high and persistent humidity. Literacy level is high at 93% across the country but no detailed information is available for the Eastern Division or the study islands.[18]

Study procedures and case definitions

SHIFT study procedures have been described elsewhere.[3] All residents of the six island communities selected were eligible and invited to participate. Prior to the study, residents were identified from the 2012 population list provided by the study nurse, and those present on the island were invited to participate by letter to the community, followed by a visit to the community from the local district nurse. Meetings were held in each selected community by a local nurse who explained the concept to residents. Subsequently, the nurse was accompanied by members of the study team who were able to answer questions and concerns the community may have had. Written consent was obtained by all residents willing to participate. Those who were illiterate or with impaired vision were provided assistance to complete the questionnaire by a member of the local study team. Informed consent for children 12 years or under was provided by parents or guardians, while for adolescents aged 13 to 17 consent was obtained by both a guardian and the participant. Those who consented provided demographic details and underwent a complete skin examination by a trained study nurse. Questions were asked in English, Fiji's official language, and translated into indigenous Fijian by trained local staff when requested by participants. At baseline, socio-demographic information and a brief medical history were collected from all participants by the study team. This included information on how many people lived in the house, the number of rooms shared and the length of residence on the island. We calculated the density of individuals per room to assess the association between scabies and the number of people sharing the same room. Participants were asked questions regarding previous diagnosis and treatment of scabies and other skin conditions. All clinical results were made available to each participant and to the local community care nurses. Study participants diagnosed with scabies or other skin conditions were provided detailed information about the condition and referred for treatment to the local nursing station. On selected islands, participants were offered treatment with oral or topical agents regardless of scabies status, and further follow up took place as part of an investigation of mass drug administration, as reported elsewhere.[3]

Scabies at baseline was defined as pruritic inflammatory papules with a typical anatomical distribution, such as hands, wrists, webs of the fingers, and ankles, following the Integrated Management of Childhood Illnesses (IMCI) guidelines.[13,21] Examination was performed on all exposed areas of the skin. Genitals and perimamillar regions were only examined if participants described symptomatic itching in these regions and consented for examination. Skin examinations were conducted in a separate, private space. Scabies severity was based on number of lesions and classified as mild, moderate or severe (1 to 10, 11 to 49 or more than 50 lesions) using a previously validated methodology. The topographic distribution of scabies lesions was recorded using ten pre-defined body regions. Infected scabies was defined as scabies plus pus-filled or crusted papules. If crusted scabies was suspected, a skin scraping was taken for microscope examination to detect mites, and a photograph sent to the team’s clinical advisors. Impetigo was defined as a papular, pustular or ulcerative lesion surrounded by erythema. Severity was counted and classified as per scabies lesion methods described above. Body distribution of impetigo lesions followed the methodology of scabies.

Statistical analysis and sample size

For the purposes of analyses reported here, the study population was made up of all those who were enrolled at the baseline visit of the SHIFT trial. Participant characteristics were summarised by demographic categories (age, sex and household density). Prevalence of scabies and impetigo were calculated for the whole population and by each of the demographic categories. Adjusted odds ratios (OR) for scabies and impetigo were calculated using a multivariate logistic regression model that incorporated the demographic factors of age, gender, number of people sleeping in the same room. Information on density of individuals per room was analysed both at individual and household level. Intraclass correlation coefficients (ICC) were estimated to determine the variation of infestation rate within and between households to assess clustering effects for both scabies and impetigo.[22] In addition, the population attributable risk (PAR) was calculated to estimate the percentage of impetigo attributed to scabies, overall and specific to body site and age.[23] All statistical analyses were conducted using STATA 14.0 (College Station, TX, USA).

Ethical approvals

SHIFT was registered with the Australian and New Zealand Trials Registry (ACTRN 12613000474752), and approved by the Fijian National Research Ethics Committee (201247) and the Royal Children's Hospital Human Research Ethics Committee (32099).

RESULTS

Study population

Overall, 2051 people consented to the study (Table 1), representing more than 85% of the population recorded on resident register, which was 99.7% indigenous Fijian (iTaukei). Participants were distributed across six island communities, in 29 villages and 527 households. The age and gender of participants were similar to those reported in the most recent national population census.[18] Most participants (51.2%) reported that they had never left their island of residence.

Prevalence and correlates of scabies

Scabies was observed in 746 participants (36.4%) of the surveyed population (Table 1). Prevalence was highest in children aged 5 to 9 years (55.7%, OR 3.7, 95% CI 2.8 – 4.9, Table 1) when compared to those aged 35 years and over. Scabies was more common in females (39.2% vs 33.7%, OR 1.3, 95% CI 1.1 – 1.5). When adjusted for age, gender and number of people per room, the results increased marginally and followed the same pattern.

Among participants with scabies, lesions were most often observed on the upper limbs (82.6%, Table 2). Although scabies lesions were present on the lower limbs less frequently in the sample overall (43.4%), this distribution was the most common in those aged less than five years (77.1%, $p<0.001$). The distribution of scabies lesions was similar in both genders, with the exception of the perineum and buttocks areas, where scabies was more observed in females ($p=0.006$).

Among participants with scabies, most had mild disease (Table 3). Children aged less than five years had more severe disease than other age groups (p=0.002). The distribution of lesions was similar between males and females (p=0.006). There was one diagnosis of crusted scabies.

Prevalence and correlates of impetigo

Impetigo was observed in 23.4% of participants (Table 1). Impetigo followed a similar age distribution to that of scabies, being most common in school-aged children. The most affected age group was the 10 -14 years (39.0%, OR 4.2, 95% CI 3.0 – 5.8), followed by the 5-9 age group with 38.4%, Table 1). Unlike scabies, impetigo was more prevalent in males (25.8%) than in females (20.7%, OR 0.8, 95% CI 0.6 – 0.9). When adjusted for age, gender and number of people per room, the results did not change.

Impetigo lesions were most frequently observed on the lower limbs (69.7%, Table 2). This trend was consistent across age groups, although more common in school aged children (Table 2). Impetigo lesions on the face, scalp and neck were more commonly observed in those aged less than five years (21.3%) than in all other age groups (p<0.001). The distribution of impetigo lesions was similar in both males and females (p=0.006).

Most participants had mild disease (76.5%, Table 3), with children aged less than 14 years, and males, more likely to have moderate or severe disease, compared to older age groups (p=0.149).

The presence of impetigo was strongly associated with a diagnosis of scabies (relative risk, RR, 2.6, 95% CI 2.2 – 3.0). Overall, more than one third (36.3%) of impetigo cases were attributed to scabies (Table 4). The same measure was calculated by age group and body site. In the age stratified analysis, significant proportions of scabies were associated with impetigo cases among children aged less than five and 5-14 years of age (71% and 46% respectively). Although not significant, approximately one third of the impetigo cases were due to scabies in participants aged 15 and over. In the site specific analysis, scabies in torso and arms/hands were both attributed to approximately 50% of the impetigo cases (Table 4). In the youngest age group, scabies in limbs and torso were responsible for 45% to 52% of the impetigo cases while just over quarter of the impetigo were attributed to the scabies in face scalp/neck. (Table 4).

Household level prevalence of scabies and impetigo

The association between scabies and overcrowding was observed both at the individual and household levels (Table 1 and 5). Participants were more likely to have scabies when four or more people were sharing the same room (38.2%, OR 1.6, 95% CI 1.2 – 2.2) compared to households with a single individual per room (27.5%, Table 1). However, the effect of room density was reduced and non-significant when adjusted for age (adjusted OR 1.2, 95% CI 0.8 – 1.7) in the same group.

Of all 527 households surveyed, only 177 (33.6%) were free of scabies. The majority of households with no scabies (56.8%) had only one or two residents living in the house, while only 7.6% of them were occupied by seven or more people (Table 5). Scabies prevalence was associated with the presence of younger children within a household, with prevalence decreasing as the median age increased. In households where inhabitants had a median age of less than 19 years, 37.3% had scabies at levels higher than 50% ($p<0.001$). Conversely, the majority (44.1%) of households where no scabies was present had residents with a median age above 45 years. The ICC due to the clustering effect of household was estimated as 13% for scabies

Similarly to scabies, participants were twice as likely to present with impetigo lesions when four or more people shared the same room (26.8%, OR 2.3, 95% CI 1.6 – 3.2) compared to households with a single individual sleeping in one room (13.9%, Table 1).). However, the significant effect of room density decreased when adjusted for age (Adjusted OR 1.7, 95% CI 1.1 – 2.5) in the same group.

The same trend was observed in relation to prevalence of impetigo and number of people per householdOf all 527 households surveyed, more than half (52.0%) had residents affected with impetigo. The majority of households with no impetigo (75.7%) had only up to two residents living in the house, while only 14.1% of them were occupied by seven or more people (Table 5). Impetigo prevalence was associated with the presence of younger children within a household, with prevalence decreasing as the median age increased. In households where inhabitants had a median age less then19 years, 32.5% had impetigo at levels higher than 33% ($p<0.001$). Conversely, 38.2% of households where no impetigo was observed had residents with a median age above 45 years. The ICC due to the clustering effect of household was estimated as 5% for impetigo.

DISCUSSION

This study describes for the first time the occurrence of scabies and impetigo in relation to participants' clinical, demographic and living characteristics in an endemic population of Fiji. The results of this study confirm that countries of the Pacific region, particularly Fiji, have a prevalence of scabies and impetigo at some of the highest levels recorded in the world, with more than one in two children affected and over one third of the general population reporting scabies. The high prevalences of scabies and impetigo in these populations of the Eastern Division are consistent with those reported by other studies in

Fiji, although considerably higher than figures described by a national prevalence study conducted several years before.[4] It is possible that this is due to the high level of remoteness of these small islands, and therefore more isolation and possible recurring lack of scabies treatment. Most participants (51.2%) reported that they had never left their island of residence; however this may include people who were on the island since birth as well as residents who may have moved there more recently after marriage or retirement.

The occurrence and clinical manifestations of scabies showed a picture consistent with that previously observed in tropical developing countries, including Fiji. Children under 14 years of age were the most heavily affected by scabies, with over 50% having the disease. However, no age group was free of scabies or impetigo, and they were present in both females and males. Besides having the highest prevalence of scabies, young children were also the group with the most severe manifestations of the disease, with one fourth of children under five having moderate to severe lesions. There were differences between the topographic distribution of scabies and impetigo papules. Overall, the first was mostly seen in upper limbs whilst the latter was more commonly observed in feet and lower limbs. These sites are more likely to be affected as they are generally not covered by clothing and are the only exposed body areas in these populations. In addition, children are often carried by carers on their arms, presumably making transmission to these body parts more likely due to prolonged contact. The presence of both diseases in the scalp and face followed a clinical manifestation typical of infants and was rarely seen in older age groups. A possible explanation is the proximity of this body part to the mother’s breast or axillary areas while lactating.

This study documents that scabies is one of the main drivers of bacterial skin infection in Fiji based on its presence in association with impetigo, as suggested by previous research in

Fiji.[4] For the first time, this study explores the association of impetigo as a risk factor for scabies also by age group and body distribution, showing that the PAR, based on observed associations, is substantially stronger in younger children. These results suggest that strategies to control scabies in endemic areas would translate into significant reduction of associated bacterial infections, particularly in infants and younger children.

Clustering of infection by household is considered to be an important epidemiological predictor for scabies. However, to our knowledge, the extent of the association between individuals of the same household and between individual belonging to different household of the same community has not been previously documented. Crowding, defined as the number of individuals per household and number of individuals per room, was strongly associated with higher prevalence of scabies and impetigo. In addition, we noted a clear correlation between young age and severity of scabies and associated bacterial infection, both at individual and household level. The ICC due to household clustering were estimated as 13% and 5% for scabies and impetigo respectively; however accounting for this clustering effect did not change the associations between the demographic factors and the outcome variables (data not show).

This study has several limitations. First, the diagnosis of scabies and impetigo was only made clinically, without the use of a confirmatory microscopy, as this method was not practical in our study setting. However, the high prevalence reported in this study is consistent with findings from earlier surveys in the Pacific region.[3-5] In addition, the study nurse who performed all skin examinations has considerable experience in scabies diagnosis having worked in the national dermatology hospital for over 20 years. We did not consistently examine breasts and genitals, areas where scabies is often common,[21,24] however we systematically asked participants whether itch, rash or discomfort were present in these parts. Second, although Fiji has two main ethnicity groups, our study only measured scabies and impetigo prevalence in the indigenous iTaukei population. Previous studies in Fiji have documented that scabies and impetigo are most common in the iTaukei population.[4,6,25] One of the explanations for this could possibly be due to a higher number of children per family and the tendency to live in houses with high density of people per room. Bacterial infections such as streptococcal and staphylococcal infections, pneumonia and rheumatic heart disease have all been more frequently reported in the iTaukei ethnicity in Fiji.[26-29] While site specific PAR was calculated to estimate the percentage of impetigo prevalence attributed to scabies, the association could have been analysed in other ways. An example could be the examination of scabies lesions anywhere in the body as a predictor of impetigo in specific body sites. Finally, although we investigated the role of living circumstances as risk factors for scabies in these communities, we did not assess in depth other socio-economic factors such as general hygiene, level of education and income factors that could potentially be associated with the presence of scabies and bacterial infections. Although we do not have this information by household, we do have extensive local knowledge of these factors for each of the islands visited.

High prevalence of scabies and related bacterial infections have previously been documented in tropical countries and in disadvantaged populations, particularly in countries of the Pacific region.[30] This study adds important data confirming the high prevalence of scabies and impetigo in Fiji. This burden of disease in resource poor communities highlights the need to undertake research to investigate the best strategies for public health control of scabies and impetigo at population level. Our data from the SHIFT study suggest that an effective public health control measure for scabies will also likely lead to a considerable reduction in the burden of impetigo. However, further studies are needed to investigate the effect of scabies control on serious secondary bacterial infections to determine whether the decline of endemic scabies would translate into a definite reduction of the burden of associated complications, such as invasive bacterial disease, post-streptococcal glomerulonephritis and potentially rheumatic heart disease.

Acknowledgements

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Table 1. Scabies and impetigo prevalence by age, gender and household density

Factor	**Sample (%)**	**Scabies**		**Impetigo**	
	N	**n (%)**	**Unadjusted OR (95% CI)**	**n (%)**	**Unadjusted OR (95% CI)**
Total	2051	746 (36.4)		479 (23.4)	
Age					
<5years	257 (12.5)	122 (47.5)	2.7 (2.0 – 3.6)	80 (31.1)	3.0 (2.1 – 4.2)
5-9 years	341 (16.6)	190 (55.7)	3.7 (2.8 – 4.9)	131 (38.4)	4.1 (3.0 – 5.6)
10-14 years	277 (13.5)	132 (47.7)	2.7 (2.0 – 3.6)	108 (39.0)	4.2 (3.0 – 5.8)
15-24 years	168 (8.2)	52 (31.0)	1.3 (0.9 – 1.9)	29 (17.3)	1.4 (0.9 – 2.2)
25-34 years	280 (13.7)	67 (23.9)	0.9 (0.7 – 1.3)	35 (12.5)	0.9 (0.6 – 1.4)
≥ 35 years	782 (35.5)	183 (25.1)	1	96 (13.2)	1
Gender					
Female	987 (48.1)	387 (39.2)	1.3 (1.1 – 1.5)	204 (20.7)	0.8 (0.6 – 0.9)
Male	1064 (51.9)	359 (33.7)	1	275 (25.8)	1
No. of people per room					
< 2 people	287 (14.0)	79 (27.5)	1	40 (13.9)	1
2 - 3 people	759 (37.0)	283 (37.3)	1.5 (1.2 – 2.1)	170 (22.4)	1.8 (1.2 – 2.6)
≥ 4 people	1005 (26.3)	384 (38.2)	1.6 (1.2 – 2.2)	269 (26.8)	2.3 (1.6 – 3.2)

Table 2. Distribution of participants with scabies and impetigo lesions by age group

Factor	Age				
	n (%)*	**n (%)***	**n (%)***	**N (%)***	**p-value**
	< 5 years (n=122)	**5- 14 years (n=322)**	**≥ 15 years (n=302)**	**Overall (N=746)**	
Location of scabies lesions					
Face/scalp/neck	13 (10.7)	13 (4.0)	16 (5.3)	42 (5.6)	<0.001
Arms/hands	88 (72.1)	283 (87.9)	245 (81.1)	616 (82.6)	<0.001
Torso#	25 (20.5.)	30 (9.3)	79 (15.2)	134 (26.2)	0.027
Legs/feet	94 (77.1)	147 (45.7)	83 (27.5)	324 (43.4)	<0.001
	< 5 years (n=80)	**5- 14 years (n=239)**	**≥ 15 years (n=160)**	**Overall (N=479)**	
Location of impetigo lesions					
Face/scalp/neck	17 (21.3)	9 (3.8)	10 (6.3)	36 (7.5)	<0.001
Arms/hands	19 (23.8)	77 (32.2)	49 (30.6)	145 (30.3)	<0.001
Torso#	4 (5.0)	11 (4.6)	13 (8.1)	28 (5.8)	0.485
Legs/feet	51 (63.8)	183 (76.6)	100 (62.5)	334 (69.7)	<0.001

* As percentage of those in the category with scabies/impetigo.

Includes perineum and buttocks areas.

Table 3. Severity of scabies and impetigo lesions by age-group *

	Age			
	n / %	**n / %**	**n / %**	**N / %**
	< 5 years (121)	**5- 14 years (320)**	**≥ 15 years (301)**	**Overall (742)**
Severity of scabies lesions				
Mild (≤ 10 lesions)	61 (50.4)	198 (61.9)	192 (63.8)	451 (60.8)
Moderate (11 – 49 lesions)	39 (32.2)	81 (25.3)	91 (30.2)	211 (28.4)
Severe (≥ 50)	21 (17.4)	41 (12.8)	18 (6.0)	80 (10.8)
	< 5 years (77)	**5- 14 years (229)**	**≥ 15 years (149)**	**Overall (455)**
Severity of impetigo lesions				
Mild (≤ 10 lesions)	52 (67.5)	173 (75.6)	123 (82.6)	348 (76.5)
Moderate (11 – 49 lesions)	15 (19.5)	34 (14.9)	17 (11.4)	66 (14.5)
Severe (≥ 50)	10 (13.0)	22 (9.6)	9 (6.0)	41 (9.0)

* $p = 0.002$ and $p = 0.149$ respectively

Table 4. Population attributable risk of scabies as a risk factor for impetigo by body site and age*

Factor	Age			
	< 5 years	**5- 14 years**	**≥ 15 years**	**Overall**
Location of lesions				
Face/scalp/neck	0.26	0.21	0.09	0.21
Arms/hands	0.52	0.35	0.41	0.45
Torso #	0.45	0.33	0.59	0.47
Legs/feet	0.47	0.15	0.21	0.26
Total	0.71	0.46	0.29*	0.36

* p = 0.108

Includes perineum and buttocks areas.

Table 5. Presence of scabies and impetigo by household size (HH: household)*

	Number of households		
HH size	Total number of HH	HH with no scabies (%)	HH with no impetigo (%)
< 3 people	185	105 (56.8)	140 (75.7)
3 - 4 people	84	29 (34.5)	40 (47.6)
5 - 6 people	166	36 (21.7)	60 (36.1)
> 6 people	92	7 (7.6)	13 (14.1)
Total	527	177 (33.6)	253 (48.0)

*p-value <0.001

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Chapter 6

6.1 Conclusions and recommendations

Scabies is a widespread public health problem and remains one of the most common skin diseases seen in the developing world and affects mostly impoverished populations in tropical developing settings. The studies published in this thesis contribute to the limited knowledge of scabies epidemiology previously available in the literature. In a world first global review of scabies prevalence, countries of the Pacific region, including Australian indigenous communities, have reported the highest prevalence rates in the world.[1-11] Fiji is currently the only country in the world to have ever implemented a national survey for scabies prevalence. The studies outlined in this thesis, have been instrumental in the development of national guidelines for the management of this skin disease that in Fiji affects nearly one in two school age children.

As evidenced by its important link with impetigo, explored in depth in this thesis, scabies has a negative impact not only on affected individuals but also imposes a burden on families and communities, particularly the most vulnerable, and mostly on young children. In addition to the severe discomfort caused by the infestation, scabies has been clearly linked to a wide range of bacterial infections that can escalate into life threatening complications, such as kidney disease and rheumatic heart disease, both largely seen in the Pacific countries.[12-15] Data reported in this manuscript highlight the important risk factors associated with scabies, which are often strongly correlated with poverty and characteristics typical of low and medium income countries. Despite a growing research and programmatic interest, and the addition to the list of neglected tropical diseases by the WHO, scabies remains largely neglected as an important public health problem.[16,17]

Despite the availability of effective agents for the treatment of scabies, control programmes targeting individuals and family members have been ineffective in reducing community prevalence in endemic populations. Low adherence, inadequate follow-up and case and contact management may be some of the reasons for re-infestation.[18]

MDA has proven to be a successful strategy to reduce scabies in high prevalence communities, both with topical and oral agents.[6,7,19] However, SHIFT has provided evidence for the first time of the superiority of oral ivermectin when compared to permethrin and standard cares for the long-term reduction of scabies prevalence in a small, isolated community of Fiji.[20] However, the efficacy and feasibility of large-scale programs for scabies has not been assessed and further research is needed to evaluate the feasibility of such programs in larger and more mobile populations.

The role of ivermectin on other parasitic and skin diseases such as soil transmitted helminths, pediculosis, strongyloides, onchocerciasis and lymphatic filariasis has been long known and ivermectin has been extensively used as treatment of choice in large MDA programs in Africa and Latin America.[21]

The main goal of MDA programs is to eliminate diseases as a public health problem by reducing prevalence rates to a level that will interrupt transmission and that will make re-emergence of the disease unlikely. Encouraging signs of the potential feasibility of this approach come from the almost complete disappearance of lymphatic filariasis in some African countries and the success of trachoma in Morocco [22,23] demonstrating that the control of these NTD is possible in some developing country settings.

In addition to being able to effectively reduce the community burden of scabies, the MDA approach is attractive for many reasons. These include the possibility of integrating scabies intervention with existing, long standing NTD programs in areas where the diseases coexist. This would allow to reduce the costs of field interventions and relieve pressure on health systems, often burdened with a number of vertical programs.[24] However, there are many limitations undermining this approach.

In most developing countries, with large populations spread across vast territories, achieving program coverage is challenging. Some studies have reported suboptimal coverage rates and difficulties in reaching some target groups. This is often due to the lack of funding or infrastructure as well as poor community participation.[25] Low coverage can also lead to programs running for an extended period of time, increasing costs and undermining sustainability. Community participation through health education and information is therefore crucial to achieve coverage and sustainability.

The risk of drug resistance is also of particular concern in view of the lack of alternative antiscabeitic, particularly oral agents, which represent a more feasible option for large-scale delivery. Although drug development is not a short-term option, recent studies have provided encouraging results on the efficacy of moxidectin for scabies.[26]

Despite a number of limitations, ivermectin MDA appears to be a highly effective and safe option for community control of scabies and related complications. However, it should be integrated with other measures, such as improved hygiene and environmental sanitation, which aim to remove factors that may contribute to the transmission of the parasite. This is essential to prevent re-emergence of the disease and achieve long term public heath control.

Further research and recommendations

Further research needs to be undertaken to address the current research gaps to achieve a long term elimination of scabies as a public health problem in resource-poor settings. The following studies have been identified as research priorities:

- *Large-scale community intervention trials for scabies* to assess the feasibility of MDA approaches and determine whether the striking results obtained by SHIFT can be replicated in larger, more mobile populations. The results from this trial will have direct implications on national public health policy in Fiji, the Pacific more generally and all regions with endemic scabies and possibly move towards the elimination of scabies.

- *Large scale community intervention trials for downstream complications of scabies*. With the results of SHIFT there is now the opportunity to expand the use of this highly effective intervention to investigate the effect of ivermectin MDA on serious downstream complications and dramatically reduce the burden of scabies in endemic areas.

- *Cluster randomized trial of one versus two doses of ivermectin for scabies*. To determine if MDA with one dose of ivermectin is as effective as MDA with two doses in reducing the prevalence of scabies at 12 months after the intervention.This would directly translate into enhanced program cost-effectiveness, also through the possible adoption of integration strategies with other NTDs, that involve a single round of MDA.

- *Integration of scabies MDA with other NTD programmes* in the Pacific region and other countries where scabies is endemic, to enhanced program cost-effectiveness, reduce the burden on health care workers and health systems.

- *Mapping and geographical information system research* to understand the ecology and epidemiology of scabies to help identify target populations most in need and to assess efficacy of MDA measures.

- *Standardised survey and diagnostic methodologies for scabies* to reach consensus among the international research communities working on scabies control. Simplified guidelines should be designed for the use in field studies in resource-poor settings.

- *Improved guidelines for surveillance and monitoring of scabies programs.*

- *Design of guidelines for MDA for scabies in resource-poor settings,* including standard operating procedures for field work and treatment guidelines and consensus on threshold of scabies prevalence that would trigger MDA in a set population.

- *Studies to assess the role of environmental strategies for scabies control* and determine whether it is crucial to incorporate them into MDA programs.

- *Development and testing of new oral therapies and vaccines for scabies* to combat drug resistance of currently available agents.

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