# Scabies: a ubiquitous neglected skin disease

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**Scabies has been a scourge among human beings for thousands of years. Its worldwide occurrence with epidemics during war, famine, and overcrowding is responsible for an estimated 300 million people currently infested. Scabies refers to the various skin lesions produced by female mites, and their eggs and scybala that are deposited in the epidermis, leading to delayed-type hypersensitivity reaction. Recent immunological findings such as cross-reactivity with house dust mite allergens and an altered T-helper-1/T-helper-2 pattern contribute to a better understanding of the pathomechanism. Furthermore, progress in molecular biology and cloning of relevant antigens could enable the development of a diagnostic ELISA system and candidate vaccines in the near future. Typical and atypical clinical presentations with pruritus as a hallmark of scabies occur in young, pregnant, immunocompromised, and elderly patients and include bullous and crusted (Norwegian) manifestations as well as those masked by steroid use (scabies incognito). This article reviews scabies management strategies in developed countries and resource-poor communities as well as typical complications, including the emergence of resistance and drug-related adverse events. Other problems such as post-scabies eczema and reinfestation, and newer treatments such as ivermectin are also discussed.**

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## Introduction

Scabies is an ectoparasite infestation. It is caused by the mite *Sarcoptes scabiei* variety *hominis* and transmitted by person-to-person contact. The name *Sarcoptes scabiei* is derived from the Greek word "sarx" (flesh) and "koptein" (to smite or to cut) and the Latin word "scabere" (to scratch). Scabies was first described more than 2500 years ago.[1] Scabies was referred to in the Old Testament and by Aristotle,[2] but it was not until 1687 that the causative organism was identified by Bonomo and Cestoni using light microscopy.[3–6]

Although the infectious agent is ubiquitous, it is endemic in impoverished communities, such as underprivileged suburban villages, where up to 9% of the population and 19% of those attending a primary health-care centre are infested.[7] By contrast, in industrialised countries, outbreaks occur in hospitals, kindergarten, and other institutions.[8] Despite common belief, scabies is only infrequently acquired from contaminated fomites (eg, clothing, towels, and bedding).[9]

## Scabies mites

*S scabiei* is a member of the family Sarcoptidae within the class of Arachnida (figure 1A). They are easily distinguished from other arachnids by the position of a distinct gnatosoma (head with mouth parts) and the lack of a division between the abdomen and cephalothorax. Adult females are around 0·4 mm long and 0·3 mm wide with males being smaller. Adult nymphs have eight legs and larvae have six. Although the mites cannot fly or jump, they may crawl as fast as 2·5 cm per min on warm skin.[10,11]

After mating, the male mite dies and the female begins to lay up to three eggs per day in skin burrows within the stratum granulosum (figure 1B). A single mite can produce up to 40 ova. Larvae hatch at 2–4 days and also dig burrows (so-called "moulting pouches"). 3 to 4 days later, the larva moults into a protonymph, which after 2–5 days moults into a tritonymph (figure 1B), from which an adult male or female emerges after another 5–6 days. In total, mature adults develop within 10–14 days. Skin entry occurs in less than 30 min and can take place during every stage by secreting enzymes that dissolve the skin, which is then ingested by the mite as nutrient (figure 1C). The average infested adult human being has an estimated ten to 15 adult female mites on the body surface at a given time.[11]

*S scabiei* is responsible for epizootic disease in livestock animals and wild populations of dogs, cats, ungulates, boars, wombats, koalas, great apes, and bovids.[12] Current estimates indicate that between 50% and 95% of pig herds worldwide are infested with *S scabiei*.[13,14] Animal scabies can be transmitted to human beings,[15] which can also result in pruritic papules (eg, pig handler's itch, cavalryman's itch).[8] In general, animal scabies is self-limiting in humans beings, since the mites cannot complete their life cycle.[16,17]

Research on scabies has historically been limited because of the difficulty in obtaining sufficient numbers of the causative organism. Recent molecular approaches have enabled substantial advances in the study of population genetics and transmission dynamics of *S scabiei*.[13] Promising data from *S scabiei* cDNA libraries have enabled the identification of several unique genes.[18] Of particular interest was the identification of *S scabiei* homologues of the known house dust mite allergens glutathione-S transferase, paramyosin, and cathepsin-L.[18] By comparison with trypsin-like serine proteases (members of group-3 allergens), which are excreted in faecal pellets,[19] one homologue has been termed Sar s 3 in analogy to Der p 3. Their most remarkable feature is that they usually do not contain an intact catalytic site, thus rendering these proteases non-functional. These inactivated proteases were designated scabies mite inactivated protease paralogues (SMIPPs). SMIPPs might, therefore, act as antagonists of active proteases by competing for peptide substrates. House dust mite code-3 and code-9 allergens that are also serine proteases

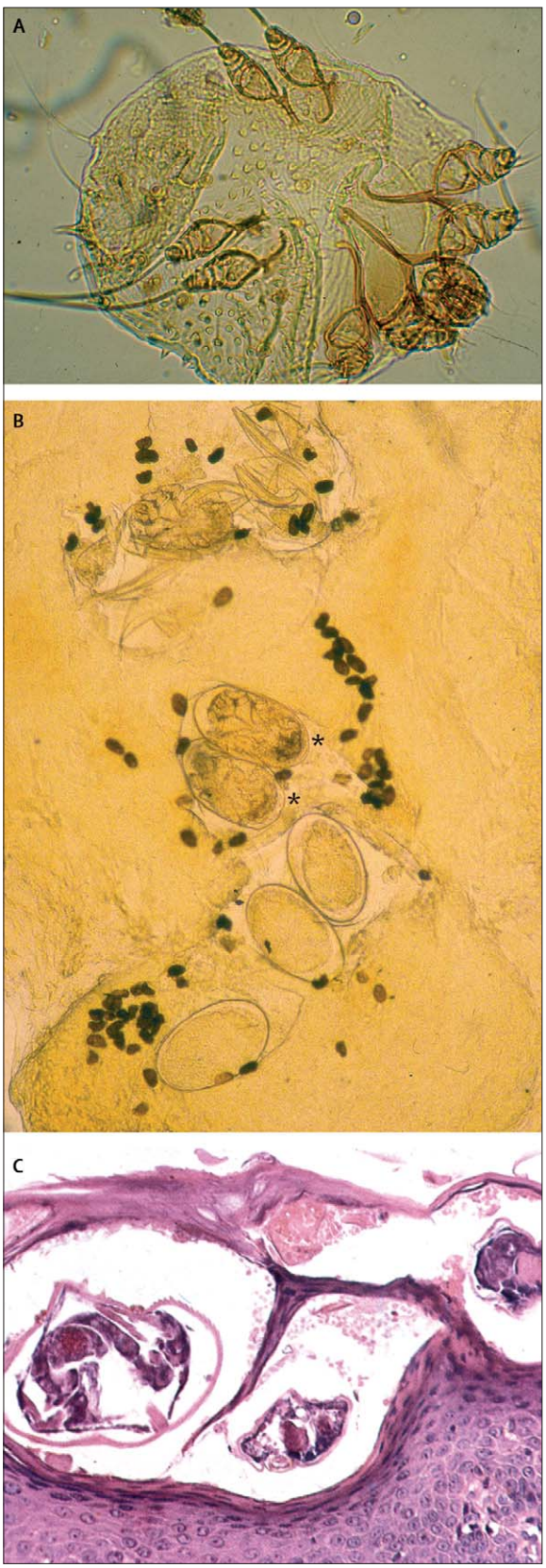


***Figure 1*: Life cycle of scabies mites**
(A) Microscopic section of *S scabiei* mite showing eight legs and the bite apparatus. (B) Skin scraping upon treatment with 10% potassium hydroxide showing eggs, nymphs (*), and scybalae (faecal pellets). (C) Histological section (haematoxylin and eosin stain) showing a burrow with the scabies mite in the upper epidermis.

are known to bind and activate protease-activated receptor (PAR)-2 on the surface of human pulmonary epithelial cells, inducing cytokine release.[20] Because PAR-2 is also present in the surface of keratinocytes, SMIPPs might be capable of binding to, but not activating, PAR-2, thus protecting the scabies mite from the inflammatory response.

## Epidemiology

Detailed figures on the epidemiology of scabies are scarce. An accurate global epidemiologic assessment does not exist.[21,22] Two rather accurate reports come from Edinburgh (between 1815 and 2000) and Denmark (1900–1970). The Royal Infirmary of Edinburgh has stored data on infectious diseases from 1815 to 2000.[21] Their statistics showed that roughly 5% of patients with skin disease in the entire period had scabies with sharp increases in incidence during wartime, when prevalence reached more than 30%.

By contrast with theories that there are fluctuations of scabies every 7–30 years (scabies is also termed "7-year itch"), wartime shows a clear coincidence with high levels of scabies.[23] Seasonality trends of scabies have been documented over a 20-year period in a large military population in the Israeli Army.[24] The results showed an overall risk ratio of 1·31 for scabies, with a higher incidence in winter than in summer. The more frequent incidence in autumn and winter might be partly because of biological characteristics of mites. Mites survive longer away from the body in cooler weather. Furthermore, colder weather encourages overcrowding in human beings. Mites also might be sensitive to antimicrobial peptides contained in human sweat, leading to reduced infestation in summer.

An epidemiological study by general practioners in England and Wales, where data of about 5 million patients were collected over a 10-year period from 1994 to 2003, showed an incidence of scabies of 351 per 100 000 person-years in males and 437 per 100 000 person-years in females.[25] Reports from northern Australia indicate that up to half of the population in some remote Aboriginal communities has scabies.[26] The same was reported from Delhi.[27,28] Global estimates account for about 300 million cases of scabies (about 5% of the world's population) towards the end of the 20th century.

It has been shown that clearance of primary scabies infestation correlates with development of immunity. Both human beings and animals have a reduced parasite burden on reinfestation, and some can even eliminate a second infestation before clinical manifestations develop.[9] However, this concept of herd immunity is challenged by both the documentation of ongoing scabies endemicity in many tropical and subtropical communities such as India, South Africa, Panama, and northern Australia, and the fact that long-term reinfestation is common.[5,29–31] It has, therefore, yet to be definitively established whether

single or multiple infestations with *S scabiei* can result in robust long-term immunity.

Scabies is most common in young children, possibly reflecting both increased exposure and, in endemic situations, lack of immunity. Scabies affects both sexes similarly. Ethnic differences in scabies epidemiology are most likely to be related to differences in overcrowding, housing, and socioeconomic and behavioural factors, rather than racial origin. Poverty, poor nutritional status, homelessness, dementia, and poor hygiene are associated risk factors.[31–33] Evidently, health-care workers are at an increased risk for scabies. Outbreaks frequently occur in institutions such as hospitals, nursing homes, prisons, or kindergartens. Recommendations for prevention and control are given in panel 1.

***Panel 1:* Guidelines for elimination of scabies in institutional outbreaks**

**Home**
- Change encasings of mattresses, carpet, clothing*
- Cleaning of rooms, furniture, couches

**Treatment**
- Topical and systemic treatment of index patients (eg, permethrin and ivermectin)
- Synchronous topical treatment of all contacts with or without skin lesions
- Evaluate potential re-treatment in week 2
- Clip nails, brush subungual folds with scabicides

**General**
- Reduce social contacts
- No reunions in nursing homes—eg, for meals
- Avoid/examine pets
- 10-day quarantine of index patient
- Use gloves, protective clothing, alcohol, and handwashing when caring for such patients

*Since transmission is unlikely to occur through contaminated fomites, this recommendation should be discussed on an individual basis.

## Transmission and pathogenesis

Studies by Mellanby[9] showed that direct person-to-person body contact was generally necessary for transmission of scabies. Only four new cases resulted from 272 attempts to infect volunteers who climbed into warm beds just vacated by heavily infected patients.[9] This finding suggested that clothing or mites shed on the floor were an unlikely means of infestation with the exception of patients with hyperinfestation (crusted or Norwegian scabies), who can shed thousands of mites daily.

Intrafamily transmission as the most common means of infestation is supported by molecular studies showing the genotypes of mites from household members to be more homogeneous than those from separate households within a community.[31] In adults, sexual contact is an important method of transmission.

## Clinical features

The pathognomonic signs of scabies are burrows, erythematous papules, and generalised pruritus (also on non-infested skin) with nocturnal predominance. Burrows are serpinginous whitish lines in the upper epidermis of several millimetres in length (figure 1C), but are only infrequently present in patients in the developing world. Burrows are typically located on the interdigital spaces of the hand, the flexure surface of the wrist, elbows, genitalia, axillae, umbilicus, belt line, nipples, buttocks, and penis shaft. Secondary papules, pustules, vesicles, and excoriations are usually present (figure 2A and figure 2B). The pruritus results from a delayed type-IV hypersensitivity reaction to the mite, its saliva, eggs, or excrements (scybala). Therefore, symptoms usually occur with a delay of up to 3 weeks after initial infestation and usually within a few days upon reinfestation.[5] The secondary lesions are more prominent than burrows, especially when the infestation has been present for some time. Notably, the rash does not correlate with the number of mites.

Whereas the diagnosis of classic scabies is straightforward, it may also present atypically. In infants scabies usually affects the axillae, head, face, diaper region, and occasionally the palms and soles, and presents with vesicles, pustules, and nodules (figure 2C).[34] Children, especially in poor countries, frequently present with scabies superinfected by group A streptococci or *Staphylococcus aureus* (figure 2D), which should be treated first. Bullous scabies may occur located on the extremities or on the trunk.[34,35]

Nodular scabies is a clinical variant occurring in about 7% of scabies cases,[5] where extremely pruritic nodules of 2–20 mm in size are present on the male genitalia, buttocks, in the groin, and the axillary regions (figure 2E). The nodules are reddish to brown and because they do not contain mites, are thought to represent intense hypersensitivity reactions to mite products. They can persist for weeks after treatment and patients might require corticosteroid injections.[5,36] Recently, a report has described the successful treatment of nodular scabies with topical pimecrolimus.[37]

Another atypical form, known as Norwegian or crusted scabies, was originally described by Danielson and Böck in 1848.[38] Nowadays, crusted scabies is frequently found in patients with HIV-infection, human T-cell lymphotropic virus type-1 infection, or following immunosuppressive therapy such as for organ transplantation.[39–43] Crusted scabies also occurs in patients with mental retardation, such as those with trisomy 21.[5,33] However, a substantial percentage (about 40% of patients) had no identifiable risk factor, suggesting the possibility of a genetic predisposition, possibly inheritable, which is yet to be determined.[43] Eosinophilia occurred in 58% and elevated IgE (mean of 17-fold) in 96% of patients, respectively, in a cohort of 78 patients.[43] Clinically, crusted scabies presents as a psoriasiform dermatitis with an acral distribution

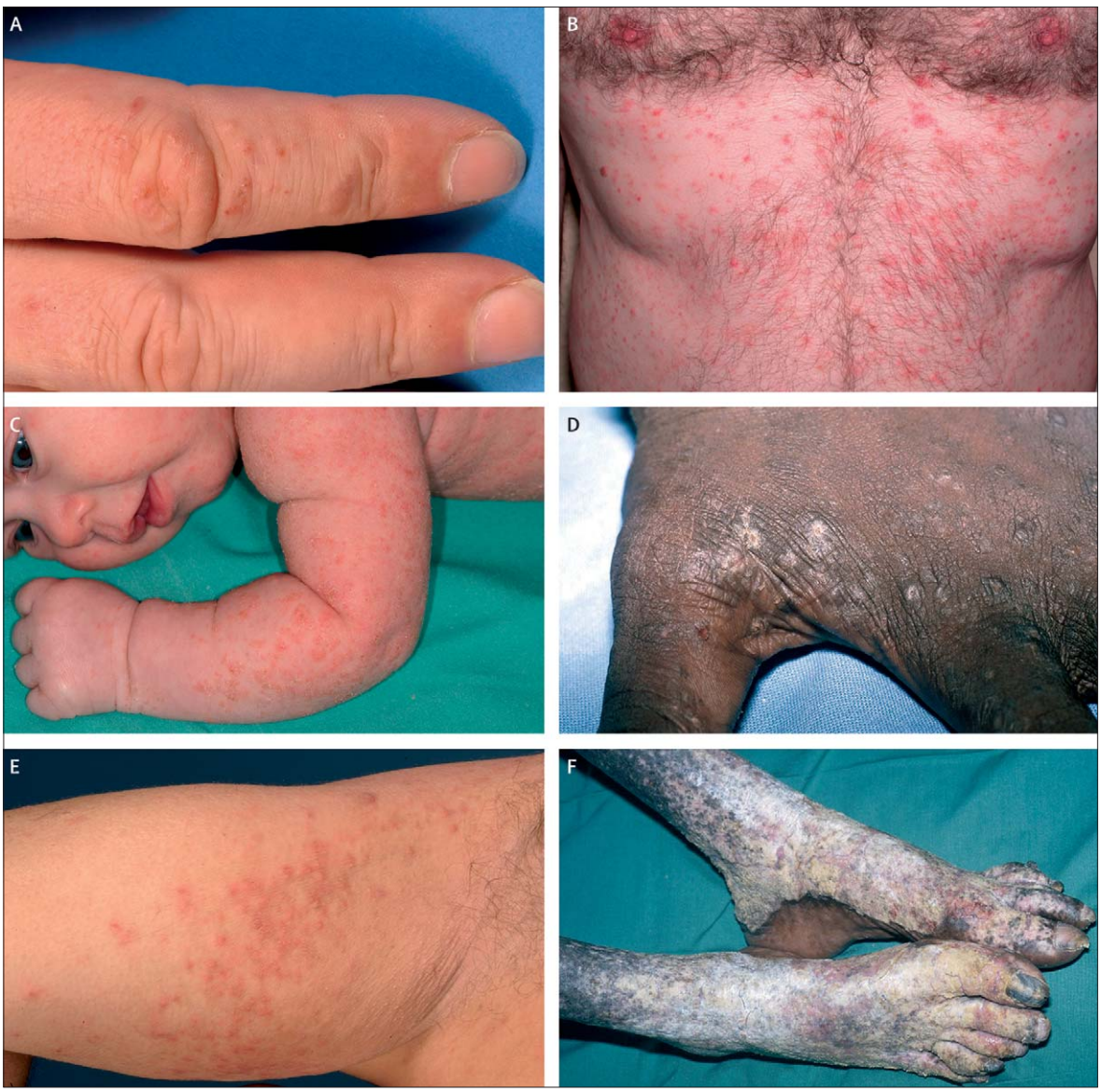


***Figure 2*: Clinical manifestations of scabies infection**
Clinical features of common scabies can include itchy papules on the index finger (A); excoriated erythematous papules on the chest and abdomen associated with intense pruritus (B); disseminated excoriations, crusts, and scaling in a baby (C); and erosions and yellowish crusts as an indication of streptococcal infection (D). Clinical features of nodular scabies can include hyperpigmented papules in the axillary region (E). Clinical features of Norwegian (crusted) scabies can include hyperkeratotic, sharp demarcated scaly plaques and crusts containing thousands of mites (F).

and variable whitish scaling (figure 2F). It usually also involves the subungual area with extensive hyperkeratoses leading to nail thickening and dystrophy.[44] Crusted scabies also might occur with predominant lesions on the scalp, face, neck, and buttocks. About half of patients with crusted scabies do not report itching.[41,44] Crusted scabies is considerably more infectious than ordinary scabies, as evidenced by nosocomial outbreaks of ordinary scabies from index cases of crusted scabies.[45] Although crusted scabies is caused by the same variety of mite that causes typical scabies, the mite population can be over 1 million per person.[46]

## Histology

A skin biopsy specimen might show mites with ova within the stratum corneum (figure 1C). A specimen from an intact burrow might show a female with eggs often behind her. An inflammatory infiltrate with spongiosis in the superficial and deep dermis is composed of lymphocytes, histiocytes, eosinophils, and occasionally neutrophils. Subepidermal oedema might also be seen. These changes can be differentiated from most other arthropod bites only by visualising the female mite or her eggs within the stratum corneum. In crusted scabies, prominent hyperkeratosis and innumerable mites can be

seen besides the inflammatory infiltrate. In nodular scabies, the inflammatory infiltrate tends to be extremely dense and mixed around the blood vessels and in the subcutaneous fat, and can occasionally mimic lymphoma or pseudolymphoma.

## Host immune response

It is generally accepted that the signs and symptoms of scabies result from delayed type-IV hypersensitivity reaction against mite and mite-product antigens.[9] The time required to induce this immune response in primary infestation could account for the latency period of up to 4 weeks, during which time the patient is free of symptoms.[47] Continuous exposure in excess of 100 days led to raised immune responses and reduced number of infesting mites in about half of infested patients.[43,45] Upon re-exposure of sensitised individuals symptoms manifest within 24 hours.[9] The occurrence of increased serum levels of total IgE and IgG combined with peripheral eosinophilia might relate to an inappropriate T-helper-2 (Th2)-type immune response. However, this pronounced humoral immune response seems non-protective, as shown by high rates of reinfestation despite increased antibody levels.[9,43]

Cell-mediated host immune responses have been analysed by investigating the inflammatory cells in dermatohistopathological sections of scabies lesions. Mites were surrounded by an inflammatory infiltrate, comprised of eosinophils, lymphocytes, and histiocytes.[48] There are no published studies to date on in-vitro T-cell responses to scabies mite antigens from scabies patients.

Because the house dust mite and scabies mites are related arthropods, it is possible that their secretions share allergens. Immunological studies have demonstrated that antisera to house dust mite allergens cross-react with extracts of *S scabiei*.[49–51] Further support comes from sensitisation experiments in rabbits, where an extract of *Dermatophagoides farinae* and *Dermatophagoides pteronyssinus* resulted in reduced levels of *S scabies* infestation.[51] By contrast, patients with hypersensitivity to *D pteronyssinus* were reported to develop a more severe rash from scabies than non-allergic patients.[52,53]

Although the mite causes marked hypersensitivity reactions, little is known about the specific scabies mite molecules in such immunologic responses. Glutathione S-transferases and SMIPPs have been suggested as important immunogenic antigens.[18,54,55]

## Diagnosis

Every individual with intense pruritus should raise a suspicion of scabies, especially if there is a family report of similar symptoms.

The usual method of scabies diagnosis is skin scraping. An oil-covered scalpel blade should be scraped across burrows; the oil helps the scraped material to adhere to the blade. Scrapings are then placed on a slide with a coverslip for microscopic examination. It is best for scraping to take place at fresh, non-excoriated burrows in the interdigital areas of the hand. Sometimes, repeated scrapings are necessary because the sensitivity is rather low. Direct microscopic examination of skin scrapings is ideal for identifying the mite and its products. Potassium hydroxide dissolves the keratin and provides a clear visualisation of the mites and eggs (figure 1B) but may dissolve the scybala, which are best seen using saline or mineral oil.[56]

An alternative method is the burrow ink test, where burrows will absorb the ink and be readily apparent.[56] Video-dermatoscopy, with magnifications of up to 600 times is especially suitable for making a diagnosis in children.[57] Dermatoscopy done directly on the skin can also aid in identifying burrows or mites.

The difficulties with the development of an ELISA for diagnosis of human scabies include the lack of an in-vitro culture system for scabies mites, the lack of an animal model for human scabies, the previous lack of recombinant purified mite antigens, the host cross-reactivity to house dust mite allergens, and technical problems (eg, contamination of mite antigen extracts with host immunoglobulin).[58]

## Differential diagnoses

The list of differential diagnoses is long and includes atopic dermatitis, contact dermatitis, lichen planus, and animal scabies—whose mites cannot complete the life cycle on the human host because they cannot create burrows (panel 2). Other insect manifestations including fleas, lice, bed bugs, chiggers, cheese mites, grain mites, foul mites, rat mites, and mosquitoes cause pruritic lesions called papular urticaria as a result of hypersensitivity.[59–61]

***Panel 2:* Differential diagnoses**

- Atopic eczema
- Contact dermatitis
- Folliculitis/impetigo
- Tinea corporis
- Bites from mosquitoes, midges, fleas, lice, bedbugs, chiggers, or other mites
- Papular urticaria
- Prurigo nodularis subacuta

- Animal scabies
- Dermatitis herpetiformis
- Herpes gestationis
- Infantile acropustulosis
- Eczema herpeticum
- Pityriasis rosea
- Pruritic urticarial papules and plaques of pregnancy (PUPPP)
- Syphilis
- Viral exanthema

The most frequent differentials are listed at the top.

| | Lindane | Benzyl benzoate | Bioallethrin with piperonyl butoxide | Crotamiton | Permethrin |
|---|---|---|---|---|---|
| Newborn babies | Not recommended | Could cause gasping syndrome | Not recommended | Recommended | Recommended (Lyclear licensed for babies >3 months in US) |
| Babies/toddlers | Possible | Possible (gasping syndrome) | Not recommended | Recommended | Recommended |
| Pregnancy | Restricted indication | Restricted indication | Not recommended | Restricted indication | Recommended |
| Lactation | Restricted indication | Recommended (exclude chest, exclude breast) | Not recommended | Restricted indication | Recommended |

*Table:* **Treatment guidelines in early childhood, and during pregnancy and lactation**

Cases of less impressive scabies are not easily diagnosed, especially when topical glucocorticosteroids mask the typical itch and inflammation; these cases frequently occur in individuals with good body hygiene and are referred to as scabies incognito.

## Treatment

Several topical scabicides are available. Oral antihistamines can be used to help alleviate pruritus. For crusted scabies, crust and scale removal is necessary for scabicides to penetrate and oral ivermectin is also recommended. Topical antipruritics such as menthol (Sarna lotion) or pramocaine hydrochloride (Prax) can additionally be used. Nodular scabies can also be treated with intralesional steroid injections or possibly with topical pimecrolimus.[37]

### Topical therapy

*Pyrethrins and pyrethroids*

The flowers in the genus chrysanthemum have been used for centuries for their insecticidal properties. The active ingredients in the flowers are the pyrethrins. They were first commercially produced in Dalmatia (Croatia) in the 1840s, reaching the USA in the 1860s as Dalmatian "insect powder". The pyrethrins were imported as dry flowers until 1956 when an extract, some 60 times more potent, made shipping cheaper. Permethrin, a pyrethroid, was approved in the USA for the treatment of scabies in 1989. Synthetic pyrethroids including permethrin represent one of the most important insecticides, accounting for over 25% of the world insecticide market.[62]

Absorption of topically applied permethrin is very low, underlining its clinical safety.[63] Permethrin has a good cosmetical acceptance and lacks allergic potential, shows low percutaneous penetration, and is excreted via the urine. According to a recent updated Cochrane review, permethrin appears to be the most effective topical scabicide, significantly better than crotamiton and lindane.[64]

Permethrin is indicated in babies (table). Topical 5% permethrin cream can cause erythema, burning, and, rarely, dystonic adverse reactions, including muscle spasms.[65] This adverse effect is probably related to permethrin's ability to delay sodium channel closure within nerve cells. Consequently, central nervous system symptoms could occasionally occur, especially in infants.

*Lindane (γ-hexachlorcyclohexane)*

Lindane is a widely prescribed topical scabicide because of its efficacy and cost-effectiveness. Dermatological adverse events include irritation; allergic contact dermatitis against parabens; and neurological symptoms (upon overdosing and accumulation in fat or milk) include insomnia, irritability, vertigo, convulsions, vomiting, diarrhea, restlessness, and collapse. This drug, therefore, has been banned in the European Union as a pesticide since 2001; it should only be used with caution when other options are not feasible (panel 3).

***Panel 3:* Measures for the safe use of lindane**

- Avoid application immediately after a bath
- Apply for no more than 6 h
- Avoid repeated applications within a short period of time
- Prevent thumb sucking in children
- Use with extreme caution in infants, pregnant women, on massively excoriated skin (eg, atopic eczema, ichthyosis, psoriasis), in patients with seizures or neurological disease

*Benzyl benzoate 10–25%*

Topical benzyl benzoate therapy has been widely used in adults and also in diluted form for children, babies, and breastfeeding mothers. Only 48% (10 of 21) of patients receiving topical benzyl benzoate were cured compared with 70% (16 of 23) of patients treated with oral ivermectin (200 μg/kg).[66] In-vitro testing has shown benzyl benzoate to kill scabies mites more rapidly than permethrin, and to be a useful alternative to permethrin in severe crusted scabies.[43,67,68] The most common adverse event is an initial severe burning sensation from local irritation, which is common with the more concentrated lotion (25%). When severe, the benzyl benzoate must be washed off; however, with analgesia and antihistamines before treatment the stinging often diminishes after 10–15 minutes, allowing the lotion to remain applied.

*Crotamiton*

Crotamiton therapy of common scabies is recommended for newborn babies and infants (table). In a double-blinded, randomised study, permethrin 5% was compared with crotamiton 10% cream for the treatment of scabies in children of 2 months to 5 years of age.[69] 2 weeks after a single overnight treatment, 14 (30%) of 47 children were

cured with permethrin 5% cream, compared with only six (13%) of 47 children treated with crotamiton. 4 weeks after treatment, 89% and 60% of patients were cured with permethrin 5% cream and crotamiton, respectively. The difference in efficacy in favour of permethrin was significant (p=0·002). Erythema and conjunctivitis may occur with topical crotamiton.

*Sulphur (5–10%)*

Despite its scabicide effects, sulphur no longer represents the treatment of choice in the developed world because of an unpleasant smell, staining of clothing, irritant effects, and variable absorption with potential side-effects in the kidney. However, it is still being used in Africa and South America.

## Systemic therapy

*Ivermectin*

Ivermectin is a synthetic derivative of the antiparasitic class of avermectins.[70,71] Ivermectin is used against a wide range of endoparasites (eg, nematodes) and ectoparasites (eg, insects, *S scabiei*, *Pediculus humanus*, *Demodex folliculorum*, and *Cheyletiella* spp). Ivermectin shows good bioavailability, is metabolised in the liver, and excreted in the faeces by more than 98% of intake. Peak concentrations are reached around 5 hours post-dosing. Minimal concentrations have been observed in human milk. No genotoxicity or teratogenicity have been observed.[71]

Ivermectin paralyses the mite by selectively binding to specific neurotransmitter receptors that function in the peripheral motor synapses of parasites (blocking glutamate-gated anion channels and γ-aminobutyric acid-gated chloride channels) .[71,72] Ivermectin was recently approved for the treatment of regular scabies in France.[70,73] A single dose of ivermectin given to 1153 prisoners cured 88% of recipients after 4 weeks and 95·5% after 8 weeks.[74] Most comparative studies have shown that oral ivermectin is equivalent for common scabies to conventional topical scabicidal treatment (benzyl benzoate, lindane, permethrin) following one or two oral doses of 200 μg/kg.[66,75,76] Only one study in 85 consecutive patients showed superior treatment with one application of 5% permethrin cream when compared with oral ivermectin.[77] A single application of permethrin was effective in 97·8% of treated patients compared with 70% who received a single oral dose of ivermectin. However, a second dose of ivermectin at a 2-week interval yielded 95% cure.[77] The temporal dissociation of clinical response suggests that ivermectin might not be effective against all stages of the scabies life cycle (eg, no ovicidal action).

The full benefit of ivermectin becomes evident when eradication of scabies in epidemic or endemic situations in nursing homes and prisons is needed since ivermectin leads to reliable disease control.[74,78–80] Along the same lines, crusted scabies has been effectively treated with ivermectin in adults[81–84] and children,[85] sometimes in combination with topical permethrin.[80,83] The failure of a single oral dose of ivermectin in some scabies patients might result from its lack of ovicidal action.[77] Therefore, several regimens often use repeated doses in 1 or 2-week intervals.[74,86]

The safety of ivermectin has been documented in millions of people with microfilarial diseases. Only 1·8% of 150 000 adverse reports caused by ivermectin were severe in nature.[87,88] Transient and mild adverse reactions included anorexia, asthenia, headache, arthralgia, myalgias, fever, eosinophilia, and maculopapular rashes. Pruritus may occur in up to 30% of treated patients.[80] Ivermectin does not normally penetrate the blood-brain barrier and consequently there is no risk of seizures; however, one recent report has indicated possible neurotoxicity in the elderly.[89] Because of limited safety data, ivermectin should not be used in children younger than 5 years of age or during pregnancy or lactation.[80]

In crusted scabies, repeated doses of ivermectin (200 μg/kg) can be given with topical scabicides (full body application, repeated initially every few days) and keratolytics.

## Drug resistance

The intensive use of pyrethrin and pyrethroids has led to the development of drug resistance in arthropods and resistance now constitutes a serious threat to many programmes for ectoparasite control. The development of resistance in human head lice has highlighted how difficult management becomes once drug resistance has emerged. Consequently, reliable in-vitro assays to define resistance and the identification of molecular tools to monitor for insecticide resistance are of great importance, together with the development of novel acaricides.[68]

The number of reports of treatment failure, possibly caused by resistance, is constantly increasing (eg, from Australia and El Salvador).[67,90,91] In-vitro mite tolerance to permethrin has been reported,[17] and a nosocomial outbreak of scabies with clinical resistance to lindane has been noted.[92–94] A simple in-vitro test has been established to assess the relative efficacy of various treatments against *S scabiei*.[68] Two mechanisms of ivermectin resistance have been proposed: alteration of P-glycoprotein, a transmembrane channel that actively transports the drug across the cell membrane; or alteration of the chloride channel receptor.

## Complications and prognosis

The most frequent complication of treatment with topical scabicides is persisting post-scabies eczema (generalised eczematous dermatitis). Because of the irritant effects of the various formulations, xerosis might increase and worsen delayed-type eczema, which could be mistaken for drug failure or reinfestation. Therefore, consequent rehydration/fattening of the skin and anti-inflammatory therapy with potent glucocorticosteroids are advised. Other complications include postinflammatory hyperpigmentation or hypopigmentation and prurigo nodules.

The prognosis of scabies is excellent with proper diagnosis and treatment, unless the patient is immunocompromised or institutionalised. However, the percentage of reinfestation is high, especially when the patient returns to their normal environment, where eradication has not been properly carried out.

### Novel drug and vaccine development

Recently, the essential oil of the tea tree (*Melaleuca alternifolia*), containing oxygenetic terpenoids, was found to have rapid scabicidal and antibacterial activity.[95,96] The active compounds have been identified as terpinene. Similarly, the essential oil of the *Lippia multiflora* Moldenke, an aromatic perennial shrub found in the west African savanna, also has scabicidal properties.[97]

Despite several efforts, protective vaccination against scabies has been unsuccessful to date. The failure of protection in animals from an experimental anti-scabies vaccine was attributed to absent protective levels of IgE.[98] The multifunctional enzyme glutathione S-transferase of *S scabiei* could represent a specific target for vaccination against human scabies.[99] Analogous to the successful development of a vaccine for cattle tick, a scabies vaccine would be very useful in veterinary settings and commercial animal husbandry as well as for human beings.[100]

## Community control

Control of scabies is hindered by difficulties with diagnosis, the costs of treatment, and evidence of emerging resistance. There is no effective vaccine. Some general recommendations can be given for locally confined outbreaks in institutions (panel 1).

Community control of scabies has been accomplished with a reduction in prevalence from 33% to less than 1% after treatment with 5% permethrin cream.[30] An example in the Cuna Indians in the San Blas islands of Panama showed that when all 280 inhabitants of the island were treated with topical 5% permethrin with systematic education and attention to logistics, scabies outbreaks could be controlled for 5 years.[30] Additionally, bacterial skin infections decreased in prevalence from 33% to less than 2%.[30] More recently, community control programmes with oral ivermectin have been successful.[30,101]

### The South American perspective

Scabies is a huge social problem in South America. Scabies is hyperendemic in the numerous poor communities in Brazil—the country most affected by the disease in South America—and is commonly associated with considerable morbidity and the continent's weakening public-health system.[7]

Recently, two studies were conducted to assess the perception and health-care seeking behaviour in relation to parasitic skin diseases and to determine their public-health effect.[102,103] Slum inhabitants were examined for the presence of scabies (8·8%), pediculosis (43·3%), tungiasis (33·6%), and cutaneous larva migrans (3·1%). Additionally, health-care seeking behaviour was assessed in patients attending a primary health-care centre adjacent to the slum. Only 28 of 54 patients from the slum with scabies sought medical assistance. The physicians of the primary health-care centre only diagnosed a parasitic skin disease when it was pointed out by the patient.[102] The results showed that scabies was the third most frequent infection, and was neglected by both population and physicians, leading to underestimation of the community prevalence.[102]

An interesting evaluation concerns the selective mass treatment with ivermectin to control both intestinal helminthiases and parasitic skin disease in this same severely affected population.[104] Prevalence rates of intestinal helminthiases and parasitic skin diseases before treatment and at 1 month and 9 months after mass treatment were: hookworm disease 28·5%, 16·4%, and 7·7%; ascariasis 17·1%, 0·4%, and 7·2%; trichuriasis 16·5%, 3·4%, and 9·4%; strongyloidiasis 11·0%, 0·6% and 0·7%; pediculosis 16·1%, 1·0%, and 10·3%; scabies 3·8%, 1·0%, and 1·5%; cutaneous larva migrans 0·7%, 0%, and 0%; and tungiasis 51·3%, 52·1% and 31·2%, respectively.[104] Adverse events occurred in 9·4% of treatments, were mild to moderate in severity, and transient. Mass treatment with ivermectin was an effective and safe means of reducing the prevalence of most of the parasitic diseases endemic in a poor community in northeast Brazil and, since the effects of treatment lasted for a prolonged time, mass treatment is probably the best option for reducing hyperendemicity of both ectoparasites and intestinal helminthiases—in conjunction with prevention and education programmes.[104] Similar data are available from other countries such as Cameroon and Liberia.[88] In tropical and subtropical countries, pyoderma caused by *Streptococcus pyogenes* and *S aureus* is a major complication of scabies that can affect rates of rheumatic fever, rheumatic heart disease, and post-streptococcal glomerulonephritis.[105,106]

### The African perspective

The prevalence of scabies in Africa is different in the various regions. Although it represents the most common skin disease in Ethiopia and Nigeria,[107,108] it is less common in eastern Africa (Uganda and Tanzania), Mali, Malawi, and Cameroon.[109] Most patients in Uganda are children. Crusted scabies was frequently diagnosed in mentally or physically handicapped children who were neglected by their relatives as well as in HIV patients from Uganda. The disease management was usually successful in boarding schools when routine procedures including disinfection of clothes and mattresses were performed.[109]

In Tanzania, the prevalence of scabies is currently low, in the range of 5%.[110] Other skin diseases—especially prurigo in HIV, psoriasis, eczema, and impetigo—are more common nowadays because doctors have learned to more efficiently treat scabies.[111]

In Nigeria, the prevalence of scabies in 1066 school children (mean age 8·8 years) was 4·7%, whereas dermatophyte infection accounted for a prevalance of 15·2%.[108] The prevalence of scabies was investigated in a displacement camp in Sierra Leone in 125 children between the ages of 1–15 years. The prevalence was age dependent, with children under 5 years accounting for 77% of scabies cases, peaking at 86% among the 5–9-year-olds, and steadily declining with an increase in age.[112] Secondary bacterial infection is very common in some areas such as Ghana.[113]

The treatment in rural Africa is generally limited to benzyl benzoate emulsion, topical sulphur, or crotamiton cream or solution,[114] because lindane is not available. In some countries 20% *Lippia multifolia* oil applied to patients with scabies for 5 consecutive days is given with similar success as benzyl benzoate.[97] Adherence in children strongly depends on the capability of their mothers.

### The Australian and Pacific perspective

In central and northern Australia scabies is currently endemic in remote Aboriginal communities, with prevalences in children as high as 50%.[105] Molecular typing of scabies mites has shown several overlapping epidemic cycles.[31] Intensive intervention programmes in selected communities, using mass topical permethrin together with household and community clean up days, has resulted in sustained lower rates of scabies.[115] However, sustainability of low scabies rates in other communities has been variable, with reintroduction occurring from untreated contacts and core transmitters who have been reinfested on several occasions after returning to their home communities.

Scabies is also endemic in many of the Pacific islands and in Papua New Guinea. A recent community intervention with oral ivermectin in several of the Solomon Islands was successful in controlling scabies and decreasing streptococcal skin disease.[101]

## Global scabies control

The obvious first step in global scabies control is for health authorities to set up national and international reporting systems, such as the one in Denmark.[22] This epidemiological foundation is a prerequisite for the start of an elimination process. There is evidence that health education combined with improved diagnosis and improved drug supply will result in a greater reduction in scabies.[30,101,104,116,117] Simple mass treatment with scabicides will produce little long-term effect. Even after long-term surveillance and treatment programmes, any interruption of vigilance or logistics will result in a significant increase in incidence.[30]

Progress in scabies molecular research and the identification of mite homologues of house dust mite allergens have fuelled the potential for novel strategies aimed towards prevention, diagnosis, treatment, control, and immunotherapy of this important but neglected parasite disease.

### Search strategy and selection criteria

Articles for this review were identified through a search of the PubMed database using the keyword "scabies". All publications in English in the last 5 years were evaluated for potential inclusion in the manuscript.

**Conflicts of interest**

We declare that we have no conflicts of interest.

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