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SUMMARY WITH CRITICAL APPRAISAL

Ivermectin for Parasitic Skin Infections of Scabies: A Review of Comparative Clinical Effectiveness, Cost-Effectiveness, and Guidelines

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Abbreviations

AE	adverse event
BASHH	British Association for Sexual Health and HIV
IUSTI	International Union Against Sexually Transmitted Infection
NMA	network meta-analysis
RCT	randomized controlled trial
SR	systematic review

Context and Policy Issues

Scabies is a skin condition caused by the parasitic infestation of the mite *Sarcoptes scabiei*. Scabies results in intense, debilitating itching and skin papules, nodules, and vesicles and is transmitted through direct contact. In a small proportion of cases, typically in those with immunosuppression, hyperinfestation and crusted scabies can develop and lead to secondary bacterial infection associated with significant morbidity and mortality.[1-3] The Global Burden of Disease study estimated that the global prevalence of scabies was approximately 200 million in 2015.[4] High prevalence of scabies is associated with tropical regions, resource-poor settings, and overcrowded settings.[1-4] Outbreaks of scabies have previously been reporting in chronic health care facilities in Canada.[5]

In Canada, common scabicides for the treatment of scabies include: topical 5% permethrin, topical crotamiton 10%, pharmacy-compounded topical sulfur 5% to 10%, and topical or oral ivermectin.[6] According to the Canadian Paediatric Society Position Statement on scabies,[6] topical treatments applied from the neck down are typically used to treat scabies and first-line treatment is topical permethrin. Some topical treatments, including permethrin, are repeated after one to two weeks to improve effectiveness as they do not affect mite eggs.[6] Treatment is recommended not only for the patient with scabies but also all close contacts at the same time to prevent transmission to others and re-infestation in the originally affected patient.[1-3,6] Similarly, washing linens and clothing in hot water is a precautionary measure to prevent fomite transmission.[2,6]

Lindane and benzyl benzoate are treatment options for scabies that are not currently approved by Health Canada.[6] There are concerns with neurotoxicity with lindane and benzyl benzoate is associated with skin irritation.[6]

Oral ivermectin previously was obtained through the Health Canada Special Access Programme for treating parasitic infections.[6,7] Recently, topical and oral ivermectin have been approved by Health Canada and their approved indications are for the treatment of rosacea and intestinal strongyloidiasis and onchocerciasis, respectively.[8,9] Therefore, these treatment options can now be evaluated for drug plan coverage decisions. Ivermectin is not approved for use in children less than 15 kg in weight or patients who are pregnant or breastfeeding.[6]

The objective of this report is to review the evidence regarding clinical effectiveness and cost-effectiveness of ivermectin for the treatment of parasitic skin infections of scabies. Additionally, this reports aims to review the evidence-based guidelines regarding the use of ivermectin for the treatment of parasitic skin infections of scabies. A 2010 CADTH report[10] summarized evidence on the clinical effectiveness and safety of treatments for lice and scabies.

Research Questions

1. What is the comparative clinical effectiveness of oral versus topical ivermectin for parasitic skin infections of scabies?
2. What is the comparative clinical effectiveness of oral ivermectin versus scabicides for parasitic skin infections of scabies?
3. What is the comparative clinical effectiveness of topical ivermectin versus scabicides for parasitic skin infections of scabies?
4. What is the comparative cost-effectiveness of oral ivermectin versus scabicides for parasitic skin infections of scabies?
5. What is the comparative cost-effectiveness of topical ivermectin versus scabicides for parasitic skin infections of scabies?
6. What are the evidence-based guidelines for the use of ivermectin for parasitic skin infections of scabies?

Key Findings

Three systematic reviews, one randomized controlled trial, and three guidelines were identified that were relevant to the research questions.

There was no conclusive evidence for a difference in clinical effectiveness in terms of cure or complete clearance between oral and topical ivermectin for the treatment of parasitic skin infections of scabies. Topical ivermectin may be associated with lower rates of persistent itching than oral ivermectin. No difference was found between oral and topical ivermectin in the percentage of patients with at least one adverse event.

Evidence from the systematic reviews suggested that oral ivermectin was less clinically effective in treating scabies than topical permethrin at one to two weeks following treatment initiation, with no difference between the treatments at later time points. There was also no difference between the treatments in terms of patients with at least one adverse event. Oral ivermectin may be more effective than crotamiton, malathion, benzyl benzoate, and lindane according to one systematic review and more effective than sulphur 10% ointment according to one randomized controlled trial of limited quality. Oral ivermectin may be associated with fewer patients with adverse events than sulfur and more patients with adverse events than synthetic pyrethrins.

Topical ivermectin may be more effective than or no different from other scabicides. There was no difference found in clinical effectiveness between topical ivermectin and permethrin in the systematic reviews. According to one systematic review, topical ivermectin may be more effective in treating scabies compared with malathion, lindane, crotamiton, and benzyl benzoate, as well as sulfur at one to two weeks after treatment initiation. Topical permethrin was associated with higher percentages of patients with adverse events compared with synthetic pyrethrins and malathion and lower percentages compared with sulfur.

While findings of clinical effectiveness of oral and topical ivermectin were largely consistent among the identified systematic reviews and the randomized controlled trial, there was considerable overlap in primary studies in the systematic reviews and the evidence base consisted mostly of randomized controlled trials of limited quality. Combined with the limited

sample sizes in the trials, there is a substantial amount of uncertainty regarding conclusions of clinical effectiveness. With regards to safety, conclusions were also limited by deficiencies in AE reporting. Generalizability to the Canadian treatment setting may be limited due to the locations where the trials were conducted and variability in the treatment regimens used.

No relevant studies were identified regarding the comparative cost-effectiveness of oral or topical ivermectin versus scabicides for parasitic skin infections of scabies.

Oral ivermectin is recommended by three guidelines for the treatment of scabies and topical ivermectin is recommended as an alternative treatment by one guideline. Oral ivermectin is recommended for the treatment of crusted scabies alone in one guideline and in combination with permethrin cream in another guideline, though these recommendations do not appear to be based on clinical evidence. The applicability of the guideline recommendations to the Canadian setting is unclear as the guidelines were developed for the European and Japanese settings.

Methods

Literature Search Methods

A limited literature search was conducted on key resources including Medline, EMBASE, The Cochrane Library, University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. No methodological filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2014 and April 17, 2019.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

Population	People of all ages, in any setting, having any severity level (i.e., regular and crusted [also known as hyperkeratotic, Norwegian or atypical]) of scabies (i.e., *Sarcoptes scabiei*).
Intervention	Q1,2,4: Oral ivermectin Q3,5: Topical ivermectin Q6: Ivermectin
Comparator	Q1: Topical ivermectin Q2-5: Scabicides (e.g.: crotamiton; permethrin; sulfur)
Outcomes	Q1-3: Clinical effectiveness (e.g., extermination of mites; complete clearance of skin lesions [e.g., burrows, papules, pustules]; relief of pruritus; number needing re-treatment); safety (e.g., side effects; number of participants with at least one adverse event) Q4-5: Cost-effectiveness outcome (e.g., cost per health benefit gained, ICER, QALY) Q6: Guidelines on appropriate use, place in therapy, and its use in treatment resistant settings.
Study Designs	Q1-3: Health technology assessments, systematic reviews, meta-analyses, randomized controlled trials,

	non-randomized studies (safety only) Q4-5: Health technology assessments, systematic reviews, meta-analyses, economic evaluations Q6: Guidelines

ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life years.

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outline in Table 1, they were duplicate publications, or were published prior to 2014. Articles were also excluded if the intervention was a mass treatment intended to prevent the spread of scabies. Guidelines with unclear methodology were excluded.

Critical Appraisal of Individual Studies

The included systematic reviews (SRs) were critically appraised by one reviewer using AMSTAR 2,[11] the included network meta-analysis (NMA) was critically appraised using the ISPOR questionnaire,[12] the RCT was critically appraised using the Downs and Black checklist,[13] and the included guidelines were assessed with the AGREE II instrument.[14] Summary scores were not calculated for the included studies; rather, a review of the strengths and limitations of each included study were described narratively.

Summary of Evidence

Quantity of Research Available

A total of 321 citations were identified in the literature search. Following screening of titles and abstracts, 301 citations were excluded and 20 potentially relevant reports from the electronic search were retrieved for full-text review. Thirteen potentially relevant publications were retrieved from the grey literature search for full text review. Of these potentially relevant articles, 26 publications were excluded for various reasons, and 7 publications met the inclusion criteria and were included in this report. These comprised three SRs, one RCT, and three evidence-based guidelines. Appendix 1 presents the PRISMA[15] flowchart of the study selection. Additional references of potential interest are provided in Appendix 6.

Summary of Study Characteristics

Additional details regarding the characteristics of included publications are provided in Appendix 2.

Study Design

Three SRs were identified regarding clinical effectiveness of oral or topical ivermectin for the treatment of parasitic skin infections of scabies. One SR and NMA published in 2019 of 52 RCTs searched databases for studies up to September 14, 2017.[16] One SR with meta-analysis published in 2018 of 15 RCTs searched databases on March 21, 2017.[17] One SR with meta-analysis published in 2018 of 15 RCTs searched databases up to April 25, 2017.[18] All three SRs included RCTs only as primary studies. Thirteen of the 15 RCTs from the two SRs with meta-analysis[17,18] were also included in the SR and NMA of 52 RCTs.[16] Each SR with meta-analysis[17,18] included one unique RCT.[17,18]

One parallel-group RCT (2018) not already included in the SRs was identified regarding the clinical effectiveness of oral ivermectin for parasitic skin infections of scabies.[19] Three

evidence-based guidelines were identified regarding the use of ivermectin for parasitic skin infections of scabies. None of the guidelines restricted the literature search by study design. One guideline on the diagnosis and management of scabies was published by the Japanese Dermatological Association in 2017,[20] one guideline on the management of scabies was produced by the International Union Against Sexually Transmitted Infection (IUSTI) in 2017,[21] and one guideline on the management of scabies was published in 2016 by the British Association for Sexual Health and HIV (BASHH).[22] Two guidelines[20,21] provided a recommendation level based on the quality of evidence assigned based on study design. One guideline used the GRADE system for formulating and stating the strength of recommendations.[22] Two guidelines[20,21] did not describe how the guideline committee arrived at its recommendations (whether through consensus, voting, or other method). One guideline[22] used the 2015 BASHH guideline methodology[23] which indicated that the Delphi technique was used to develop consensus and that the GRADE grid was used to resolve disagreements.

Country of Origin

The SRs were led by authors in Thailand,[16] South Africa,[17] and Germany.[18]

The RCT was conducted in Iraq.[19]

One guideline was intended for use in Japan[20] and one in the UK,[22] and one in Europe.[21]

Patient Population

The three SRs[16-18] included patients with scabies, with one specifying a diagnosis of classical scabies[18] and one specifying diagnosis based on microscopic or clinical exam.[16] Most of the included primary RCTs in the SRs[16-18] included both adult and pediatric patients, though some RCTs restricted eligibility to patients within a certain age range. In the SRs,[16-18] patients with crusted scabies at baseline were excluded where reported, with the exception of 1.5% of patients in one primary RCT in one SR.[16]

Patients in the RCT (N = 150) were 12 years of age or older, had scabies with no severe chronic illness, and were adherent to treatment and follow-up.[19] The treatment setting was not described.

The target populations in each of the three guidelines were as follows: patients with scabies,[20] patients with scabies and those in endemic areas,[21] and patients over 16 years of age presenting to sexual health clinics in the UK.[22] The intended users were dermatologists in Japan in one guideline[20] and clinicians at sexual health clinics in the UK in another guideline.[22] One guideline did not specify the intended users.[21]

Interventions and Comparators

The number of administrations of oral ivermectin at a dosage of 200 µg/kg ranged from one to three times in two of the SRs.[17,18] Oral ivermectin was administered at a dosage of 100 µg/kg to 250 µg/kg once or twice in one SR.[16] Topical ivermectin 1% was administered in one or two applications in one SR,[16] one to three applications in one SR,[17] and one application in one SR.[18]

Topical permethrin 2.5% to 5% was the comparator in the SRs, and was administered in one to six applications,[16,17] and in one to five applications.[18] In one SR,[16] the following comparators were also included: topical permethrin and oral ivermectin combined (single dose and application, respectively), topical sulfur 5% to 10% (where reported) in three to

seven applications, topical benzyl benzoate 10% to 25% in one to six applications, topical malathion 0.5% in two applications, topical crotamiton 10% (where reported) in one to five applications, synergized pyrethrins 0.165%, placebo, white soft paraffin, and herbal medicine.

In the RCT,[19] oral ivermectin at a dosage of 200 µg/kg was administered once at baseline and again one week later, and was compared with both sulphur 10% ointment and with permethrin 5% cream. Sulphur 10% ointment was applied for three consecutive days and again one week later and permethrin 5% cream was applied at baseline and again one week later.[19] Topical treatments in the RCT were applied over the whole body below the neck.[19]

One guideline considered oral ivermectin treatment without further details,[20] one guideline considered oral ivermectin 200 µg/kg as two doses one week apart,[21], and one guideline considered oral ivermectin 200 µg/kg as two doses two weeks apart.[22] For the treatment of crusted scabies, one guideline considered oral ivermectin 200 µg/kg on days 1, 2, and 8 with additional treatments potentially required on days 9 and 15 or on days 9, 15, 22, and 29.[21] One guideline considered a combination of topical permethrin once daily for seven days followed by twice weekly until cure and oral ivermectin 200 µg/kg on days 1, 2, 8, 9, and 15 with additional treatment potentially required on days 22 and 29.[22] One guideline also considered topical ivermectin 1% lotion compared with topical permethrin 5% cream.[21]

Outcomes

The primary outcome was cure (clinical or microscopic/parasitic cure) at one to two weeks and at three to six weeks as defined in the primary RCTs in one SR,[16] complete clearance of lesions at one, two, and four weeks in one SR,[18] and treatment failure (the definition had to include persistent lesions, new lesions, or confirmation of a live mite) in one SR.[17] Secondary efficacy outcomes reported were persistent itching in two SRs[16,17] (defined as presence of itch or nocturnal itch that did not improve or did not improve by at least 50% in one SR[16]), re-infestation,[16] and number of patients re-treated.[18] Assessment of itching was not described. The number of patients with at least one adverse event (AE) was reported in two SRs.[16,18] and one SR reported withdrawals due to AE.[18]

The RCT reported cure according to number of lesions (no new lesions detected) and cure according to severity of itching.[19]

The three guidelines[20-22] considered clinical effectiveness and safety in the recommendations regarding ivermectin treatment.

Summary of Critical Appraisal

Additional details regarding the strengths and limitations of included publications are provided in Appendix 3.

Systematic Reviews

The following strengths were common to all three SRs[16-18]: the components of PICO were described in the research questions and inclusion criteria, multiple databases were searched, study selection and data extraction were performed in duplicate, the primary studies were described in adequate detail, the Cochrane Risk of Bias tool was used to assess study quality, appropriate methods were used to combine study results, sources of heterogeneity were investigated (and consistency between direct and indirect evidence was assessed in the NMA[16]), and the review authors declared no conflicts of interest. In two

SRs,[16,18] the review protocol was registered and a list of excluded studies and reasons for exclusion was provided, while it was unclear in one SR[17] whether the methods were established prior to conduct of the review.

The following limitations were common to all three SRs:[16-18] a rationale was not provided for including RCTs only, the potential impact of risk of bias in the primary RCTs was not assessed or discussed, and funding sources were not reported for the primary RCTs. Trial registries and grey literature were not searched in two SRs.[16,17] All three SRs[16-18] reported that patients and personnel were not blinded to treatment assignment in most of the primary RCTs and that there was a high risk of performance bias (as well as detection bias as noted in two SRs: for all outcomes in one SR[18] and for non-cure outcomes in one SR[16]). As well, incomplete outcome data and high or unclear risk of attrition bias was noted for most primary RCTs in two SRs.[16,18] The impact of these sources of bias on the results for individual RCTs and meta-analyses was unclear.

The generalizability of the SR results to the Canadian setting is unclear as most of the primary RCTs in the three SRs[16-18] were conducted in countries in Asia. One SR[18] noted that all of its primary RCTs were conducted in regions with a high prevalence of scabies and in resource-poor countries. Patients with crusted scabies tended to be excluded from the primary RCTs included in the SRs[16-18] and the evidence in this subpopulation is lacking. It is also unclear how generalizable the results from the interventions are to the treatment regimens described in the CPS position statement as the numbers and schedules of treatment administrations varied. In addition, the reporting of whether close contacts were treated and steps were taken to prevent fomite transmission was inconsistent in the primary RCTs of the SRs.[16-18]

RCT

While the study objective and interventions were clearly described in the RCT[19] and the statistical tests for the main outcomes were appropriate, many important details were not reported. It was not clear how patients were recruited, consented, and randomized, how allocation was concealed, whether patients and personnel were blinded to treatment assignment, and how many patients were lost to follow-up or had poor adherence to study treatment. Also, sample size considerations were not described, the diagnosis of scabies in patients and outcomes were not defined, and harms were not assessed. Therefore, there were several potential sources of bias that could have affected the results. The RCT was conducted in Iraq and the treatment setting was not described, and therefore the generalizability of the results to the Canadian setting remains unclear.

Guidelines

Two guidelines[20,22] provided sufficient descriptions of the overall objective, the health questions covered, and the target population. The intended users were clearly defined in one guideline.[20] Two guidelines[20,22] indicated that the view and preferences of the target population had been sought and one guideline was developed by a group that included individuals from all relevant professional groups.[20]

All three guidelines[20-22] used systematic search methods and provided a link between recommendations and supporting evidence. However, none of the guidelines[20-22] clearly described the criteria for selecting the evidence, described the strengths and limitations of the body of evidence, or underwent external review by experts prior to publication. Two guidelines[20,22] considered health benefit, side effects, and risks in formulating

recommendations and one guideline[22] followed a published methodology for formulating the recommendations as well as the procedure for updating the guideline.

All three guidelines[20-22] gave specific recommendations, presented the different options for management of the condition, made the key recommendations easily identifiable, and were not funded from an external source. Competing interests were recorded and addressed in two of the guidelines.[20,22] None of the guidelines[20-22] described facilitators and barriers to their application, provided advice on putting the recommendations into the practice, or considered potential resource implications of applying the recommendations.

Summary of Findings

Appendix 4 presents tables of the main study findings and authors' conclusions.

Clinical Effectiveness of Oral Versus Topical Ivermectin

Cure and Complete Clearance

Cure and clearance were reported in two SRs comparing oral and topical ivermectin. In one SR with NMA, cure rate was reported to be higher with topical ivermectin than with oral ivermectin (with marginal statistical significance) one to two weeks after treatment initiation and not different between the treatments three to six weeks after treatment initiation.[16] One SR[18] found no significant difference between oral and topical ivermectin for complete clearance rate at one, two, and four weeks (low to moderate certainty of evidence according to GRADE). The primary RCTs included in these comparisons were also included in the SR with NMA.[16] The discrepancy between the results for the two aforementioned SRs for cure or clearance at one and two weeks may have been due to the different analysis methods (direct comparison meta-analysis versus network-meta-analysis) and/or the decision in one of the SRs to pool the two time points.

Re-infestation and Re-Treatment

Re-infestation was reported in one SR[16] and one of its included RCTs found no recurrences four weeks after treatment initiation in patients receiving oral or topical ivermectin.

The percentage of non-responders re-treated was reported in one SR[18] and was numerically higher with oral ivermectin than with topical ivermectin in one of the included RCTs.

Persistent Itching

Persistent itching occurred at lower rates with topical ivermectin than with oral ivermectin in one SR,[16] though the definition of persistent itching was unclear.

Adverse Events

One SR[16] reported that there was no significant difference in patients with at least one AE between oral and topical ivermectin treatment.

Clinical Effectiveness of Oral Ivermectin Versus Other Scabicides

Cure and Complete Clearance

Two SRs and the one RCT reported cure and clearance with oral ivermectin compared with other scabicides. At one to two weeks after treatment initiation, oral ivermectin had a higher cure rate than crotamiton and lower cure rate than topical permethrin in one SR with

NMA.[16] There was no difference between oral ivermectin and synthetic pyrethrins, sulfur, combination permethrin and oral ivermectin, malathion, lindane, and benzyl benzoate in cure rate at this time point.[16] One SR[18] compared complete clearance rates at one, two, and four weeks after treatment initiation between oral ivermectin and permethrin 5% cream and included one RCT not included in the SR with an NMA.[16] Oral ivermectin in this SR[18] had a lower cure rate than permethrin cream at one week and there was no difference between oral ivermectin and permethrin cream at two weeks (with a low certainty of evidence according to GRADE for both time points).

At three to six weeks after treatment initiation, oral ivermectin had a higher cure rate than crotamiton, malathion, benzyl benzoate, and lindane in one SR with an NMA.[16] In the same SR, there was no difference in cure rate between oral ivermectin and topical permethrin, synthetic pyrethrins, sulfur, and combination permethrin and oral ivermectin at this time point.[16] In the SR comparing complete clearance rates,[18] there was no difference between oral ivermectin and permethrin cream at four weeks (low certainty of evidence according to GRADE).

In the one relevant RCT that was identified,[19] cure rate at one week and at two weeks after treatment initiation according to either severity of lesions or severity of itching (neither end point being well-defined) was higher with oral ivermectin than with sulphur 10% ointment and no different between oral ivermectin and permethrin 5% cream.

Treatment Failure, Re-Infestation, and Re-Treatment

One SR reported treatment failure, one SR reported re-infestation, and one SR reported re-treatment with oral ivermectin compared with other scabicides. One SR[17] compared treatment failure rates without specifying a time point of evaluation and included two RCTs that were not included in the other SRs.[16,18] The SR[17] found a higher failure rate with oral ivermectin than with topical permethrin.

In one SR,[16] individual RCTs reported no relapses at 30 days with oral ivermectin or benzyl benzoate (two RCTs), no recurrences at 8 weeks with oral ivermectin or permethrin (one RCT), and the same re-infestation rate with oral ivermectin and benzyl benzoate at two weeks (one RCT).

According to one SR,[18] the re-treatment rate was higher with oral ivermectin than with permethrin cream in one RCT.

Persistent Itching

Two SRs reported persistent itching for oral ivermectin compared with permethrin and found no difference between the two treatments.[16,17] There was a lower rate of persistent itching with oral ivermectin than with benzyl benzoate and no difference between oral ivermectin and synthetic pyrethrins, sulfur, lindane, and crotamiton in one SR.[16]

Adverse Events

Two SRs reported the proportion of patients with at least one AE for oral ivermectin compared with permethrin and found no difference between the treatments.[16,18] One SR[16] reported that the proportion of patients with at least one AE was higher for oral ivermectin versus synthetic pyrethrins, lower for oral ivermectin versus sulfur, and no difference was found between oral ivermectin and combination permethrin and oral ivermectin, malathion, lindane, crotamiton, and benzyl benzoate. One SR[18] reported that in four RCTs comparing oral ivermectin and topical permethrin, there were no withdrawals due to AE.

Clinical Effectiveness of Topical Ivermectin Versus Other Scabicides

Cure and Treatment Failure

At one to two weeks after treatment initiation, topical ivermectin had a higher cure rate than sulfur, malathion, lindane, crotamiton, and benzyl benzoate in one SR with NMA.[16] There was no difference between topical ivermectin and synthetic pyrethrins, combination permethrin and oral ivermectin, and permethrin in cure rate at this time point.[16]

At three to six weeks after treatment initiation, topical ivermectin had a higher cure rate than malathion, lindane, crotamiton, and benzyl benzoate in the SR with an NMA.[16] There was no difference between topical ivermectin and synthetic pyrethrins, combination permethrin and oral ivermectin, sulfur, and permethrin in cure rate at this time point.[16] One SR found no difference in complete clearance rate at four weeks between topical ivermectin and permethrin cream (moderate certainty of evidence according to GRADE).

One SR[17] found no difference in treatment failure rate between topical ivermectin and permethrin.

Persistent Itching

There was no difference in persistent itching with topical ivermectin and synthetic pyrethrins, combination permethrin and oral ivermectin, sulfur, permethrin, crotamiton, lindane, and benzyl benzoate in one SR.[16]

Adverse Events

In the SR with an NMA,[16] the proportion of patients with at least one AE was higher for topical ivermectin versus synthetic pyrethrins and malathion and lower for topical ivermectin versus sulfur. There were no differences between topical ivermectin and permethrin, combination permethrin and oral ivermectin, lindane, crotamiton, and benzyl benzoate.[16]

Cost-Effectiveness of Ivermectin

No relevant evidence regarding the cost-effectiveness of oral or topical ivermectin versus scabicides for parasitic skin infections of scabies was identified; therefore, no summary can be provided.

Evidence-Based Guidelines for the Use of Ivermectin

The three relevant guidelines[20-22] that were identified recommend oral ivermectin for the treatment of scabies. One guideline strongly recommends the use of oral ivermectin for treating scabies,[20] one guideline lists oral ivermectin 200 µg/kg in two doses one week apart as a recommended treatment,[21] and one guideline lists oral ivermectin 200 µg/kg in two doses two weeks apart in patients weighing over 15 kg as an alternative treatment regimen that can be used when initial treatment is not sufficient (as a strong recommendation).[22] Ivermectin 1% lotion is recommended as an alternative treatment in one guideline.[21] In this guideline, the distinction between recommended and alternative treatments was based on the clinical evidence though it was also noted that availability of treatments differs among the European countries.[21] One guideline[20] from Japan states that permethrin is more effective than oral ivermectin in treating scabies, but does not strongly recommend permethrin because it is not covered by Japanese health insurance.

For crusted scabies, one guideline[21] recommends a topical scabicide (permethrin or benzyl benzoate) applied daily for seven days followed by twice a week application until cure

combined with oral ivermectin 200 µg/kg on days 1, 2, and 8 with additional ivermectin for persistent infestation on days 9 and 15 or on days 9, 15, 22, and 29. This recommendation was based on *"expert committee reports or opinions and/or clinical experience of respected authorities"*.[21] One guideline[22] recommends a combination of topical permethrin cream once daily for seven days followed by twice weekly until cure and oral ivermectin 200 µg/kg on days 1, 2, 8, 9, and 15 with additional treatment for severe infestations on days 22 and 29. This recommendation was not assigned a level of evidence or recommendation level.

Limitations

The overall quality of the primary RCTs in the three SRs[16-18] was found to be poor, as numerous potential sources of bias were identified in most of the primary RCTs in the SRs.[16-18] In addition, the included RCT[19] also had a number of sources of bias that may have contributed substantial uncertainty to the results. Two SRs[16,18] noted that limited sample sizes also contributed uncertainty to the results. One SR[18] excluded RCTs from a specific author due to suspicion of flawed data and at least seven RCTs in one SR[16] and three RCTs in another SR[17] were co-authored by this individual.

Two SRs[16,18] noted that there were sources of between-trial heterogeneity while one SR did not find any significant sources of heterogeneity.[17] Many aspects of the interventions and comparators were either variable between studies or not reported and any of these may have contributed to heterogeneity in the SRs. For example, reporting of whether there was treatment of close contacts and prevention of fomite transmission was inconsistent, the number of doses or applications for each therapeutic agent varied between studies, and one SR[18] noted that the number of patients re-treated was not reported in most of the included RCTs. Two of the SRs[17,18] included oral ivermectin, topical ivermectin, and permethrin as relevant interventions and evidence for the clinical effectiveness of ivermectin compared with other treatments was informed by one SR[16] and one RCT.[19]

As noted in two SRs,[16,17] the findings may have limited applicability to crusted scabies as patients with crusted scabies were excluded from most primary RCTs. While two guidelines[21,22] recommend treatment regimens for crusted scabies, these recommendations were not directly linked to clinical evidence. No relevant articles were found that addressed the treatment of patients with treatment-resistant scabies. Specific AEs were not reported in the SRs[16-18] and one SR[18] noted that AE reporting was poor. Re-infestation was not reported in most primary RCTs and the available results were from varying time points.

The generalizability of the SR[16-18] and RCT[19] results to the Canadian setting is unclear as most of the clinical evidence is from countries in Asia, regions with high prevalence of scabies and resource-poor countries. Also, the guidelines[20-22] were developed by groups in the UK, Europe, and Japan and it is unclear whether availability of treatments for scabies is similar between those regions and Canada.

Conclusions and Implications for Decision or Policy Making

Three SRs,[16-18] one RCT not included in the SRs,[19] and three guidelines[20-22] were identified that were relevant to the research questions.

There was no conclusive evidence for a difference in clinical effectiveness between oral and topical ivermectin.[16,18] Topical ivermectin may be associated with lower rates of persistent itching than oral ivermectin.[16] There was no evidence for a difference between oral and topical ivermectin in the percentage of patients with at least one AE.[16]

Evidence from meta-analyses suggested that oral ivermectin may be less clinically effective in treating scabies than permethrin at one to two weeks following treatment initiation[16,18] There was no evidence for a difference in effectiveness between oral ivermectin and permethrin at later time points[16,18] or for a difference in percentage of patients with at least one AE.[16]

Although oral ivermectin was reported to be less clinically effective than permethrin at one to two weeks following treatment in two SRs,[16,18] it may be more effective or no different than the other scabicides.[16] The findings suggested that oral ivermectin was more clinically effective than crotamiton, malathion, benzyl benzoate, and lindane (the latter three at three to six weeks after treatment initiation) and not significantly different from synthetic pyrethrins, sulfur, and combination permethrin and oral ivermectin in cure rate. Oral ivermectin may be associated with a lower rate of persistent itching compared with benzyl benzoate.[16,17] In one RCT with limited quality,[19] cure rate was higher at one and two weeks with oral ivermectin than with sulphur 10% ointment. In the SR,[16] oral ivermectin was associated with lower percentages of patients with AEs compared with sulfur and higher percentages compared with synthetic pyrethrins.

Topical ivermectin may be more effective than or no different from other scabicides. There was no evidence for a difference in clinical effectiveness between topical ivermectin and permethrin in three SRs.[16-18] One SR[16] found a higher cure rate with topical ivermectin compared with malathion, lindane, crotamiton, and benzyl benzoate up to six weeks after treatment initiation and a higher cure rate compared with sulfur at one to two weeks after treatment initiation. Topical ivermectin was associated with higher percentages of patients with AEs compared with synthetic pyrethrins and malathion and lower percentages compared with sulfur.[16]

There were several limitations in the identified body of evidence. There was considerable overlap in primary RCTs in the SRs[16-18] and risk of bias in most of the primary RCTs arising from lack of blinding and incomplete outcome reporting. One SR[18] reported the level of certainty of the evidence as low or moderate for all relevant comparisons. Also, two SRs[16,18] noted that sample sizes were small in the primary RCTs. Therefore, there is a substantial amount of uncertainty regarding conclusions of clinical effectiveness. In terms of safety, conclusions were also limited by deficiencies in AE reporting.

Variability in the dosage regimens for each drug and inconsistent of reporting of re-treatment, treatment of close contacts, and prevention of fomite transmission may have contributed towards the heterogeneity detected in the results of two SRs.[16,18]

Additional high quality RCTs with larger sample sizes, standardized treatment regimens, and comprehensive AE reporting would help reduce uncertainty in the comparative clinical effectiveness and safety of ivermectin for treating scabies.

A 2010 CADTH report on clinical effectiveness and safety of treatments for lice and scabies[10] found that the available evidence suggested permethrin and oral ivermectin were the most clinically effective treatments for scabies. The 2010 report identified limitations in the body of evidence similar to those identified in the present report.

No relevant studies were identified regarding the comparative cost-effectiveness of oral or topical ivermectin versus scabicides for parasitic skin infections of scabies.

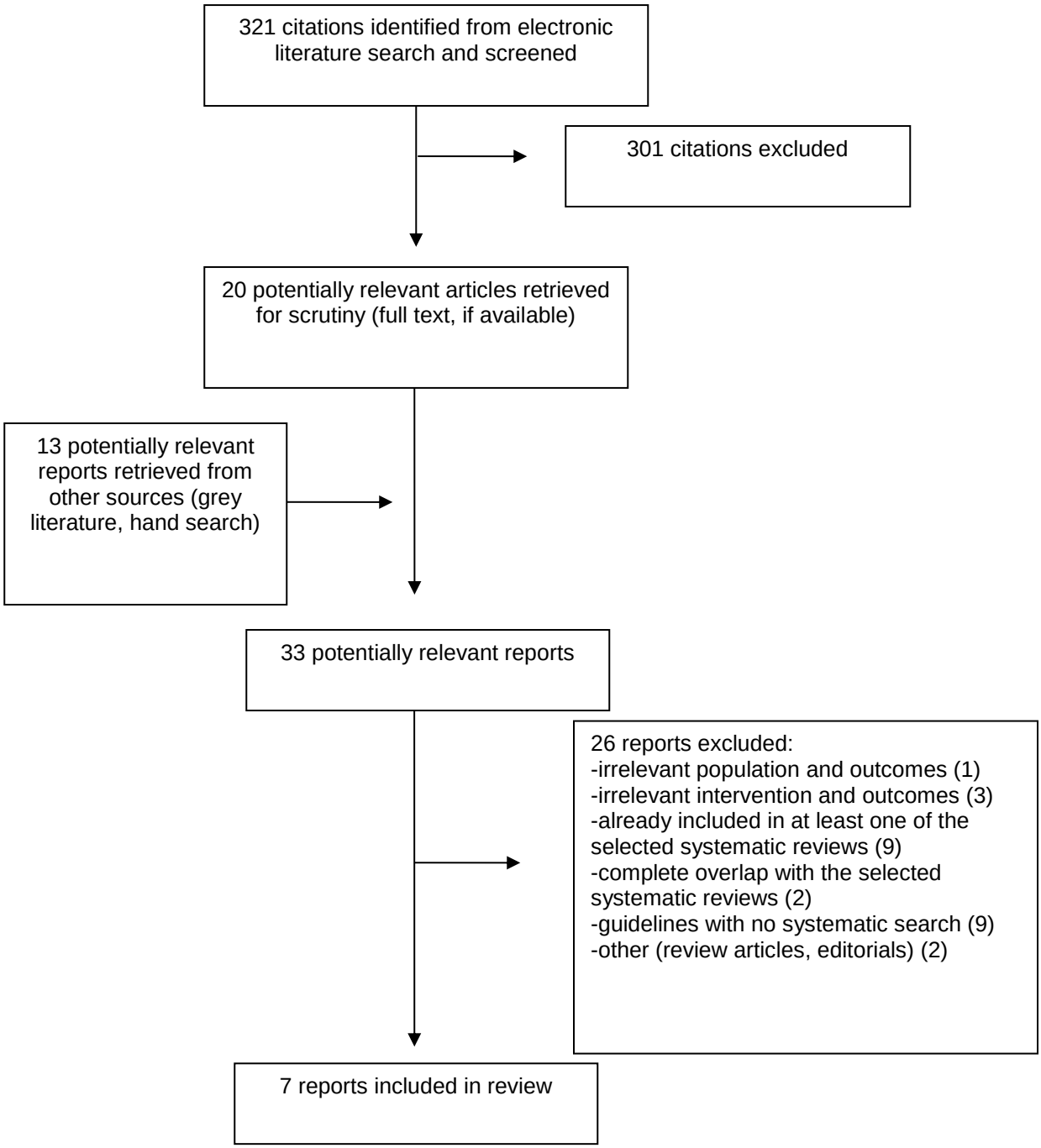
Oral ivermectin is recommended in three guidelines for the treatment of scabies[20-22] and topical ivermectin is recommended as an alternative treatment in one of the guidelines.[21] Oral ivermectin is recommended for the treatment of crusted scabies alone in one guideline[21] and in combination with permethrin cream in another guideline,[22] though these recommendations do not appear to be based on clinical evidence.

The generalizability of the SR[16-18] and RCT[19] results and guideline[20-22] recommendations to the Canadian setting is unclear as most of the clinical evidence is from countries in Asia and the guidelines were developed by groups in the UK, Europe, and Japan. Clinical evidence is lacking in patients with crusted scabies and no evidence or recommendations were found regarding treatment resistant scabies. Preventative treatment, which may be relevant in outbreaks of scabies, is outside the scope of this report.

References

1. Chandler DJ, Fuller LC. A review of scabies: an infestation more than skin deep. *Dermatology.* 2019;235(2):79-90.
2. McCarthy JS, Kemp DJ, Walton SF, Currie BJ. Scabies: more than just an irritation. *Postgrad Med J.* 2004;80(945):382-387.
3. Thean LJ, Engelman D, Kaldor J, Steer AC. Scabies: new opportunities for management and population control. *Pediatr Infect Dis J.* 2019;38(2):211-213.
4. Karimkhani C, Colombara DV, Drucker AM, et al. The global burden of scabies: a cross-sectional analysis from the Global Burden of Disease Study 2015. *Lancet Infect Dis.* 2017;17(12):1247-1254.
5. Holness DL, DeKoven JG, Nethercott JR. Scabies in chronic health care institutions. *Arch Dermatol.* 1992;128(9):1257-1260.
6. Banerji A. Scabies. *Paediatr Child Health.* 2015;20(7):395-402.
7. Houston AR, Blais C-M, Houston S, Ward BJ. Reforming Canada's Special Access Programme (SAP) to improve access to off-patent essential medicines. *Journal of the Association of Medical Microbiology and Infectious Disease Canada.* 2018;3(2):100-107.
8. Product monograph: Rosiver ivermectin cream, 1% w/w topical rosacea therapy. Thornhill (ON): Galderma Canada Inc. ; 2015 Apr: https://pdf.hres.ca/dpd_pm/00030271.PDF. Accessed 2019 May 16.
9. Product monograph including patient medication information: Stromectol ivermectin tablet, USP 3mg antiparasitic agent. Kirkland (QC): Merck Canada Inc.; 2018: https://pdf.hres.ca/dpd_pm/00047237.PDF. Accessed 2019 May 16.
10. Health Techology Inquiry Service. Lindane and other treatments for lice and scabies: a review of clinical effectiveness and safety. Ottawa (ON): CADTH; 2010 Jun: https://cadth.ca/lindane-and-other-treatments-lice-and-scabies-review-clinical-effectiveness-and-safety-0. Accessed 2019 May 16.
11. Shea BJ, Reeves BC, Wells G, et al. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. *BMJ.* 2017;358:j4008. http://www.bmj.com/content/bmj/358/bmj.j4008.full.pdf. Accessed 2019 May 16.
12. Jansen JP, Trikalinos T, Cappelleri JC, et al. Indirect treatment comparison/network meta-analysis study questionnaire to assess relevance and credibility to inform health care decision making: an ISPOR-AMCP-NPC Good Practice Task Force report. *Value Health.* 2014;17(2):157-173.
13. Downs SH, Black N. The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. *J Epidemiol Community Health.* 1998;52(6):377-384. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1756728/pdf/v052p00377.pdf. Accessed 2019 May 16.
14. Agree Next Steps Consortium. The AGREE II Instrument. [Hamilton, ON]: AGREE Enterprise; 2017: https://www.agreetrust.org/wp-content/uploads/2017/12/AGREE-II-Users-Manual-and-23-item-Instrument-2009-Update-2017.pdf. Accessed 2019 May 16.
15. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *J Clin Epidemiol.* 2009;62(10):e1-e34.
16. Thadanipon K, Anothaisintawee T, Rattanasiri S, Thakkinstian A, Attia J. Efficacy and safety of antiscabietic agents: A systematic review and network meta-analysis of randomized controlled trials. *J Am Acad Dermatol.* 2019;80(5):1435-1444.
17. Dhana A, Yen H, Okhovat JP, Cho E, Keum N, Khumalo NP. Ivermectin versus permethrin in the treatment of scabies: a systematic review and meta-analysis of randomized controlled trials. *J Am Acad Dermatol.* 2018;78(1):194-198.
18. Rosumeck S, Nast A, Dressler C. Ivermectin and permethrin for treating scabies. *Cochrane Database Syst Rev.* 2018;4:CD012994.
19. Al Jaff DAA, Amin MHM. Comparison the effectiveness of sulphur ointment, permethrin and oral ivermectin in treatment of scabies. *Research Journal of Pharmaceutical, Biological and Chemical Sciences.* 2018;9(1):670-676.
20. Executive Committee of Guideline for the Diagnosis and Treatment of Scabies. Guideline for the diagnosis and treatment of scabies in Japan (third edition): Executive Committee of Guideline for the Diagnosis and Treatment of Scabies. *J Dermatol.* 2017;44(9):991-1014.
21. Salavastru CM, Chosidow O, Boffa MJ, Janier M, Tiplica GS. European guideline for the management of scabies. *J Eur Acad Dermatol Venereol.* 2017;31(8):1248-1253.
22. Sashidharan PN, Basavaraj S, Bates CM. 2016 UK national guideline on the management of scabies. Macclesfield (GB): British Association for Sexual Health and HIV; 2016: https://www.bashhguidelines.org/media/1137/scabies-2016.pdf. Accessed 2019 May 16.
23. Kingston M, Radcliffe K, Cousins D, et al. British Association for Sexual Health and HIV: framework for guideline development and assessment. *Int J STD AIDS.* 2015;27(3):165-177.

Appendix 1: Selection of Included Studies



Appendix 2: Characteristics of Included Publications

Table 2: Characteristics of Included Systematic Reviews and Meta-Analyses

First Author, Publication Year, Country	Study Designs and Numbers of Primary Studies Included	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
Thadanipon, 2019, Thailand	52 RCTs	• Patients with scabies • Diagnosis was based on microscopic or clinical exam • 3 RCTs in children, 7 RCTs in adults, 42 RCTs in both children and adults • 24 RCTs reported severity of scabies at baseline (range of 1.7% to 100% of cases) • Cases of crusted scabies were absent where reported, except for 1.5% of cases in one RCT	• RCTs comparing ≥ 2 different treatments for scabies were eligible • 13 treatments were included: ○ Oral ivermectin in 1 or 2 doses ▪ 200 µg/kg in 41 RCTs ▪ 150 to 200 µg/kg in 2 RCTs ▪ 100 µg/kg in 2 RCTs ○ Topical ivermectin 1% in 1 or 2 applications (5 RCTs) ○ Permethrin in 1 to 6 applications ▪ 5% in 29 RCTs (including 1 RCT where children were given 2.5%) ▪ 2.5% in 2 RCTs ○ Permethrin and oral ivermectin combined in 1 dose/application (1 RCT) ○ Sulfur in 3 to 7 applications ▪ 10% in 5 RCTs (including 1 RCT where children were given 5%) ▪ Dose NR in 1 RCT ○ Benzyl benzoate 10% to 25% (including Tenutex) in 1 to 6 applications (15 RCTs) ○ Lindane in 1 to 2 applications ▪ 1% in 15 RCTs ▪ 0.5% in 1 RCT ○ Malathion 0.5% in 2 applications (1 RCT) ○ Crotamiton in 1 to 5 applications ▪ 10% in 5 RCTs ▪ Dose NR in 1 RCT ○ Synergized pyrethrins 0.165% (2 RCTs) ○ Placebo (1 RCT) ○ White soft paraffin (1 RCT) ○ Herbal medicine (2 RCTs) • Treatment groups were combined regardless of formulation or dosage regimen • Treatment of close contacts reported in 65.4% of RCTs (NR otherwise) • Prevention of fomite transmission reported in 26.9% of RCTs (NR otherwise)	• Cure at 1 to 2 weeks • Cure at 3 to 6 weeks • Re-infestation • Persistent itching • Patients with ≥ 1 AE

Table 2: Characteristics of Included Systematic Reviews and Meta-Analyses

First Author, Publication Year, Country	Study Designs and Numbers of Primary Studies Included	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
Dhana, 2018, South Africa	15 RCTs	• Patients with scabies • 6 RCTs excluded children < 5 years of age • 3 RCTs excluded children less than 10 or 12 years of age • 1 RCT excluded patients < 18 years of age • 9 RCTs excluded patients with crusted scabies	• 14 RCTs included treatment with oral ivermectin 200 µg/kg in 1 to 3 doses • 2 RCTs included treatment with topical ivermectin 1% in 1 to 3 applications • All RCTs included permethrin 2.5% or 5% in 1 to 6 applications • Treatment of close contacts in 9 RCTs • Prevention of fomite transmission in 5 RCTs	• Treatment failure (persistent lesions, new lesions, or confirmation of a live mite) • Persistent itching
Rosumeck, 2018, Germany	15 RCTs	• Patients with a diagnosis of classical scabies • 11 RCTs included adult and pediatric patients • 1 RCT included patients aged 18 to 60 years • 1 RCT included patients aged 5 to 15 years	• All RCTs included treatment with oral ivermectin 200 µg/kg in 1 to 3 doses • 13 RCTs included treatment with permethrin 5% (2.5% for children in one RCT) in 1 to 5 applications ○ Permethrin 5% cream and permethrin 5% lotion were distinct interventions • 2 RCTs included treatment with topical ivermectin 1% in 1 application • Treatment of close contacts in 9 RCTs • Prevention of fomite transmission in 2 RCTs	• Complete clearance at 7, 14, and 30 days • Number of patients re-treated • Patients with ≥ 1 AE • Withdrawals due to AE

AE = adverse event; NR = not reported; RCT = randomized controlled trial.

Table 3: Characteristics of Included Primary Clinical Study

First Author, Publication Year, Country	Study Design	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
Al Jaff, 2018, Iraq	Parallel-group RCT	• > or ≥ 12 years old (unclear) • Patients with scabies • Patients adherent to treatment and follow-up • No severe chronic illness	• 3 treatment groups: ○ Oral ivermectin 200 µg/kg at baseline and 1 week later ○ Sulphur 10% ointment for 3 consecutive days and repeated after 1 week ○ Permethrin 5% cream at baseline and 1 week later	At 1 and 2 weeks follow-up and overall: • Cure according to number of lesions (no new lesions detected) • Cure according to severity of itching

Table 3: Characteristics of Included Primary Clinical Study

First Author, Publication Year, Country	Study Design	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
		• N = 75 in each treatment group	• Treatment of close contacts	

RCT = randomized controlled trial

Table 4: Characteristics of Included Guidelines

Intended Users, Target Population	Intervention and Practice Considered	Major Outcomes Considered	Evidence Collection, Selection, and Synthesis	Evidence Quality Assessment	Recommendations Development and Evaluation	Guideline Validation
The Japanese Dermatological Association, 2017[20]						
Dermatologists in Japan, patients with scabies	Diagnosis, treatment, and prevention of scabies	Clinical effectiveness and safety	Database search in PubMed (January 2009 to May 2014) and Japan Medical Abstracts Society Web (up to May 2014)	Classification of evidence level (based on study design[s] informing the recommenda-tion) and classification of recommendation level (based on evidence level and quality)	Not described	Public comment was invited
Salavastru, 2017[21]						
Intended users unclear, patients with scabies and those in endemic areas	Management of scabies	Clinical effectiveness and safety	Review of existing guidelines and database search (Pubmed, Biomedical Reference Collection, Medline, and Cochrane Collaboration Databases; search dates not provided)	Classification of evidence level (based on study design[s] informing the recommenda-tion) and classification of recommendation level (based on evidence level and quality)	Not described	Not described
Sashidharan et al., 2016[22]						
Clinicians at Level 3 sexual health clinics in	Diagnosis and management of scabies	Clinical effectiveness and safety	Database searches (Medline,	The GRADE system was used for	According to the BASHH guideline methodology,[23] the	*"The first draft was produced by*

Table 4: Characteristics of Included Guidelines

Intended Users, Target Population	Intervention and Practice Considered	Major Outcomes Considered	Evidence Collection, Selection, and Synthesis	Evidence Quality Assessment	Recommendations Development and Evaluation	Guideline Validation
the UK, patients > 16 years old presenting to such clinics			Pubmed, and Embase [January 2002 to July 2015], Cochrane Collaboration Databases, CDC website on scabies, NICE Guidelines, and IUSTI guidelines	formulating and stating the strength of recommend-ations	Delphi technique was used and in the case of disagreement the GRADE grid was used.	*the writing group and then circulated to BASHH CEG for review using the AGREE appraisal tool. The second draft of the guideline is being piloted on BASHH website for wider consultation and also simultaneous ly reviewed by the patient/public panel. The final draft will be presented to the CEG for review and piloting in their clinics."*

BASHH = British Association for Sexual Health; CDC = Center for Disease Control; CEG = Clinical Effectiveness Group; IUSTI = International Union against Sexually Transmitted Infections; NICE = The National Institute for Health and Care Excellence.

Appendix 3: Critical Appraisal of Included Publications

Table 5: Strengths and Limitations of Systematic Reviews and Meta-Analyses using AMSTAR 2[11]

Strengths	Limitations
Dhana, 2018[17]	
• The research questions and inclusion criteria for the review included the components of PICO • Multiple databases and references of included studies were searched and keywords were provided • Study selection, data extraction, and quality assessment were performed in duplicate • Included studies were described in adequate detail • Risk of bias was assessed using the Cochrane Risk of bias assessment tool • Appropriate methods were used to combine study results and random-effects models were used • Interpretation and discussion of the results accounted for risk of bias • Meta-regression was performed to investigate sources of heterogeneity; none were identified • Funnel plots and Egger's test were used to assess publication bias • The review authors declared no conflicts of interest	• It was unclear whether review methods were established prior to conduct of the review • An explanation was not given for including only RCTs • Trial registries and grey literature were not searched • A list of excluded studies was not provided • Sources of funding for the included studies were not provided • The potential impact of risk of bias in primary studies on the results of the meta-analysis was not assessed
Rosumeck, 2018[18]	
• The research questions and inclusion criteria for the review included the components of PICO • Review methods were comprehensively pre-specified in a registered protocol and deviations were justified • Multiple databases and trial registries were searched, keywords were provided for the search, and grey literature and reference lists of included studies were searched • Study selection, data extraction, and quality assessment were performed in duplicate with consensus achieved • A list of excluded studies and reasons for exclusion were provided • Included studies were described in adequate detail • Risk of bias was assessed using the Cochrane Risk of bias assessment tool • Sources of funding for the included studies were provided where available • Appropriate methods were used to combine study results and the use of random-effects models was justified • Interpretation and discussion of the results accounted for risk of bias • Sources of substantial heterogeneity were investigated and discussed • Publication bias was assessed based on study size and funding due to the small number of studies pooled • The review authors declared no conflicts of interest	• An explanation was not given for including only RCTs • The potential impact of risk of bias in primary studies on the results of the meta-analysis was not assessed

RCT = randomized controlled trials.

Table 6: Strengths and Limitations of Systematic Review and Network Meta-Analysis using the ISPOR Questionnaire[12]

Strengths	Limitations
Thadanipon, 2019[16]	
Relevance • All RCTs with patients treated for scabies were included regardless of patient or disease characteristics • Patients included adults and children, those with severe and non-severe cases, and those diagnosed with or without microscopy • All treatments for scabies mentioned in the CPS Position Statement were included • Where reported, close contacts were also treated • Relevant outcomes were reported **Credibility** • The research questions and inclusion criteria for the review included the components of PICO • A comprehensive literature search was conducted with multiple databases searched, search strategy reported, PRISMA reporting guidelines followed, and protocol registered • Study selection and data extraction were performed in duplicate with disagreement resolved by consensus with a third reviewer • A list of excluded studies and reasons for exclusion was provided • Detailed characteristics of included studies were reported • All RCTs were connected in a single evidence network for each outcome • Cochrane Risk of Bias tool was used to assess study quality • Funnel plots were used to assess publication bias • Meta-regression results in direct meta-analyses were used to identify sources of heterogeneity to guide subgroup analyses • Direct meta-analyses used appropriate models (random-effects models when $I^2 \geq 25\%$) • Appropriate methods were used for network meta-analysis (2-stage network meta-analysis using a multivariate meta-analysis with consistency model; distinct between-studies variance for each contrast) • Consistency between direct and indirect evidence was assessed using a design-by-treatment interaction model and no evidence of inconsistency was found • The following were reported: evidence networks for each outcome, individual RCT results, results of direct comparisons and network meta-analysis, pairwise contrasts with 95% confidence intervals, treatment rankings, and subgroup analyses for direct comparisons • Funnel plots were used to assess publication bias • The authors disclosed no conflicts of interest	**Relevance** • Most RCTs were conducted in Asia • Evidence in patients with crusted scabies was limited as crusted scabies was absent, not reported (or reported in 1.5% of patients in one RCT) • Some RCTs had more topical treatment applications in the permethrin, benzyl benzoate, crotamiton, and sulfur treatment groups than in the regimens outlined in the CPS Position Statement • Most RCTs did not report whether there was prevention of fomite transmission **Credibility** • Grouping of cure by time point (1 to 2 week and 3 to 6 weeks) may not have been pre-specified • Poor quality studies were included: in most RCTs, risk of bias was reported as high for blinding of participants and personnel for all outcomes, high or unclear for blinding of outcome assessment, and high for incomplete outcome data • Risk of selective reporting bias was reported as high for 33% of the RCTs • Sources of funding for the RCTs were not provided • There were no sensitivity analyses excluding low quality RCTs • Baseline characteristics were not reported per treatment group and an assessment of imbalances was not reported • Percentage of severe cases varied from 1.7% to 100% • The conclusions were not balanced: they were based on the treatment rankings as opposed to the pairwise comparisons and did not address concerns with potential bias or the evidence base

CPS = Canadian Paediatric Society; ISPOR = International Society for Pharmacoeconomics and Outcomes Research; PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RCT = randomized controlled trial.

Table 7: Strengths and Limitations of Included Primary Clinical Study using the Downs and Black Checklist[13]

Strengths	Limitations
Al Jaff, 2018[19]	
• Study objective was clearly described • Interventions were clearly described • Simple outcome data was provided for the results • The time period between initial treatment and outcome assessment was the same for all patients • The statistical tests for assessing the main outcomes were appropriate	• Outcomes, particularly methods for determining cure, were not clearly described • Inclusion and exclusion criteria did not explicitly state that patients had to have scabies and did not specify how it was diagnosed • A list of principal confounders was not provided and distributions of expected confounders were not described • Adverse events were not assessed • Patient disposition was not reported and it was not clear if any patients were lost to follow-up • Actual *P* values were not reported (only whether they were above or below 0.05) • Patient recruitment and consenting was not described • Treatment setting was not described • There was no description of blinding patients or outcome assessors to treatment allocation • Adherence to treatment was not reported • Randomization method was not reported • Sample size calculations were not described and it was unclear whether the study was sufficiently powered to detect a difference

Table 8: Strengths and Limitations of Guidelines using AGREE II[14]

Item	Guideline		
	The Japanese Dermatological Association, 2017[20]	Salavastru, 2017[21]	Sashidharan, 2016[22]
Domain 1: Scope and Purpose			
1. The overall objective(s) of the guideline is (are) specifically described.	✓	×	✓
2. The health question(s) covered by the guideline is (are) specifically described.	✓	×	✓
3. The population (patients, public, etc.) to whom the guideline is meant to apply is specifically described.	✓	×	✓
Domain 2: Stakeholder Involvement			
4. The guideline development group includes individuals from all relevant professional groups.	✓	×	×
5. The views and preferences of the target	✓	×	✓

Table 8: Strengths and Limitations of Guidelines using AGREE II[14]

Item	Guideline		
population (patients, public, etc.) have been sought.			
6. The target users of the guideline are clearly defined.	✓	×	×
Domain 3: Rigour of Development			
7. Systematic methods were used to search for evidence.	✓	✓	✓
8. The criteria for selecting the evidence are clearly described.	×	×	×
9. The strengths and limitations of the body of evidence are clearly described.	×	×	×
10. The methods for formulating the recommendations are clearly described.	×	×	✓
11. The health benefits, side effects, and risks have been considered in formulating the recommendations.	✓	×	✓
12. There is an explicit link between the recommendations and the supporting evidence.	✓	✓	✓
13. The guideline has been externally reviewed by experts prior to its publication.	×	×	×
14. A procedure for updating the guideline is provided.	×	×	✓
Domain 4: Clarity of Presentation			
15. The recommendations are specific and unambiguous.	✓	✓	✓
16. The different options for management of the condition or health issue are clearly presented.	✓	✓	✓
17. Key recommendations are easily identifiable.	✓	✓	✓
Domain 5: Applicability			
18. The guideline describes facilitators and barriers to its application.	×	×	×
19. The guideline provides advice and/or tools on how the recommendations can be put into practice.	×	×	×
20. The potential resource implications of applying the recommendations have been considered.	×	×	×
21. The guideline presents monitoring and/or auditing criteria.	×	✓	✓
Domain 6: Editorial Independence			
22. The views of the funding body have not	✓	✓	✓

Table 8: Strengths and Limitations of Guidelines using AGREE II[14]

Item	Guideline		
influenced the content of the guideline.			
23. Competing interests of guideline development group members have been recorded and addressed.	✓	×	✓

Appendix 4: Main Study Findings and Authors' Conclusions

Table 9: Summary of Findings Included Systematic Reviews and Meta-Analyses

Main Study Findings	Authors' Conclusion
Thadanipon, 2019[16]	

<u>Oral vs. topical ivermectin</u>
 	
Cure at 1 to 2 weeks: Significantly higher cure rate at 1 to 2 weeks with topical ivermectin vs. oral ivermectin; RR = 1.18 (95% CI, 1.00 to 1.41)
 	
Cure at 3 to 6 weeks: No significant difference in cure rate at 3 to 6 weeks between topical and oral ivermectin; RR = 1.02 (95% CI, 0.90 to 1.15)
 	
Re-infestation: In 1 RCT (N = 62; Ahmad et al., 2016), there were no recurrences at 4 weeks in patients receiving topical ivermectin or oral ivermectin
 	
Persistent itching: Significantly lower rate of persistent itching with topical vs. oral ivermectin; RR = 0.26 (95% CI, 0.10 to 0.71)
 	
Patients with ≥ 1 AE: No significant difference in AE rate between topical and oral ivermectin; RR = 1.42 (95% CI, 0.91 to 2.22)
 	
<u>Oral ivermectin vs. other scabicides</u>
 	
Cure at 1 to 2 weeks:
• Significantly higher cure rate at 1 to 2 weeks with oral ivermectin vs. crotamiton; RR = 1.34 (95% CI, 1.08 to 1.65)
• Significantly higher cure rate at 1 to 2 weeks with permethrin vs. oral ivermectin; RR = 1.16 (95% CI, 1.05 to 1.27)
• No significant difference in cure rate at 1 to 2 weeks between oral ivermectin and the following: synthetic pyrethrins, sulfur, permethrin + oral ivermectin, malathion, lindane, and benzyl benzoate
 	
Cure at 3 to 6 weeks:
• Significantly higher cure rate at 3 to 6 weeks with oral ivermectin vs.:
  ○ malathion; RR = 1.38 (95% CI, 1.05 to 1.82)
  ○ lindane; RR = 1.20 (95% CI, 1.09 to 1.32)
  ○ crotamiton; RR = 1.25 (95% CI, 1.09 to 1.43)
  ○ benzyl benzoate; RR = 1.18 (95% CI, 1.03 to 1.35)
• No significant difference in cure rate at 3 to 6 weeks between oral ivermectin and the following: synthetic pyrethrins, sulfur, permethrin, and permethrin + oral ivermectin
 	
Re-infestation:
• In 2 RCTs (N = 44 in Glaziou et al., 1993; N = 58 in Nnoruka et al., 2001), there were no relapses at 30 days in patients receiving oral ivermectin or benzyl benzoate
• In 1 RCT (N = 120; Saqib et al., 2012), 6.7% of patients in both the oral ivermectin and benzyl benzoate group had re-infestation at 2 weeks
• In 1 RCT (N = 95; Usha et al., 2000), there were no recurrences at 8 weeks in patients receiving oral ivermectin or permethrin
	"Combination permethrin plus oral ivermectin, topical ivermectin, and synergized pyrethrins had the strongest evidence for highest cure, lowest chance of persistent itching, and lowest adverse reactions, respectively. There was no 1 treatment that ranked highest in all aspects. Physicians should not only consider the efficacy and safety profiles of the medication, but also its ease of administration."[16] [p. 1442]

Table 9: Summary of Findings Included Systematic Reviews and Meta-Analyses

Main Study Findings	Authors' Conclusion

Persistent itching:
• Significantly lower rate of persistent itching with oral ivermectin vs. benzyl benzoate; RR = 0.57 (95% CI, 0.34 to 0.95)
• No significant difference in rate of persistent itching between oral ivermectin and the following: synthetic pyrethrins, sulfur, permethrin, lindane, and crotamiton
 	
Patients with ≥ 1 AE
• Significantly lower AE rate with synthetic pyrethrins vs. oral ivermectin; RR = 0.21 (95% CI, 0.07 to 0.58)
• Significantly lower AE rate with oral ivermectin vs. sulfur; RR = 5.27 (95% CI, 3.00 to 9.26) for sulfur vs. oral ivermectin
• No significant difference in AE rate between oral ivermectin and the following: permethrin, permethrin + oral ivermectin, malathion, lindane, crotamiton, and benzyl benzoate
 	
<u>Topical ivermectin vs. other scabicides</u>
 	
Cure at 1 to 2 weeks:
• Significantly higher cure rate with topical ivermectin vs.:
  ○ sulfur; RR = 1.62 (95% CI, 1.26 to 2.09)
  ○ malathion; RR = 1.70 (95% CI, 1.10 to 2.63)
  ○ lindane; RR = 1.45 (95% CI, 1.18 to 1.80)
  ○ crotamiton; RR = 1.58 (95% CI, 1.25 to 2.00)
  ○ benzyl benzoate; RR = 1.31 (95% CI, 1.07 to 1.60)
• No significant difference in cure rate between topical ivermectin and the following: synthetic pyrethrins, permethrin, and permethrin + oral ivermectin
 	
Cure at 3 to 6 weeks:
• Significantly higher cure rate with topical ivermectin vs.:
  ○ malathion; RR = 1.41 (95% CI, 1.04 to 1.90)
  ○ lindane; RR = 1.22 (95% CI, 1.06 to 1.41)
  ○ crotamiton; RR = 1.27 (95% CI, 1.09 to 1.48)
  ○ benzyl benzoate; RR = 1.20 (95% CI, 1.03 to 1.40)
• No significant difference in cure rate between topical ivermectin and the following: synthetic pyrethrins, sulfur, permethrin, and permethrin + oral ivermectin
 	
Persistent itching:
• No significant difference in rate of persistent itching between topical ivermectin and the following: synthetic pyrethrins, sulfur, permethrin, lindane, crotamiton, and benzyl benzoate
 	
Patients with ≥ 1 AE:
• Significantly higher AE rate with topical ivermectin vs.:
  ○ synthetic pyrethrins; RR = 6.88 (95% CI, 2.36 to 20.05)
  ○ malathion; RR = 2.40 (95% CI, 1.04 to 5.55)
• Significantly lower AE rate with topical ivermectin vs. sulfur; RR = 0.27 (95% CI, 0.14 to 0.52)
• No significant difference in AE rate between topical ivermectin and	

Table 9: Summary of Findings Included Systematic Reviews and Meta-Analyses

Main Study Findings	Authors' Conclusion
the following: permethrin, permethrin + oral ivermectin, lindane, crotamiton, and benzyl benzoate	
Dhana, 2018[17]	
Treatment failure was not a reported outcome in Thadanipon et al. and is therefore reported here. Also, the results for oral ivermectin vs. permethrin for treatment failure involve two RCTs (Maurya et al., 2014 and Wankhade et al., 2013) not included in Thadanipon et al. **Oral ivermectin vs. permethrin** **Treatment failure:** Significantly higher treatment failure rate with oral ivermectin vs. permethrin; RR = 1.33 (95% CI, 1.04 to 1.72); N = 1691 **Persistent itch:** No significant difference in persistent itch between oral ivermectin and permethrin; RR = 1.32 (95% CI, 0.91 to 1.93); N = 821 **Topical ivermectin vs. permethrin** **Treatment failure:** No significant difference in treatment failure rate between topical ivermectin and permethrin; RR = 1.49 (95% CI, 0.88 to 2.51); N = 580 **Note:** There was complete overlap in the included studies for this comparison with those for cure and persistent itch in Thadanipon et al.	*"In summary, oral ivermectin is less effective than topical permethrin. Topical ivermectin may have a similar efficacy to topical permethrin, but further trials are warranted given the small sample size used for this comparison. All 3 agents, however, have low treatment failure rates and are well tolerated."*[17] [p. 197-198]
Rosumeck, 2018[18]	
Since complete clearance was reported in Rosumeck et al. for 1, 2, and 4 weeks as opposed to 1 to 2 weeks and 3 to 6 weeks as in Thadanipon et al., the results are reported here. Unless other indicated, the included RCTs for these comparisons were also included RCTs in Thadanipon et al. The number of patients re-treated and withdrawals due to AE were not reported outcomes in Thadanipon et al. and are therefore reported here. **Oral vs. topical ivermectin** **Complete clearance at 1 week:** In 1 RCT (N = 62), no significant difference in complete clearance rate between oral and topical ivermectin; RR = 0.84 (95% CI, 0.65 to 1.08); low certainty of evidence according to GRADE **Complete clearance at 2 weeks:** In 1 RCT (N = 62), no significant difference in complete clearance rate between oral and topical ivermectin; RR = 1.00 (95% CI, 0.94 to 1.06); moderate certainty of evidence according to GRADE **Complete clearance at 4 weeks:** In 2 RCTs, no significant difference in complete clearance rate between oral and topical ivermectin; RR = 0.99 (95% CI, 0.95 to 1.03); N = 272; moderate certainty of evidence according to GRADE	*"We found that for the most part, there was no difference detected in the efficacy of permethrin compared to systemic or topical ivermectin. Overall, few and mild adverse events were reported. Our confidence in the effect estimates was mostly low to moderate. Poor reporting is a major limitation."*[18] [p. 2]

Table 9: Summary of Findings Included Systematic Reviews and Meta-Analyses

Main Study Findings	Authors' Conclusion
Note: There was complete overlap in the included studies for the above comparisons with those for cure in Thadanipon et al. **Withdrawals due to AE at week 4**: In 1 RCT (N = 62) comparing oral and topical ivermectin, no patients withdrew due to AE by week 4. GRADE certainty of evidence was moderate. **Oral ivermectin vs. permethrin** **Complete clearance at 1 week:** Significantly lower complete clearance rate with oral ivermectin vs. permethrin cream; RR = 0.65 (95% CI, 0.54 to 0.78); N = 613 **Complete clearance at 2 weeks:** No significant difference in complete clearance rate between oral ivermectin and permethrin cream; RR = 0.91 (95% CI, 0.76 to 1.08); N = 459 **Complete clearance at 4 weeks:** No significant difference in complete clearance rate between oral ivermectin and permethrin cream; RR = 0.92 (95% CI, 0.82 to 1.03); N = 581 **Improvement clinically at 4 weeks:** In 1 RCT (N = 100; Das et al., 2006), % of patients with "improvement clinically" was 90.0% vs. 96.0% for permethrin vs. oral ivermectin **Patients with ≥ 1 AE at 4 weeks:** No significant difference in patients with ≥ 1 AE between oral ivermectin and permethrin cream; RR = 1.30 (95% CI, 0.35 to 4.83); N = 502; low certainty of evidence according to GRADE **Number of patients re-treated (non-responders only):** In 1 RCT (N = 68; Bachewar et al., 2009), 44.4% vs. 17.86% of patients receiving oral ivermectin 200 µg/kg vs. permethrin 5% were re-treated **Withdrawals due to AE at week 4**: In 3 RCTs (N = 305) comparing oral ivermectin and permethrin cream, and one RCT (N = 120) comparing oral ivermectin and permethrin lotion, no patients withdrew due to AE by week 4. GRADE certainty of evidence for oral ivermectin vs. permethrin cream was moderate. **Notes for complete clearance:** • The results include one RCT (Rohatgi et al., 2013) that was not included in Thadanipon et al. • GRADE certainty of evidence was low **Topical ivermectin vs. permethrin** **Complete clearance at 4 weeks:** In 1 RCT (N = 210), no significant difference in complete clearance rate between topical ivermectin and permethrin cream; RR = 1.02 (95% CI, 0.96 to 1.08); moderate certainty of evidence according to GRADE	

Table 9: Summary of Findings Included Systematic Reviews and Meta-Analyses

Main Study Findings	Authors' Conclusion
Note: The above RCT was included in the comparisons for cure in Thadanipon et al.	

AE = adverse event; CI = confidence interval; NMA = network meta-analysis; RCT = randomized controlled trials; RR = relative risk.

Table 10: Summary of Findings of Included Primary Clinical Study

Main Study Findings	Authors' Conclusion
Al Jaff, 2018[19]	
Cure at 1 to 2 weeks according to number of lesions • Cure rate was between 85.4% for oral ivermectin, 56.0% for sulphur, and 77.3% for permethrin (N = 225) • According to the LSD test following ANOVA, cure rate was significantly different ($P < 0.05$) between oral ivermectin and sulphur • There was no significant difference in cure rate between oral ivermectin and permethrin **Cure at 1 to 2 weeks according to severity of itching** • Cure rate was between 89.3% for oral ivermectin, 53.3% for sulphur, and 76.0% for permethrin (N = 225) • According to the LSD test following ANOVA, cure rate was significantly different ($P < 0.05$) between oral ivermectin and sulphur • There was no significant difference in cure rate between oral ivermectin and permethrin	*"There was no differences in effectiveness of both oral ivermectin and topical permethrin cream against severity of disease (No. of lesions) and Pruritus (P value > 0.05), however topical sulphur ointment was less effective than both topical permethrin cream and oral ivermectin against severity of disease (No. of lesions) and Pruritus"*[19] [p. 674-675]

ANOVA = analysis of variance; LSD = least significant difference.

Table 11: Summary of Recommendations in Included Guidelines

Recommendations	Strength of Evidence and Recommendations
The Japanese Dermatological Association, 2017[20]	
1. [Oral] Ivermectin is effective for treating scabies. Evidence: *"[…] an RCT was conducted in Mexico with 55 subjects, using a single dose of 200 lg/kg. The cure rate in the ivermectin group was reported to be 74%, compared with 15% in the placebo group, demonstrating the efficacy of ivermectin, and no adverse reactions were seen. There is a wealth of usage experience with ivermectin in the treatment of animal scabies or non-scabies parasitosis in humans. There are also a number of RCT comparing the efficacy of ivermectin with that of other drugs in the treatment of human scabies. Ivermectin is currently widely used in Japan as the only oral drug for human scabies and the results of postmarketing surveillance of all 807 patients have been published (the evidence level is low, but the number of cases is high)."*[20] [p. 998] 2. Permethrin is more effective in the treatment of scabies than [oral] ivermectin. Evidence: *"There are RCT and meta-analysis which demonstrate that*	1. Recommendation level: A (use of the treatment is strongly recommended; there is at least one SR/MA or good quality RCT demonstrating efficacy) 2. Recommendation level: C1 (use of the treatment may be considered, but there is insufficient evidence; inferior quality non-randomized controlled trial or analytical epidemiological study [cohort study, case-control trial], a number of good quality descriptive studies [case report, case series], or a committee-approved opinion of specialist committee or specialist individual)

Table 11: Summary of Recommendations in Included Guidelines

Recommendations	Strength of Evidence and Recommendations
permethrin is significantly superior to ivermectin in terms of efficacy. Permethrin has almost no adverse effects. However, permethrin is not covered by health insurance in Japan, and considering that this guideline is essentially a guideline for Japan, the recommendation level is set at C1."[20] [p. 999]	
Salavastru, 2017[21]	
1. As a recommended treatment: *"Oral ivermectin (taken with food) 200 micrograms/kg as two doses 1 week apart"*[21] [p. 1249] 2. As an alternative treatment: *"Ivermectin 1% lotion was reported to be as effective as permethrin cream 5%"*[21] [p. 1250] 3. For crusted scabies: *"A topical scabicide (permethrin 5% cream or benzyl benzoate lotion 25%) repeated daily for 7 days then 2x weekly until cure AND Oral ivermectin 200 micrograms/kg on days 1, 2 and 8. For severe cases, based on persistent live mites on skin scrapings at follow-up visit, additional ivermectin treatment might be required on days 9 and 15 or on days 9, 15, 22 and 29"*[21] [p. 1250]	1. Level of evidence: Ib (at least one RCT) Recommendation grade: A (Requires at least one RCT as part of the body of literature of overall good quality and consistency addressing the specific recommendation.) 2. Level of evidence: Ib (at least one RCT) Recommendation grade: A (Requires at least one RCT as part of the body of literature of overall good quality and consistency addressing the specific recommendation.) 3. Level of evidence: IV (expert committee reports or opinions and/or clinical experience of respected authorities) Recommendation grade: C (Requires evidence from expert committee reports or opinions and/or clinical experience of respected authorities. Indicates absence of directly applicable studies of good quality.)
Sashidharan, 2016[22]	
1. As an alternative regimen: *"Ivermectin in a dose of 200 mcg/kg 2 weeks apart in patients weighing >15kg"*[22] 2. For crusted scabies: *"Combination regimen of topical permethrin cream once daily for 7 days, then twice weekly until cure plus oral ivermectin (200 mcg/kg) on days 1,2,8,9 and 15. Patients with severe infestations may require additional doses on day 22 and 29."*[22]	1. Level of evidence: A (high quality meta-analyses, systematic reviews of and RCTs directly applicable to the target population) Recommendation level: 1b (strong recommendation; moderate quality evidence; benefits clearly outweigh risk and burdens, or vice versa) 2. No level of evidence or recommendation level assigned

MA = meta-analysis, RCT = randomized controlled trial; SR = systematic review.

Appendix 5: Overlap between Included Systematic Reviews

Table 12: Primary Study Overlap between Included Systematic Reviews

Primary Study Citation	Systematic Review Citation		
	Thadanipon, 2019[16]	Dhana, 2018[17]	Rosumeck, 2018[18]
Abdel-Raheem, 2016	✓	✓	✓
Aggarwal, 2014	✓	✓	
Ahmad, 2016	✓		✓
Alipour, 2015	✓		
Bachewar, 2009	✓	✓	✓
Brooks, 2002	✓		
Chhaiya, 2012	✓	✓	✓
Chouela, 1999	✓		
Daneshpajooh, 1999	✓		
Das, 2006	✓		✓
Glaziou, 1993	✓		
Goldust, 2014 (Cutan Ocul Toxicol)	✓		
Goldust, 2014 (Int J Dermatol)	✓		
Goldust, 2014 (Skinmed)	✓		
Goldust, 2013 (Ann Parasitol)	✓		
Goldust, 2013 (Int J Dermatol)	✓	✓	
Goldust, 2012	✓	✓	
Kanwar, 2016	✓	✓	
Khan, 2007	✓		
Ly, 2009	✓		
Madan, 2001	✓		
Manjhi, 2014	✓	✓	✓
Maurya, 2014		✓	
Meenakshi, 2014	✓		✓
Mohebbipour, 2012	✓		

Table 12: Primary Study Overlap between Included Systematic Reviews

Primary Study Citation	Systematic Review Citation		
	Thadanipon, 2019[16]	Dhana, 2018[17]	Rosumeck, 2018[18]
Mushtaq, 2010	✓	✓	✓
Nnoruka, 2001	✓		
Ranjkesh, 2013	✓	✓	
Razaee, 2015	✓		
Rohatgi, 2013			✓
Saqib, 2012	✓	✓	✓
Shaheen, 2017	✓		
Sharma, 2011	✓	✓	✓
Usha, 2000	✓	✓	✓
Wankhade, 2013		✓	✓
Wankhade, 2016	✓		✓

NOTE: For the Thadanipon systematic review and network meta-analysis, only primary studies with at least one oral or topical ivermectin treatment group were included in this table.

Appendix 6: Additional References of Potential Interest

Position Statement Relevant to the Canadian Setting

1. Banerji A. Scabies. *Paediatr Child Health*. 2015 Oct;20(7):395-402. [Reaffirmed 2018 Feb 28]: https://www.cps.ca/en/documents/position/scabies. Accessed 2019 May 16.

Non-Systematic Review of Clinical Effectiveness of Oral Ivermectin for Scabies Treatment

1. National Institute for Health and Care Excellence (NICE). Difficult-to-treat scabies: oral ivermectin. Evidence summary. London (GB): NICE; 2014 Mar: https://www.nice.org.uk/advice/esuom29/resources/difficulttotreat-scabies-oral-ivermectin-pdf-54116459009974213. Accessed 2019 May 16.

Case Reports and Non-Systematic Review Relevant to Safety of Oral Ivermectin

1. Gilbert BW, Slechta J. A case of ivermectin-induced warfarin toxicity: first published report. *Hosp Pharm*. 2018 01 Dec;53(6):393-394.

2. Kerneuzet I, Blind E, Darrieux L, Moreau S, Safa G. Ivermectin-induced drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome. *JAAD Case Rep*. 2018 July;4(6):524-527.

3. Kircik LH, Del Rosso JQ, Layton AM, Schauber J. Over 25 years of clinical experience with ivermectin: an overview of safety for an increasing number of indications. *Journal Drugs Dermatol*. 2016 Mar;15(3):325-332.