Aus der Klinik für Dermatologie, Venerologie und Allergologie
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DISSERTATION

Ivermectin and permethrin for treating scabies

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1 Abstracts

Background

Scabies is an intensely itchy parasitic skin infection. Our objective was to assess the efficacy and safety of topical permethrin and topical or systemic ivermectin.

Methods

We followed the methods as recommended by Cochrane. The Cochrane Infectious Diseases Group Specialized Register, CENTRAL, MEDLINE, Embase, LILACS, and IndMED were searched up to April 2017. We also searched trial registers and grey literature. Two review authors independently screened records, extracted data, and performed risk of bias evaluations.

We summarized dichotomous outcomes using risk ratios with 95% confidence intervals and meta-analysed the data using a random-effects model. We assessed the certainty of the evidence using the GRADE approach.

Results

We included fifteen studies (1896 participants).

Ivermectin (200 µg/kg) may lead to slightly lower rates of complete clearance after one week compared to permethrin 5% cream. After one dose of ivermectin or one application of permethrin 5% lotion, there is probably little or no difference in complete clearance rates. After two weeks, one dose ivermectin compared to one application of permethrin lotion may lead to similar complete clearance rates (low to moderate-certainty evidence).

There is no difference in rates of complete clearance between systemic ivermectin and ivermectin 1% lotion after four weeks (moderate-certainty evidence). Likewise, after four weeks, ivermectin lotion probably leads to little or no difference in rates of complete clearance when compared to permethrin cream (moderate-certainty evidence).

Safety reporting was suboptimal. After two weeks, there is no difference in the number of participants with ≥ 1 adverse event (AE) comparing systemic ivermectin and permethrin cream (moderate-certainty evidence). After four weeks, ivermectin may lead to a slightly larger proportion of patients with ≥ 1AE (low-certainty evidence).

AEs in participants treated with topical ivermectin were rare and comparable to those with systemic ivermectin. It is uncertain whether there is any difference in the number of participants with ≥ 1 AE. No withdrawals due to AE occurred (very low- and moderate-certainty evidence).

It is uncertain whether topical ivermectin or permethrin differ in the number of participants with ≥ 1 AE (very low-certainty evidence).

Conclusion

For the most part, we found no difference in the efficacy of permethrin compared to systemic or topical ivermectin. Overall, few and mild AEs were reported. Confidence in the effect estimates was mostly low to moderate.

Modifiziert aus:

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Hintergrund

Skabies ist eine intensiv juckende parasitäre Hautinfektion. Ziel war es, die Wirksamkeit und Sicherheit von topischem Permethrin und topischem oder systemischem Ivermectin zu untersuchen.

Methodik

Das Specialized Register der Cochrane Infectious Diseases Group, CENTRAL, MEDLINE, Embase, LILACS und IndMED wurden bis April 2017 durchsucht. Des Weiteren haben wir Studienregister durchsucht und nach grauer Literatur recherchiert. Zwei Review-Autorinnen sichteten unabhängig voneinander die Treffer, extrahierten Daten und bewerteten das Verzerrungspotenzial der eingeschlossenen Studien.

Dichotome Endpunkte wurden als relatives Risiko mit 95-%-Konfidenzintervall dargestellt. Die Studien wurden mittels Random-Effects-Modell metaanalysiert. Die Bewertung der Qualität der Evidenz erfolgte gemäß der GRADE-Methodik.

Ergebnisse

Fünfzehn Studien wurden eingeschlossen (1896 Studienteilnehmer).

Im Vergleich zu Permethrin 5% Creme führt Ivermectin (200 µg/kg) nach einer Woche zu einer geringfügig niedrigeren Rate der kompletten Abheilung. Eine einmalige Dosis Ivermectin bzw. die einmalige Anwendung von Permethrin 5% Lotion führt wahrscheinlich nur zu einem geringen oder gar keinem Unterschied in der Rate der kompletten Abheilung. Nach zwei Wochen führt Ivermectin zu einer ähnlichen Rate der kompletten Abheilung wie Permethrin Lotion (jeweils einmalig; Evidenz von niedriger bis moderater Vertrauenswürdigkeit).

Nach vier Wochen gibt es keinen Unterschied in der Rate der kompletten Abheilung von systemischem Ivermectin und Ivermectin 1% Lotion (Evidenz von moderater Vertrauenswürdigkeit). Ebenso, gibt es wahrscheinlich nur einen geringen oder gar keinen Unterschied in der Rate der kompletten Abheilung nach vier Wochen Ivermectin Lotion oder Permethrin Creme.

Die Berichterstattung bezüglich der Medikamentensicherheit war suboptimal. Nach zwei Wochen besteht kein Unterschied in der Anzahl der Studienteilnehmer mit ≥ 1 unerwünschten Ereignis (UE) bei systemischem Ivermectin und Permethrin Creme (Evidenz von moderater Vertrauenswürdigkeit). Jedoch führt Ivermectin nach vier Wochen zu einer etwas höheren Anzahl an Studienteilnehmern mit ≥ 1 UE (Evidenz von niedriger Vertrauenswürdigkeit).

Unerwünschte Ereignisse bei Studienteilnehmern behandelt mit topischem Ivermectin waren selten und vergleichbar mit denen bei systemischem Ivermectin. Es ist unklar, ob es einen Unterschied in der Anzahl der Studienteilnehmer mit ≥ 1 UE gibt. Es gab keine Studienabbrüche aufgrund von UE (Evidenz von sehr niedriger bzw. moderater Vertrauenswürdigkeit). Ebenfalls ist unklar, ob topisches Ivermectin oder Permethrin zu einer unterschiedlichen Anzahl von Studienteilnehmern mit ≥ 1 UE führen (Evidenz von sehr niedriger Vertrauenswürdigkeit).

Schlussfolgerung

Größtenteils fanden wir keinen Unterschied in der Wirksamkeit von Permethrin im Vergleich zu systemischem oder topischem Ivermectin. Insgesamt wurden wenige und leichte unerwünschte Ereignisse berichtet. Das Vertrauen in die Effektschätzer war meist niedrig bis moderat.

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2 Manteltext

‚Ivermectin and permethrin for treating scabies' - Ein Cochrane Review

Die Publikation mit dem Titel „Ivermectin and permethrin for treating scabies" [1] ist eine systematische Übersichtsarbeit. Die Erstellung erfolgte entsprechend den methodischen Regeln der Cochrane Collaboration, welche im ‚Cochrane Handbook for Systematic Reviews of Interventions' [2] zusammengefasst sind. Mit der systematischen Erarbeitung und den spezifischen methodischen Anforderungen an die Erstellung von Cochrane Reviews wird das kritische Hinterfragen eines potenziellen Verzerrungsrisikos einzelner Studien und somit das bestmögliche Vermeiden von systematischen Fehlern bei der Evidenzsynthese intendiert. Zudem wird jeder Cochrane Review umfangreich extern begutachtet und stellt somit eine hochwertige und verlässliche Grundlage für eine evidenzbasierte Gesundheitsversorgung, gesundheitspolitische Entscheidungen und den weiteren Forschungsbedarf dar.

Hintergrund

Skabies, bekannt als Krätze, ist eine intensiv juckende parasitäre Infektion der Haut, die durch die weibliche Krätzemilbe (*Sarcoptes scabiei*) verursacht wird.

Die Krätzemilbe gräbt Gänge in die oberste Schicht der Epidermis, legt dort Eier ab und ist bis zu 60 Tage lebensfähig [3]. Außerhalb des menschlichen Körpers überlebt sie jedoch nur maximal drei Tage [4]. Die Übertragung findet normalerweise über direkten Hautkontakt statt, unter Umständen aber auch über kontaminiertes Material, wie Kleidung oder Bettwaren [5]. Erkrankte leiden an Hautausschlag, mit papulösen oder vesikulären Eruptionen, und quälendem (vor allem nächtlichem) Pruritus. Neben der Gefahr von bakteriellen Superinfektionen kann es unbehandelt zu chronischen Verläufen kommen.

Unter anderem aufgrund einer derzeit vermehrten Anzahl von Massenunterkünften in Deutschland bedingt durch die erhöhten Flüchtlingszahlen, ist die Frage eines möglichen verstärkten Aufkommens von Krätzefällen belangvoll. Asylsuchende sind nicht allein durch die beengte Raumsituation in Flüchtlingsunterkünften, sondern auch durch die Strapazen der langen Reise und dem Erleben von strapaziösen Ereignissen empfänglicher für Krankheiten - und somit auch für Skabies.

Weitere Ausführungen finden sich im Abschnitt ‚Description of the condition' auf Seite 8 der Publikation.

Die klinische Diagnose basiert in der Regel auf Juckreiz in der Anamnese, vor allem wenn Kontaktpersonen ebenfalls betroffen sind, und dem Auffinden von typischen Läsionen an den Prädilektionsstellen. In den meisten Fällen kann die Diagnose mikroskopisch, durch den Nachweis von Milben, Eiern oder Milbenkot aus Hautmaterial (Hautgeschabsel) gesichert werden [6] (*vgl. Abschnitt ‚Diagnosis', Seite 8 der Publikation*).

Verschiedene Optionen stehen zur Behandlung der Skabies zur Verfügung. Dazu gehören Schwefelverbindungen, Benzylbenzoat, Crotamiton, Hexachlorcyclohexan, Malathion, Permethrin, Ivermectin sowie einige pflanzliche Heilmittel. In den letzten Jahren sind dabei topisches Permethrin und orales Ivermectin die relevantesten Behandlungsmöglichkeiten für Skabies geworden [7, 8]. In Deutschland ist topisches Permethrin seit Oktober 2004 [9, 10] und systemisches Ivermectin seit Februar 2016 [11] zugelassen. Topisches Ivermectin dagegen, bisher zugelassen für die Behandlung von Kopfläusen [12] und Rosazea [13], wurde in den letzten Jahren wegen der erwarteten therapeutischen Wirksamkeit bei Skabies zwar beforscht, ist aber noch nicht zugelassen.

Ivermectin ist ein nicht-ovizidales Breitband-Anthelminthikum, welches das Nervensystem der Skabiesmilbe befällt und sie somit abtötet [14]. Es wird oral in einer Dosis von 200 Mikrogramm Ivermectin pro kg Körpergewicht verabreicht [11, 15].

Permethrin ist in der Regel als 5%-ige Creme oder Lösung erhältlich. Es ist ein synthetisches Pyrethroid, welches ovizidal wirkt, d. h. es tötet die Krätzemilbe und deren Eier [15].

Weitere Informationen hierzu finden sich im Abschnitt ‚Description of the intervention' und ‚How the intervention might work' auf den Seiten 8 und 9 der Publikation.

Fragestellung und Zielsetzung

Es ergibt sich aktuell die Frage, ob eine systemische Therapie mit Ivermectin zu einem besseren und sicheren Behandlungserfolg gegenüber topischem Permethrin bzw. topischem Ivermectin führt.

In einem aus unserer Arbeitsgruppe verfassten systematischen Review aus dem Jahr 2016 [16], an dem ich substantiell mitgearbeitet hatte und welches sich methodisch ebenfalls an den Empfehlungen von Cochrane orientiert, wurde ein breiteres Spektrum an Skabies-Interventionen betrachtet. Derzeit gibt es keine aktuelle systematische

Übersichtsarbeit, die die verfügbare Evidenz zu Ivermectin und Permethrin darlegt, obwohl dies eine der wichtigsten Fragestellung ist (persönliche Kommunikation mit Prof. Paul Garner, Editor der Cochrane Infectious Diseases Group; vgl. Empfehlungen vom Robert Koch-Institut [8] und der deutschen S1-Leitlinie zur Diagnostik und Therapie der Skabies [17]).

Ziel des Cochrane Reviews ist es, die verfügbare Evidenz zur Wirksamkeit und Sicherheit von topischem Permethrin und topischem Ivermectin sowie systemischem Ivermectin zur Behandlung von Skabies systematisch aufzuarbeiten und unter anderem Klinikern, die mit der aktuellen Versorgungssituation in Deutschland konfrontiert sind, eine Übersicht bezüglich der vorhandenen Evidenz zu geben.

Die Abschnitte ‚Why it is important to do this review' und *‚Objectives' auf den Seiten 9 und 10 der Publikation beschreiben vertiefend die Fragestellung und das Ziel der Arbeit.*

Methodik

Für die Erstellung des Cochrane Reviews wurde vorab das methodische Vorgehen in einem Studienprotokoll definiert und dieses im ‚International Prospective Register for Systematic Reviews' (PROSPERO, CRD42016048685) registriert [18].

Für den Review berücksichtigt wurden alle randomisierten kontrollierten Studien (RCTs) unabhängig vom Publikationsstatus oder der Publikationssprache. Tabelle 1 listet die Einschlusskriterien anhand der klinischen Fragestellung im PICO-Schema (PICO: Patient – Intervention – Comparison – Outcome) [19] auf.

Tabelle 1: PICO-Schema

PICO	Beschreibung
Patient	- Erwachsene und Kinder mit Skabies
Intervention	- Permethrin topisch - Ivermectin topisch - Ivermectin systemisch
Vergleichsintervention	- eine der genannten Interventionen
Zielgröße	Primärer Endpunkt: - Rate der kompletten Abheilung (Tag 7, 14, und 30 nach Behandlungsbeginn) Sekundäre Endpunkte: - Anzahl der Teilnehmer, die erneut behandelt wurden - Anzahl der Teilnehmer mit ≥ 1 unerwünschten Ereignis

PICO	Beschreibung
	(Bewertung am Ende der aktiven Studienphase) - Anzahl der Studienabbrüche aufgrund von unerwünschten Ereignissen (Bewertung am Ende der aktiven Studienphase)

Vergleiche hierzu Abschnitt ‚Criteria for considering studies for this review' auf Seite 10 der Publikation.

Um alle relevanten publizierten und unpublizierten RCTs zu identifizieren wurde bis zum 25. April 2017 umfangreich u. a. in den folgenden elektronischen Datenbanken gesucht:

- Cochrane Infectious Disease Group Specialized Register,
- Cochrane Central Register of Controlled Trials (CENTRAL),
- MEDLINE (PubMed),
- Embase Ovid,
- LILACS und
- IndMED.

Die Recherche schloss zudem Quellen für Graue Literatur sowie sechs Studienregister ein. Des Weiteren wurden die Referenzlisten aller eingeschlossenen RCTs in Hinblick auf weitere Studien gesichtet sowie Erstautoren kontaktiert um unveröffentlichte Studiendaten zu erhalten.

Detaillierte Informationen finden sich im Abschnitt ‚Search methods for identification of studies' auf den Seiten 10 und 11 der Publikation.

Die Datensammlung sowie die Analyse der Daten orientierte sich an den Rahmenbedingungen des Cochrane Handbooks [2]. Zwei Review-Autorinnen sichteten unabhängig voneinander die Treffer der Literatursuche und extrahierten die Studiendaten. Alle eingeschlossenen Studien wurden mit Hilfe des Cochrane Risk of Bias Assessment Tools hinsichtlich ihres potenziellen Verzerrungsrisikos (englisch: Risk of Bias) beurteilt.

Dichotome Endpunkte wurden als relatives Risiko (RR) mit 95-%-Konfidenzintervall dargestellt (95-%-KI). Bei ausreichender Homogenität wurden die Studienergebnisse mittels Random-Effects-Modell metaanalysiert.

Für jeden Vergleich wurde eine sogenannte ‚Summary of Findings'-Tabelle erstellt. Diese enthält für jeden Endpunkt eine Einschätzung der Qualität der identifizierten Evidenz gemäß der Methodik der Grading of Recommendations Assessment,

Development and Evaluation (GRADE) Arbeitsgruppe [20]. Hierbei wird das Vorliegen von Studienlimitationen, Inkonsistenz, Indirektheit, unzureichende Präzision und Publikationsbias berücksichtig und die Vertrauenswürdigkeit der vorliegenden Evidenz als hoch, moderat, niedrig oder sehr niedrig bewertet (vgl. Tabelle 2) [2, 21].

Tabelle 2: Bewertung der Qualität der Evidenz (Vertrauen in die Effektschätzer) nach GRADE [21]

Hoch (++++)	Wir sind sehr sicher, dass der wahre Effekt nahe bei dem Effektschätzer liegt.
Moderat (+++)	Wir haben mäßig viel Vertrauen in den Effektschätzer: Der wahre Effekt ist wahrscheinlich nahe bei dem Effektschätzer, aber es besteht die Möglichkeit, dass er relevant verschieden ist.
Niedrig (++)	Unser Vertrauen in den Effektschätzer ist begrenzt: Der wahre Effekt kann durchaus relevant verschieden vom Effektschätzer sein.
Sehr niedrig (+)	Wir haben nur sehr wenig Vertrauen in den Effektschätzer: Der wahre Effekt ist wahrscheinlich relevant verschieden vom Effektschätzer.

Das genaue methodische Vorgehen bei der Datensammlung und Datenanalyse ist in Abschnitt ‚Data collection and analysis' auf den Seite 11 bis 13 der Publikation beschrieben.

Ergebnisse

Nach Sichtung der 459 Treffer aus der systematischen Recherche und Anwendung der Ein- bzw. Ausschlusskriterien wurden 15 Studien mit 1896 Studienteilnehmern eingeschlossen. Fast alle Studien wurden in Südasien oder Nordafrika durchgeführt. Verglichen wurde systemisches Ivermectin mit topischem Permethrin, topisches Ivermectin mit topischem Permethrin oder systemisches Ivermectin mit topischem Ivermectin zur Behandlung der Skabies. Für jede eingeschlossene Studie wurden die Studiencharakteristika extrahiert und tabellarisch aufbereitet. Alle Studien waren monozentrisch mit meist geringen Teilnehmerzahlen pro Studiengruppe.

An dieser Stelle besonders zu erwähnen ist, dass drei Studien aus dem Iran, vom selben (Korrespondenz-) Autor publiziert, ausgeschlossen wurden (*vgl. Abschnitt ‚Excluded studies', Seite 16 und 17 der Publikation*). Aus vorherigen Arbeiten sind uns noch weitere Skabies-Studien dieser iranischen Autorengruppe bekannt, deren Daten unstimmig und mangelhaft bzw. wiederholend berichtet wurden. Dies führte dazu, dass wir die Validität der Studien als fraglich und das Risiko einer verzerrten Darstellung der Ergebnisse als sehr wahrscheinlich einschätzen. Details hierzu wurden bereits an

anderer Stelle berichtet [16] und in einem Letter-to-Editor im Journal Annals of Parasitology publiziert [22]. Des Weiteren wurde das Thema auf der Jahrestagung der Cochrane Skin Group am 9. und 10. Januar 2017 in Berlin vorgestellt und diskutiert, mit dem einstimmigen Ergebnis, dass diese Studien wegen des Verdachts fehlerhafter Daten vom Cochrane Review ausgeschlossen werden.
Eine ausführliche Beschreibung der Charakteristika der ein- bzw. ausgeschlossenen Studien findet sich in Abschnitt ‚Description of studies' auf den Seiten 13 bis 17 der Publikation.

Zur Bewertung des Risikos für eine systematische Verzerrung der Studienergebnisse wurde für jede eingeschlossene Studie die Aspekte ‚selection bias', ‚performance bias', ‚detection bias', ‚attrition bias', ‚reporting bias' und ‚other bias' berücksichtigt.
Lediglich vier der eingeschlossenen Studien wurden mit einem geringen Risiko für Selektionsbias bzgl. der Generierung der Randomisierungssequenz sowie der verdeckten Gruppenzuteilung, bewertet. Fast alle Studien weisen ein hohes Risiko für eine Verzerrung aufgrund der Studiendurchführung durch eine fehlende Verblindung der Studienteilnehmer und des Studienpersonals sowie der Endpunkterheber auf. Bezogen auf einen Bias bei der Vollständigkeit der erhobenen Endpunktdaten divergieren die eingeschlossenen Studien; die Bewertung ist annähernd gleich verteilt und zeigt ein geringes bis hohes Risiko. Das Risiko einer selektiven Berichterstattung wurde für fast alle Studien als unklar bewertet, da die Erstellung eines Studienprotokolls vorab durch die jeweiligen Autoren nicht erwähnt wurde und dies auch nicht herauszufinden war. Andere Ursachen für ein Bias-Risiko wurden ebenfalls für fast alle Studien als unklar bewertet.
Details für jede eingeschlossene Studie sind im Abschnitt ‚Risk of bias in included studies' auf den Seiten 17 bis 20 der Publikation aufgeführt.

Für die folgenden sechs Vergleiche konnten Studien identifiziert werden:

- Ivermectin 200 µg/kg Körpergewicht (1 bis 3 Dosen) versus Permethrin 5% Creme (1 bis 3 Anwendungen)
- Ivermectin 200 µg/kg Körpergewicht (1 bis 2 Dosen) versus Permethrin 5% Lotion (1 bis 5 Anwendungen)
- Ivermectin 200 µg/kg Körpergewicht (1 Dosis) versus Permethrin 5% (unbekannte Grundlage, 1 Anwendung)

- Ivermectin 200 µg/kg Körpergewicht (1 bis 3 Dosen) versus Ivermectin 1% Lotion/Lösung (1 bis 3 Anwendungen)
- Ivermectin 1% Lotion (1 bis 3 Anwendungen) versus Permethrin 5% Creme (1 bis 3 Anwendungen)
- Ivermectin systemisch (1 Dosis) versus Ivermectin systemisch (2 bis 3 Dosen).

Exemplarisch sind nachfolgend die Ergebnisse für den primären Endpunkt (Rate der kompletten Abheilung aller Skabies-Läsionen) sowie einige Endpunkte bezüglich Medikamentensicherheit aufgeführt.

Ivermectin in der Standarddosis von 200 µg/kg Körpergewicht führt nach einer Woche vermutlich zu geringfügig niedrigeren Heilungsraten als Permethrin 5% Creme (RR 0,65, 95-%-KI 0,54 bis 0,78; 613 Studienteilnehmer, 6 Studien; Evidenz von niedriger Vertrauenswürdigkeit). Nach zwei bzw. vier Wochen gibt es vermutlich nur einen geringen oder gar keinen Unterschied in der Rate der kompletten Abheilung (RR 0,91, 95-%-KI 0,76 bis 1,08; 459 Studienteilnehmer, 5 Studien; Evidenz von niedriger Vertrauenswürdigkeit bzw. RR 0,92, 95-%-KI 0,82 bis 1,03; 581 Studienteilnehmer, 5 Studien; Evidenz von niedriger Vertrauenswürdigkeit).

Einmalig Ivermectin in der Standarddosis verglichen mit einer einmaligen Anwendung von Permethrin 5% Lotion führt nach einer Woche vermutlich zu einem geringen oder gar keinen Unterschied in der Rate der kompletten Abheilung (RR 0,93, 95-%-KI 0,74 bis 1,17; 120 Studienteilnehmer, 1 Studie; Evidenz von moderater Vertrauens-würdigkeit). Dies ändert sich auch nach zwei Wochen nicht (RR 1,00, 95-%-KI 0,78 bis 1,29; 120 Studienteilnehmer, 1 Studie; Evidenz von niedriger Vertrauenswürdigkeit).

Vier Wochen nach Behandlungsbeginn besteht wahrscheinlich nur ein geringer oder gar kein Unterschied in der Rate der kompletten Abheilung zwischen systemischem Ivermectin und Ivermectin 1% (RR 0,99, 95-%-KI 0,95 bis 1,03; 272 Studienteilnehmer, 2 Studien; Evidenz von moderater Vertrauenswürdigkeit).

In ähnlicher Weise gibt es vermutlich nach vier Wochen nur einen geringen oder gar keinen Unterschied in der Rate der kompletten Abheilung im Vergleich von Ivermectin 1% Lotion und Permethrin 5% Creme (RR 1,02, 95-%-KI 0,96 bis 1,08; 210 Studienteilnehmer, 1 Studie; Evidenz von moderater Vertrauenswürdigkeit) bzw. im Vergleich von ein und zwei Dosen systemischem Ivermectin (RR 0,97, 95-%-KI 0,83 bis 1,14; 80 Studienteilnehmer, 1 Studie; Evidenz von hoher Vertrauenswürdigkeit).

Die Berichterstattung bezogen auf die Medikamentensicherheit war im Allgemeinen suboptimal. Nach zwei Wochen gab es keine Studienabbrüche aufgrund von unerwünschten Ereignissen im Vergleich von systemischem Ivermectin und Permethrin 5% Lotion (120 Studienteilnehmer, 1 Studie; Evidenz von moderater Vertrauenswürdigkeit).

Ebenfalls, nach vier Wochen gab es keine Studienabbrüche aufgrund von unerwünschten Ereignissen im Vergleich von systemischem Ivermectin und Permethrin 5% Creme (305 Studienteilnehmer, 3 Studien; Evidenz von moderater Vertrauenswürdigkeit).

Nach zwei Wochen gibt es vermutlich keinen Unterschied in der Anzahl der Studienteilnehmer mit ≥ 1 unerwünschten Ereignis (UE) bei systemischem Ivermectin und Permethrin Creme (55 Studienteilnehmer, 1 Studie; Evidenz von moderater Vertrauenswürdigkeit). Jedoch führt Ivermectin nach vier Wochen vermutlich zu einer etwas höheren Anzahl an Studienteilnehmern mit ≥ 1 UE (RR 1,30, 95-%-KI 0,35 bis 4,83; 502 Studienteilnehmer, 4 Studien; Evidenz von niedriger Vertrauenswürdigkeit).

Unerwünschte Ereignisse bei Studienteilnehmern behandelt mit topischem Ivermectin waren selten und vergleichbar mit denen bei systemischem Ivermectin. Zudem ist unklar, ob es einen Unterschied in der Anzahl der Studienteilnehmer mit ≥ 1 UE gibt (RR 5,05, 95-%-KI 0,25 bis 103,87; 201 Studienteilnehmer, 1 Studie; Evidenz von sehr niedriger Vertrauenswürdigkeit). Studienabbrüche aufgrund von UE traten nicht auf (62 Studienteilnehmer, 1 Studie, Evidenz von moderater Vertrauenswürdigkeit).

Ebenfalls ist unklar, ob Ivermectin 1% Lotion und Permethrin 5% Creme nach vier Wochen zu einer unterschiedlichen Anzahl von Studienteilnehmern mit ≥ 1 UE führen (RR 0,33, 95-%-KI 0,01 bis 7,93; 200 Studienteilnehmer, 1 Studie; Evidenz von sehr niedriger Vertrauenswürdigkeit).

Alle Ergebnisse und Metaanalysen der einzelnen Endpunkte und Erhebungszeiträume sind im Abschnitt ‚Effects of interventions' auf den Seiten 20 bis 33 der Publikation ausführlich dargestellt.

Diskussion

Es wurde ein systematischer Review zur Therapie der Skabies mit Permethrin sowie topischem und systemischem Ivermectin durchgeführt. Zusammenfassend ist zu sagen, dass die Unterschiede in der Wirksamkeit, der Anzahl der Teilnehmer mit ≥ 1

unerwünschten Ereignis und die Anzahl der Studienabbrüche aufgrund von unerwünschten Ereignissen gering waren.
Außer der Überlegenheit in der Wirksamkeit von Permethrin 5% Creme nach einer Woche gegenüber systemischem Ivermectin konnten keine anderen Wirkungsunterschiede festgestellt werden. Unsere Ergebnisse erlauben keinen Rückschluss auf den Wirkungseintritt von topischer im Vergleich zu systemischer Therapie, da dies nicht direkt untersucht wurde.
Im Allgemeinen können systemische und topische Medikamente zu verschiedenen Arten von Nebenwirkungen führen. In den eingeschlossenen Studien scheinen nur sehr wenige unerwünschte Ereignisse aufgetreten zu sein; die Berichterstattung diesbezüglich war jedoch suboptimal. Selbst in Studien, in denen die Medikation mehrfach verabreicht wurde, wurden keine höheren Zahlen an unerwünschten Ereignissen berichtet. Hinzu kommt, dass weder unter systemischem Ivermectin noch unter Permethrin oder topischem Ivermectin Studienabbrüche aufgrund von unerwünschten Ereignissen berichtet wurden.

Die Übertragbarkeit der Studienergebnisse auf westliche Länder und die externe Validität ist insofern limitiert, da die Studien ausschließlich in Regionen mit hoher Skabies-Prävalenz durchgeführt wurden. Die meisten der eingeschlossenen Studien wurden in Ländern mit niedrigem bis mittlerem Einkommen (Indien, Pakistan und Ägypten) durchgeführt. Alle Studien wurden in ressourcenarmen Ländern mit einer jeweils kleinen Anzahl an Studienteilnehmern pro Studiengruppe durchgeführt. Die eingeschlossenen Studien waren inkonsistent in ihren Beschreibungen sowie den Definitionen und Bewertungen der Rate der kompletten Abheilung. Keine der Studien erläuterte zudem die wissenschaftliche Grundlage für die a priori definierten Häufigkeiten der Anwendung der Medikationen, die sich stark unterschieden.

Wir haben die Vertrauenswürdigkeit der vorliegenden Evidenz nach dem GRADE-Ansatz bewertet und die Ergebnisse in fünf sogenannten "Summary of findings"-Tabellen dargestellt. Eine ungenügende methodische Qualität der Studien und eine unzureichende Präzision der Ergebnisse waren Hauptgründe für die Herabstufung der Vertrauenswürdigkeit. In zwei Metaanalysen besteht substantielle Heterogenität in den Studienergebnissen. Durchgeführte Sensitivitätsanalysen konnten jedoch nicht dazu beitragen deren Ursache zu erklären. Das Vertrauen in diese Ergebnisse ist daher eingeschränkt.

Da alle Studien in ressourcenarmen Ländern durchgeführt wurden, kann nicht ausgeschlossen werden, dass weitere Studien durchgeführt, aber nicht veröffentlicht oder nicht durch unsere umfassenden Recherchen identifiziert wurden. Ein Fünftel der eingeschlossenen Studien wurden nicht durch die systematische Literaturrecherche, sondern durch eine Internetrecherche bzw. dem Sichten der Referenzlisten eingeschlossener Studien identifiziert. Publikationsbias kann somit nicht ausgeschlossen werden.
Ebenfalls ist unklar, welchen Einfluss die drei ausgeschlossenen iranischen Studien - deren Validität fragwürdig ist - auf die Ergebnisse dieses Reviews hätten.
Eine tiefgründige Diskussion der Ergebnisse findet sich im Abschnitt ‚Discussion' auf den Seite 34 bis 36 der Publikation.

Schlussfolgerungen

Topisches Permethrin, topisches Ivermectin und systemisches Ivermectin sind sehr wirksam bei der Behandlung von Skabies. In den identifizierten Studien konnten keine relevanten Wirkungsunterschiede festgestellt werden. Berichtete unerwünschte Ereignisse waren selten und von milder Intensität. Die individuelle Wahl der Therapie ist daher von der Praktikabilität, der Verfügbarkeit, der Arzneimittelzulassung sowie der jeweiligen Kosten abhängig.
Permethrin und topisches Ivermectin sind für Patientinnen und Patienten geeignet, bei denen die korrekte Anwendung am ganzen Körper gewährleistet werden kann. Alternativ kann systemisches Ivermectin verabreicht werden; vor allem bei der Behandlung von großen Patientengruppen.
In der deutschen S1-Leitlinie werden Empfehlungen für unterschiedliche Patientengruppen ausgesprochen [17]. Systemisches Ivermectin ist z. B. während der Schwangerschaft oder bei Kindern mit einem Körpergewicht unter 15 kg nicht indiziert.
Wahrscheinlich ist für die meisten Patientinnen und Patienten eine einmalige Behandlung ausreichend. Das Ausmaß der Erkrankung, die Anzahl der infizierten Kontaktpersonen, der Immunstatus sowie das klinische Ansprechen während der Nachbeobachtung können jedoch eine zweite Anwendung erforderlich machen.

Die Vertrauenswürdigkeit in die gefundene Evidenz ist u. a. aufgrund suboptimaler Studiendurchführung, -design oder -berichterstattung eingeschränkt. Randomisierte kontrollierte Studien mit guter methodischer Qualität, die entsprechend aktueller Standards (z. B. CONSORT) berichtet werden, sind notwendig um das Verzerrungspotenzial zu verringern und die Evidenzbasis zu verbessern.

Die Frage der wiederholten Behandlung (wann und wie oft) kann nicht abschließend beantwortet werden. Hierfür sind weitere Studien mit klaren und strikteren Behandlungsschemata erforderlich. Ebenfalls traten unerwünschte Ereignisse in den eingeschlossenen Studien selten auf und waren schlecht berichtet. Studien mit einer größeren Stichprobe und einer besseren Dokumentation und Klassifizierung der unerwünschten Ereignisse könnten hier weitere Daten liefern.

Vereinzelt gibt es Diskussionen über Resistenzen gegen Skabizide. Bekannte Fälle sind aber regional begrenzt und die Evidenz hierzu rar. In Zukunft könnten Studien, die die Resistenzentwicklung untersuchen notwendig sein.

Fragen der öffentlichen Gesundheit wie Massenmedikation zur Prävention und Behandlung von Skabies waren nicht Bestandteil dieser Arbeit, könnten aber Teil weiterer Forschung sein.

Details zu den Schlussfolgerungen finden sich im Abschnitt ‚Authors' conclusions' auf Seite 36 der Publikation.

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3 Eidesstattliche Versicherung und Anteilserklärung

Eidesstattliche Versicherung

„Ich, Stefanie Rosumeck, versichere an Eides statt durch meine eigenhändige Unterschrift, dass ich die vorgelegte Dissertation mit dem Thema: "Ivermectin and permethrin for treating scabies“ selbstständig und ohne nicht offengelegte Hilfe Dritter verfasst und keine anderen als die angegebenen Quellen und Hilfsmittel genutzt habe.
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Mein Anteil an der ausgewählten Publikation entspricht dem, der in der untenstehenden gemeinsamen Erklärung mit dem Betreuer, angegeben ist. Sämtliche Publikationen, die aus dieser Dissertation hervorgegangen sind und bei denen ich Autor bin, entsprechen den URM (s.o.) und werden von mir verantwortet.
Die Bedeutung dieser eidesstattlichen Versicherung und die strafrechtlichen Folgen einer unwahren eidesstattlichen Versicherung (§156,161 des Strafgesetzbuches) sind mir bekannt und bewusst.“

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Datum Unterschrift

Ausführliche Anteilserklärung an der erfolgten Publikation

Rosumeck S, Nast A, Dressler C.
Ivermectin and permethrin for treating scabies.
Cochrane Database of Systematic Reviews 2018, Issue 4. Art. No.: CD012994.
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Entsprechend der methodischen Vorgaben der ‚Cochrane editorial base' wurden die untenstehenden Punkte 3, 7 und 8 von zwei Autorinnen (Stefanie Rosumeck und Corinna Dressler) jeweils selbständig und unabhängig voneinander durchgeführt. Die weiteren Punkte wurden von der Doktorandin eigenständig erbracht:

1. Erstellung des Protokolls und Registrierung bei PROSPERO.
2. Kontaktperson für die ‚editorial base' der Cochrane Infectious Diseases Group und Koordination der jeweiligen Beiträge der Co-Autoren.
3. Identifizierung geeigneter Studien aus den Ergebnissen der elektronischen Literaturrecherchen, die von der Cochrane ‚editorial base' durchgeführt wurden.
4. Identifizierung geeigneter Artikel bzw. Abstracts aus den Referenzlisten der eingeschlossenen Studien.
5. Volltext-Beschaffung der eingeschlossenen Studien.
6. Korrespondenz mit Autoren zur Beschaffung fehlender Daten und Informationen.
7. Überprüfung und Bewertung der methodischen Qualität der eingeschlossenen Studien anhand des ‚Cochrane Risk of Bias Tool'.
8. Bewertung der Qualität der Evidenz anhand der GRADE-Methodik (Grading of Recommendations Assessment, Development and Evaluation).
9. Systematische Datenextraktion aus den eingeschlossenen Studien mithilfe von Review Manager (RevMan) und Microsoft Word.
10. Analyse und Interpretation der extrahierten Daten und Ergebnisse.
11. Überarbeitung des Abschnitts Hintergrund basierend auf Strong 2007.
12. Inhaltliche Ausarbeitung und schriftliches Verfassen der Abschnitte Abstract, Plain language summary, Methodik, Ergebnisse und Diskussion.
13. Beantwortung und Bearbeitung der Fragen der Cochrane-Gutachter.

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Unterschrift der Doktorandin

4 Auszug aus der Journal Summary List (ISI Web of Knowledge)

Journal Data Filtered By: **Selected JCR Year: 2016** Selected Editions: SCIE,SSCI
Selected Categories: **"MEDICINE, GENERAL and INTERNAL"**
Selected Category Scheme: WoS
Gesamtanzahl: 154 Journale

Rank	Full Journal Title	Total Cites	Journal Impact Factor	Eigenfactor Score
1	NEW ENGLAND JOURNAL OF MEDICINE	315,143	72.406	0.700770
2	LANCET	214,732	47.831	0.404930
3	JAMA-JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION	141,015	44.405	0.280910
4	BMJ-British Medical Journal	100,535	20.785	0.160310
5	ANNALS OF INTERNAL MEDICINE	53,770	17.135	0.099970
6	JAMA Internal Medicine	8,760	16.538	0.057200
7	PLOS MEDICINE	22,665	11.862	0.059550
8	Journal of Cachexia Sarcopenia and Muscle	1,310	9.697	0.003780
9	BMC Medicine	9,765	7.901	0.039390
10	JOURNAL OF INTERNAL MEDICINE	9,903	7.598	0.017500
11	CANADIAN MEDICAL ASSOCIATION JOURNAL	13,176	6.784	0.018580
12	MAYO CLINIC PROCEEDINGS	12,492	6.686	0.024640
13	Nature Reviews Disease Primers	315	6.389	0.001330
14	Cochrane Database of Systematic Reviews	54,740	6.124	0.166300
15	AMERICAN JOURNAL OF MEDICINE	24,050	5.550	0.026830
16	ANNALS OF FAMILY MEDICINE	4,266	4.917	0.010810
17	Translational Research	2,992	4.652	0.008560
18	Deutsches Arzteblatt International	3,124	4.257	0.007190
19	PALLIATIVE MEDICINE	4,309	4.220	0.007430
20	AMERICAN JOURNAL OF PREVENTIVE MEDICINE	18,936	4.020	0.042310
21	ANNALS OF MEDICINE	4,194	3.715	0.007100
22	JOURNAL OF GENERAL INTERNAL MEDICINE	16,296	3.701	0.028930

Selected JCR Year: 2016; Selected Categories: "MEDICINE, GENERAL und INTERNAL"

5 Druckexemplar der Publikation

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[Intervention Review]

Ivermectin and permethrin for treating scabies

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ABSTRACT

Background

Scabies is an intensely itchy parasitic infection of the skin. It occurs worldwide, but is particularly problematic in areas of poor sanitation, overcrowding, and social disruption. In recent years, permethrin and ivermectin have become the most relevant treatment options for scabies.

Objectives

To assess the efficacy and safety of topical permethrin and topical or systemic ivermectin for scabies in people of all ages.

Search methods

We searched the following databases up to 25 April 2017: the Cochrane Infectious Diseases Group Specialized Register, CENTRAL, MEDLINE, Embase, LILACS, and IndMED. We searched the World Health Organization International Clinical Trials Registry Platform, the ISRCTN registry, CenterWatch Clinical Trials Listing, ClinicalTrials.gov, TrialsCentral, and the UK Department of Health National Research Register for ongoing trials. We also searched multiple sources for grey literature and checked reference lists of included studies for additional trials.

Selection criteria

We included randomized controlled trials that compared permethrin or ivermectin against each other for people with scabies of all ages and either sex.

Data collection and analysis

Two review authors independently screened the identified records, extracted data, and assessed the risk of bias for the included trials.

The primary outcome was complete clearance of scabies. Secondary outcomes were number of participants re-treated, number of participants with at least one adverse event, and number of participants withdrawn from study due to an adverse event.

We summarized dichotomous outcomes using risk ratios (RR) with 95% confidence intervals (CI). If it was not possible to calculate the point estimate, we described the data qualitatively. Where appropriate, we calculated combined effect estimates using a random-

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effects model and assessed heterogeneity. We calculated numbers needed to treat for an additional beneficial outcome when we found a difference.

We assessed the certainty of the evidence using the GRADE approach. We used the control rate average to provide illustrative clearance rates in the comparison groups.

Main results

Fifteen studies (1896 participants) comparing topical permethrin, systemic ivermectin, or topical ivermectin met the inclusion criteria. Overall, the risk of bias in the included trials was moderate: reporting in many studies was poor. Nearly all studies were conducted in South Asia or North Africa, where the disease is more common, and is associated with poverty.

Efficacy

Oral ivermectin (at a standard dose of 200 μg/kg) may lead to slightly lower rates of complete clearance after one week compared to permethrin 5% cream. Using the average clearance rate of 65% in the trials with permethrin, the illustrative clearance with ivermectin is 43% (RR 0.65, 95% CI 0.54 to 0.78; 613 participants, 6 studies; *low-certainty evidence*). However, by week two there may be little or no difference (illustrative clearance of permethrin 74% compared to ivermectin 68%; RR 0.91, 95% CI 0.76 to 1.08; 459 participants, 5 studies; *low-certainty evidence*). Treatments with one to three doses of ivermectin or one to three applications of permethrin may lead to little or no difference in rates of complete clearance after four weeks' follow-up (illustrative cures with 1 to 3 applications of permethrin 93% and with 1 to 3 doses of ivermectin 86%; RR 0.92, 95% CI 0.82 to 1.03; 581 participants, 5 studies; *low-certainty evidence*).

After one week of treatment with oral ivermectin at a standard dose of 200 μg/kg or one application of permethrin 5% lotion, there is probably little or no difference in complete clearance rates (illustrative cure rates: permethrin 73%, ivermectin 68%; RR 0.93, 95% CI 0.74 to 1.17; 120 participants, 1 study; *moderate-certainty evidence*). After two weeks of treatment, one dose of systemic ivermectin compared to one application of permethrin lotion may lead to similar complete clearance rates (extrapolated cure rates: 67% in both groups; RR 1.00, 95% CI 0.78 to 1.29; 120 participants, 1 study; *low-certainty evidence*).

There is probably little or no difference in rates of complete clearance between systemic ivermectin at standard dose and topical ivermectin 1% lotion four weeks after initiation of treatment (illustrative cure rates: oral ivermectin 97%, ivermectin lotion 96%; RR 0.99, 95% CI 0.95 to 1.03; 272 participants, 2 studies; *moderate-certainty evidence*). Likewise, after four weeks, ivermectin lotion probably leads to little or no difference in rates of complete clearance when compared to permethrin cream (extrapolated cure rates: permethrin cream 94%, ivermectin lotion 96%; RR 1.02, 95% CI 0.96 to 1.08; 210 participants, 1 study; *moderate-certainty evidence*), and there is little or no difference among systemic ivermectin in different doses (extrapolated cure rates: 2 doses 90%, 1 dose 87%; RR 0.97, 95% CI 0.83 to 1.14; 80 participants, 1 study; *high-certainty evidence*).

Safety

Reporting of adverse events in the included studies was suboptimal. No withdrawals due to adverse events occurred in either the systemic ivermectin or the permethrin group (*moderate-certainty evidence*). Two weeks after treatment initiation, there is probably little or no difference in the proportion of participants treated with systemic ivermectin or permethrin cream who experienced at least one adverse event (55 participants, 1 study; *moderate-certainty evidence*). After four weeks, ivermectin may lead to a slightly larger proportion of participants with at least one adverse event (extrapolated rates: permethrin 4%, ivermectin 5%; RR 1.30, 95% CI 0.35 to 4.83; 502 participants, 4 studies; *low-certainty evidence*).

Adverse events in participants treated with topical ivermectin were rare and of mild intensity and comparable to those with systemic ivermectin. For this comparison, it is uncertain whether there is any difference in the number of participants with at least one adverse event (*very low-certainty evidence*). No withdrawals due to adverse events occurred (62 participants, 1 study; *moderate-certainty evidence*).

It is uncertain whether topical ivermectin or permethrin differ in the number of participants with at least one adverse event (*very low-certainty evidence*). We found no studies comparing systemic ivermectin in different doses that assessed safety outcomes.

Authors' conclusions

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.

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PLAIN LANGUAGE SUMMARY

Ivermectin and permethrin for treating scabies

What is the aim of this review?

The aim of this Cochrane Review was to assess the efficacy and safety of topical permethrin and topical or systemic ivermectin for scabies in people of all ages. We searched for all relevant studies to answer this question and found 15 studies, which we collected and analysed.

Key messages

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 of studies was a major limitation.

Additional high-certainty studies are needed to strengthen the confidence in the results and improve the evidence base.

What was studied in the review?

Scabies is an intensely itchy parasitic infection of the skin. It occurs throughout the world, but is particularly problematic in areas of poor sanitation, overcrowding, and social disruption. In recent years, permethrin and ivermectin have become the most relevant treatment options for scabies.

We examined topical permethrin, topical ivermectin, and systemic ivermectin as a treatment for scabies in women and men of all ages. We assessed efficacy as complete clearance of skin lesions at different time points after the start of the treatment. Other outcomes were the number of participants re-treated, the number of participants with at least one adverse event, and the number of participants who stopped participating in the study because they experienced an adverse event.

What are the main results of the review?

We found 15 relevant studies. Nearly all studies were set in South Asia or North Africa. These studies compared systemic ivermectin with topical permethrin, topical ivermectin with topical permethrin, or systemic ivermectin with topical ivermectin to treat people with scabies. All studies were conducted at a single centre with mostly small numbers of participants per study group.

Oral ivermectin may lead to slightly lower rates of complete clearance after one week compared to permethrin cream (*low-certainty evidence*), but little or no difference in rates of complete clearance by week two (*low-certainty evidence*). Treatments with one to three doses of ivermectin or one to three applications of permethrin may lead to little or no difference in rates of complete clearance after four weeks (*low-certainty evidence*).

There is probably little or no difference in complete clearance rates after one week of treatment with oral ivermectin or one application of permethrin lotion (*moderate-certainty evidence*).

There is probably little or no difference in rates of complete clearance between systemic ivermectin at standard dose and topical ivermectin lotion four weeks after initiation of treatment (*moderate-certainty evidence*). Likewise, after four weeks, ivermectin lotion probably leads to little or no difference in rates of complete clearance when compared to permethrin cream (*moderate-certainty evidence*), and there is little or no difference among treatments with systemic ivermectin in different doses (*high-certainty evidence*).

No participants in the systemic ivermectin or the permethrin group stopped participating in the study because they experienced an adverse event (*moderate-certainty evidence*). Two weeks after treatment initiation, there is probably little or no difference in the proportion of participants treated with systemic ivermectin or permethrin cream who experienced at least one adverse event (*moderate-certainty evidence*). After four weeks, ivermectin may lead to a slightly larger proportion of participants with at least one adverse event (*low-certainty evidence*).

Adverse events in participants treated with topical ivermectin were rare and of mild intensity and comparable to those with systemic ivermectin. For this comparison, it is uncertain whether there is any difference in the number of participants with at least one adverse event (*very low-certainty evidence*). No participants in the topical or systemic ivermectin group stopped participating in the study because they experienced an adverse event (*moderate-certainty evidence*).

It is uncertain whether topical ivermectin and permethrin differ in the number of participants with at least one adverse event (*very low-certainty evidence*). We found no studies comparing one dose versus two doses of systemic ivermectin that assessed safety outcomes.

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How up-to-date is this review?

We searched for studies published up to 25 April 2017.

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SUMMARY OF FINDINGS FOR THE MAIN COMPARISON *[Explanation]*

Oral ivermectin 200 μg/kg (1 to 3 doses) compared to topical permethrin 5% cream (1 to 3 applications) for treating scabies

Patient or population: people with scabies, 2 to 80 years of age
Location: India, Pakistan
Intervention: oral ivermectin 200 μg/kg
Comparison: topical permethrin 5% cream

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Number of participants (trials)	Certainty of the evidence (GRADE)	Comments
	Risk with permethrin 5% cream	Risk with ivermectin 200 μg/kg				
Complete clearance - week 1	654 per 1000	425 per 1000 (353 to 510)	RR 0.65 (0.54 to 0.78)	613 (6 RCTs)[1]	⊕⊕◯◯ LOW[2,3]	-
Complete clearance - week 2	744 per 1000	677 per 1000 (565 to 804)	RR 0.91 (0.76 to 1.08)	459 (5 RCTs)[4]	⊕⊕◯◯ LOW[2,5]	In 1 study non-responders were re-treated after 1 week; in 1 study 44.44% of participants (IVER) and 17.86% of participants (PER) were re-treated after 1 week (absolute numbers are unclear)
Complete clearance - week 4 - IVER 1 dose versus PER 1 application	900 per 1000	900 per 1000 (774 to 1000)	RR 1.00 (0.86 to 1.16)	80 (1 RCT)[6]	⊕⊕⊕⊕ HIGH	-
Complete clearance - week 4 - IVER 1 to 3 doses versus PER 1 to 3 applications	932 per 1000	857 per 1000 (764 to 959)	RR 0.92 (0.82 to 1.03)	581 (5 RCTs)[7]	⊕⊕◯◯ LOW[2,8]	In 3 studies non-responders were re-treated once; in 1 study non-responders were re-

						treated after 2 and/or 3 weeks (absolute numbers are unclear); in 1 study 12 participants (IVER) and 1 participant (PER) were re-treated after 2 weeks
Complete clearance - week 4 - IVER 2 doses versus PER 1 application	900 per 1000	873 per 1000 (747 to 1000)	RR 0.97 (0.83 to 1.14)	80 (1 RCT)[6]	⊕⊕⊕⊕ HIGH	-
Number of participants with ≥ 1 AE - week 2	0 per 1000	0 per 1000 (0 to 0)	Not estimable	55 (1 RCT)[9]	⊕⊕⊕◯ MODERATE[2]	0 events; 44.44% of participants (IVER) and 17.86% of participants (PER) were re-treated after 1 week (absolute numbers are unclear)
Number of participants with ≥ 1 AE - week 4	39 per 1000	51 per 1000 (14 to 190)	RR 1.30 (0.35 to 4.83)	502 (4 RCTs)[10]	⊕⊕◯◯ LOW[2,11]	In 1 study non-responders were re-treated after 2 weeks; in 1 study non-responders were re-treated after 2 and 3 weeks; in 1 study participants in IVER group were re-treated (absolute numbers are unclear)
Withdrawal due to AE - week 4	See comment	See comment	-	305 (3 RCTs)[12]	⊕⊕⊕◯ MODERATE[2]	0 events; in 1 study non-responders were re-treated after 1 week (absolute numbers are unclear); in 1 study 12 participants (IVER)

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				and 1 participant (PER) were re-treated after 2 weeks

*__The risk in the intervention group__ (and its 95% CI) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).
Abbreviations: AE: adverse event; **CI:** confidence interval; **IVER:** ivermectin; **PER:** permethrin; **RCT:** randomized controlled trial; **RR:** risk ratio.

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

[1]Usha 2000; Bachewar 2009; Sharma 2011; Rohatgi 2013; Meenakshi 2014; Wankhade 2016.
[2]Downgraded by 1 for serious risk of bias: assessed as moderate.
[3]Downgraded by 1 for serious imprecision: CI crosses minimal clinically important difference threshold: statistically significant difference of uncertain clinical importance.
[4]Usha 2000; Bachewar 2009; Mushtaq 2010; Sharma 2011; Rohatgi 2013.
[5]Downgraded by 1 for serious inconsistency: I^2 = 61% (P = 0.04).
[6]Sharma 2011.
[7]Usha 2000; Mushtaq 2010; Chhaiya 2012; Rohatgi 2013; Wankhade 2016.
[8]Downgraded by 1 for serious inconsistency: I^2 = 74% (P = 0.004).
[9]Bachewar 2009.
[10]Mushtaq 2010; Sharma 2011; Chhaiya 2012; Wankhade 2016.
[11]Downgraded by 1 for serious imprecision: CI crosses line of no effect and minimal clinically important difference thresholds: uncertain whether there is any difference.
[12]Usha 2000; Manjhi 2014; Wankhade 2016.

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BACKGROUND

This section is based on Strong 2007.

Description of the condition

Scabies is an intensely itchy parasitic infection of the skin that is caused by the *Sarcoptes scabiei* mite. It occurs worldwide, but is particularly problematic in areas of poor sanitation, overcrowding, and social disruption. The global prevalence of scabies ranges from 0.2% to 71.4%, with large variations in geographical region (Romani 2015a). Highest scabies prevalence is noted in Pacific and Central/South American regions. Children are particularly affected (Romani 2015a); for example, in Germany, infectious disease surveillance data on centralized homes for asylum seekers from 2004 to 2014 revealed 119 outbreaks. Of 615 people diagnosed with an infectious disease, 19% had scabies (Kühne 2016). The Global Burden of Disease Study 2015 concluded that 0.21% of all disability-adjusted life-years were caused by scabies worldwide (Karimkhani 2017).

In resource-rich communities, scabies tends to occur in cyclical epidemics, particularly within institutional living situations such as nursing homes (Scheinfeld 2004), or the army (Mimouni 1998; Mimouni 2003). There is some seasonal variation, with incidence being greater in the winter than in the summer, perhaps related to a tendency of indoor overcrowding, as well as increased mite survival in colder weather (Downs 1999; Hay 2012). In resource-poor communities, the occurrence pattern is quite different, with the disease being endemic in many areas (Chosidow 2000). The prevalence of infections in a community is potentially influenced by changes in social attitudes, population movements, wars, misdiagnosis, inadequate treatment, and changes in the immune status of the population. Scabies infestation represents a considerable burden of ill health in many communities, and although the disease is rarely life-threatening, it causes widespread debilitation and misery (Green 1989).

The *S scabiei* life cycle begins with the pregnant female laying two to three eggs a day in burrows several millimetres to several centimetres in length in the stratum corneum (outermost layer) of the skin. After about 50 to 72 hours, larvae emerge and make new burrows. They mature, mate, and repeat this 10- to 17-day cycle. Mites usually live for 30 to 60 days (Green 1989). Mites survive for up to three days outside of the human body (CDC 2017a).

Humans are the main reservoir for *S scabiei* var. *hominis* (variety of the mite named to reflect the main host species). Scabies is usually spread person to person via direct skin contact, including sexual contact, though transfer via inanimate objects such as clothing or furnishings is also possible (Hay 2004). The mite can burrow beneath the skin within 2.5 minutes, though around 20 minutes is more usual (Alexander 1984). The level of infectiousness of an individual depends in part on the number of mites harboured, which can vary from just a single mite to millions (Chosidow 2000).

Humans can also be transiently infected by the genetically distinct animal varieties of *S scabiei* (for example, var. *canis*), though cross-infectivity is low (Fain 1978; Walton 2004a).

Clinical infection with the scabies mite causes discomfort and often intense itching of the skin, particularly at night, with irritating papular or vesicular eruptions. While infestation with the scabies mite is not life-threatening, the severe, persistent itch debilitates and depresses people (Green 1989). The classical sites of infestation are between the fingers, the wrists, axillary areas, female breasts (particularly the skin of the nipples), peri-umbilical area, penis, scrotum, and buttocks. Infants are usually affected on the face, scalp, palms, and soles of the feet. Much of the itching associated with scabies is a result of the host immune reaction, and symptoms can take several weeks to appear after initial infection in a person exposed to scabies for the first time. Symptoms appear after a much shorter interval (one to two days) after re-infestation (Arlian 1989).

A more severe or 'crusted' presentation of infestation is associated with extreme incapacity and with disorders of the immune system, such as HIV infection. Clinically this atypical form of scabies presents with a hyperkeratotic dermatosis resembling psoriasis. Lymphadenopathy and eosinophilia can be present, but itching may be unexpectedly mild. People with crusted scabies may harbour millions of mites and are highly infectious (Meinking 1995). The dermatological distribution of mites in such people is often atypical (for example, including the head), and treatment in hospital is advised (Chosidow 2000; Sunderkötter 2016).

Complications are few, although secondary bacterial infection of the skin lesions by group A *Streptococcus pyogenes* or *Staphylococcus aureus*, or both, can occur following repeated scratching, particularly in warmer climates (Meinking 1995). Secondary infection with group A *Streptococcus* can lead to acute glomerulonephritis, outbreaks of which have been associated with scabies (Green 1989; Hoy 2012; Hay 2013).

Diagnosis

Diagnosis on clinical grounds is usually made based on a history of itching (particularly if contacts are also affected) and the finding of lesions at the classical sites. The diagnosis can in most cases be confirmed by microscopically identifying a mite, egg, or mite faeces in a skin scraping, or by extracting a mite from a burrow (Chosidow 2000).

Description of the intervention

Various treatments are available for scabies. These include sulfur compounds, benzyl benzoate, crotamiton, hexachlorocyclohexane, malathion, permethrin, and ivermectin. A number of herbal remedies have also been proposed, including tea tree oil, lippia oil,

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T ointment, and kakawati poultice (Banez 1999; Oladimeji 2000; Alebiosu 2003; Walton 2004b; Oladimeji 2005).

In recent years, topical permethrin and oral ivermectin have become the most relevant treatment options for scabies (Banerji 2015; RKI 2016).

Topical permethrin 5% was first licensed in 1989 by the US Food and Drug Administration (Currie 2010). It was approved in Germany in October 2004 (Hamm 2006; InfectoScab 2016). In low- and middle-income countries such as India, where permethrin was approved for treating scabies in 1995 (CDSCO), the treatment is considered expensive, while oral ivermectin seems to be cheaper (Sharma 2011).

In contrast, oral ivermectin was first approved for the treatment of scabies in France in 2001 (Currie 2010); in the past few years it has been approved in Australia and the Netherlands (AusPAR 2013; Merck 2015). Oral ivermectin was approved for the treatment of scabies in Germany in February 2016 (Scabioral 2016), whereas in the USA it is still used off-label (CDC 2017b).

Topical ivermectin has also been investigated for the treatment of scabies in recent years due to the expected therapeutic efficacy. It is not approved for the treatment of scabies, but for treating head lice (0.5% lotion, FDA 2012) and inflammatory lesions of rosacea (1% cream, FDA 2014).

Systemic ivermectin is associated with adverse reactions such as nausea, rash, dizziness, itching, abdominal pain, and fever. Many of these symptoms may be an allergic reaction to the dead parasites rather than to ivermectin itself (Fawcett 2003). An increased risk of death amongst elderly patients in a long-term care facility has been reported with the use of ivermectin (Barkwell 1997). However, the validity of this report has been discussed considerably (Bredal 1997; Coyne 1997; Diazgranados 1997; Reintjes 1997), and its findings could not be confirmed by multiple subsequent studies.

Rare adverse reactions have been reported with the use of permethrin, including neck dystonia (Coleman 2005), pruritus, burning, and stinging (Fawcett 2003).

Prevention

Prevention is based on principles common to most infectious diseases, that is limitation of contact with the mite. An infested person can spread scabies even if no symptoms are present. The probability of transmission is highest with direct and close skin-to-skin contact and happens most frequently between family members. Linen used and worn three days before the start of treatment should be washed thoroughly to avoid spreading scabies (CDC 2017a). Contacts of cases are usually advised to treat themselves at the same time as the case in order to reduce the risk of re-exposure and re-infestation (Sunderkötter 2016).

How the intervention might work

Ivermectin is a broad-spectrum anthelmintic agent, which affects the nervous system of the scabies mite and causes its death (AusPAR 2013). Unlike permethrin, it is not ovicidal. Ivermectin is available as systemic antiscabies drug (200 µg/kg/dose; CDC 2017b). Permethrin is usually available as a 5% cream or 5% lotion. It is a synthetic pyrethroid, which kills the scabies mite and the eggs (CDC 2017b).

In general, permethrin is applied as 5% cream to all areas of the body from head/neck to toe. It is left on overnight or up to 24 hours and then rinsed off. Application is sometimes repeated once, about one to two weeks later. Children aged two months or older can also be treated (Currie 2010; Banerji 2015; CDC 2015; Sunderkötter 2016; CDC 2017b; Salavastru 2017).

Ivermectin is taken orally as a tablet with a dosage of 200 µg/kg body weight, usually once but sometimes a second time after one to two weeks. It has not been tested in pregnant or lactating woman and children weighing less than 15 kg. Furthermore, opinions diverge on whether the tablet should be taken with food or on an empty stomach (Currie 2010; Banerji 2015; CDC 2015; Sunderkötter 2016; CDC 2017b; Salavastru 2017).

A follow-up visit to determine whether the patient is cured should ideally occur one month after the initiation of treatment. This time allows for lesions to heal and for any eggs and mites to reach maturity in case the treatment did not work (that is, beyond the longest incubation interval). Patients should be advised that itching may persist for one to two weeks after treatment, even if the mite is successfully eradicated (Buffet 2003). Because of this delay in symptom relief, it may sometimes be difficult to distinguish re-infestation from primary treatment failure.

Why it is important to do this review

Apart from a non-Cochrane systematic review that considered several scabies treatments (Dressler 2016a), there is currently no systematic review focusing on the available evidence comparing ivermectin with permethrin. Using data from randomized controlled trials, this review summarizes and evaluates the existing evidence on the efficacy and safety of permethrin and ivermectin for scabies. We aimed to answer the following questions in relation to safety and efficacy.

- Is oral ivermectin superior to topical permethrin?
- Is oral ivermectin superior to topical ivermectin?
- Is topical ivermectin superior to topical permethrin?
- Is a single dose of oral ivermectin superior to multiple doses of oral ivermectin?

Global epidemics and an increasing number of asylum seekers due to the Middle Eastern population migration highlights the importance of this review to investigate and understand scabies interventions (Kühne 2016; Bloch-Infanger 2017).

A Cochrane Review on 'Interventions for treating scabies' was published in 2007 (Strong 2007). This includes an evaluation

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of crotamiton, lindane, sulfur, and benzyl benzoate; Strong 2007 and earlier published versions are listed in the 'Other published versions of this review' section.

OBJECTIVES

To assess the efficacy and safety of topical permethrin and topical or systemic ivermectin for scabies in people of all ages.

METHODS

Criteria for considering studies for this review

Types of studies

We only included randomized controlled trials (RCTs). We considered all study reports irrespective of their publication status and language of publication.

The review protocol was registered with PROSPERO International prospective register of systematic reviews in October 2016 (Rosumeck 2016). Very few changes have been made to the proposed methods; see the 'Differences between protocol and review' section.

Types of participants

Children or adults of both sexes with a diagnosis of classical scabies, as defined by the study authors.

Types of interventions

Intervention

- Topical permethrin.
- Topical ivermectin.
- Systemic ivermectin.

Control

- One of the above mentioned interventions.

Types of outcome measures

Primary outcomes

- Complete clearance (outcome assessment at 7, 14, and 30 days' post-initiation of treatment).

Secondary outcomes

- Number of people re-treated.
- Number of people with at least one adverse event (outcome assessment at the end of active study period).
- Number of people withdrawn from study due to adverse event (outcome assessment at the end of active study period).

Search methods for identification of studies

We attempted to identify all RCTs regardless of language or publication status (published, unpublished, in press, or in progress).

Electronic searches

Databases

We searched the following databases up to 25 April 2017 using the search terms and strategy described in Appendix 1: the Cochrane Infectious Disease Group Specialized Register; the Cochrane Central Register of Controlled Trials (CENTRAL, published in the Cochrane Library; Issue 4, 2017); MEDLINE (PubMed, from 1946); Embase Ovid (from 1974); LILACS (Latin American and Caribbean Center on Health Sciences Information) (lilacs.bvsalud.org/, from 1982), and IndMED (indmed.nic.in/, from 1985). We also searched EconLit (Economic Literature database, EBSCOHost, from 1993 to 26 July 2016) and ERIC (Education Resources Information Center, EBSCOHost, from 1966 to 26 July 2016).

Grey literature

We searched the following sources for published and unpublished trials up to 26 July 2016:

- British Library Index of Conference Proceedings (explorecatalogue.bl.uk/), search term: "scabies" AND ("trial" OR "study" OR "treatment");
- British Library for Development Studies (blds.ids.ac.uk/), search term: "scabies";
- BRIDGE (www.bridge.ids.ac.uk/), search term: "scabies";
- Social Care Online (www.scie-socialcareonline.org.uk/), search term: "scabies";
- Institute for Development Studies (www.ids.ac.uk/search), search term: "scabies";
- IIED (www.iied.org/), search term: "scabies"; and
- Science.gov (www.science.gov/), search term: "scabies" AND ("trial" OR "study" OR "treatment").

Trials registers

We searched the following sources for registered trials using the term "scabies" up to 25 April 2017:

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- World Health Organization International Clinical Trials Registry Platform (WHO ICTRP, apps.who.int/trialsearch);
- ISRCTN registry (www.isrctn.com);
- CenterWatch Clinical Trials Listing (www.centerwatch.com);
- US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (www.clinicaltrials.gov);
- TrialsCentral (www.trialscentral.org); and
- UK Department of Health National Research Register (www.nihr.ac.uk).

Searching other resources

Reference lists

We scanned the reference lists of all included RCTs for further studies.

Correspondence

We attempted to obtain unpublished data via e-mail correspondence with first authors if contact details were available or could be identified.

Data collection and analysis

Several of the following sections may be identical to parts of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

Selection of studies

Two review authors independently screened the titles and abstracts of all studies identified by the search to determine those that were potentially relevant. The full texts of all records assessed as eligible by at least one of the review authors were obtained. We read all available full texts to assess study eligibility according to the inclusion criteria.

We scrutinized the trial reports to ensure that multiple publications from the same trial were identified so that data were only included once (see the Characteristics of included studies table). Reasons for the exclusion of studies during the full-text screening phase are listed in the Characteristics of excluded studies table.

We illustrated the study selection process in a PRISMA flow diagram.

Data extraction and management

Two review authors (SR and CD) independently extracted data from the included trial reports using a standardized data extraction form (Microsoft Word). Items extracted include study characteristics, inclusion and exclusion criteria, baseline data, definition of outcomes, adverse events, and whether participants were re-treated. The form was piloted.

We extracted the number of participants randomized as well as the number of participants analysed for each study arm. For each dichotomous outcomes, we recorded the number of participants experiencing the event in each arm of the trial. If efficacy data were not reported using an intention-to-treat approach, we imputed these data employing a non-responder imputation approach for all intervention and control groups.

Where primary or secondary outcomes were measured at more than one time point, we aimed to extract all relevant data corresponding to 7, 14, and 30 days post-treatment initiation.

For one study, Usha 2000, we extracted percentages of participants achieving 'complete clearance of lesions' (graded as good improvement) from a graph using the Engauge Digitizer software (Engauge Digitizer). We converted the percentages into absolute numbers, as no withdrawals or dropouts were reported.

After comparing the extracted data and resolving any differences through discussion, one review author (SR) entered the data into Review Manager 5 (RevMan 5) (RevMan 2014), and a second review author (CD) checked the data for accuracy.

Assessment of risk of bias in included studies

For each included study, two review authors independently assessed the methodological quality using the Cochrane 'Risk of bias' assessment tool (Higgins 2011). We assessed the following seven domains.

- Random sequence generation.
- Allocation concealment.
- Blinding of participants and personnel.
- Blinding of outcome assessment.
- Completeness of outcome data.
- Selective reporting.
- Other sources of bias.

For each trial, to assess 'selection bias' we described the methods used to generate the randomization list and how the allocation was concealed; to assess 'performance and detection bias' we stated who was blinded and, if reported, how this was done. In order to assess 'attrition bias', we reported the number of participants lost to follow-up and the method study authors used to deal with missing data. If more than 10% of the participants were lost to follow-up in at least one of the study groups, and no imputation method was used to analyse the study outcomes, we evaluated the risk of bias as high. To assess 'reporting bias', we described any discrepancies between the methods section (planned measurements) and the results as reported in the included records. For the domain 'other bias', we have listed and assessed any other potential sources of bias that may have influenced the studies' results.

For each of the domains 'selection bias', 'reporting bias', and 'other bias', we made one assessment ('low risk', 'high risk', or 'unclear risk' of bias). For the domains 'performance bias', 'detection bias', and 'attrition bias', we made two assessments: one for all efficacy

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outcomes and one for all safety outcomes per study. Discrepancies in assessments were resolved by discussion.
Review authors' judgements about each 'Risk of bias' item for each included study are presented in the 'Risk of bias' summary figure.

Measures of treatment effect

We presented results as risk ratios (RRs) with corresponding 95% confidence intervals (CIs). If an outcome was positive (for example, clearance), RRs greater than one demonstrate a favourable outcome of the intervention of interest, and these were presented to the right of the line of no effect. In case of negative outcomes (for example, safety), RRs smaller than one demonstrate a favourable outcome of the intervention of interest (represented to the left of the line of no effect). We expressed all statistically significant results as numbers needed to treat for an additional beneficial outcome (NNTB) with 95% CIs (Christensen 2006).
To avoid the problem of multiplicity, we chose only one primary outcome and a limited number of secondary outcomes.

Unit of analysis issues

To avoid unit of analysis errors, we included every study only once in each comparison (for each outcome at each time point). We also used this approach for multi-arm studies given that for each comparison a single effect measure was calculated. This precluded the same group of participants being included more than once in the same meta-analysis.
In one comparison, we combined two arms of a three-arm study for the outcome 'complete clearance' (Sharma 2011). In both arms oral ivermectin 200 μg/kg body weight was administered on day one. After two weeks, participants in one of these arms received an additional dose of oral ivermectin. We considered both arms as treated equally and hence combined the number of events and participants when assessing the outcome after one and two weeks of treatment.

Dealing with missing data

For dichotomous efficacy data, we performed an intention-to-treat analysis. We imputed outcome data for the missing participants using a non-responder imputation approach for the intervention and the control groups, meaning that we assumed treatment failure for all missing participant data (conservative approach, Higgins 2011). Participants were analysed in the group to which they had been randomized. We specified the amount of imputed participant data as footnotes in the forest plots.
Some study authors reported insufficient information on safety outcomes. In such cases we reported data as presented by the study authors.
If there were inconsistencies within a publication regarding the reported data, we asked the author for clarification. We sent two e-mails if contact details were provided in the publication or if we were able to identify them elsewhere.

Assessment of heterogeneity

We assessed heterogeneity by visually inspecting forest plots, calculating an I^2 statistic, and carrying out a Chi^2 test for heterogeneity using RevMan 5 (RevMan 2014). If we detected heterogeneity (that is, I^2 statistic > 50%), we undertook subgroup or sensitivity analysis, or both, to explore the causes of the heterogeneity (Higgins 2011).
If heterogeneity was low or not detected, we pooled results from trials using a random-effects meta-analysis model, because we anticipated that the different studies would estimate different intervention effects (DerSimonian 1986; Higgins 2011).

Assessment of reporting biases

Had we included 10 or more studies comparing the same intervention, we would have evaluated a funnel plot. However, this was not the case, and we were unable to assess publication bias. We aimed at avoiding the introduction of other types of reporting bias at the systematic review level by conducting extensive searches and including all languages.

Data synthesis

We have summarized and presented qualitative information (for example, study design, description of participants, study groups, outcome measurements) in the Characteristics of included studies tables. We calculated RRs and 95% CIs using Review Manager 5 for each of the preselected outcomes and pooled data using a random-effects model if appropriate (RevMan 2014).
Where a meta-analysis could not be performed (for example, due to effects being reported as percentages only), we described the results in the text.

'Summary of findings' tables

For each assessed comparison we created a 'Summary of findings' table, which included an evaluation of the certainty of evidence according to the GRADE approach described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011; Schünemann 2013). Using the online tool GRADEpro GDT, we assessed the certainty of the evidence as either high, moderate, low, or very low (GRADEpro GDT). Randomized controlled trials start as high-certainty evidence and are rated down depending on the presence of study limitations (risk of bias), inconsistency, indirectness, imprecision, and publication bias.

Risk of bias

If most of the information was from studies with an overall assessment of moderate or high risk of bias, we downgraded one (serious limitations) or two levels (very serious limitations) (Guyatt 2011a).

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Inconsistency

We judged large and unexplained inconsistency based on similarity of point estimates and the extent of overlap of CIs. Depending on the magnitude of inconsistency in study results, we rated down by one or two levels (Guyatt 2011d).

Imprecision

We examined 95% CI for imprecision. If the confidence limit crossed the minimal clinically important difference thresholds, we downgraded one level. Minimal important difference represents the smallest difference between treatment groups for an outcome that clinicians or patients identify as meaningful. By default, these thresholds are 0.75 for appreciable harm and 1.25 for appreciable benefit. If both thresholds were crossed and CIs were wide, we downgraded the certainty by two levels (Guyatt 2011c).

Indirectness

We assessed differences in patient populations, (co-)interventions, and measurement of the outcomes of the pooled studies. Depending on the extent of differences, we downgraded one or two levels (Guyatt 2011e).

Publication bias

Due to the small number of studies pooled, it was inappropriate to evaluate a funnel plot. We rated the likelihood of publication bias based on study size and sponsorship. In case of publication bias, we rated down by one level (Guyatt 2011b).

We justified and documented our assessment in the 'Summary of findings' tables (that is, in case of downgrading) using footnotes.

Subgroup analysis and investigation of heterogeneity

Due to the different study designs with respect to drug dosing, we analysed subgroups according to the number of treatment doses - one, one to two, or two doses - for ivermectin 200 μg/kg body weight compared to permethrin 5% cream (for the outcome 'complete clearance' assessed after four weeks of treatment).

We investigated statistical heterogeneity by means of sensitivity analysis.

Sensitivity analysis

For two comparisons and outcomes, we conducted sensitivity analyses due to statistical heterogeneity. We could not identify meaningful groups of studies based on 'Risk of bias' assessments that would help explain the heterogeneity. We reported effect estimates excluding studies with slightly different treatment schemes or with a contrary result, separately (see Appendix 2).

RESULTS

Description of studies

Results of the search

The electronic searches (see Electronic searches) retrieved 692 references. We found another article coincidentally through a search of the Internet, which we included.

We screened the titles and abstracts of 441 records retrieved through database searches and assessed 19 full-text records for eligibility.

We screened the reference lists of already included trials and found three more potentially relevant studies, two of which met the inclusion criteria.

A total of 15 trials met the inclusion criteria of the review.

Trial register searches identified 17 further studies (including two duplicates); we could include one ongoing trial.

The study selection process can be seen in Figure 1.

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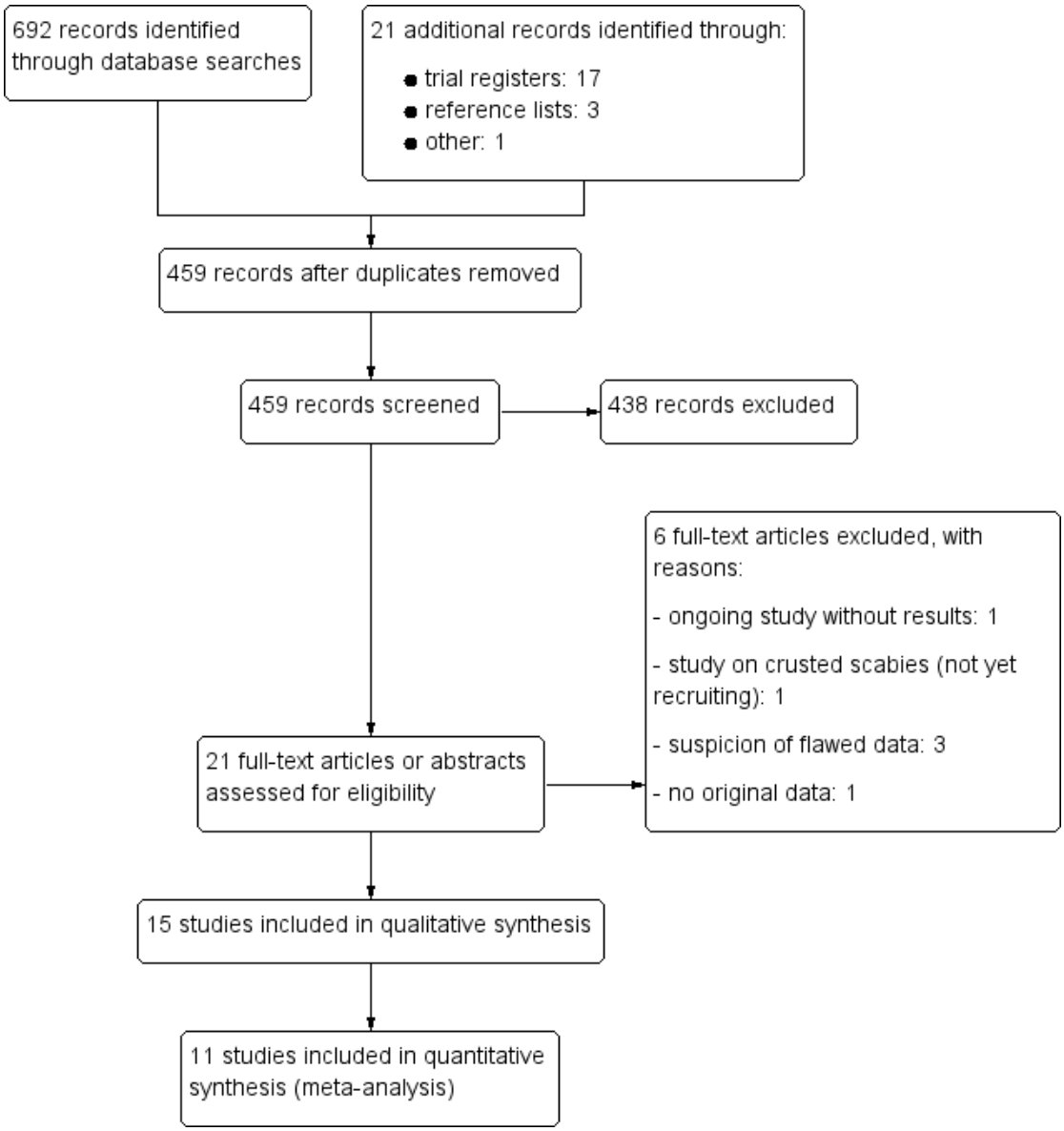
Figure 1. Study flow diagram.



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Included studies

We included 15 RCTs that investigated 1896 participants treated with ivermectin or permethrin. Details of all included studies are provided in the Characteristics of included studies tables.

We contacted the authors of six studies to obtain missing data or to clarify inconsistent information (Das 2006; Mushtaq 2010; Saqib 2012; Rohatgi 2013; Wankhade 2013; Manjhi 2014); the authors of two studies replied (Saqib 2012; Rohatgi 2013). Details are reported in the respective Characteristics of included studies tables.

Design

All included studies were parallel-group RCTs, and most were conducted as open-label trials. Participants and personnel were blinded to treatment assignment in only one study (Sharma 2011). In a second study, the outcome assessor was blinded (Saqib 2012). We assumed that all studies recruited participants from one centre, but this was not stated clearly in all study reports.

Seven studies compared two treatment groups. Five of these studies evaluated topical permethrin and systemic ivermectin (Usha 2000; Mushtaq 2010; Saqib 2012; Rohatgi 2013; Wankhade 2013); one study compared topical ivermectin with systemic ivermectin (Ahmad 2016); and the remaining study compared one versus three treatments of systemic ivermectin (Macotela-Ruiz 1996).

Five studies compared three treatment groups. One study investigated permethrin, systemic ivermectin, and topical ivermectin (Chhaiya 2012); one study compared permethrin with two different regimens of systemic ivermectin (Sharma 2011); and the remaining three studies investigated systemic ivermectin and permethrin as well as another treatment not addressed in this review (benzyl benzoate 25% lotion (Bachewar 2009); gamma benzene hexachloride 1% lotion (Meenakshi 2014); combination of topical permethrin and systemic ivermectin (Wankhade 2016)).

Three studies compared four treatment groups. Abdel-Raheem 2016 investigated topical permethrin and systemic ivermectin (plus two groups treated with sulfur ointment or benzyl benzoate cream not included in this review). Das 2006 also examined the effect of gamma benzene hexachloride 1% and included a placebo group. Manjhi 2014 investigated topical permethrin and systemic ivermectin (plus two groups treated with gamma benzene hexachloride 1% lotion or benzyl benzoate 20% lotion not included in this review).

In two studies, uncured participants were switched to another treatment (Usha 2000; Chhaiya 2012).

The oldest included study was conducted from 1993 to 1995 and was published in 1996 (Macotela-Ruiz 1996), while the three most recent ones were published in 2016 (Abdel-Raheem 2016; Ahmad 2016; Wankhade 2016).

Sample sizes

The sample size varied from 62, in Ahmad 2016, to 315, in Chhaiya 2012. In two studies the numbers of randomized participants per study group were not reported (Mushtaq 2010; Wankhade 2013).

Study settings

All studies took place in dermatological outpatient clinics/dermatological departments of medical colleges or hospitals.

Age

Eleven studies included children and adults, with an age range of two to 80 years (Usha 2000; Das 2006; Bachewar 2009; Mushtaq 2010; Sharma 2011; Chhaiya 2012; Manjhi 2014; Meenakshi 2014; Abdel-Raheem 2016; Ahmad 2016; Wankhade 2016).

Saqib 2012 included only adults aged 18 to 60. One trial enrolled only children from five to 15 years of age (Rohatgi 2013).

Only three studies reported the mean age at baseline of all included participants. In the study by Abdel-Raheem 2016, the mean age of the 200 participants who completed the study was 25.33 years (standard deviation (SD) 12.84). The mean age at baseline of the 62 randomized participants in the study by Ahmad 2016 was 21.8 years (SD 15). Macotela-Ruiz 1996 did not report the age of participants, but stated a mean age of 12 and 16 years for male and female participants, respectively, in the group treated with one dose of ivermectin 250 μg/kg body weight, and a mean age of 18 and 20 for male and female participants, respectively, in the three-dose group.

Another study by Wankhade 2013, which was available only as an abstract, did not report age.

Sex

All studies recruited both women and men. Eleven studies reported the proportion of female participants, including 639 women (45.22%) and 774 men (Macotela-Ruiz 1996; Usha 2000; Bachewar 2009; Mushtaq 2010; Sharma 2011; Chhaiya 2012; Rohatgi 2013; Meenakshi 2014; Abdel-Raheem 2016; Ahmad 2016; Wankhade 2016).

Geographical region

Ten studies were conducted in India (Usha 2000; Das 2006; Bachewar 2009; Sharma 2011; Chhaiya 2012; Rohatgi 2013;

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Wankhade 2013; Manjhi 2014; Meenakshi 2014; Wankhade 2016), two in Pakistan (Mushtaq 2010; Saqib 2012), two in Egypt (Abdel-Raheem 2016; Ahmad 2016), and one in Mexico (Macotela-Ruiz 1996).

Diagnosis of scabies

A detailed description of how scabies was diagnosed in each study is provided as part of the Characteristics of included studies tables. Diagnostic procedures differed greatly. In six studies clinical diagnosis was confirmed by microscopic examination (Das 2006; Chhaiya 2012; Saqib 2012; Rohatgi 2013; Abdel-Raheem 2016; Ahmad 2016). In the study by Wankhade 2016, participants were included based on clinical criteria, even when the microscopic examination was negative. In four studies scabies was diagnosed clinically only (Usha 2000; Bachewar 2009; Sharma 2011; Meenakshi 2014). In the study by Mushtaq 2010, only in cases of uncertainty confirmation of the clinical diagnosis was sought by an additional microscopic examination. Three studies did not report diagnostic procedures (Macotela-Ruiz 1996; Wankhade 2013; Manjhi 2014).

Interventions

Treatment duration, frequency, and formulation

The treatment frequency of permethrin ranged from a single application in most included studies (Usha 2000; Das 2006; Bachewar 2009; Mushtaq 2010; Sharma 2011; Chhaiya 2012; Saqib 2012; Rohatgi 2013; Wankhade 2013; Manjhi 2014; Wankhade 2016), to a single application daily on five days/nights in a row (Abdel-Raheem 2016). In one study, permethrin was applied on day one and again after one week (Meenakshi 2014).

Most of the included studies administered permethrin as a 5% cream (Usha 2000; Das 2006; Bachewar 2009; Mushtaq 2010; Sharma 2011; Chhaiya 2012; Rohatgi 2013; Manjhi 2014; Meenakshi 2014; Wankhade 2016). Two studies investigated permethrin as a lotion (Abdel-Raheem 2016: 5% for adults, 2.5% for children and Saqib 2012: 5%). One study, available as an abstract only, did not report the galenic formulation (Wankhade 2013).

Systemic ivermectin was administered once in 12 studies (Macotela-Ruiz 1996; Usha 2000; Bachewar 2009; Mushtaq 2010; Sharma 2011; Chhaiya 2012; Saqib 2012; Rohatgi 2013; Wankhade 2013; Manjhi 2014; Ahmad 2016; Wankhade 2016). In two studies, systemic ivermectin was administered on day one and again one week later (Meenakshi 2014; Abdel-Raheem 2016). In another two studies, two doses of ivermectin - on day one and again after two weeks - were dispensed (Das 2006; Sharma 2011). In Macotela-Ruiz 1996, ivermectin was given three times: on day one, day seven, and day 10.

Systemic ivermectin was administered orally, in five studies in tablet form (Das 2006; Chhaiya 2012; Rohatgi 2013; Meenakshi 2014; Wankhade 2016). The other 10 studies did not specify whether a tablet or a capsule was used (Macotela-Ruiz 1996; Usha 2000; Das 2006; Mushtaq 2010; Sharma 2011; Saqib 2012; Wankhade 2013; Manjhi 2014; Abdel-Raheem 2016; Ahmad 2016).

Two studies investigated a single application of topical ivermectin (Chhaiya 2012; Ahmad 2016), administered as 1% lotion, in Chhaiya 2012, or as 1% solution, in Ahmad 2016.

Re-treatment

Most studies did not report the absolute numbers of participants needing re-treatment or being re-treated. Only two trials comparing ivermectin with permethrin reported numbers of participants needing a second treatment due to non-response, which was higher in the systemic ivermectin group than in the permethrin group.

We specified any available information on number of participants re-treated as footnotes in the forest plots and in Appendix 3.

Treatment of family members and close contacts

In nine studies, members of the family or close contacts, or both, were treated alongside the study participants.

In four studies, family members, Usha 2000; Rohatgi 2013; Abdel-Raheem 2016, or all contacts of the participants, Saqib 2012, received the same medication as the study participant.

In three studies, contacts were treated irrespective of the participant's treatment as follows: Sharma 2011 provided all family contacts with topical permethrin 5% cream for single overnight application. Macotela-Ruiz 1996 treated 95 contacts with an oral single dose of 250 μg/kg body weight ivermectin. Bachewar 2009 gave benzyl benzoate 25% lotion to all participants so family members could be treated simultaneously.

Meenakshi 2014 explicitly explained to all participants the importance of treating their family members. Whether medication was dispensed or not was not reported. Ahmad 2016 reported that contacts were treated; the nature and extent of the treatment were not described.

Definition and diagnosis of complete clearance

Three studies provided no definition of 'clinical cure of scabietic lesions' (Chhaiya 2012), 'improvement clinically' (Das 2006), or 'cure rate' (Wankhade 2013). The other studies provided details of the definition and diagnosis of complete clearance, which are given in Appendix 4.

Excluded studies

We excluded five studies after full-text assessment (see Figure 1). Reasons for the exclusion of studies are listed in the Characteristics of excluded studies table.

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The objective of Chhaiya 2013 was a cost-effectiveness analysis of topical permethrin versus oral ivermectin. The analysis consists of two study groups of Chhaiya 2012. The study did not report any additional relevant data.

We excluded one study on people with crusted scabies, which was not yet open for participant recruitment (NCT02841215). The aim of this study is to assess the efficacy of ivermectin 400 μg/kg body weight compared to ivermectin 200 μg/kg body weight in severe forms of scabies.

We excluded three studies co-authored by Mohamad Goldust due to suspicion of flawed data (Goldust 2012; Goldust 2013; Ranjkesh 2013). We are aware of several other publications on scabies by Goldust and colleagues. Details are reported elsewhere (Dressler 2016b). The issue was presented and discussed at the annual meeting of the Cochrane Skin Group on 9-10 January 2017 in Berlin: a unanimous decision was made to exclude these studies from the review due to the suspicion of flawed data.

Ongoing studies

One study is still recruiting (NCT02407782), hence results are not yet available.

Risk of bias in included studies

See Figure 2 for the 'Risk of bias' evaluations of the included trials. For more details on each assessment, see the 'Risk of bias table' for each individual study in the Characteristics of included studies tables.

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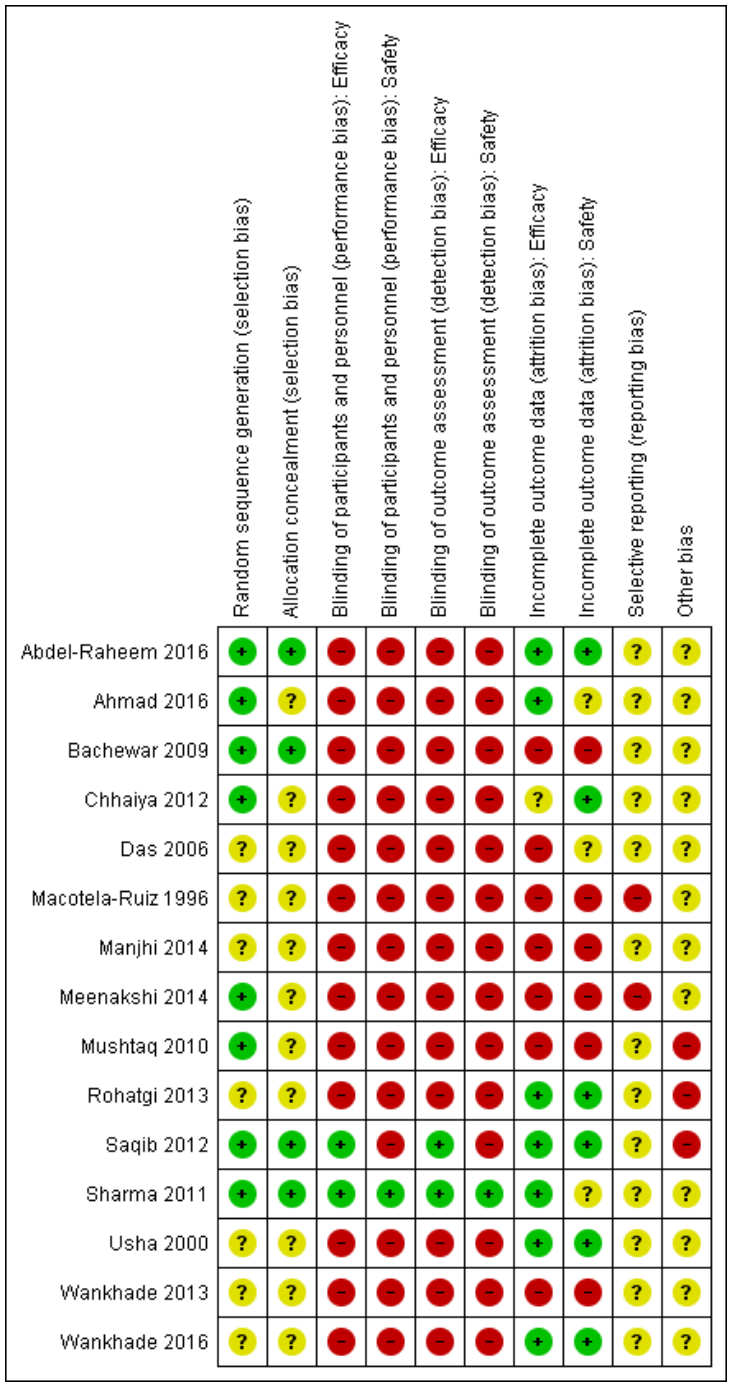
Figure 2. 'Risk of bias' summary: review authors' judgements about each risk of bias item for each included trial.



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Allocation

More than half of the included studies used adequate methods to generate random sequence (Bachewar 2009; Mushtaq 2010; Sharma 2011; Chhaiya 2012; Saqib 2012; Meenakshi 2014; Abdel-Raheem 2016; Ahmad 2016). The other seven studies did not report the methods used (Macotela-Ruiz 1996; Usha 2000; Das 2006; Rohatgi 2013; Wankhade 2013; Manjhi 2014; Wankhade 2016).

Four studies reported methods that assured adequate allocation concealment (Bachewar 2009; Sharma 2011; Saqib 2012; Abdel-Raheem 2016). We assessed the remaining 11 studies as at unclear risk of bias (Macotela-Ruiz 1996; Usha 2000; Das 2006; Mushtaq 2010; Chhaiya 2012; Rohatgi 2013; Wankhade 2013; Manjhi 2014; Meenakshi 2014; Ahmad 2016; Wankhade 2016).

Consequently, we judged only four out of 15 studies to be at low risk of selection bias (Bachewar 2009; Sharma 2011; Saqib 2012; Abdel-Raheem 2016).

Blinding

We assessed performance and detection bias for efficacy and safety outcomes separately. There were only minor differences. We assessed nearly all included studies as at high risk of performance and detection bias.

Thirteen studies were at high risk of bias with regard to blinding. Of these, seven studies were not blinded (Macotela-Ruiz 1996; Bachewar 2009; Chhaiya 2012; Rohatgi 2013; Meenakshi 2014; Abdel-Raheem 2016; Wankhade 2016), and six study authors did not report anything about steps taken to ensure blinding of participants or personnel, or both (Usha 2000; Das 2006; Mushtaq 2010; Wankhade 2013; Manjhi 2014; Ahmad 2016). We assessed Sharma 2011, which was was double-blind, as at low risk of performance and detection bias. We assessed Saqib 2012 as at low risk of bias regarding efficacy outcomes as at least the physician was blinded to treatment assignment (single-blind study). We rated this study as at high risk of bias regarding adverse events because participants who are aware of their treatment (no blinding) may pay more attention to adverse events related to the specific mode of application (topical versus oral), which introduces bias.

Incomplete outcome data

We assessed attrition bias for efficacy and safety outcomes separately, which led to different assessments in four studies (Das 2006; Sharma 2011; Chhaiya 2012; Ahmad 2016).

Efficacy outcome

In seven studies none or less than 10% of the randomized participants in at least one of the study groups were lost to follow-up over the duration of the study. We assessed the risk of attrition bias in these studies as low (Usha 2000; Sharma 2011; Saqib 2012; Rohatgi 2013; Abdel-Raheem 2016; Ahmad 2016; Wankhade 2016).

More than 10% of the randomized participants in at least one of the study groups were lost to follow-up in Bachewar 2009, Mushtaq 2010, and Meenakshi 2014. Das 2006 reported results as percentages only; the number of participants evaluated and thus the number of participants eventually lost to follow-up is unclear. Macotela-Ruiz 1996 and Wankhade 2013 reported no numerical outcome data, therefore we assessed the risk of bias as high. A clear explanation of the scales or items used to assess the outcome was missing in Manjhi 2014, which led to an assessment of high risk of bias regarding the reported efficacy outcomes.

We rated the remaining study by Chhaiya 2012 as at unclear risk of bias because the number of participants lost to follow-up was less than 10% (15/315), but the number of participants analysed at week two and three was unclear.

Safety outcome

In six studies, none or less than 10% of the randomized participants in at least one of the study groups were lost to follow-up. We assessed the risk of attrition bias in these studies as being low (Usha 2000; Chhaiya 2012; Saqib 2012; Rohatgi 2013; Abdel-Raheem 2016; Wankhade 2016).

In contrast, more than 10% of the randomized participants in at least one of the study groups were lost to follow-up in Bachewar 2009, Mushtaq 2010, and Meenakshi 2014. No numerical outcome data were reported in Macotela-Ruiz 1996, Wankhade 2013, and Manjhi 2014. We rated these six studies as at high risk of attrition bias. We assessed the remaining three studies as at unclear risk of bias. In Das 2006, the number of participants evaluated for safety was unclear. Sharma 2011 did not report adverse events for each study group separately, and Ahmad 2016 did not report numerical data on participants with adverse events per study group.

Selective reporting

We rated two studies as at high risk of reporting bias. Macotela-Ruiz 1996 and Meenakshi 2014 defined outcomes in the corresponding methods sections but did not report results for these outcomes. We assessed the remaining studies as at unclear risk of reporting bias (Usha 2000; Das 2006; Bachewar 2009; Mushtaq 2010; Sharma 2011; Chhaiya 2012; Saqib 2012; Rohatgi 2013; Wankhade 2013; Manjhi 2014; Abdel-Raheem 2016; Ahmad 2016; Wankhade 2016). None of the included studies provided information about a study protocol.

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Other potential sources of bias

We judged three studies as at high risk of other sources of bias. Mushtaq 2010 and Saqib 2012 reported baseline differences between intervention and control group. In addition, there were minor inconsistencies in the publications. The reports by Rohatgi 2013 revealed discrepancies in response data between the abstract and the doctoral thesis the study author provided. We judged all other included studies to be of unclear risk of other sources of bias.

Effects of interventions

See: **Summary of findings for the main comparison** Oral ivermectin 200 μg/kg (1 to 3 doses) compared to topical permethrin 5% cream (1 to 3 applications); **Summary of findings 2** Oral ivermectin 200 μg/kg (1 to 2 doses) compared to topical permethrin 5% lotion (1 to 5 applications); **Summary of findings 3** Oral ivermectin 200 μg/kg (1 to 3 doses) compared to topical ivermectin 1% lotion/solution (1 to 3 applications); **Summary of findings 4** Topical ivermectin 1% lotion (1 to 3 applications) compared to topical permethrin 5% cream (1 to 3 applications); **Summary of findings 5** Oral ivermectin 200 μg/kg (1 dose) compared to oral ivermectin 200 μg/kg (2 doses)
See the 'Summary of findings' tables section.
The included studies investigated the following four comparisons.

- Oral ivermectin versus topical permethrin.
- Oral ivermectin versus topical ivermectin.
- Topical ivermectin versus topical permethrin.
- Oral ivermectin versus oral ivermectin in different doses.

Data on the following six comparisons are reported here.

- Ivermectin 200 μg/kg body weight (1 to 3 doses) versus permethrin 5% cream (1 to 3 applications).
- Ivermectin 200 μg/kg body weight (1 to 2 doses) versus permethrin 5% lotion (1 to 5 applications).
- Ivermectin 200 μg/kg body weight (1 dose) versus permethrin 5% (of unknown ointment base, 1 application).
- Ivermectin 200 μg/kg body weight (1 to 3 doses) versus ivermectin 1% lotion/solution (1 to 3 applications).
- Ivermectin 1% lotion (1 to 3 applications) versus permethrin 5% cream (1 to 3 applications).
- Ivermectin systemic (1 dose) versus ivermectin systemic (2 to 3 doses).

We have reported comparisons addressing our predefined outcomes in more detail below. If there is no paragraph describing an outcome or a specific time point, it was not reported in any of the included studies.

Oral ivermectin versus topical permethrin

Ivermectin 200 μg/kg body weight (1 to 3 doses) versus permethrin 5% cream (1 to 3 applications) (1129 participants, 10 trials)

Ten studies compared ivermectin oral with permethrin 5% cream (Usha 2000; Das 2006; Bachewar 2009; Mushtaq 2010; Sharma 2011; Chhaiya 2012; Rohatgi 2013; Manjhi 2014; Meenakshi 2014; Wankhade 2016).

Complete clearance

One-week follow-up

Eight studies reported the outcome 'complete clearance' one week after treatment initiation.
Six studies including a total of 613 participants could be pooled using a random-effects meta-analysis model (Usha 2000; Bachewar 2009; Sharma 2011; Rohatgi 2013; Meenakshi 2014; Wankhade 2016). Heterogenerity was not significant (I^2 = 35%, P = 0.18). The pooled estimate shows that permethrin may be slightly more effective than ivermectin (risk ratio (RR) 0.65, 95% confidence interval (CI) 0.54 to 0.78; Analysis 1.1, Figure 3). This translates to 229 fewer patients per 1000 achieving complete clearance in the ivermectin group (from 144 fewer to 301 fewer; Summary of findings for the main comparison). We rated the certainty of evidence as low; see Summary of findings for the main comparison.

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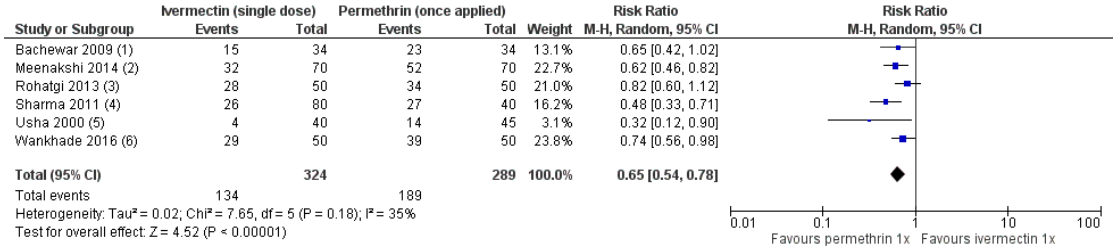
Figure 3. Forest plot of comparison: 1 Ivermectin 200 μg/kg versus permethrin 5% cream, outcome: 1.1 Complete clearance - week 1.



Footnotes
(1) IVER: 7/34 imputed (NRI); PER: 6/34 imputed (NRI)
(2) IVER: 12/70 imputed (NRI); PER: 8/70 imputed (NRI)
(3) IVER: 2/50 ITT-NRI; PER: 2/50 ITT-NRI
(4) IVER: 1/80 imputed (NRI); PER: 2/40 imputed (NRI)
(5) No imputation
(6) No imputation

These results are in line with the results reported by Chhaiya 2012, who stated that after one week of treatment 74.8% of participants treated with permethrin and 30.0% of participants treated with ivermectin achieved complete clearance; absolute numbers were not reported and could not be deducted.

Manjhi 2014 investigated 'complete improvement' based on pruritus and lesions separately. A difference for complete improvement based on lesions alone was found in favour of permethrin (RR 0.74, 95% CI 0.56 to 0.99; 120 participants); for complete improvement based on pruritus no difference was found (RR 0.82, 95% CI 0.60 to 1.11; 120 participants).

Two weeks' follow-up

Six studies reported the outcome 'complete clearance' after two weeks of treatment (Usha 2000; Bachewar 2009; Mushtaq 2010; Sharma 2011; Chhaiya 2012; Rohatgi 2013). Of these, Chhaiya 2012 reported results as percentages only: 99.0% of participants treated with permethrin and 63.0% of participants treated with ivermectin achieved complete clearance after two weeks. Absolute numbers could not be deducted. The combined effect estimate of the remaining five studies showed no difference between the treatment groups (RR 0.91, 95% CI 0.76 to 1.08; 459 participants; Analysis 1.2, Figure 4). A statistically significant heterogeneity test (I^2 = 61%, P = 0.04) led us to further investigate the source of heterogeneity. Risk of bias was low to high and very divergent between studies. We could not identify meaningful groups of studies based on the 'Risk of bias' assessments that would help explain heterogeneity. In the studies by Bachewar 2009 and Rohatgi 2013, uncured participants had been re-treated after one week; absolute numbers were not provided. Visual inspection of the forest plot suggests that the trial by Usha 2000 may be one of the causes of substantial statistical heterogeneity, though we could not identify any clinical or methodological reasons. Omitting either of these studies from the meta-analysis did not substantially change the effect estimate. Sensitivity analyses neither changed the point estimates nor whether the CI crossed the line of no effect (Appendix 2). Hence, we pooled data from all five studies. We rated the certainty of the evidence as low (Summary of findings for the main comparison).

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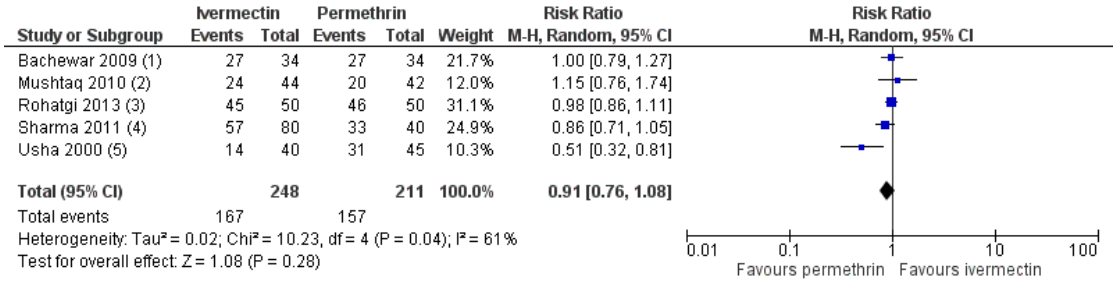
Figure 4. Forest plot of comparison: 1 Ivermectin 200 μg/kg versus permethrin 5% cream, outcome: 1.2 Complete clearance - week 2.



Footnotes
(1) IVER: 44.44% of participants were re-treated after 1 week, 7/34 imputed (NRI); PER: 17.86% of participants were re-treated after 1 week,...
(2) IVER: single dose, per-protocol analysis; PER: single application, per-protocol analysis
(3) IVER, PER: participants who showed no signs of cure at 1st follow-up were given same treatment again, 2/50 ITT-NRI for each group
(4) IVER: single dose, supervised, 1/80 imputed (NRI); PER: single application, 2/40 imputed (NRI)
(5) IVER: single dose, supervised, no imputation; PER: single application, no imputation

Four weeks' follow-up

Seven studies reported 'complete clearance' after four weeks (Usha 2000; Das 2006; Mushtaq 2010; Sharma 2011; Chhaiya 2012; Rohatgi 2013; Wankhade 2016).

A study by Sharma 2011 compared one dose of ivermectin with one application of permethrin 5% cream. After four weeks of follow-up no difference was found (RR 1.00, 95% CI 0.86 to 1.16; 80 participants). We rated the certainty of the evidence as high (Analysis 1.3: subgroup 1, Figure 5, and Summary of findings for the main comparison).

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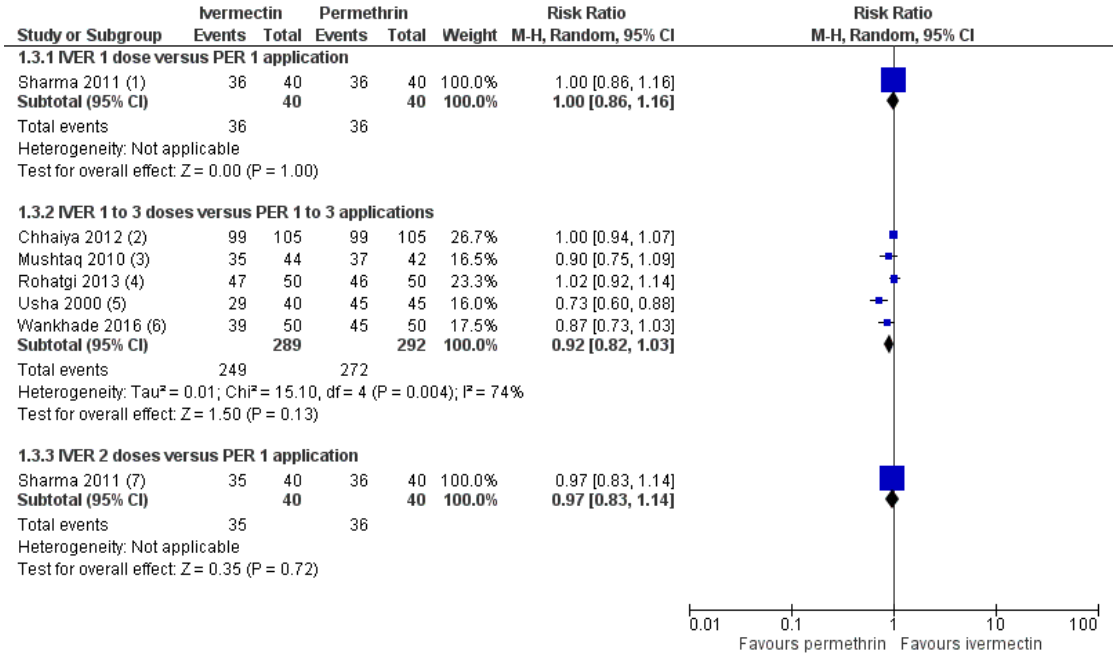
Figure 5. Forest plot of comparison: 1 Ivermectin 200 μg/kg (1 to 3 doses) versus permethrin 5% cream (1 to 3 applications), outcome: 1.3 Complete clearance - week 4.



Footnotes
(1) IVER: single dose, no imputation; PER: single application, self-applied, no imputation
(2) IVER, PER: participants who were not cured were prescribed repeat intervention along with anti-histaminic at week 2 and week 3; IVER:...
(3) IVER, PER: non-responders to 1st treatment were given 2nd dose at week 2 in their respective groups, per-protocol analysis
(4) IVER, PER: participants who showed no signs of cure at 1st follow-up were given same treatment again, 2/50 ITT-NRI for each group
(5) IVER: 12 participants were re-treated at week 2, no imputation; PER: 1 participant was re-treated at week 2, no imputation
(6) IVER, PER: non-responders to 1st treatment were given 2nd dose at week 1 in their respective groups, no imputation
(7) IVER: two doses, 1/40 imputed (NRI); PER: single application, self-applied, 2/40 imputed (NRI)

In five studies uncured participants were re-treated after one week, Chhaiya 2012; Rohatgi 2013; Wankhade 2016, and/or after two weeks (Usha 2000; Mushtaq 2010; Chhaiya 2012; Wankhade 2016). Additionally, Chhaiya 2012 planned to switch non-responders to permethrin 5% after three weeks. This could have affected only one participant in the ivermectin group (not clearly stated).
We observed statistically significant heterogeneity between the five trials (I^2 = 74%, P = 0.004), but could not identify potential reasons based on either the direction of the effect or due to a different treatment regimen. We also performed subgroup analyses, creating a subgroup excluding the two studies from sensitivity analysis. The test for subgroup differences was non-significant (I^2 = 6%, P = 0.30, see Analysis 1.4). Irrespective of the number of pooled studies, the combined estimates showed no differences between the groups (RR 0.92, 95% CI 0.82 to 1.03; 581 participants, 5 trials; Analysis 1.3: subgroup 2, Figure 5, Appendix 2 for sensitivity analysis). We rated the certainty of the evidence as low (Summary of findings for the main comparison).
Das 2006 and Sharma 2011 treated participants with two doses of ivermectin (initial treatment and at two weeks' follow-up) compared to one application of permethrin 5% cream. After four weeks, no difference could be found based on the results reported by Sharma 2011 (RR 0.97, 95% CI 0.83 to 1.14; 80 participants; Analysis 1.3: subgroup 3, Figure 5). We rated the certainty of the evidence as high (Summary of findings for the main comparison). In the trial by Das 2006, 90.0% of participants treated with permethrin and 96.0% of participants treated with ivermectin achieved 'improvement clinically' after four weeks (no further information provided).

Number of participants re-treated

None of the included studies had a predefined outcome measure assessing the 'number of participants re-treated'. Hence, reporting differed greatly. Most studies did not report absolute numbers or proportions of participants having been re-treated. In Appendix 3, we have provided an overview of when treatment was repeated. Only two studies did not repeat their intervention - neither as part

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of the treatment schedule nor in response to uncured participants.

Number of participants with at least one adverse event

The reporting of adverse events was poor.

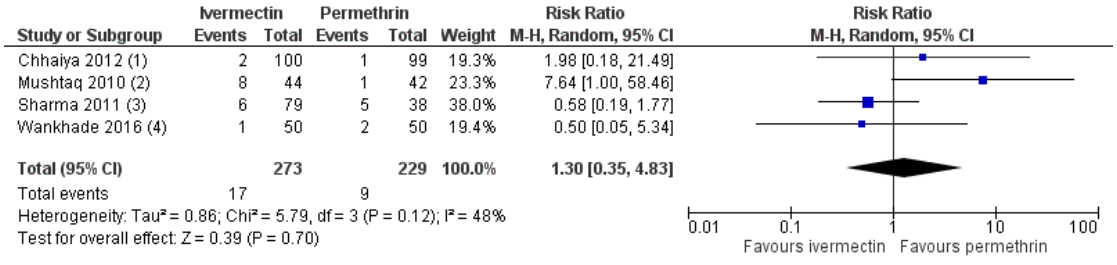
Two weeks' follow-up

In the study by Bachewar 2009, none of the 55 participants experienced any adverse events. An effect estimate is not calculable; we rated the certainty of the evidence as moderate (Analysis 1.5 and Summary of findings for the main comparison).

Four weeks' follow-up

Four studies including 502 participants reported data for participants experiencing at least one adverse event after four weeks (Mushtaq 2010; Sharma 2011; Chhaiya 2012; Wankhade 2016). We found low-certainty evidence that ivermectin may lead to a slightly larger proportion of participants with at least one adverse event (RR 1.30, 95% CI 0.35 to 4.83; moderate heterogeneity: I^2 = 48%, P = 0.12; Analysis 1.6, Figure 6, Summary of findings for the main comparison).

Figure 6. Forest plot of comparison: 1 Ivermectin 200 μg/kg versus permethrin 5% cream, outcome: 1.5 Number of participants with ≥ 1 adverse event - week 4.



Footnotes
(1) IVER, PER: participants who were not cured were prescribed repeat intervention along with anti-histaminic at week 2 and week 3
(2) Inconsistent data (p. 229 and 300): 8 versus 7 patients with adverse events; IVER, PER: non-responders to 1st treatment were given 2nd...
(3) IVER: participants from 2 groups combined, participants were treated 1x or 2x, almost in same proportion; PER: single application
(4) IVER: single dose; PER: single application

Das 2006 and Rohatgi 2013 reported zero events per group, however the number of participants assessed at week four is unclear. In the trial by Usha 2000, participants were evaluated after eight weeks. In the ivermectin group, three out of 40 participants experienced at least one adverse event, while none of the 45 analysed participants in the permethrin group experienced an event.

Number of participants withdrawn from study due to adverse event

Four weeks' follow-up

In three studies with 305 randomized participants (Usha 2000; Manjhi 2014; Wankhade 2016), no withdrawals due to adverse events occurred (Analysis 1.7). We rated the certainty of the evidence as moderate (Summary of findings for the main comparison).

Ivermectin 200 μg/kg body weight (1 to 2 doses) versus permethrin 5% lotion (1 or 5 applications) (227 participants, 2 trials)

Two studies compared oral ivermectin 200 μg/kg body weight with permethrin 5% lotion (Saqib 2012; Abdel-Raheem 2016). In the study by Abdel-Raheem 2016, children randomized to the permethrin group below the age of 10 were treated with permethrin 2.5% lotion.

Complete clearance

One and two weeks' follow-up

In Saqib 2012, participants were treated with either a single dose of ivermectin or a single application of permethrin 5% lotion.

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Complete clearance was defined as no itching, cutaneous lesions/burrows, and negative microscopy. There was no difference between study groups (week one: RR 0.93, 95% CI 0.74 to 1.17; Analysis 2.1: subgroup 1; week two: RR 1.00, 95% CI 0.78 to 1.29; Analysis 2.2: subgroup 1; 120 participants each). We rated the certainty of the evidence as moderate and low, respectively (Summary of findings 2).

In the study by Abdel-Raheem 2016, 107 participants were treated either with a single dose of ivermectin or with permethrin 5% lotion on five consecutive nights. Complete clearance was defined as negative parasitological examination of the participant with complete absence of new lesions. After one week, permethrin may have lead to slightly more participants with complete clearance (RR 0.70, 95% CI 0.47 to 1.03; Analysis 2.1: subgroup 2). After two weeks, no difference was found (RR 0.97, 95% CI 0.81 to 1.17; Analysis 2.2: subgroup 2). We rated the certainty of the evidence as low and moderate, respectively (Summary of findings 2).

Number of participants re-treated

The two studies comparing ivermectin 200 µg/kg with permethrin 5% lotion had different treatment schedules, as shown in Appendix 3.

Number of participants with at least one adverse event

Two weeks' follow-up

Abdel-Raheem 2016 found no difference between groups in number of participants with at least one adverse event (RR 5.00, 95% CI 0.25 to 101.58; 100 participants; Analysis 2.3). We rated the certainty of the evidence as very low (Summary of findings 2).

Number of participants withdrawn from study due to adverse event

Two weeks' follow-up

Saqib 2012 reported that no participants withdrew from the study due to adverse events in either group (120 participants; Analysis 2.4). We rated the certainty of the evidence as moderate (Summary of findings 2).

Ivermectin 200 µg/kg body weight (1 dose) versus permethrin 5% (1 application) (100 participants, 1 trial)

We identified only one study, Wankhade 2013, whose data were published as an abstract only.

Complete clearance

Wankhade 2013 investigated ivermectin 200 µg/kg body weight and permethrin 5% of unknown ointment base. Participants were evaluated one and two weeks' post-treatment initiation. The authors state that "Permethrin had significantly better cure rate than ivermectin" (Wankhade 2013). The number of randomized participants per group, the definition of 'cure', and the time point of evaluation were not reported.

Number of participants re-treated

Wankhade 2013 stated that participants with no sign of cure received the same treatments again after one week (Appendix 3).

Oral ivermectin versus topical ivermectin

Ivermectin 200 µg/kg body weight (1 to 3 doses) versus ivermectin 1% lotion/solution (1 to 3 applications) (272 participants, 2 trials)

Two studies compared ivermectin oral with ivermectin 1% lotion, Chhaiya 2012, or 1% solution, Ahmad 2016.

Complete clearance

One-week follow-up

In Ahmad 2016, there was no difference between study groups after one week of follow-up (RR 0.84, 95% CI 0.65 to 1.08; 62 participants; Analysis 3.1). We rated the certainty of evidence as low (Summary of findings 3).

In Chhaiya 2012, 30.0% of participants treated with ivermectin 200 µg/kg body weight and 69.3% of participants treated with ivermectin 1% lotion achieved 'complete clearance' after one week. Reported data were insufficient for calculating an effect estimate.

Two weeks' follow-up

In Ahmad 2016, there was no difference between study groups after two weeks of follow-up (RR 1.00, 95% CI 0.94 to 1.06; 62 participants; Analysis 3.2). We rated the certainty of evidence as moderate (Summary of findings 3).

In Chhaiya 2012, 63.0% of participants treated with ivermectin 200 µg/kg body weight achieved 'complete clearance', whereas 100.0% of participants treated with ivermectin 1% lotion were cleared after two weeks of follow-up. Absolute numbers of participants were not reported (Chhaiya 2012).

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Four weeks' follow-up

Pooled data from Chhaiya 2012 and Ahmad 2016 revealed no difference between study groups for 'complete clearance' after four weeks of follow-up (RR 0.99, 95% CI 0.95 to 1.03; 272 participants; Analysis 3.3). We rated the certainty of evidence as moderate (Summary of findings 3).

Number of participants re-treated

Ahmad 2016 re-treated non-responders after one week. Four out of 32 participants in the topical ivermectin group and eight out of 30 participants in the systemic ivermectin group were re-treated. Chhaiya 2012 re-treated those participants who were not cured at week one and week two. Non-responders at week three switched to permethrin. Absolute numbers were not reported (Appendix 3).

Number of participants with at least one adverse event

Four weeks' follow-up

We found no difference between groups for the number of participants with at least one adverse event within four weeks of follow-up (RR 5.05, 95% CI 0.25 to 103.87; 201 participants; Analysis 3.4). We rated the certainty of the evidence as very low (Summary of findings 3).

Number of participants withdrawn from study due to adverse event

Four weeks' follow-up

None of the 62 randomized participants in Ahmad 2016 withdrew due to an adverse event (Analysis 3.5). We rated the certainty of evidence as moderate (Summary of findings 3).

Topical ivermectin versus topical permethrin

Ivermectin 1% lotion (1 to 3 applications) versus permethrin 5% cream (1 to 3 applications) (210 participants, 1 trial)

Complete clearance

One-week follow-up

In Chhaiya 2012, 69.3% of participants treated with ivermectin 1% lotion and 74.8% of participants treated with permethrin 5% cream achieved 'complete clearance' after one week. Reported data were insufficient to calculate an effect estimate.

Two weeks' follow-up

After two weeks of follow-up, 100.0% of the participants treated with ivermectin 1% lotion achieved 'complete clearance' and 99.0% of the participants treated with permethrin 5% cream were cleared. Absolute numbers of participants were not reported.

Four weeks' follow-up

Data reported by Chhaiya 2012 showed no difference between the study groups after four weeks of follow-up for complete clearance (RR 1.02, 95% CI 0.96 to 1.08; 210 participants; Analysis 4.1). We rated the certainty of the evidence as moderate (Summary of findings 4).

Number of participants re-treated

Chhaiya 2012 re-treated those participants who were not cured at week one and week two. Non-responders at week three were switched to permethrin. Absolute numbers were not reported (Appendix 3).

Number of participants with at least one adverse event

Four weeks' follow-up

We could find no difference between the groups for the number of participants with at least one adverse event within four weeks of follow-up (RR 0.33, 95% CI 0.01 to 7.93; 200 participants; Analysis 4.2). We rated the certainty of the evidence as very low (Summary of findings 4).

Oral ivermectin versus oral ivermectin in different doses

Ivermectin 200 μg/kg body weight (1 dose) versus ivermectin 200 μg/kg body weight (2 doses) (80 participants, 1 trial)

Complete clearance

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Four weeks' follow-up

Sharma 2011, which included 80 participants, found no difference between one and two doses of oral ivermectin for 'complete clearance' after four weeks of follow-up (RR 0.97, 95% CI 0.83 to 1.14; Analysis 5.1; Summary of findings 5). We rated the certainty of the evidence as high.

Number of participants re-treated

As planned by Sharma 2011, none of the participants were re-treated, except as defined in the study protocol (Appendix 3).

Ivermectin 250 μg/kg body weight (1 dose) versus ivermectin 250 μg/kg body weight (3 doses) (273 participants, 1 trial)

Complete clearance

Macotela-Ruiz 1996, which involved 273 participants, investigated a single dose ivermectin at day 1 versus three doses of ivermectin on day 1, 3, and 10. Absolute numbers were not reported. All participants were cured within 45 days of follow-up. 'Cure' was defined as considerable improvement of dermatosis, no pruritus, and no new lesions. The exact time point of evaluation is unclear.

Number of participants re-treated

Macotela-Ruiz 1996 did not report on additional re-treatment of participants, except as stipulated in the study protocol (Appendix 3).

Number of participants with at least one adverse event

The authors reported that there were no adverse drug reactions (Macotela-Ruiz 1996).

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ADDITIONAL SUMMARY OF FINDINGS [Explanation]

Oral ivermectin 200 μg/kg (1 to 2 doses) compared to topical permethrin 5% lotion (1 to 5 applications) for treating scabies

Patient or population: people with scabies, 5 to 60 years of age
Location: Egypt, Pakistan
Intervention: oral ivermectin 200 μg/kg
Comparison: topical permethrin 5% lotion

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Number of participants (trials)	Certainty of the evidence (GRADE)	Comments
	Risk with permethrin 5% lotion	Risk with ivermectin 200 μg/kg				
Complete clearance - week 1 - IVER 1 dose versus PER 1 application	733 per 1000	682 per 1000 (543 to 858)	RR 0.93 (0.74 to 1.17)	120 (1 RCT)[1]	⊕⊕⊕◯ MODERATE[2]	-
Complete clearance - week 1 - IVER 1 dose versus PER on 5 consecutive nights	593 per 1000	415 per 1000 (279 to 610)	RR 0.70 (0.47 to 1.03)	107 (1 RCT)[3]	⊕⊕◯◯ LOW[2,4]	-
Complete clearance - week 2 - IVER 1 dose versus PER 1 application	667 per 1000	667 per 1000 (520 to 860)	RR 1.00 (0.78 to 1.29)	120 (1 RCT)[1]	⊕⊕◯◯ LOW [2,4]	-
Complete clearance - week 2 - IVER 2 doses versus PER on 5 consecutive nights	815 per 1000	790 per 1000 (660 to 953)	RR 0.97 (0.81 to 1.17)	107 (1 RCT)[3]	⊕⊕⊕◯ MODERATE[2]	-

Number of participants with ≥ 1 AE - week 2 - IVER 2 doses versus PER on 5 consecutive nights	0 per 1000	0 per 1000 (0 to 0)	RR 5.00 (0.25 to 101.58)	100 (1 RCT)[1]	⊕◯◯◯ VERY LOW [2,5]	-
Withdrawal due to AE - week 2 - IVER 1 dose versus PER 1 application	0 per 1000	0 per 1000 (0 to 0)	Not estimable	120 (1 RCT)[1]	⊕⊕⊕◯ MODERATE[2]	0 events

*__The risk in the intervention group__ (and its 95% CI) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).
Abbreviations: AE: adverse event; **CI:** confidence interval; **IVER:** ivermectin; **PER:** permethrin; **RCT:** randomized controlled trial; **RR:** risk ratio

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

[1] Saqib 2012.
[2] Downgraded by 1 for serious risk of bias: assessed as moderate.
[3] Abdel-Raheem 2016.
[4] Downgraded by 1 for serious imprecision: CI crosses line of no effect and minimal clinically important difference thresholds: uncertain whether there is any difference.
[5] Downgraded by 2 for very serious imprecision: CI crosses line of no effect and minimal clinically important difference thresholds: uncertain whether there is any difference and wide CI.

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Oral ivermectin 200 μg/kg (1 to 3 doses) compared to topical ivermectin 1% lotion/solution (1 to 3 applications) for treating scabies

Patient or population: people with scabies, 5 to 80 years of age
Location: Egypt, India
Intervention: oral ivermectin 200 μg/kg
Comparison: topical ivermectin 1% lotion/solution

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Number of participants (trials)	Certainty of the evidence (GRADE)	Comments
	Risk with ivermectin 1% lotion/solution	Risk with ivermectin 200 μg/kg				
Complete clearance - week 1	875 per 1000	735 per 1000 (569 to 945)	RR 0.84 (0.65 to 1.08)	62 (1 RCT)[1]	⊕⊕◯◯ LOW[2,3]	-
Complete clearance - week 2	1000 per 1000	1000 per 1000 (940 to 1000)	RR 1.00 (0.94 to 1.06)	62 (1 RCT)[1]	⊕⊕⊕◯ MODERATE[2]	8 participants (oral IVER) and 4 participants (topical IVER) were re-treated after 1 week
Complete clearance - week 4	971 per 1000	961 per 1000 (922 to 1000)	RR 0.99 (0.95 to 1.03)	272 (2 RCTs)[1,4]	⊕⊕⊕◯ MODERATE[2]	In 1 study 8 participants (oral IVER) and 4 participants (topical IVER) were re-treated after 1 week; in 1 study non-responders were re-treated after 2 and/or 3 weeks (absolute numbers are unclear)
Number of participants with ≥ 1 AE - week 4	0 per 1000	0 per 1000 (0 to 0)	RR 5.05 (0.25 to 103.87)	201 (1 RCT)[4]	⊕◯◯◯ VERY LOW[2,5]	Non-responders were re-treated after 2 and/or 3 weeks (absolute numbers are unclear)

Withdrawal due to AE - week 4	0 per 1000	0 per 1000 (0 to 0)	Not estimable	62 (1 RCT)[4]	⊕⊕⊕◯ MODERATE[2]	0 events; 8 participants (oral IVER) and 4 participants (topical IVER) were re-treated after 1 week

*__The risk in the intervention group__ (and its 95% CI) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).
Abbreviations: AE: adverse event; CI: confidence interval; IVER: ivermectin; RCT: randomized controlled trial; RR: risk ratio

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

[1]Ahmad 2016.
[2]Downgraded by 1 for serious risk of bias: assessed as moderate.
[3]Downgraded by 1 for serious imprecision: CI crosses line of no effect and minimal clinically important difference thresholds: uncertain whether there is any difference.
[4]Chhaiya 2012.
[5]Downgraded by 2 for very serious imprecision: CI crosses line of no effect and minimal clinically important difference thresholds: uncertain whether there is any difference and wide CI.

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Topical ivermectin 1% lotion (1 to 3 applications) compared to topical permethrin 5% cream (1 to 3 applications) for treating scabies

Patient or population: people with scabies, 5 to 80 years of age
Location: India
Intervention: topical ivermectin 1% lotion
Comparison: topical permethrin 5% cream

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Number of participants (trials)	Certainty of the evidence (GRADE)	Comments
	Risk with permethrin 5% cream	Risk with ivermectin 1% lotion				
Complete clearance - week 4	943 per 1000	962 per 1000 (905 to 1000)	RR 1.02 (0.96 to 1.08)	210 (1 RCT)[1]	⊕⊕⊕◯ MODERATE[2]	Non-responders were re-treated after 2 and/or 3 weeks (absolute numbers are unclear)
Number of participants with ≥ 1 AE - week 4	10 per 1000	3 per 1000 (0 to 80)	RR 0.33 (0.01 to 7.93)	200 (1 RCT)[1]	⊕◯◯◯ VERY LOW[2,3]	Non-responders were re-treated after 2 and/or 3 weeks (absolute numbers are unclear)

*__The risk in the intervention group__ (and its 95% CI) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).
Abbreviations: AE: adverse event; CI: confidence interval; RCT: randomized controlled trial; RR: risk ratio

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

[1] Chhaiya 2012.
[2] Downgraded by 1 for serious risk of bias: assessed as moderate.
[3] Downgraded by 2 for very serious imprecision: CI crosses line of no effect and minimal clinically important difference thresholds: uncertain whether there is any difference and wide CI.

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Oral ivermectin 200 μg/kg (1 dose) compared to oral ivermectin 200 μg/kg (2 doses) for treating scabies

Patient or population: people with scabies, over 5 years of age
Location: India
Intervention: oral ivermectin 200 μg/kg 1 dose
Comparison: oral ivermectin 200 μg/kg 2 doses

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Number of participants (trials)	Certainty of the evidence (GRADE)	Comments
	Risk with ivermectin 200 μg/kg 2 doses	Risk with ivermectin 200 μg/kg 1 dose				
Complete clearance - week 4	900 per 1000	873 per 1000 (747 to 1000)	RR 0.97 (0.83 to 1.14)	80 (1 RCT)[1]	⊕⊕⊕⊕ HIGH	-

***The risk in the intervention group** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
Abbreviations: CI: confidence interval; RR: risk ratio.

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of effect

[1] Sharma 2011.

DISCUSSION

Summary of main results

Fifteen trials, comprising 1896 participants treated with ivermectin or permethrin, met our inclusion criteria. Nearly all studies were conducted in South Asia or North Africa, where many people live in poor, overcrowded conditions. We have presented our findings in five 'Summary of findings' tables (Summary of findings for the main comparison; Summary of findings 2; Summary of findings 3; Summary of findings 4; Summary of findings 5).

The differences in the efficacy results, the number of participants with adverse events, and the number of participants withdrawn due to adverse events were small.

Efficacy

We analysed 13 studies comprising 1456 participants evaluating systemic ivermectin versus permethrin. Oral ivermectin at a standard dose of 200 μg/kg may lead to slightly lower rates of complete clearance after one week compared to permethrin 5% cream (extrapolated cure rates based on anticipated absolute effects: permethrin 65%, ivermectin 43%; RR 0.65, 95% CI 0.54 to 0.78; 613 participants, 6 studies; low-certainty evidence), but may lead to little or no difference in rates of complete clearance by week two (extrapolated cure rates based on anticipated absolute effects: permethrin 74%, ivermectin 68%; RR 0.91, 95% CI 0.76 to 1.08; 459 participants, 5 studies; low-certainty evidence).

In two out of 13 studies (Saqib 2012; Manjhi 2014), the re-treatment of participants was not planned. Uncured participants in seven studies were re-treated (Usha 2000; Bachewar 2009; Mushtaq 2010; Chhaiya 2012; Rohatgi 2013; Wankhade 2013; Wankhade 2016); however, only two of these studies reported numbers (Usha 2000; Bachewar 2009), finding that more participants in the systemic ivermectin groups were re-treated than in the permethrin groups. It is unclear whether the re-treatment of participants in these seven studies who did not show complete clearance had been planned or not. Additionally, three studies reported that all participants in the ivermectin group were re-treated after one or two weeks, irrespective of treatment response (Das 2006; Sharma 2011; Abdel-Raheem 2016). Meenakshi 2014 repeated treatment in all participants.

Study investigators may have chosen to repeat the treatment because ivermectin, unlike permethrin, only affects the mite and not the egg. After one dose, considering the life cycle of the scabies mite (10 to 17 days), a second treatment with ivermectin might be necessary. Alternatively, ivermectin might have a slower onset of action. Studies that included some form of re-treatment (see Appendix 3) comparing permethrin cream and oral ivermectin may lead to little or no difference in rates of complete clearance after four weeks (extrapolated cure rates based on anticipated absolute effects: 1 to 3 applications of permethrin 93%, 1 to 3 doses of ivermectin 86%; RR 0.92, 95% CI 0.82 to 1.03; 581 participants, 5 studies; low-certainty evidence). Considering the cure rates after one or two weeks of treatment, we assume that the number of participants needing re-treatment was low to medium. However, suboptimal reporting precludes further judgement.

Likewise, after four weeks ivermectin lotion probably leads to little or no difference in rates of complete clearance when compared to permethrin cream (extrapolated cure rates based on anticipated absolute effects: permethrin cream 94%, ivermectin lotion 96%; RR 1.02, 95% CI 0.96 to 1.08; 210 participants, 1 study; moderate-certainty evidence, up to two re-treatments of non-responders, numbers unclear; Chhaiya 2012), which may support the above mentioned assumptions. Furthermore, there is probably little or no difference in rates of complete clearance between oral ivermectin at standard dose and topical ivermectin 1% lotion four weeks after initiation of treatment (extrapolated cure rates based on anticipated absolute effects: oral ivermectin 97%, ivermectin lotion 96%; RR 0.99, 95% CI 0.95 to 1.03; 272 participants, 2 studies; moderate-certainty evidence; up to two re-treatments of non-responders, numbers unclear; Chhaiya 2012 and Ahmad 2016). The dose comparison study showed that one dose of systemic ivermectin led to little or no difference in rates of complete clearance compared to two doses of systemic ivermectin (extrapolated cure rates based on anticipated absolute effects: 2 doses 90%, 1 dose 87%; RR 0.97, 95% CI 0.83 to 1.14; 80 participants, 1 study; high-certainty evidence). This finding weakens our assumptions as described above. While this study had one of the smallest sample sizes, the methodological conduct and reporting appeared best, giving it more weight.

We did not identify any differences in efficacy between permethrin and ivermectin other than after one week of treatment. Our findings do not allow for a conclusion about the onset of action in topical treatments compared to systemic treatments, as this was not directly assessed.

Safety

Generally, systemic and topical drugs can lead to different types of events, endangering blinding. Only two of the studies included in this review were blinded. While the reporting of adverse events in the included studies was suboptimal, it appears that very few adverse events occurred. Two weeks after treatment initiation, there is probably little or no difference in the proportion of participants treated with systemic ivermectin or permethrin cream who experienced at least one adverse event (55 participants, 1 study; moderate-certainty evidence). After four weeks, ivermectin may lead to a slightly larger proportion of participants with at least one adverse event (extrapolated rates: permethrin 4%, ivermectin 5%; RR 1.30, 95% CI 0.35 to 4.83; 502 participants, 4 studies; low-certainty evidence). In scabies treatment, medications are sometimes given more than once. However, even the studies with repeated applications did not report more adverse events. To add, no withdrawals due to adverse events occurred in either the systemic ivermectin or the permethrin group (moderate-certainty ev-

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idence). In most studies in which participants were treated only once, a possible explanation for zero withdrawals could be that participants who experienced adverse events after their first (and only) treatment remained in study because they had already had their treatment.

The studies analysed for this review reported severe itching, secondary bacterial infections, headache, and nausea in people treated with systemic ivermectin (Mushtaq 2010; Sharma 2011).

Regarding permethrin, the analysed studies in this review rarely stated the frequency of adverse events and did not designate their types. Only erythema, burning, and pruritus were reported during permethrin treatment (Mushtaq 2010; Sharma 2011).

Two analysed studies evaluating systemic versus topical ivermectin reported that adverse events were rare and of mild intensity and comparable in both study groups (Chhaiya 2012; Ahmad 2016). It is uncertain whether there was any difference in the proportion of participants with at least one adverse event (very low-certainty evidence). No withdrawals due to adverse events occurred, which supports these findings (62 participants, 1 study; moderate-certainty evidence).

Furthermore, it is uncertain whether topical ivermectin or permethrin differ in the number of participants with at least one adverse event (very low-certainty evidence). We found no studies comparing systemic ivermectin in different doses that assessed our predefined safety outcomes.

Overall completeness and applicability of evidence

Applicability to Western countries and external validity - apart from the obvious differences between RCT conditions and real-world conditions - is limited due to studies being conducted in regions with a high prevalence of scabies. Most included trials were conducted in lower-middle-income countries (India, Pakistan, and Egypt). Only one study was undertaken in Mexico in the beginning of the 1990s (middle-income country). All studies were conducted in resource-poor countries.

We identified only single-centre studies that included predominately small numbers of participants per study group. The included studies were inconsistent in their descriptions, definitions, and assessments of cure as well as in the frequencies of treatment application. Pooling data or comparing data across participant groups was therefore difficult or inappropriate.

Although permethrin is an ovicidal medication, in some of the included studies it was applied twice. Conversely, in some studies evaluating ivermectin, a non-ovicidal medication, the drug was administered only once. None of these studies explained the scientific rationale behind these a priori defined dosages, although permethrin is often administered twice due to compliance and reinfestation issues (see How the intervention might work).

Quality of the evidence

We assessed the certainty of the evidence according to the GRADE approach and presented it in five 'Summary of findings' tables (Summary of findings for the main comparison; Summary of findings 2; Summary of findings 3; Summary of findings 4; Summary of findings 5).

The main reasons for downgrading the certainty of the evidence were the quality of the trials and imprecision in the results. In general, the methodological quality of the trials included in this review was moderate. We assessed most of the studies as having a high risk of performance and detection bias. We rated attrition bias as high in nearly half of the included studies. We downgraded certainty for imprecision, mainly because minimal clinically important difference thresholds were crossed by the CIs or the CIs were wide.

Substantial heterogeneity between trials became apparent in two meta-analyses (Analysis 1.2 and Analysis 1.3). This could be explained by variations in the numbers of re-treated participants, which were not stated in most studies. However, the sensitivity analyses (Appendix 2) did not help to further explain this, and it restricts our confidence in the results.

Potential biases in the review process

While we considered publication bias to be undetected, we cannot rule it out. Nearly all included studies were conducted in resource-poor nations. It is unknown if studies were conducted but not published or not identified through our comprehensive searches. One-fifth of the included studies were not identified via the systematic searches of academic, trial, and grey literature repositories, but through web searches (n = 1) and through screening of reference lists (n = 2). We did not consult experts.

It should be noted that it is not clear what impact the three excluded studies - whose validity is questionable (see Excluded studies) - would have on the overall findings of this review.

Despite clear inclusion criteria, individual interpretation or human mistakes may lead to different results in data extraction. We attempted to preclude this potential bias by ensuring that two review authors read all full texts and extracted data independently. All disagreements were discussed fully.

In some cases, we were unable to extract all relevant data because reporting was poor or incomplete (for example, absolute numbers of evaluated participants) in publications. We contacted study authors in an effort to overcome these issues. However, most authors did not respond to our inquiries.

In order to avoid the issue of multiplicity, we chose only one primary outcome at three time points and only reported effects measures/CIs instead of testing for significance.

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Agreements and disagreements with other studies or reviews

Our results comparing permethrin and systemic ivermectin are similar to our recently published comprehensive systematic review considering several scabies treatments (Dressler 2016a). Dressler 2016a concluded that there is no difference between a single dose of permethrin 5% and systemic ivermectin.
Of interest is also a larger study by Romani 2015b, who randomized three island communities in Fiji to either permethrin for only affected patients and their contacts (standard treatment) or permethrin for all island inhabitants or ivermectin for all inhabitants. After 12 months, systemic ivermectin was found to be superior to topical permethrin (Dressler 2016a). Romani 2015b reported that the prevalence declined by 49% in the standard treatment group, 62% in the permethrin group, and 94% in the ivermectin group after one year.

AUTHORS' CONCLUSIONS

Implications for practice

Topical permethrin, topical ivermectin, and systemic ivermectin all lead to high clearance rates in the treatment of scabies. Highly relevant differences could not be seen in the identified trials.

The choice of one of these three treatments can be guided by considerations of practicability, availability, drug licensing, and costs depending on the individual setting.

Permethrin and ivermectin as topical treatments are appropriate for patients in which the correct application to the whole body can be properly ensured. Systemic ivermectin may be given preference if proper application cannot be ensured or if very large groups of patients need to be treated and proper instructions and topical application is not feasible.

Further limitations apply with regard to the age of the patients and in case of pregnancy and breastfeeding. Systemic ivermectin is not indicated during pregnancy or for children weighing less than 15 kg.

The need for a single versus a repeated application cannot be properly answered based on the identified trial results. For most patients, a single treatment is likely sufficient. The treating physician may take into account the extent of the disease, the number of contact persons affected, the likeliness of correct application, the immune status, and the clinical response during follow-up as an indicator for the need of a second application.

Implications for research

Due to suboptimal study conduct, design, or reporting and, for example, the small sample sizes, the certainty of the level of evidence is restricted, which limits our confidence in the effect estimates. Randomized controlled trials of good methodological quality complying with current reporting standards (for example, CONSORT) are necessary to reduce risk of bias and and improve the evidence base.

The question of repeated treatment, that is when and how often, cannot be answered conclusively. Further studies with clear and strict treatment regimens are needed.

Adverse events were rare and poorly reported in the included studies. Studies with a larger sample size and better documentation and classification of adverse events could overcome this issue.

The proportion of participants withdrawn due to non-response or adverse events is poorly reported. It is unlikely that new studies from middle-income countries investigating systemic ivermectin versus topical permethrin will change the results (Mounsey 2009).

Discussions on resistance to scabious treatments have emerged, however such cases have been regionally limited, and the overall evidence is scarce. Studies focusing on a possible development of resistance may become necessary in the future.

Public health questions like mass drug interventions for prevention and treatment of scabies were not addressed in this review but could be part of further research and other reviews (Romani 2015b).

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* *Indicates the major publication for the study*

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CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Abdel-Raheem 2016

Methods	Single-centre, parallel-group randomized trial Duration: 7 months, from November 2012 to May 2013
Participants	**Inclusion criteria** • Aged 5 to 50 years • Clinical presentation of scabies: people experiencing itching and had characteristic lesions (that is, burrows, vesicles, papules, nodules or pustules) on anatomical sites of predilection for scabies (that is, the interdigital folds of the hands, the elbows, the wrists, the buttocks, the axillary folds, the nipple areolas in women and the male external genitalia); detailed physical and dermatological examination was done including description of the lesions and their distribution on the body and assessment of the degree of pruritus • Identification of a mite: parasitological examination of lesions was performed by low-power microscopy; at least 4 to 6 scrapings per participant from separate locations were obtained, placed in a drop of 10% potassium hydroxide solution on a glass slide, and examined for the presence of living *Sarcoptes scabiei* (that is, adult forms), eggs, or faecal pellets **Exclusion criteria** • Pregnant or lactating women • Body weight less than 15 kg • People with a systemic condition such as abnormal liver and kidney functions, known thyroid disease, cardiac disorders, nervous system disorders and psychiatric illnesses • People with history of diabetes mellitus, hypertension, or chronic infectious diseases • People having any other associated skin disease that could alter the picture of scabies • Immunocompromised individuals • Atypical presentations like crusted scabies • People with any antiscabietic treatment in the preceding month **Baseline characteristics** (n = 50 completers in each group) • Age (mean ± SD): group A: 27.84 ± 9.46, B: 25.28 ± 13.73, C: 22.52 ± 12.77, D: 28.40 ± 13.42 • Males/females: group A: 26/24, B: 14/36, C: 24/26, D: 20/30
Interventions	A: Oral ivermectin 200 μg/kg body weight at day 1 and 7, taken with meals; tablets were taken in the presence of the physician (n = 53 participants) B: Permethrin 2.5% (for children below 10 years) or 5% (for adults) lotion applied by participant and left overnight to the whole body below neck for 5 consecutive nights (n = 54 participants) Not included in this review: C: Benzyl benzoate 20% cream applied by participant and left overnight to the whole body below neck for 5 consecutive nights (n = 55 participants) D: Sulfur ointment, 5% (for children below 10 years) or 10% (for adults) applied by

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	participant and left overnight to the whole body below neck for 5 consecutive nights (n = 54 participants) • Participants were first treated from secondary bacterial infection, if present, with azithromycin once daily for 3 days. • Cured participants were prescribed antihistaminic for symptomatic treatment of remaining pruritus and/or nodules, and the uncured participants were prescribed repeated intervention along with antihistaminic. • Members of the same family not enrolled in the study were given the same drugs according to their age or any other suitable regimen.
Outcomes	• Complete cure (negative parasitological examination of the participant with complete absence of new lesions; residual and all new lesions were scraped for detection of mites; if only 1 mite was detected, this was considered as treatment failure; week 1 and 2) • Number of participants re-treated (week 1) • Number of participant with ≥ 1 adverse event
Funding source	Quote (page 478): "This research was funded by authors themselves, and received support From Faculty of Medicine Fayoum University."
Declarations of interest	Quote (page 478): "The authors report no conflicts of interest."
Notes	Location: Al Fayoum, Egypt Clinical trial registry: PACTR201505001116484

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote (page 474): "random allocation number generated through computer"
Allocation concealment (selection bias)	Low risk	Quote (page 474): "randomly allocated" Quote from Pan African Clinical Trials Registry: "Sealed opaque envelopes"
Blinding of participants and personnel (performance bias) Efficacy	High risk	Quote from Pan African Clinical Trials Registry: "Open-label (masking not used)"
Blinding of participants and personnel (performance bias) Safety	High risk	Quote from Pan African Clinical Trials Registry: "Open-label (masking not used)"
Blinding of outcome assessment (detection bias) Efficacy	High risk	Quote from Pan African Clinical Trials Registry: "Open-label (masking not used)"

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Abdel-Raheem 2016 (*Continued*)

Blinding of outcome assessment (detection bias) Safety	High risk	Quote from Pan African Clinical Trials Registry: "Open-label (masking not used)"
Incomplete outcome data (attrition bias) Efficacy	Low risk	16/216 participants lost to follow-up (permethrin group: 4; oral ivermectin group: 3; benzoyl benzoate group: 5; sulfur group: 4) No intention-to-treat analysis performed. Quote (page 475, Figure 1)
Incomplete outcome data (attrition bias) Safety	Low risk	16/216 participants lost to follow-up (permethrin group: 4; oral ivermectin group: 3; benzoyl benzoate group: 5; sulfur group: 4) Quote (page 475, Figure 1)
Selective reporting (reporting bias)	Unclear risk	Outcomes stated in Pan African Clinical Trials Registry, but registration was on 25 April 2015 (after completion of study)
Other bias	Unclear risk	-

Ahmad 2016

Methods	Single-centre, randomized trial Duration: not stated
Participants	**Inclusion criteria** • Age ≥ 5 years and > 15 kg body weight • Clinically and laboratory diagnosed scabies: ○ Clinical diagnosis was based on the presence of ≥ 3 out of 4 criteria: nocturnal pruritus, family history of similar illness, clinical demonstration of burrows, scabies lesions at typical sites ○ Laboratory diagnosis: demonstration of mites and/or mite products (eggs, larva, or faecal pellets) in scrapings from skin lesions (burrows or scabetic papules from classical sites) using light microscopy after incubation in 15% potassium hydroxide **Exclusion criteria** • Pregnant and lactating women • People with crusted (Norwegian) scabies • People with history of epileptic fits, immunodeficiency, secondary cutaneous infection or eczematization, and coexisting skin disease that could interfere with treatment evaluation • People with history of recent scabetic treatment • Known hypersensitivity to ivermectin **Baseline characteristics** • Age (mean ± SD): 21.8 ± 15 • Males/females: 26/36

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Ahmad 2016 (*Continued*)

Interventions	A: Ivermectin 1% solution applied once to entire body below neck at night (n = 32 participants) B: Oral ivermectin 200 μg/kg body weight after food on day 1 (n = 30 participants) • Treatment was repeated after 1 week only in participants with persistent symptoms. • Treatment of contacts and proper hygienic measures were emphasized.
Outcomes	• Cure ('effective' = marked to excellent improvement in pruritus (score 0) and no lesions, absence of mites and their products on microscopy; score: 0 = no pruritus, no skin lesions; 1 = mild pruritus, $\leq$ 10 lesions; 2 = moderate pruritus, 11 to 49 lesions; 3 = marked pruritus, $\geq$ 50 lesions; week 1, 2, and 4) • Number of participants withdrawn from study due to adverse event
Funding source	Not stated
Declarations of interest	Not stated
Notes	Location: Minia, Egypt

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (page 59): "adaptive biased-coin randomization"
Allocation concealment (selection bias)	Unclear risk	Insufficient information
Blinding of participants and personnel (performance bias) Efficacy	High risk	No information
Blinding of participants and personnel (performance bias) Safety	High risk	No information
Blinding of outcome assessment (detection bias) Efficacy	High risk	No information
Blinding of outcome assessment (detection bias) Safety	High risk	No information
Incomplete outcome data (attrition bias) Efficacy	Low risk	All data reported, no loss to follow-up.

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Ahmad 2016 (*Continued*)

Incomplete outcome data (attrition bias) Safety	Unclear risk	No numerical data on participants with adverse events per study group
Selective reporting (reporting bias)	Unclear risk	Insufficient information
Other bias	Unclear risk	-

Bachewar 2009

Methods	Single-centre, parallel-group randomized trial Duration: 5 months, from March to July 2007
Participants	**Inclusion criteria** • Above 12 years of age • Newly diagnosed with scabies (diagnosis was based on clinical symptoms and clinical history) • Person had to satisfy ≥ 3 of following criteria: history of contact with a person with scabies, complaint of nocturnal itching, history of involvement of family members, presence of classical burrows on clinical examination, presence of typical scabetic lesions like papules, nodules, or vesicles **Exclusion criteria** • Pregnant or lactating women; women of childbearing age or planning for conception in near future • Abnormal liver and kidney functions, known thyroid disease, cardiac disorders, nervous system disorders, and psychiatric illnesses; people with history of diabetes mellitus, hypertension, or chronic infectious diseases • Any concurrent medication for other illness, consuming tobacco in any form, alcohol, or any substance of abuse • Any other associated skin disease that could alter the picture of scabies • Known/suspected immunocompromised individuals • Scabies with atypical presentations • Intake of any antiscabetic treatment in the preceding week • Noncompliant participants **Baseline characteristics** • Males/females: group A: 22/12, B: 18/16, C: 23/12
Interventions	A: Permethrin 5% cream applied once to whole body below neck, left overnight (n = 34 participants) B: Oral ivermectin 200 μg/kg body weight as single dose, given as supervised medication along with printed handouts of "do's" in the local vernacular language (n = 34 participants) • Same treatment was repeated if there were no signs of cure after 1 week. • All participants were issued 25% benzyl benzoate lotion for topical application for family members and close contacts. Not included in this review: C: Benzyl benzoate 25% lotion applied to whole body below neck, left overnight, on 2 consecutive nights (n = 35 participants)

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Bachewar 2009 (*Continued*)

Outcomes	• Cure (no new lesions (papules, vesicles, and classical burrows), examined by dermatologist and principal investigator; week 1 and 2) • Number of participants with ≥ 1 adverse event
Funding source	Not stated
Declarations of interest	Not stated
Notes	Location: Nagpur, India

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "random allocation number generated through computer"
Allocation concealment (selection bias)	Low risk	Quote: "number [...] provided with any one of the chosen three therapeutic interventions"
Blinding of participants and personnel (performance bias) Efficacy	High risk	Quote: "our study was biased due to non-blinding" Not blinded
Blinding of participants and personnel (performance bias) Safety	High risk	Quote: "our study was biased due to non-blinding" Not blinded
Blinding of outcome assessment (detection bias) Efficacy	High risk	Quote: "our study was biased due to non-blinding" Not blinded
Blinding of outcome assessment (detection bias) Safety	High risk	Quote: "our study was biased due to non-blinding" Not blinded
Incomplete outcome data (attrition bias) Efficacy	High risk	23/103 participants lost to follow-up (permethrin group: 6; oral ivermectin group: 7; benzyl benzoate group: 10) No intention-to-treat analysis performed. Quote: Table 1 and 2
Incomplete outcome data (attrition bias) Safety	High risk	23/103 participants lost to follow-up (permethrin group: 6; oral ivermectin group: 7; benzyl benzoate group: 10) Quote: Table 1 and 2

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Bachewar 2009 (*Continued*)

Selective reporting (reporting bias)	Unclear risk	Insufficient information
Other bias	Unclear risk	-

Chhaiya 2012

Methods	Single-centre, parallel-group randomized trial Duration: 1 year and 8 months, from June 2007 to January 2009
Participants	**Inclusion criteria** • Aged 5 to 80 years • Clinically diagnosed scabies: ○ Microscopically diagnosed scabies (demonstration of egg, larvae, mite, or faecal material) ○ In case of negative microscopic examination, person had to satisfy ≥ 3 of following criteria: presence of typical scabietic lesions (papules, nodules, or vesicles at classical sites), presence of classical burrows on clinical examination, nocturnal pruritus, history of involvement of family member or similar symptoms in contacts **Exclusion criteria** • Pregnant women and lactating mothers • Person treated with any topical scabicidal therapy in the month before entry • People taking any topical or systemic antibiotic therapy in the week before entry into the study • Immunologically compromised patients • Having scabies with atypical presentation like crusted scabies or scabies incognito • People with secondary bacterial infection • History of allergy to any of the study drugs • Blood pressure < 100/60 mmHg **Baseline characteristics** • Age (mean ± SD): group A: 23.40 ± 13.55, B: 21.97 ± 13.26, C: 22.52 ± 12.69 • Males/females: group A: 58/47, B: 58/47, C: 59/46
Interventions	A: Permethrin 5% cream applied once to whole body covering neck to toe, left for ≥ 8 hours, along with printed information sheet in the local vernacular language (n = 105 participants) B: Oral ivermectin 200 μg/kg body weight as single dose, self administered along with printed information sheet in the local vernacular language (n = 105 participants) C: Ivermectin 1% lotion, left for ≥ 8 hours, along with printed information sheet in the local vernacular language, containing details regarding application of drug and other instructions (n = 105 participants) • Participants who were not cured were prescribed repeat intervention along with antihistaminic at each follow-up. • Participants who were not cured at the end of 3rd week were switched over to standard treatment with 5% permethrin. • All participants received oral hydroxyzine 10 mg or 25 mg twice daily for symptomatic treatment of pruritus.

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Chhaiya 2012 (*Continued*)

Outcomes	• Clinical cure of scabietic lesions (no definition; week 1, 2, 3, and 4) • Number of participants re-treated (week 1, 2, 3, and 4) • Number of participants with ≥ 1 adverse event
Funding source	Quote: "Source of Support: None"
Declarations of interest	Quote: "Conflict of Interest: None"
Notes	Location: Surendranagar, India

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "random allocation number generated through computer"
Allocation concealment (selection bias)	Unclear risk	Insufficient information
Blinding of participants and personnel (performance bias) Efficacy	High risk	Quote: "The study was open-labeled.", "Possible variation, if any, due to different formulations- lotion and cream, cannot be ruled out."
Blinding of participants and personnel (performance bias) Safety	High risk	Quote: "The study was open-labeled.", "Possible variation, if any, due to different formulations- lotion and cream, cannot be ruled out."
Blinding of outcome assessment (detection bias) Efficacy	High risk	Quote: "The study was open-labeled.", "Possible variation, if any, due to different formulations- lotion and cream, cannot be ruled out."
Blinding of outcome assessment (detection bias) Safety	High risk	Quote: "The study was open-labeled.", "Possible variation, if any, due to different formulations- lotion and cream, cannot be ruled out."
Incomplete outcome data (attrition bias) Efficacy	Unclear risk	15/315 participants lost to follow-up (permethrin group: 6; oral ivermectin group: 5; topical ivermectin group: 4) Quote: Figure 1 No intention-to-treat analysis performed. Number of participants analysed in week 2 and 3 is unclear.

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Chhaiya 2012 (*Continued*)

Incomplete outcome data (attrition bias) Safety	Low risk	15/315 participants lost to follow-up (permethrin group: 6; oral ivermectin group: 5; topical ivermectin group: 4) Quote: Figure 1
Selective reporting (reporting bias)	Unclear risk	Insufficient information
Other bias	Unclear risk	-

Das 2006

Methods	Single-centre, parallel-group randomized trial Duration: not stated
Participants	**Inclusion criteria** • At least 2 years of age • Scabies (microscopic and clinical confirmation) **Exclusion criteria** • Pregnant women **Baseline characteristics** • Age: 3 to 71 (age 0 to 5: 9%, age 6 to 15: 22%, age 16 to 30: 22%, age 30 to 50: 9%, age ≥ 51: 7%; total does not equal 100%) • Males/females: 140/60
Interventions	A: Permethrin 5% cream overnight, single application from neck to toes in all family members (n = 50 participants) B: Oral ivermectin 200 μg/kg body weight d1 and d14 (n = 50 participants) Not included in this review: C: Gamma benzene hexachloride 1% for 2 consecutive overnight applications to all family members (n = 50 participants) D: White soft paraffin in a manner similar to group A (n = 50 participants)
Outcomes	• "Improvement clinically" (no definition; week 4)
Funding source	Quote: "Source of Support: None"
Declarations of interest	Quote: "Conflict of Interest: None"
Notes	Location: Kolkata, India We contacted first author twice via e-mail but did not receive a response

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "randomly distributed"

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Das 2006 (*Continued*)

Allocation concealment (selection bias)	Unclear risk	Insufficient information
Blinding of participants and personnel (performance bias) Efficacy	High risk	No information
Blinding of participants and personnel (performance bias) Safety	High risk	No information
Blinding of outcome assessment (detection bias) Efficacy	High risk	No information
Blinding of outcome assessment (detection bias) Safety	High risk	No information
Incomplete outcome data (attrition bias) Efficacy	High risk	Percentage of "improved clinically" reported, no definition. Results for groups C and D not reported.
Incomplete outcome data (attrition bias) Safety	Unclear risk	Quote: "We however did not experience any adverse effect in all four groups." Unclear number of evaluated completers
Selective reporting (reporting bias)	Unclear risk	Insufficient information
Other bias	Unclear risk	-

Macotela-Ruiz 1996

Methods	Single-centre, parallel-group randomized trial Duration: 3 years, from January 1993 to December 1995
Participants	**Inclusion criteria** • Scabies (indisputable, no information about methods of diagnosing scabies) • No age limit **Exclusion criteria** • Pregnant or lactating women • People with renal or hepatic insufficiency • People with antiscabietic treatment in 6 weeks prior to study **Baseline characteristics** • Age (mean): group A: male: 12, female: 16; B: male: 18, female: 20 • Males/females: group A: 56/96, B: 53/32; unclear data, sum of males and females does not correspond to total number of included participants

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Macotela-Ruiz 1996 (*Continued*)

Interventions	A: Oral ivermectin 250 μg/kg body weight on day 1 (n = 152 participants) B: Oral ivermectin 250 μg/kg body weight on day 1, 3, and 10 (n = 121 participants) • 9 participants in group A and 10 participants in group B with secondary infection received dicloxacillin 75 mg/kg body weight per day. • 95 healthy contacts received an oral single dose of 250 μg/kg body weight ivermectin.
Outcomes	• Cure (considerable improvement of dermatosis, no pruritus, no new lesions; up to 45 days)
Funding source	Not stated
Declarations of interest	Not stated
Notes	Location: Santiago Yancuitlalpan, Mexico

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (page 179): "patients were randomized in two groups"
Allocation concealment (selection bias)	Unclear risk	Insufficient information
Blinding of participants and personnel (performance bias) Efficacy	High risk	Quote (page 179): "An open therapeutic study" Not blinded
Blinding of participants and personnel (performance bias) Safety	High risk	Quote (page 179): "An open therapeutic study" Not blinded
Blinding of outcome assessment (detection bias) Efficacy	High risk	Quote (page 179): "An open therapeutic study" Not blinded
Blinding of outcome assessment (detection bias) Safety	High risk	Quote (page 179): "An open therapeutic study" Not blinded
Incomplete outcome data (attrition bias) Efficacy	High risk	No information on dropouts, unclear time point of evaluation, no absolute numbers
Incomplete outcome data (attrition bias) Safety	High risk	No information on dropouts, unclear time point of evaluation, no absolute numbers

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Macotela-Ruiz 1996 (*Continued*)

Selective reporting (reporting bias)	High risk	No data on defined outcomes such as pruritus, papules, excoriation, crusts, etc
Other bias	Unclear risk	-

Manjhi 2014

Methods	Single-centre, parallel-group randomized trial Duration: 1 year, from April 2011 to March 2012
Participants	**Inclusion criteria** • Age above 5 and below 60 years • People of both sexes • People willing to receive either topical or oral therapy • People willing to follow-up at 1st and 6th week or if any complaints in between • Scabies (no information about methods of diagnosing) **Exclusion criteria** • Pregnant and lactating women • People who were not willing to come for follow-up • Any serious systemic illness **Baseline characteristics** • Not stated
Interventions	A: Oral ivermectin 200 μg/kg body weight, single dose (n = 60 participants) B: Permethrin 5% cream, single application below the jaw line after scrub bath and left overnight (n = 60 participants) Not included in this review: C: Gamma benzene hexachloride 1% lotion, single application (n = 60 participants) D: Benzyl benzoate 25% lotion, single application (n = 60 participants)
Outcomes	• Complete improvement based on severity of pruritus or lesions (lesion count: < 10 - mild, 11 to 49 - moderate, > 50 - severe; pruritus: 10-centimetre visual analogue scale: 0 - no pruritus, 1 to 3 - mild, 4 to 6 - moderate, 7 to 10 - severe; week 1 and 6) • Number of participants withdrawn from study due to adverse event
Funding source	Not stated
Declarations of interest	Not stated
Notes	Location: Patna, India Children "below 5y" were excluded; unclear if children of 5 years of age were included or excluded We contacted first author twice via e-mail but did not receive a response

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

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Manjhi 2014 (*Continued*)

Random sequence generation (selection bias)	Unclear risk	Quote (page 1): "simple random sampling" Insufficient information
Allocation concealment (selection bias)	Unclear risk	Quote (page 2): "randomly allocated" Insufficient information
Blinding of participants and personnel (performance bias) Efficacy	High risk	No information
Blinding of participants and personnel (performance bias) Safety	High risk	No information
Blinding of outcome assessment (detection bias) Efficacy	High risk	No information
Blinding of outcome assessment (detection bias) Safety	High risk	No information
Incomplete outcome data (attrition bias) Efficacy	High risk	Quote (page 2): Table/Fig-1 - Table/Fig-5 Results are reported for all 60 randomized participants per treatment group, but actual results of the outcomes scales are not reported; clear explanation of how 'improvement' is reflected in the scales is missing
Incomplete outcome data (attrition bias) Safety	High risk	Quote (page 1): "The main objective of the study is to know the efficacy and safety of Oral Ivermectin in comparison to commonly used topical antiscabies drugs […]" Quote (page 3): "Oral Ivermectin is well tolerated, non irritant to skin, does not show central nervous system side effects because it does not cross blood brain barrier. " No information about safety issues in other treatment groups; no numerical data on safety were reported
Selective reporting (reporting bias)	Unclear risk	Insufficient information
Other bias	Unclear risk	No information on baseline data

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Meenakshi 2014

Methods	Single-centre, parallel-group randomized trial Duration: 10 months, from January to October 2011
Participants	**Inclusion criteria** • Age was at least 12 years • Newly diagnosed scabies: made on basis of history and clinical examination; presence of diffuse itching and visible lesions associated either with ≥ 2 typical locations of scabies (interdigital folds, flexor aspect of wrist and elbow, genitals, anterior axillary folds) or with a household member with itching **Exclusion criteria** • Pregnant or lactating females • Any history of diabetes, hypertension, or any chronic disease • Any psychiatric illness or neurological disorder, any other associated skin disease which can affect the study due to same presentation like atopic dermatitis, dyshidrotic eczema, insect bite reaction, etc. **Baseline characteristics** • Age (mean): group A: 23.55, B: 27.74, C: 28.89 • Males/females: group A: 49/21, B: 41/29, C: 51/19
Interventions	A: Permethrin 5% cream on day 1 and 7, applied over whole body below neck and scrub bath taken 12 hours later (n = 70 participants) B: Oral ivermectin 200 μg/kg body weight on day 1 and 7, applied any time of day (n = 70 participants) Not included in this review: C: Gamma benzene hexachloride 1% lotion on day 1 and 7 applied over whole body below neck and scrub bath taken 12 hours later (n = 70 participants) • Participants of group A and C were instructed to take warm-water bath before application of medicine and then after application of medicine next morning. • They were advised about also treating the family members and prevention of transmission by washing all clothes and bedding that came in contact.
Outcomes	• Complete clinical cure (week 1 and 3; reduction in clinical grading score (up to grade 0 or 1) and itching grading score (up to grade 0, 1, or 2); "moderate or good improvement"): ○ Clinical grading score: scale of 0 to 3: 0 = free of lesions (no lesions), 1 = 10 or fewer lesions (mild), 2 = 11 to 49 lesions (moderate), 3 = 50 or more lesions (severe) ○ Itching grading score: participant was asked for reduction in pruritus, grading was done on given scale by the observer: scale of 0 to 4: 0 = 0% (no pruritus), 1 = 1% to 25% (mild pruritus), 2 = 26% to 50% (moderate pruritus), 3 = 51% to 75% (severe pruritus), 4 = 76% to 100% (very severe pruritus • Number of participants with ≥ 1 adverse event
Funding source	Quote (page 15): "Source of support: Nil"
Declarations of interest	Quote (page 15): "Conflict of interest: Nil"
Notes	Location: Jhansi, India
Risk of bias	

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Meenakshi 2014 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (page 16): "randomly on basis of a computer generated random table"
Allocation concealment (selection bias)	Unclear risk	Insufficient information
Blinding of participants and personnel (performance bias) Efficacy	High risk	Quote (page 15): "open label"
Blinding of participants and personnel (performance bias) Safety	High risk	Quote (page 15): "open label"
Blinding of outcome assessment (detection bias) Efficacy	High risk	Quote (page 15): "open label"
Blinding of outcome assessment (detection bias) Safety	High risk	Quote (page 15): "open label"
Incomplete outcome data (attrition bias) Efficacy	High risk	35/210 participants lost to follow-up or non-compliant (permethrin group: 8; oral ivermectin group: 12; GBH group: 15) Quote (page 18 and Table 2): "several patients were lost during follow up" No intention-to-treat analysis performed.
Incomplete outcome data (attrition bias) Safety	High risk	35/210 participants lost to follow-up or non-compliant (permethrin group: 8; oral ivermectin group: 12; GBH group: 15) Quote (page 18 and Table 2): "several patients were lost during follow up"
Selective reporting (reporting bias)	High risk	Cure (moderate or good improvement) and not cured (no or mild improvement) were defined but not reported Assessment of safety was planned, but not reported numerically
Other bias	Unclear risk	-

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Mushtaq 2010

Methods	Single-centre, parallel-group randomized trial Duration: not stated
Participants	**Inclusion criteria** • Aged 2 to 60 years • Diagnosed as having scabies on history and examination; scraping for mite was performed in cases of doubt **Exclusion criteria** • Pregnant and lactating females • Immunocompromised patients • People having bacterial, fungal, or viral infections of skin • People receiving any treatment for systemic disorders • People who received treatment for scabies in last 4 weeks **Baseline characteristics** (for completers only) • Males/females: group A: 24/20, B: 20/22
Interventions	A: Oral ivermectin 200 μg/kg body weight as a single dose (n = 44 participants completed) B: Permethrin 5% cream at night on whole body for 12 hours, single application (n = 42 participants completed) • 100 participants randomized, number of randomized participants per study group unclear. • Non-responders to first treatment were given second dose at second week in their respective group.
Outcomes	• Cure of disease (no lesions; week 1, 2, and 4) • Number of participants re-treated (week 2) • Number of participants with $\geq$ 1 adverse event
Funding source	Not stated
Declarations of interest	Not stated
Notes	Location: Lahore, Pakistan Probably baseline differences: page 229: "more patients in the ivermectin group had moderate and severe lesions as compared to permethrin group" We contacted first author twice via e-mail but did not receive a response

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "divided by using random number table into group A and group B"
Allocation concealment (selection bias)	Unclear risk	Insufficient information

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Blinding of participants and personnel (performance bias) Efficacy	High risk	No information
Blinding of participants and personnel (performance bias) Safety	High risk	No information
Blinding of outcome assessment (detection bias) Efficacy	High risk	No information
Blinding of outcome assessment (detection bias) Safety	High risk	No information
Incomplete outcome data (attrition bias) Efficacy	High risk	14/100 participants lost to follow-up (unclear how many in each group, probably 6 in ivermectin group, 8 in permethrin group) Quote: "14 participants lost to follow up" No intention-to-treat analysis performed; number of randomized participants per study group unclear
Incomplete outcome data (attrition bias) Safety	High risk	14/100 participants lost to follow-up (unclear how many in each group, probably 6 in ivermectin group, 8 in permethrin group) Quote: "14 participants lost to follow up" Unclear number of randomized participants per study group
Selective reporting (reporting bias)	Unclear risk	Insufficient information
Other bias	High risk	Sex distribution in Table 1 seems to be reversed. Probably baseline differences in severity: "more patients in the ivermectin group had moderate and severe lesions as compared to permethrin group" Inconsistent data for safety (page 229 and 300): 8 versus 7 participants with adverse events

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Rohatgi 2013

Methods	Single-centre, parallel-group randomized trial Duration: 1 year and 7 months, from November 2011 to May 2013
Participants	**Inclusion criteria** • Aged 5 to 15 years • Newly diagnosed with scabies • Diagnosed by dermatologist: people with severity score 1, 2, or 3 were eligible; assessed by counting the number of lesions and assigning a score: 0 (free of lesions - no scabies), 1 (10 or fewer lesions - mild), 2 (11 to 49 lesions - moderate), 3 (50 or more lesions - severe), 4 (crusty - very severe) • Diagnosis confirmed by microscopic examination of mite in "many patients", by biopsy of the skin lesions in "few patients" • Body weight > 15 kg **Exclusion criteria** • Abnormal liver and kidney functions, known thyroid disease, cardiac disorders, nervous system disorders, psychiatric illnesses; people with history of diabetes mellitus, hypertension, or infectious diseases • Any concurrent medication for other illness • Any other associated skin disease that could alter the picture of scabies, or complications of scabies like pyoderma • Known/suspected immunocompromised individuals or parents diagnosed as HIV, having scabies with atypical presentations • Intake of any antiscabetic treatment in the preceding 4 weeks • Intake of topical steroid in the previous 4 weeks • Known hypersensitivity to oral or topical preparations • People whose family/household members or classmates have scabies at the same time • Noncompliant people/guardians **Baseline characteristics** • Males/females: group A: 31/19, group B: 30/20 • Age (mean): group A: 10.5, group B: 9.6
Interventions	A: Permethrin 5% cream, single application to whole body below neck, left overnight (n = 50 participants) B: Oral ivermectin 200 μg/kg body weight as a single dose (n = 50 participants) • All participants were given antipruritic or antihistaminic medication for pruritus. • Participants who showed no signs of cure at first follow-up were given same treatment again only once. • All family contacts received same treatment as the study participant (children < 5 years of age and pregnant women were treated with 12.5% to 25% benzyl benzoate emulsion, supplied free of cost).
Outcomes	• Cure (absence of clinical lesions and no new lesions like papules, vesicles, and classical burrows suggestive of live parasite; week 1, 2, and 4) • Number of participants re-treated (week 1) • Number of participants with $\geq$ 1 adverse event
Funding source	Not stated

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Rohatgi 2013 (*Continued*)

Declarations of interest	Not stated
Notes	Location: Bangalore, India Abstract available, and first author provided unpublished data (doctoral thesis); not all questions were answered by contact author

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (doctoral thesis, page 42): "Simple random sampling" Insufficient information
Allocation concealment (selection bias)	Unclear risk	Insufficient information
Blinding of participants and personnel (performance bias) Efficacy	High risk	Quote (abstract): "open labelled"
Blinding of participants and personnel (performance bias) Safety	High risk	Quote (abstract): "open labelled"
Blinding of outcome assessment (detection bias) Efficacy	High risk	Quote (abstract): "open labelled"
Blinding of outcome assessment (detection bias) Safety	High risk	Quote (abstract): "open labelled"
Incomplete outcome data (attrition bias) Efficacy	Low risk	4/100 participants lost to follow-up (permethrin group: 2; oral ivermectin group: 2) Intention-to-treat analysis performed.
Incomplete outcome data (attrition bias) Safety	Low risk	4/100 participants lost to follow-up (permethrin group: 2; oral ivermectin group: 2)
Selective reporting (reporting bias)	Unclear risk	Insufficient information
Other bias	High risk	Inconsistent data for male/female ratio (page 55/56: 61 males/39 females; page 76: 63 males/37 females) Inconsistent response data in abstract and doctoral thesis; conservative approach was

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		followed

Saqib 2012

Methods	Single-centre, parallel-group randomized trial Duration: not stated
Participants	**Inclusion criteria** • Aged 18 to 60 years • Confirmed diagnosis of scabies by burrow detection by ink method and microscopic evidence of *Sarcoptes scabiei* mite in any of its development stage or its faeces **Exclusion criteria** • Pregnant or lactating women • Hypersensitivity to permethrin or ivermectin • Prior use of topical or systemic scabicide in last 4 weeks • People on radiotherapy, steroids or other immunosuppressive drugs for any systemic or cutaneous indication • People with any chronic debilitating disorders, neoplasias, with neurological, hepatic, or renal dysfunction **Baseline characteristics** • Age (mean ± SD): group A: 31.45 ± 9.78, B: 29.45 ± 9.72 (data from Table 1)
Interventions	A: Permethrin 5% lotion form on whole body (from neck to toe) for 10 to 12 hours followed by a bath, single application; participants received explicit written instructions about topical application (n = 60 participants) B: Oral ivermectin 200 μg/kg body weight as a single dose, taken in the presence of the investigator (n = 60 participants) • All participants were given antihistamines at bedtime during first week. • Secondary infection, when present, was treated with a 7-day course of antibiotic. • Contacts of the participants of both groups were treated at the same time with same treatment (< 5 years of age and pregnant or lactating women were treated with 5% to 10% sulphur ointment).
Outcomes	• Cure (no itching, cutaneous lesions/burrows, and microscopy; week 1 and 2) • Number of participants withdrawn from study due to adverse event
Funding source	Not stated
Declarations of interest	Not stated
Notes	Location: Lahore, Pakistan Statistically significant baseline differences: page 47: "history of scabies in contacts was present more in group A than in group B" Inconsistent data for mean age in abstract and Table 1 We contacted author for more details to assess risk of bias.
Risk of bias	

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Saqib 2012 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "randomly divided" Author confirmed via e-mail: "random number table"
Allocation concealment (selection bias)	Low risk	Author confirmed via e-mail: "assignment by nurse, treated by physician blind to assignment"
Blinding of participants and personnel (performance bias) Efficacy	Low risk	Author confirmed via e-mail: "treated by physician blind to assignment"
Blinding of participants and personnel (performance bias) Safety	High risk	Probably not blinded
Blinding of outcome assessment (detection bias) Efficacy	Low risk	Author confirmed via e-mail: "treated by physician blind to assignment"
Blinding of outcome assessment (detection bias) Safety	High risk	Probably not blinded
Incomplete outcome data (attrition bias) Efficacy	Low risk	Quote: "All 120 patients completed the study."
Incomplete outcome data (attrition bias) Safety	Low risk	Quote: "All 120 patients completed the study."
Selective reporting (reporting bias)	Unclear risk	Insufficient information
Other bias	High risk	Inconsistent data for mean age in abstract and Table 1 Statistically significant baseline differences: page 47: "history of scabies in contacts was present more in group A than in group B"

Sharma 2011

Methods	Single-centre, parallel-group randomized trial Duration: 1 year and 4 months, from December 2006 to March 2008
Participants	**Inclusion criteria** • Age over 5 years and/or > 15 kg

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	• Clinically diagnosed scabies: demonstration of eggs, larva, mites/mite products, or faecal pellets by light microscopy in the scrapings from multiple representative or suspected skin lesions in 10% potassium hydroxide and/or the presence of ≥ 3 of the following clinical criteria: demonstration of burrow; presence of scabetic lesions at the classical sites; nocturnal pruritus; family history of similar illness **Exclusion criteria** • Pregnant and lactating women • People with immunodeficiency or severe systemic disease or with heavily crusted or nodular lesions, secondary infection or eczematization and coexisting dermatological disease that could interfere with the diagnosis and subsequent monitoring of scabies • Antiscabetic or topical steroid in the previous 4 weeks • Known hypersensitivity to the trial drugs **Baseline characteristics** • Age (mean ± SD): group A: 21.38 ± 13.17, B: 23.40 ± 11.03, C: 23.53 ± 12.73 • Males/females: group A: 19/21, B: 29/11, C: 24/16
Interventions	A: Permethrin 5% cream, self applied on day 1 and placebo tablets of vitamin B-complex on day 1 and 15 (n = 40 participants) B: Placebo cream, self applied on day 1 and oral ivermectin 200 μg/kg body weight on day 1 and placebo tablet of vitamin B-complex on day 15 (n = 40 participants) C: Placebo cream, self applied on day 1 and oral ivermectin 200 μg/kg body weight on day 1 and 15 (n = 40 participants) • Participants were instructed to apply the medication all over the body below the neck at night. • All family contacts were provided with permethrin 5% cream for single overnight application, free of cost.
Outcomes	• Complete clinical cure (defined as reduction in both the number of lesions as well as the grade of pruritus by more than or equal to 50% (that is, moderate and good improvement) and negative microscopy; week 1, 2, and 4) • Number of participants with ≥ 1 adverse event (data for group B and C combined)
Funding source	Not stated
Declarations of interest	Not stated
Notes	Location: New Delhi, India

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "computer-generated random numbers"
Allocation concealment (selection bias)	Low risk	Quote: "dispensed by a trained staff nurse in identical pre-coded and numbered container"

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Sharma 2011 (*Continued*)

Blinding of participants and personnel (performance bias) Efficacy	Low risk	Quote: "placebos were similar to the trial drugs in color, shape, size, and consistency and were dispensed by a trained staff nurse in identical pre-coded and numbered container"
Blinding of participants and personnel (performance bias) Safety	Low risk	Quote: "placebos were similar to the trial drugs in color, shape, size, and consistency and were dispensed by a trained staff nurse in identical pre-coded and numbered container"
Blinding of outcome assessment (detection bias) Efficacy	Low risk	Quote: "neither the investigator nor the patients were aware of the composition of drugs allocated and the code was revealed only after the completion of the study"
Blinding of outcome assessment (detection bias) Safety	Low risk	Quote: "neither the investigator nor the patients were aware of the composition of drugs allocated and the code was revealed only after the completion of the study"
Incomplete outcome data (attrition bias) Efficacy	Low risk	3/120 participants lost to follow-up (permethrin group: 2; oral ivermectin - 2 doses group: 1) No withdrawal at 1 week follow-up; no intention-to-treat analysis for week 2 and 4
Incomplete outcome data (attrition bias) Safety	Unclear risk	3/120 participants lost to follow-up (permethrin group: 2; oral ivermectin - 2 doses group: 1) Number of adverse events reported for ivermectin groups were combined
Selective reporting (reporting bias)	Unclear risk	Insufficient information
Other bias	Unclear risk	-

Usha 2000

Methods	Single-centre, parallel-group randomized trial Duration: 1 year and 5 months, from August 1996 to December 1997
Participants	**Inclusion criteria** • Older than 5 years of age • Scabies: diagnosed by the demonstration of eggs, larva, mites, or faecal pellets by light microscopy or by the presence of ≥ 3 of the following clinical criteria confirmed independently by 2 consultants: demonstration of burrow, presence of scabietic lesions

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	at the classical sites, nocturnal pruritus, family history of similar illness **Exclusion criteria** • Pregnant and lactating women • Any antiscabietic treatment in the previous month • People with serious central nervous system, hepatic, cardiac, or renal disease **Baseline characteristics** • Age (mean ± SD): group A: 21.28 ± 13.44, B: 22.4 ± 12.6 • Males/females: group A: 26/14, B: 33/12
Interventions	A: Oral ivermectin 200 μg/kg body weight, single dose, supervised (n = 40 participants) B: Permethrin 5% cream, single application overnight (n = 45 participants) • All participants received standard instructions (about the mode of application, general measures, importance of treating the family contacts, prevention of fomite transmission). • Participants with treatment failure (no improvement in pruritus and skin lesions, appearance of new lesions, or presence of mites or their products on microscopy) at week 2 received another dose of same treatment; at week 4 cross-over to other group. • Secondary infection was treated with a 7-day course of erythromycin 250 mg 4 times daily. • All family contacts received same treatment as the study participant (children < 5 years of age and pregnant women were treated with 12.5% to 25% benzyl benzoate emulsion).
Outcomes	• Complete clearance (good improvement; week 1, 2, 4, and 8) • Number of participants re-treated (week 2 and 4) • Number of participants with ≥ 1 adverse event • Number of participants withdrawn from study due to adverse event
Funding source	Not stated
Declarations of interest	Not stated
Notes	Location: Trivandrum, India

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote (page 237): "randomly allocated" Insufficient information
Allocation concealment (selection bias)	Unclear risk	Quote (page 237): "randomly allocated" Insufficient information
Blinding of participants and personnel (performance bias) Efficacy	High risk	No information

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Usha 2000 (*Continued*)

Blinding of participants and personnel (performance bias) Safety	High risk	No information
Blinding of outcome assessment (detection bias) Efficacy	High risk	No information
Blinding of outcome assessment (detection bias) Safety	High risk	No information
Incomplete outcome data (attrition bias) Efficacy	Low risk	No missing outcome data
Incomplete outcome data (attrition bias) Safety	Low risk	No missing outcome data
Selective reporting (reporting bias)	Unclear risk	Insufficient information
Other bias	Unclear risk	Data for 'complete clearance' reported in figure only; numerical data were extracted from chart for meta-analysis

Wankhade 2013

Methods	Single-centre, parallel-group randomized trial Duration: not stated
Participants	**Inclusion criteria** • People with scabies **Exclusion criteria** • Not stated **Baseline characteristics** • Not stated
Interventions	A: Permethrin 5% (type of formulation not stated; n = unclear) B: Oral ivermectin 200 μg/kg body weight as a single dose (n = unclear) • 100 participants were allocated. • If there was no sign of cure, same treatment was repeated.
Outcomes	• Cure rate (no definition; time point of evaluation unclear)
Funding source	Not stated
Declarations of interest	Not stated

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Wankhade 2013 (*Continued*)

Notes	Location: Nanded, India Only abstract available We contacted first author twice via e-mail but did not receive a response

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomely allocated" Insufficient information
Allocation concealment (selection bias)	Unclear risk	Quote: "randomely allocated" Insufficient information
Blinding of participants and personnel (performance bias) Efficacy	High risk	No information
Blinding of participants and personnel (performance bias) Safety	High risk	No information
Blinding of outcome assessment (detection bias) Efficacy	High risk	No information
Blinding of outcome assessment (detection bias) Safety	High risk	No information
Incomplete outcome data (attrition bias) Efficacy	High risk	No numerical data given.
Incomplete outcome data (attrition bias) Safety	High risk	No numerical data given.
Selective reporting (reporting bias)	Unclear risk	Insufficient information
Other bias	Unclear risk	-

Wankhade 2016

Methods	Single-centre, parallel-group randomized trial Duration: 1 year and 1 month, from March 2013 to March 2014
Participants	**Inclusion criteria** • Age between 5 to 60 years

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	• New patients of scabies as diagnosed by dermatologist • History of involvement of family member or similar symptoms in contacts • Presence of nocturnal itching • For those whose microscopic examination was negative, inclusion in study was based on clinical criteria **Exclusion criteria** • Pregnant and lactating women • People with any other associated skin disease that could alter the picture of scabies, or complications of scabies like pyoderma • Known or suspected immunocompromised individuals like HIV • History of topical steroid use in the previous 4 weeks or use of topical or systemic antibiotic therapy in the week before entry into the study • Received any antiscabetic treatment in the past 4 weeks • Noncompliant participants or guardians • People not willing to come for follow-up • People having scabies with atypical presentation like crusted scabies or scabies incognito • History of allergy to any of the study drugs • People with associated comorbid condition like hypertension, diabetes, liver, kidney disorder **Baseline characteristics** • Age (mean ± SD): group A: 16.74 ± 9.90, B: 22.04 ± 10.61, C: 23.74 ± 9.91 • Males/females: group A: 30/20, B: 28/22, C: 29/21
Interventions	A: Permethrin 5% cream, single application (n = 50 participants) B: Oral ivermectin 200 μg/kg body weight, single application (n = 50 participants) Not included in this review: C: Combination of topical permethrin with oral ivermectin (n = 50 participants) • If there were no signs of cure, the same intervention was repeated at the end of week 1 only once.
Outcomes	• Cure (no new clinical lesions and improvement in pruritus, no new lesions like papules, vesicles, and classical burrows suggestive of live parasite should be seen; week 1 and 4) • Number of participants with $\geq$ 1 adverse event • Number of participants withdrawn due to adverse event
Funding source	Quote (page 71): "Funding: None"
Declarations of interest	Quote (page 71): "Conflict of interest: None declared"
Notes	Location: Nanded, India

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote (page 68): "randomised" Insufficient information

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Wankhade 2016 (*Continued*)

Allocation concealment (selection bias)	Unclear risk	Quote (page 69): "randomly allocated" Insufficient information
Blinding of participants and personnel (performance bias) Efficacy	High risk	Quote (page 68): "open-label"
Blinding of participants and personnel (performance bias) Safety	High risk	Quote (page 68): "open-label"
Blinding of outcome assessment (detection bias) Efficacy	High risk	Quote (page 68): "open-label"
Blinding of outcome assessment (detection bias) Safety	High risk	Quote (page 68): "open-label"
Incomplete outcome data (attrition bias) Efficacy	Low risk	No missing outcome data
Incomplete outcome data (attrition bias) Safety	Low risk	No missing outcome data
Selective reporting (reporting bias)	Unclear risk	Insufficient information
Other bias	Unclear risk	-

Abbreviations: GBH: gamma benzene hexachloride; SD: standard deviation.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Chhaiya 2013	No original data, same study population as in Chhaiya 2012
Goldust 2012	Suspicion of flawed data Issue was presented and discussed at the annual meeting of the Cochrane Skin Group on 9-10 January 2017 in Berlin: unanimous decision to exclude the study
Goldust 2013	Suspicion of flawed data Issue was presented and discussed at the annual meeting of the Cochrane Skin Group on 9-10 January 2017 in Berlin: unanimous decision to exclude the study

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(*Continued*)

NCT02841215	Study of people with crusted scabies; not yet open for participant recruitment
Ranjkesh 2013	Suspicion of flawed data Issue was presented and discussed at the annual meeting of the Cochrane Skin Group on 9-10 January 2017 in Berlin: unanimous decision to exclude the study

Characteristics of ongoing studies *[ordered by study ID]*

NCT02407782

Trial name or title	Oral Ivermectin Versus Topical Permethrin to Treat Scabies in Children (SCRATCH)
Methods	Multicentre, randomized trial Duration: 1 year and 9 months, from January 2016 to September 2017 (estimated)
Participants	**Inclusion criteria** • Children up to 16 years of age • Weight > 15 kg • Documented diagnosis of scabies, defined by positive dermoscopic examination **Exclusion criteria** • Previous scabies therapy during the past 4 weeks • Known allergy to ivermectin or permethrin • Widespread eczematization or impetiginization • Liver and renal failure
Interventions	A: Permethrin 5% cream on day 1 and 10 B: Oral ivermectin 200 μg/kg body weight on day 1 and 10 • Estimated enrolment: 502 participants
Outcomes	• Assessment of skin lesions and healing at day 28
Starting date	January 2016
Contact information	Franck BORALEVI, Professor 05 56 79 59 41 franck.boralevi@chu-bordeaux.fr Fabienne NACKA, PhD 05 57 82 01 08 fabienne.nacka@chu-bordeaux.fr
Study ID	Clinical trial registry: NCT02407782 Other study ID number: CHUBX 2011/16
Notes	Location: Bordeaux, France Source: clinicaltrials.gov/ct2/show/NCT02407782 (last updated: 3 June 2016)

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DATA AND ANALYSES

Comparison 1. Ivermectin 200 μg/kg (1 to 3 doses) versus permethrin 5% cream (1 to 3 applications)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Complete clearance - week 1	6	613	Risk Ratio (M-H, Random, 95% CI)	0.65 [0.54, 0.78]
2 Complete clearance - week 2	5	459	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.76, 1.08]
3 Complete clearance - week 4	6		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.1 IVER 1 dose versus PER 1 application	1	80	Risk Ratio (M-H, Random, 95% CI)	1.0 [0.86, 1.16]
3.2 IVER 1 to 3 doses versus PER 1 to 3 applications	5	581	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.82, 1.03]
3.3 IVER 2 doses versus PER 1 application	1	80	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.83, 1.14]
4 Subgroup analysis for 1.3.2 - complete clearance - week 4	5		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
4.1 IVER 1 to 3 doses versus PER 1 to 3 applications - 5 studies	5	581	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.82, 1.03]
4.2 IVER 1 to 3 doses versus PER 1 to 3 applications - 3 studies	3	410	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.91, 1.06]
5 Number of participants with ≥ 1 adverse event - week 2	1	55	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
6 Number of participants with ≥ 1 adverse event - week 4	4	502	Risk Ratio (M-H, Random, 95% CI)	1.30 [0.35, 4.83]
7 Withdrawal due to adverse event - week 4	3	305	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

Comparison 2. Ivermectin 200 μg/kg (1 to 2 doses) versus permethrin 5% lotion (1 to 5 applications)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Complete clearance - week 1	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 IVER 1 dose versus PER 1 application	1	120	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.74, 1.17]
1.2 IVER 1 dose versus PER on 5 consecutive nights	1	107	Risk Ratio (M-H, Random, 95% CI)	0.70 [0.47, 1.03]
2 Complete clearance - week 2	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 IVER 1 dose versus PER 1 application	1	120	Risk Ratio (M-H, Random, 95% CI)	1.0 [0.78, 1.29]
2.2 IVER 2 doses versus PER on 5 consecutive nights	1	107	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.81, 1.17]

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3 Number of participants with ≥ 1 adverse event - week 2	1	100	Risk Ratio (M-H, Random, 95% CI)	5.00 [0.25, 101.58]
4 Withdrawal due to adverse event - week 2	1	120	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

Comparison 3. Ivermectin 200 μg/kg (1 to 3 doses) versus ivermectin 1% lotion/solution (1 to 3 applications)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Complete clearance - week 1	1	62	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.65, 1.08]
2 Complete clearance - week 2	1	62	Risk Ratio (M-H, Random, 95% CI)	1.0 [0.94, 1.06]
3 Complete clearance - week 4	2	272	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.95, 1.03]
4 Number of participants with ≥ 1 adverse event - week 4	1	201	Risk Ratio (M-H, Random, 95% CI)	5.05 [0.25, 103.87]
5 Withdrawal due to adverse event - week 4	1	62	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

Comparison 4. Ivermectin 1% lotion (1 to 3 applications) versus permethrin 5% cream (1 to 3 applications)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Complete clearance - week 4	1	210	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.96, 1.08]
2 Number of participants with ≥ 1 adverse event - week 4	1	200	Risk Ratio (M-H, Random, 95% CI)	0.33 [0.01, 7.93]

Comparison 5. Ivermectin 200 μg/kg (1 dose) versus ivermectin 200 μg/kg (2 doses)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Complete clearance - week 4	1	80	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.83, 1.14]

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Analysis 1.1. Comparison 1 Ivermectin 200 μg/kg (1 to 3 doses) versus permethrin 5% cream (1 to 3 applications), Outcome 1 Complete clearance - week 1.

Review: Ivermectin and permethrin for treating scabies

Comparison: 1 Ivermectin 200 μ g/kg (1 to 3 doses) versus permethrin 5% cream (1 to 3 applications)

Outcome: 1 Complete clearance - week 1

Study or subgroup	Ivermectin (single dose) n/N	Permethrin (once applied) n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Bachewar 2009 (1)	15/34	23/34		13.1 %	0.65 [0.42, 1.02]
Meenakshi 2014 (2)	32/70	52/70		22.7 %	0.62 [0.46, 0.82]
Rohatgi 2013 (3)	28/50	34/50		21.0 %	0.82 [0.60, 1.12]
Sharma 2011 (4)	26/80	27/40		16.2 %	0.48 [0.33, 0.71]
Usha 2000 (5)	4/40	14/45		3.1 %	0.32 [0.12, 0.90]
Wankhade 2016 (6)	29/50	39/50		23.8 %	0.74 [0.56, 0.98]
Total (95% CI)	**324**	**289**		**100.0 %**	**0.65 [0.54, 0.78]**

Total events: 134 (Ivermectin (single dose)), 189 (Permethrin (once applied))

Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 7.65$, df = 5 (P = 0.18); $I^2 = 35\%$

Test for overall effect: Z = 4.52 (P < 0.00001)

Test for subgroup differences: Not applicable

(1) IVER: 7/34 imputed (NRI); PER: 6/34 imputed (NRI)

(2) IVER: 12/70 imputed (NRI); PER: 8/70 imputed (NRI)

(3) IVER: 2/50 ITT-NRI; PER: 2/50 ITT-NRI

(4) IVER: 1/80 imputed (NRI); PER: 2/40 imputed (NRI)

(5) No imputation

(6) No imputation

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Analysis 1.2. Comparison 1 Ivermectin 200 μg/kg (1 to 3 doses) versus permethrin 5% cream (1 to 3 applications), Outcome 2 Complete clearance - week 2.

Review: Ivermectin and permethrin for treating scabies

Comparison: 1 Ivermectin 200 μ g/kg (1 to 3 doses) versus permethrin 5% cream (1 to 3 applications)

Outcome: 2 Complete clearance - week 2

Study or subgroup	Ivermectin n/N	Permethrin n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Bachewar 2009 (1)	27/34	27/34		21.7 %	1.00 [0.79, 1.27]
Mushtaq 2010 (2)	24/44	20/42		12.0 %	1.15 [0.76, 1.74]
Rohatgi 2013 (3)	45/50	46/50		31.1 %	0.98 [0.86, 1.11]
Sharma 2011 (4)	57/80	33/40		24.9 %	0.86 [0.71, 1.05]
Usha 2000 (5)	14/40	31/45		10.3 %	0.51 [0.32, 0.81]
Total (95% CI)	**248**	**211**		**100.0 %**	**0.91 [0.76, 1.08]**

Total events: 167 (Ivermectin), 157 (Permethrin)

Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 10.23$, df = 4 (P = 0.04); $I^2 = 61\%$

Test for overall effect: Z = 1.08 (P = 0.28)

Test for subgroup differences: Not applicable

(1) IVER: 44.44% of participants were re-treated after 1 week, 7/34 imputed (NRI); PER: 17.86% of participants were re-treated after 1 week, 6/34 imputed (NRI)

(2) IVER: single dose, per-protocol analysis; PER: single application, per-protocol analysis

(3) IVER, PER: participants who showed no signs of cure at 1st follow-up were given same treatment again, 2/50 ITT-NRI for each group

(4) IVER: single dose, supervised, 1/80 imputed (NRI); PER: single application, 2/40 imputed (NRI)

(5) IVER: single dose, supervised, no imputation; PER: single application, no imputation

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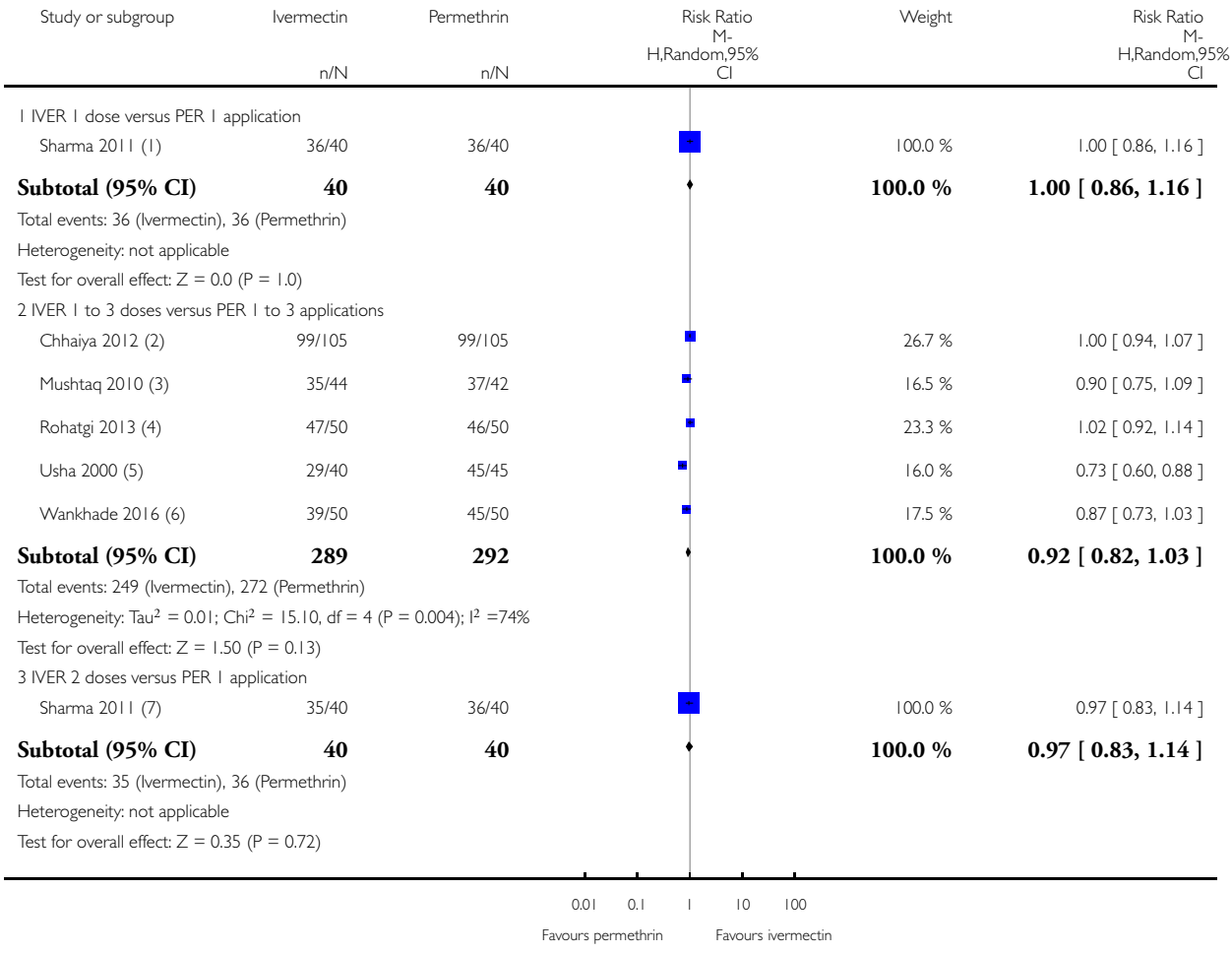
Analysis 1.3. Comparison 1 Ivermectin 200 μg/kg (1 to 3 doses) versus permethrin 5% cream (1 to 3 applications), Outcome 3 Complete clearance - week 4.

Review: Ivermectin and permethrin for treating scabies

Comparison: 1 Ivermectin 200 μ g/kg (1 to 3 doses) versus permethrin 5% cream (1 to 3 applications)

Outcome: 3 Complete clearance - week 4



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(1) IVER: single dose, no imputation; PER: single application, self-applied, no imputation

(2) IVER, PER: participants who were not cured were prescribed repeat intervention along with anti-histaminic at week 2 and week 3; IVER: 5/105 imputed (NRI); PER: 6/105 imputed (NRI)

(3) IVER, PER: non-responders to 1st treatment were given 2nd dose at week 2 in their respective groups, per-protocol analysis

(4) IVER, PER: participants who showed no signs of cure at 1st follow-up were given same treatment again, 2/50 ITT-NRI for each group

(5) IVER: 12 participants were re-treated at week 2, no imputation; PER: 1 participant was re-treated at week 2, no imputation

(6) IVER, PER: non-responders to 1st treatment were given 2nd dose at week 1 in their respective groups, no imputation

(7) IVER: two doses, 1/40 imputed (NRI); PER: single application, self-applied, 2/40 imputed (NRI)

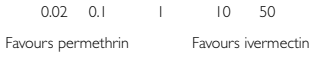
Analysis 1.4. Comparison 1 Ivermectin 200 μg/kg (1 to 3 doses) versus permethrin 5% cream (1 to 3 applications), Outcome 4 Subgroup analysis for 1.3.2 - complete clearance - week 4.

Review: Ivermectin and permethrin for treating scabies

Comparison: 1 Ivermectin 200 μ g/kg (1 to 3 doses) versus permethrin 5% cream (1 to 3 applications)

Outcome: 4 Subgroup analysis for 1.3.2 - complete clearance - week 4

Study or subgroup	Ivermectin n/N	Permethrin n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 IVER 1 to 3 doses versus PER 1 to 3 applications - 5 studies					
Chhaiya 2012 (1)	99/105	99/105		26.7 %	1.00 [0.94, 1.07]
Mushtaq 2010 (2)	35/44	37/42		16.5 %	0.90 [0.75, 1.09]
Rohatgi 2013 (3)	47/50	46/50		23.3 %	1.02 [0.92, 1.14]
Usha 2000 (4)	29/40	45/45		16.0 %	0.73 [0.60, 0.88]
Wankhade 2016 (5)	39/50	45/50		17.5 %	0.87 [0.73, 1.03]
Subtotal (95% CI)	**289**	**292**		**100.0 %**	**0.92 [0.82, 1.03]**
Total events: 249 (Ivermectin), 272 (Permethrin)					
Heterogeneity: Tau^2 = 0.01; Chi^2 = 15.10, df = 4 (P = 0.004); I^2 =74%					
Test for overall effect: Z = 1.50 (P = 0.13)					
2 IVER 1 to 3 doses versus PER 1 to 3 applications - 3 studies					
Chhaiya 2012 (6)	99/105	99/105		52.6 %	1.00 [0.94, 1.07]
Rohatgi 2013 (7)	47/50	46/50		31.7 %	1.02 [0.92, 1.14]
Wankhade 2016 (8)	39/50	45/50		15.6 %	0.87 [0.73, 1.03]
Subtotal (95% CI)	**205**	**205**		**100.0 %**	**0.98 [0.91, 1.06]**
Total events: 185 (Ivermectin), 190 (Permethrin)					



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Study or subgroup	Ivermectin n/N	Permethrin n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Heterogeneity: Tau² = 0.00; Chi² = 3.11, df = 2 (P = 0.21); I² =36%					
Test for overall effect: Z = 0.40 (P = 0.69)					
Test for subgroup differences: Chi² = 1.06, df = 1 (P = 0.30), I² =6%					

(1) IVER, PER: participants who were not cured were prescribed repeat intervention along with anti-histaminic at week 2 and week 3; IVER: 5/105 imputed (NRI); PER: 6/105 imputed (NRI)

(2) IVER, PER: non-responders to 1st treatment were given 2nd dose at week 2 in their respective groups, per-protocol analysis

(3) IVER, PER: participants who showed no signs of cure at 1st follow-up were given same treatment again, 2/50 ITT-NRI for each group

(4) IVER: 12 participants were re-treated at week 2, no imputation; PER: 1 participant was re-treated at week 2, no imputation

(5) IVER, PER: non-responders to 1st treatment were given 2nd dose at week 1 in their respective groups, no imputation

(6) IVER, PER: participants who were not cured were prescribed repeat intervention along with anti-histaminic at week 2 and week 3; IVER: 5/105 imputed (NRI); PER: 6/105 imputed (NRI)

(7) IVER, PER: participants who showed no signs of cure at 1st follow-up were given same treatment again, 2/50 ITT-NRI for each group

(8) IVER, PER: non-responders to 1st treatment were given 2nd dose at week 1 in their respective groups, no imputation

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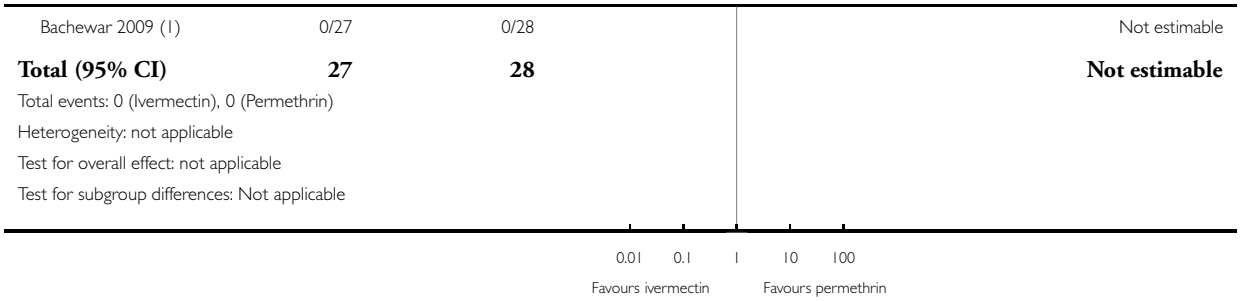
Analysis 1.5. Comparison 1 Ivermectin 200 μg/kg (1 to 3 doses) versus permethrin 5% cream (1 to 3 applications), Outcome 5 Number of participants with ≥ 1 adverse event - week 2.

Review: Ivermectin and permethrin for treating scabies

Comparison: 1 Ivermectin 200 μ g/kg (1 to 3 doses) versus permethrin 5% cream (1 to 3 applications)

Outcome: 5 Number of participants with ≥ 1 adverse event - week 2

Study or subgroup	Ivermectin n/N	Permethrin n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Bachewar 2009 (1)	0/27	0/28			Not estimable
Total (95% CI)	**27**	**28**			**Not estimable**
Total events: 0 (Ivermectin), 0 (Permethrin)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
Test for subgroup differences: Not applicable					



(1) IVER: 44.44% of participants were re-treated after 1 week; PER: 17.86% of participants were re-treated after 1w

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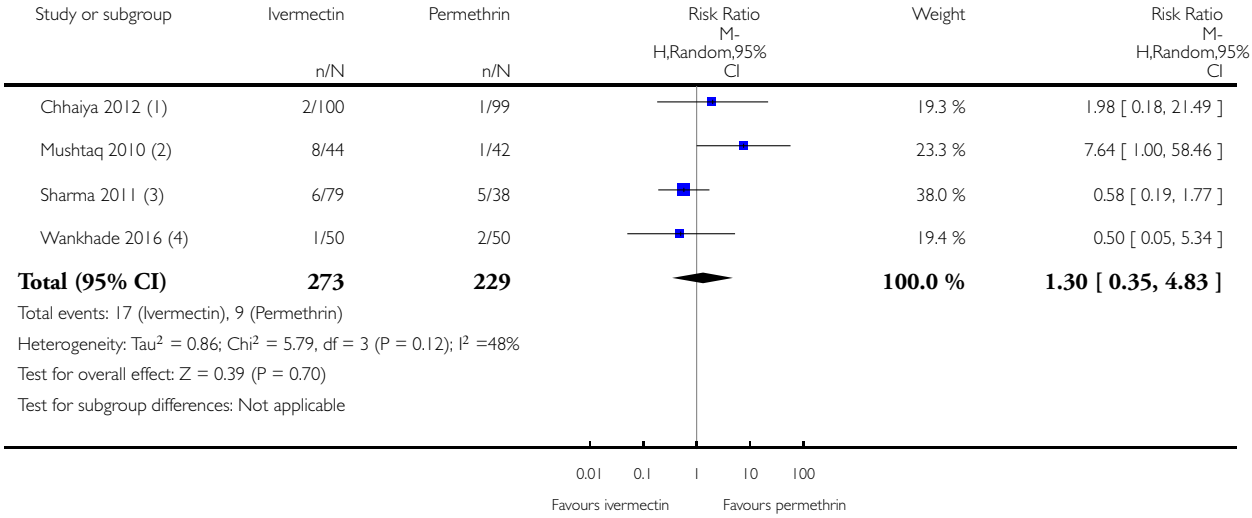
Analysis 1.6. Comparison 1 Ivermectin 200 μg/kg (1 to 3 doses) versus permethrin 5% cream (1 to 3 applications), Outcome 6 Number of participants with ≥ 1 adverse event - week 4.

Review: Ivermectin and permethrin for treating scabies

Comparison: 1 Ivermectin 200 μ g/kg (1 to 3 doses) versus permethrin 5% cream (1 to 3 applications)

Outcome: 6 Number of participants with ≥ 1 adverse event - week 4



(1) IVER, PER: participants who were not cured were prescribed repeat intervention along with anti-histaminic at week 2 and week 3

(2) Inconsistent data (p. 229 and 300): 8 versus 7 patients with adverse events; IVER, PER: non-responders to 1st treatment were given 2nd dose at week 2 in their respective groups

(3) IVER: participants from 2 groups combined, participants were treated 1x or 2x, almost in same proportion; PER: single application

(4) IVER: single dose; PER: single application

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Analysis 1.7. Comparison 1 Ivermectin 200 μg/kg (1 to 3 doses) versus permethrin 5% cream (1 to 3 applications), Outcome 7 Withdrawal due to adverse event - week 4.

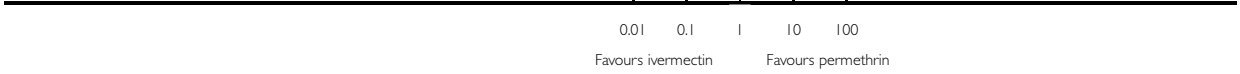
Review: Ivermectin and permethrin for treating scabies

Comparison: 1 Ivermectin 200 μ g/kg (1 to 3 doses) versus permethrin 5% cream (1 to 3 applications)

Outcome: 7 Withdrawal due to adverse event - week 4

Study or subgroup	Ivermectin n/N	Permethrin n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Manjhi 2014 (1)	0/60	0/60			Not estimable
Usha 2000 (2)	0/40	0/45			Not estimable
Wankhade 2016 (3)	0/50	0/50			Not estimable
Total (95% CI)	**150**	**155**			**Not estimable**

Total events: 0 (Ivermectin), 0 (Permethrin)
Heterogeneity: not applicable
Test for overall effect: not applicable
Test for subgroup differences: Not applicable



(1) IVER: single dose; PER: single application

(2) IVER: 12 participants were re-treated at week 2; PER: 1 participant was re-treated at week 2

(3) IVER, PER: non-responders re-treated at week 1

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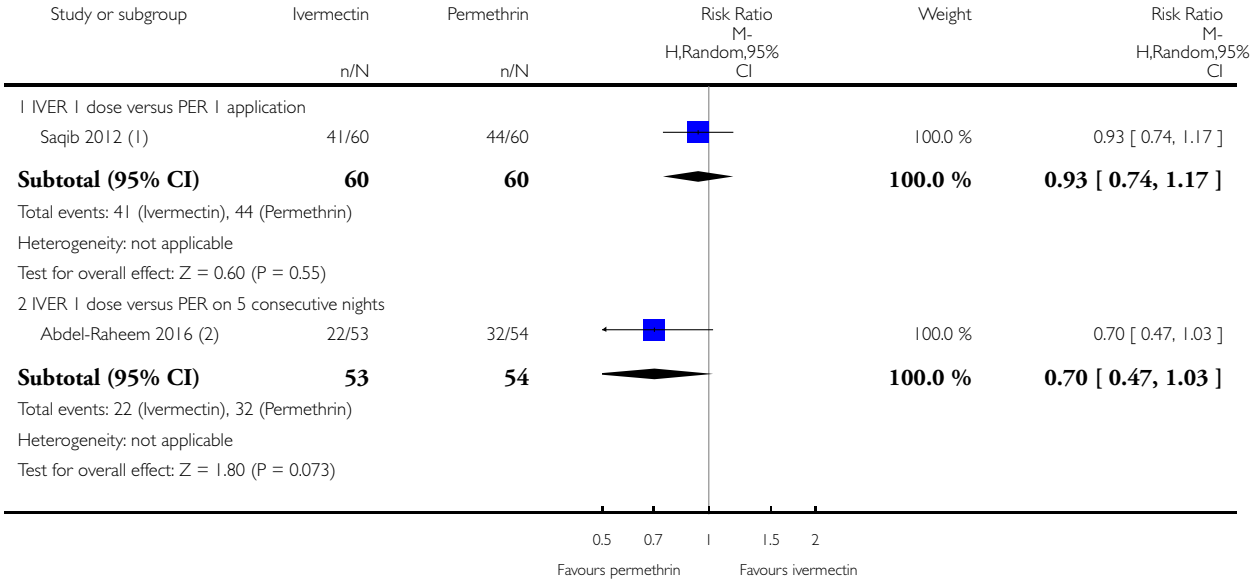
Analysis 2.1. Comparison 2 Ivermectin 200 μg/kg (1 to 2 doses) versus permethrin 5% lotion (1 to 5 applications), Outcome 1 Complete clearance - week 1.

Review: Ivermectin and permethrin for treating scabies

Comparison: 2 Ivermectin 200 μ g/kg (1 to 2 doses) versus permethrin 5% lotion (1 to 5 applications)

Outcome: 1 Complete clearance - week 1



(1) IVER: single dose, supervised, no imputation; PER: single application, patient-applied, no imputation

(2) IVER: single dose, supervised, 3/53 imputed (NRI); PER: on 5 consecutive nights, patient-applied; 2.5% for children below 10 years, 4/54 imputed (NRI)

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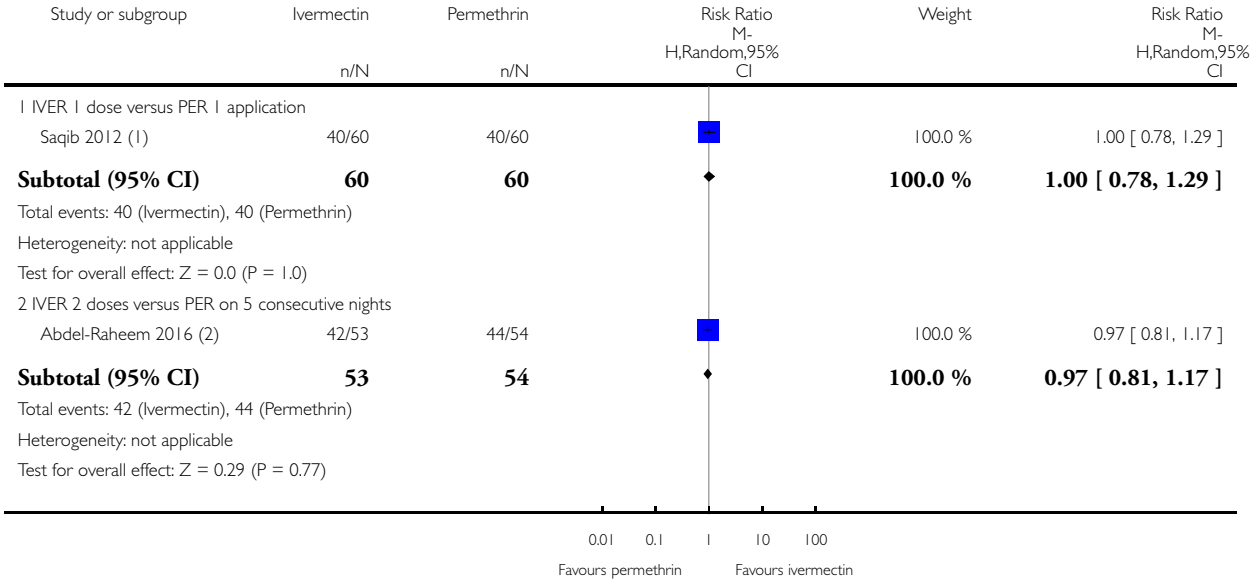
Analysis 2.2. Comparison 2 Ivermectin 200 μg/kg (1 to 2 doses) versus permethrin 5% lotion (1 to 5 applications), Outcome 2 Complete clearance - week 2.

Review: Ivermectin and permethrin for treating scabies

Comparison: 2 Ivermectin 200 μ g/kg (1 to 2 doses) versus permethrin 5% lotion (1 to 5 applications)

Outcome: 2 Complete clearance - week 2



(1) IVER: single dose, supervised, no imputation; PER: single application, patient-applied, no imputation

(2) IVER: all participants were re-treated at week 1, 3/53 imputed (NRI); PER: patient-applied; 2.5% for children below 10 years, 4/54 imputed (NRI)

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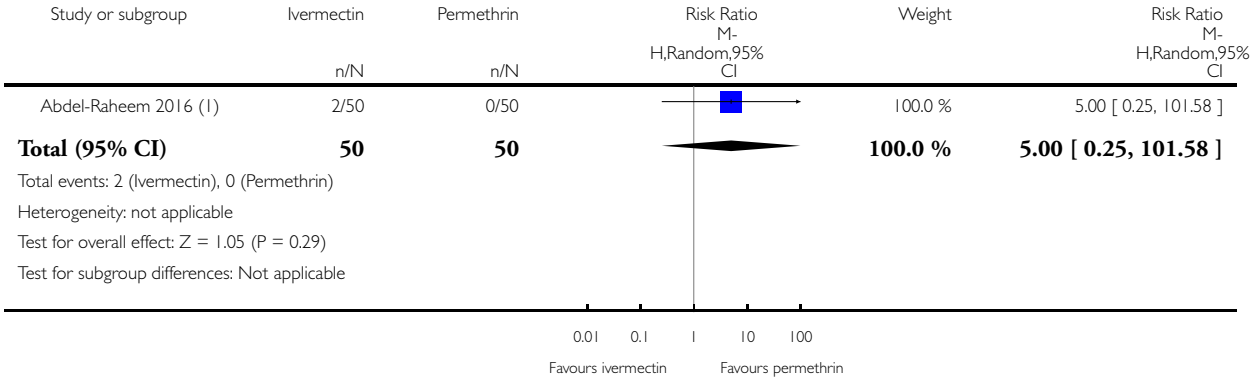
Analysis 2.3. Comparison 2 Ivermectin 200 μg/kg (1 to 2 doses) versus permethrin 5% lotion (1 to 5 applications), Outcome 3 Number of participants with ≥ 1 adverse event - week 2.

Review: Ivermectin and permethrin for treating scabies

Comparison: 2 Ivermectin 200 μ g/kg (1 to 2 doses) versus permethrin 5% lotion (1 to 5 applications)

Outcome: 3 Number of participants with ≥ 1 adverse event - week 2



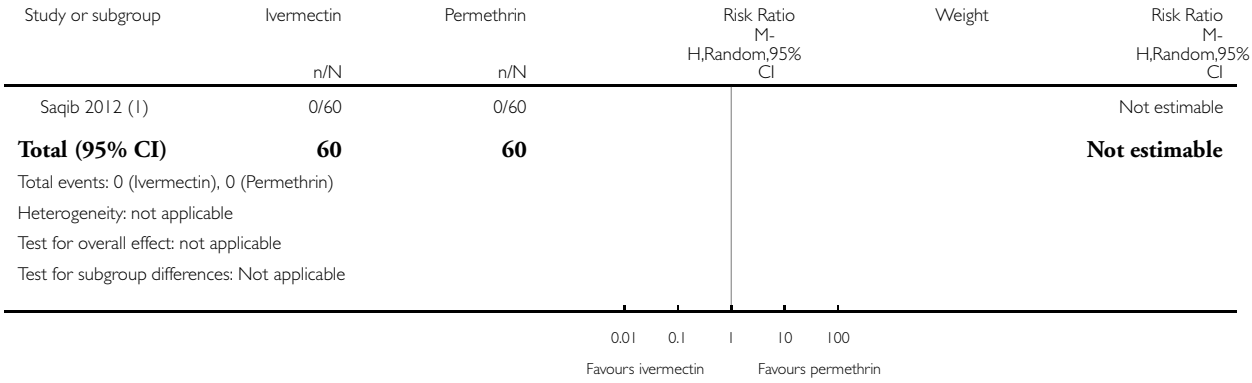
(1) IVER: all participants were re-treated at week 1; PER: patient-applied; 2.5% for children below 10 years

Analysis 2.4. Comparison 2 Ivermectin 200 μg/kg (1 to 2 doses) versus permethrin 5% lotion (1 to 5 applications), Outcome 4 Withdrawal due to adverse event - week 2.

Review: Ivermectin and permethrin for treating scabies

Comparison: 2 Ivermectin 200 μ g/kg (1 to 2 doses) versus permethrin 5% lotion (1 to 5 applications)

Outcome: 4 Withdrawal due to adverse event - week 2



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(1) IVER: single dose, supervised; PER: single application, patient-applied

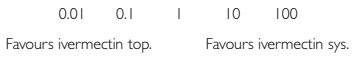
Analysis 3.1. Comparison 3 Ivermectin 200 μg/kg (1 to 3 doses) versus ivermectin 1% lotion/solution (1 to 3 applications), Outcome 1 Complete clearance - week 1.

Review: Ivermectin and permethrin for treating scabies

Comparison: 3 Ivermectin 200 μ g/kg (1 to 3 doses) versus ivermectin 1% lotion/solution (1 to 3 applications)

Outcome: 1 Complete clearance - week 1

Study or subgroup	Ivermectin sys. n/N	Ivermectin top. n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Ahmad 2016 (1)	22/30	28/32		100.0 %	0.84 [0.65, 1.08]
Total (95% CI)	**30**	**32**		**100.0 %**	**0.84 [0.65, 1.08]**
Total events: 22 (Ivermectin sys.), 28 (Ivermectin top.)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.37 (P = 0.17)					
Test for subgroup differences: Not applicable					



(1) No imputation

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Analysis 3.2. Comparison 3 Ivermectin 200 μg/kg (1 to 3 doses) versus ivermectin 1% lotion/solution (1 to 3 applications), Outcome 2 Complete clearance - week 2.

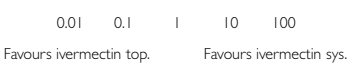
Review: Ivermectin and permethrin for treating scabies

Comparison: 3 Ivermectin 200 μ g/kg (1 to 3 doses) versus ivermectin 1% lotion/solution (1 to 3 applications)

Outcome: 2 Complete clearance - week 2

Study or subgroup	Ivermectin sys. n/N	Ivermectin top. n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Ahmad 2016 (1)	30/30	32/32		100.0 %	1.00 [0.94, 1.06]
Total (95% CI)	**30**	**32**		**100.0 %**	**1.00 [0.94, 1.06]**

Total events: 30 (Ivermectin sys.), 32 (Ivermectin top.)
Heterogeneity: not applicable
Test for overall effect: Z = 0.0 (P = 1.0)
Test for subgroup differences: Not applicable



(1) IVER sys: 8 participants were re-treated at week 1, no imputation; IVER top: 4 participants were re-treated at week 1, no imputation

Analysis 3.3. Comparison 3 Ivermectin 200 μg/kg (1 to 3 doses) versus ivermectin 1% lotion/solution (1 to 3 applications), Outcome 3 Complete clearance - week 4.

Review: Ivermectin and permethrin for treating scabies

Comparison: 3 Ivermectin 200 μ g/kg (1 to 3 doses) versus ivermectin 1% lotion/solution (1 to 3 applications)

Outcome: 3 Complete clearance - week 4

Study or subgroup	Ivermectin sys. n/N	Ivermectin top. n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Ahmad 2016 (1)	30/30	32/32		49.0 %	1.00 [0.94, 1.06]
Chhaiya 2012 (2)	99/105	101/105		51.0 %	0.98 [0.92, 1.04]
Total (95% CI)	**135**	**137**		**100.0 %**	**0.99 [0.95, 1.03]**

Total events: 129 (Ivermectin sys.), 133 (Ivermectin top.)
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.26, df = 1 (P = 0.61); I^2 =0.0%
Test for overall effect: Z = 0.46 (P = 0.64)
Test for subgroup differences: Not applicable

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(1) IVER sys: 8 participants were re-treated at week 1, no imputation; IVER top: 4 participants were re-treated at week 1, no imputation

(2) IVER: participants who were not cured were prescribed repeat intervention along with anti-histaminic at week 2 and week 3; IVER sys: 5/105 imputed (NRI); IVER top: 6/105 imputed (NRI)

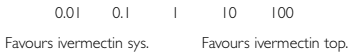
Analysis 3.4. Comparison 3 Ivermectin 200 μg/kg (1 to 3 doses) versus ivermectin 1% lotion/solution (1 to 3 applications), Outcome 4 Number of participants with ≥ 1 adverse event - week 4.

Review: Ivermectin and permethrin for treating scabies

Comparison: 3 Ivermectin 200 μ g/kg (1 to 3 doses) versus ivermectin 1% lotion/solution (1 to 3 applications)

Outcome: 4 Number of participants with ≥ 1 adverse event - week 4

Study or subgroup	Ivermectin sys. n/N	Ivermectin top. n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Chhaiya 2012 (1)	2/100	0/101		100.0 %	5.05 [0.25, 103.87]
Total (95% CI)	**100**	**101**		**100.0 %**	**5.05 [0.25, 103.87]**
Total events: 2 (Ivermectin sys.), 0 (Ivermectin top.)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.05 (P = 0.29)					
Test for subgroup differences: Not applicable					



(1) IVER: participants who were not cured were prescribed repeat intervention along with anti-histaminic at week 2 and week 3

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Analysis 3.5. Comparison 3 Ivermectin 200 μg/kg (1 to 3 doses) versus ivermectin 1% lotion/solution (1 to 3 applications), Outcome 5 Withdrawal due to adverse event - week 4.

Review: Ivermectin and permethrin for treating scabies

Comparison: 3 Ivermectin 200 μ g/kg (1 to 3 doses) versus ivermectin 1% lotion/solution (1 to 3 applications)

Outcome: 5 Withdrawal due to adverse event - week 4

Study or subgroup	Ivermectin sys. n/N	Ivermectin top. n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Ahmad 2016 (1)	0/30	0/32			Not estimable
Total (95% CI)	**30**	**32**			**Not estimable**

Total events: 0 (Ivermectin sys.), 0 (Ivermectin top.)
Heterogeneity: not applicable
Test for overall effect: not applicable
Test for subgroup differences: Not applicable

(1) IVER sys: 8 participants were re-treated at week 1; IVER top: 4 participants were re-treated at week 1

Analysis 4.1. Comparison 4 Ivermectin 1% lotion (1 to 3 applications) versus permethrin 5% cream (1 to 3 applications), Outcome 1 Complete clearance - week 4.

Review: Ivermectin and permethrin for treating scabies

Comparison: 4 Ivermectin 1% lotion (1 to 3 applications) versus permethrin 5% cream (1 to 3 applications)

Outcome: 1 Complete clearance - week 4

Study or subgroup	Ivermectin n/N	Permethrin n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Chhaiya 2012 (1)	101/105	99/105		100.0 %	1.02 [0.96, 1.08]
Total (95% CI)	**105**	**105**		**100.0 %**	**1.02 [0.96, 1.08]**

Total events: 101 (Ivermectin), 99 (Permethrin)
Heterogeneity: not applicable
Test for overall effect: Z = 0.65 (P = 0.52)
Test for subgroup differences: Not applicable

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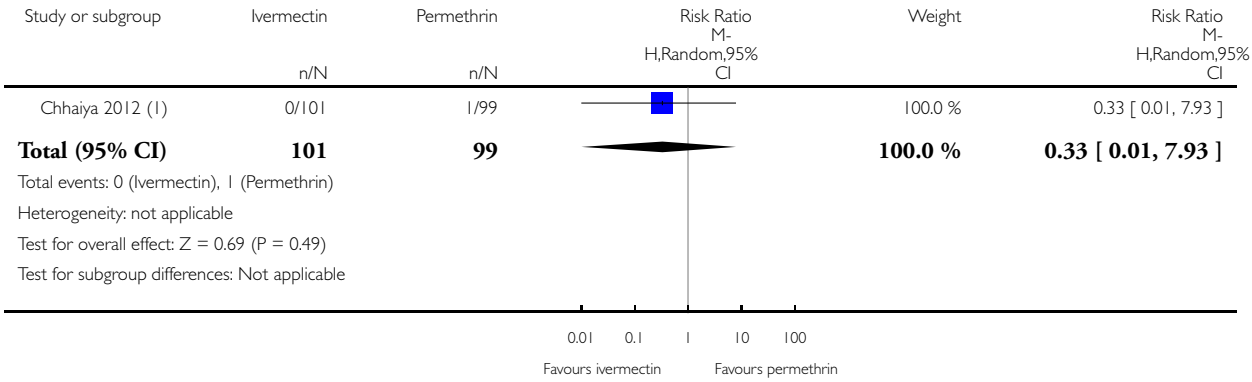
(1) IVER, PER: participants who were not cured were prescribed repeat intervention along with anti-histaminic at week 2 and week 3; IVER: 4/105 imputed (NRI); PER: 6/105 imputed (NRI)

Analysis 4.2. Comparison 4 Ivermectin 1% lotion (1 to 3 applications) versus permethrin 5% cream (1 to 3 applications), Outcome 2 Number of participants with ≥ 1 adverse event - week 4.

Review: Ivermectin and permethrin for treating scabies

Comparison: 4 Ivermectin 1% lotion (1 to 3 applications) versus permethrin 5% cream (1 to 3 applications)

Outcome: 2 Number of participants with ≥ 1 adverse event - week 4



(1) IVER, PER: participants who were not cured were prescribed repeat intervention along with anti-histaminic at week 2 and week 3

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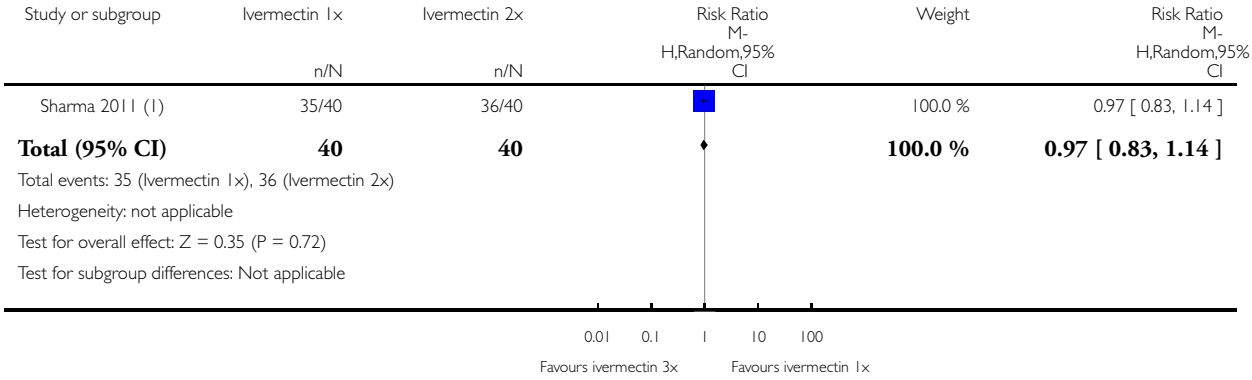
Analysis 5.1. Comparison 5 Ivermectin 200 μg/kg (1 dose) versus ivermectin 200 μg/kg (2 doses), Outcome 1 Complete clearance - week 4.

Review: Ivermectin and permethrin for treating scabies

Comparison: 5 Ivermectin 200 μ g/kg (1 dose) versus ivermectin 200 μ g/kg (2 doses)

Outcome: 1 Complete clearance - week 4



(1) IVER 1x: no imputation; IVER 3x: 1/40 imputed (NRI)

APPENDICES

Appendix 1. Search strategy

Search set	CIDG SR[a] / Econ-Lit/ ERIC	CENTRAL	MEDLINE/Embase[b]	LILACS[b]	IndMED
1	scabies	scabies ti, ab	scabies ti, ab	scabies	scabies
2	-	"scabies" [MeSH]	"scabies" [MeSH/ Emtree]	permethrin	sarcoptes scabiei
3	-	"sarcoptes scabiei" [MeSH]	"sarcoptes scabiei" [MeSH/Emtree]	ivermectin	1 or 2
4	-	1 or 2 or 3	1 or 2 or 3	2 or 3	-
5	-	permethrin ti, ab	permethrin ti, ab	1 and 4	-

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(*Continued*)

6	-	"permethrin" [MeSH]	"permethrin" [MeSH/Emtree]	-	-
7	-	"pyrethrins" [MeSH]	"pyrethrins" [MeSH]	-	-
8	-	ivermectin ti, ab	"pyrethroid" [Emtree]	-	-
9	-	"ivermectin" [MeSH]	ivermectin ti, ab	-	-
10	-	5 or 6 or 7 or 8 or 9	"ivermectin" [MeSH/Emtree]	-	-
11	-	4 and 10	5 or 6 or 7 or 8 or 9 or 10	-	-
12	-	-	4 and 11	-	-

[a] Cochrane Infectious Diseases Group Specialized Register.
[b] Search terms used in combination with the search strategy for retrieving trials developed by the Cochrane Collaboration (Lefebvre 2011).

Appendix 2. Sensitivity analyses: summary table

Comparison	Subgroup	Outcome	Sensitivity analysis	Meta-analysis
Ivermectin 200 μg/kg versus permethrin 5% cream	-	Complete clearance - week 2	Without Usha 2000 (significant effect estimate): RR 0.96, 95% CI 0.88 to 1.06 (I^2 statistic = 0%) Without Bachewar 2009; Rohatgi 2013 (some participants were re-treated after 1 week): RR 0.81, 95% CI 0.56 to 1.19 (I^2 statistic = 71%)	RR 0.91, 95% CI 0.76 to 1.08 (I^2 statistic = 61%)
	IVER 1 to 3 doses versus PER 1 to 3 doses	Complete clearance - week 4	Without Usha 2000 (significant effect estimate): RR 0.97, 95% CI 0.91 to 1.05 (I^2 statistic = 31%) Without Usha 2000; Mushtaq 2010 (non-responders re-treated after 2 weeks):	RR 0.92, 95% CI 0.82 to 1.03 (I^2 statistic = 74%)

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(*Continued*)

			RR 0.98, 95% CI 0.91 to 1.06 (I^2 statistic = 36%)	

Abbreviations: CI: confidence interval; IVER: ivermectin; PER: permethrin; RR: risk ratio.

Appendix 3. Number of participants re-treated

Study	Initial treatment	Follow-up week 1	Follow-up week 2	Follow-up week 3	Follow-up week 4
Studies that treated participants once					
Manjhi 2014	1 x IVER 200 µg/kg	-	-	-	-
	1 x PER 5%	-	-	-	-
Saqib 2012	1 x IVER 200 µg/kg	-	-	-	-
	1 x PER 5%	-	-	-	-
Studies that treated participants once and re-treated only non-responders					
Ahmad 2016	1 x IVER 1%	Yes, 4/32 participants	-	-	-
	1 x IVER 200 µg/kg	Yes, 8/30 participants	-	-	-
Bachewar 2009	1 x IVER 200 µg/kg	Yes, 44.44% of participants	-	-	-
	1 x PER 5%	Yes, 17.86% of participants	-	-	-
Chhaiya 2012	1 x IVER 200 µg/kg	Yes, n unclear	Yes, n unclear	Switch over to PER 5%	-
	1 x IVER 1%	Yes, n unclear	Yes, n unclear	Switch over to PER 5%	-
	1 x PER 5%	Yes, n unclear	Yes, n unclear	Yes, n unclear	-
Mushtaq 2010	1 x IVER 200 µg/kg	-	Yes, n unclear	-	-
	1 x PER 5%	-	Yes, n unclear	-	-
Rohatgi 2013	1 x IVER 200 µg/kg	Yes, n unclear	-	-	-

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(*Continued*)

	1 x PER 5%	Yes, n unclear	-	-	-
Usha 2000	1 x IVER 200 µg/kg	-	Yes, 12 participants	-	Cross-over if treatment failure
	1 x PER 5%	-	Yes, 1 participant	-	Cross-over if treatment failure
Wankhade 2013	1 x IVER 200 µg/kg	Yes, n unclear	-	-	-
	1 x PER 5%	Yes, n unclear	-	-	-
Wankhade 2016	1 x IVER 200 µg/kg	Yes, n unclear	-	-	-
	1 x PER 5%	Yes, n unclear	-	-	-
Studies that treated all participants with more than 1 dose					
Abdel-Raheem 2016	1 x IVER 200 µg/kg	1 x IVER 200 µg/kg	Yes, time and n unclear		
	PER 5% for 5 consecutive nights	-			
Das 2006	1 x IVER 200 µg/kg	-	1 x IVER 200 µg/kg	-	-
	1 x PER 5%	-	-	-	-
Macotela-Ruiz 1996	1 x IVER 250 µg/kg	-	-	-	-
	1 x IVER 250 µg/kg	Day 3: 1 x IVER 250 µg/kg	Day 10: 1 x IVER 250 µg/kg	-	-
Meenakshi 2014	1 x IVER 200 µg/kg	1 x IVER 200 µg/kg	-	-	-
	1 x PER 5%	1 x PER 5%	-	-	-
Sharma 2011	1 x IVER 200 µg/kg	-	-	-	-
	1 x IVER 200 µg/kg	-	Day 15: 1 x IVER 200 µg/kg	-	-
	1 x PER 5%	-	-	-	-

Abbreviations: IVER: ivermectin; PER: permethrin.

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Appendix 4. Definition and diagnosis of complete clearance

Study	Name of outcome	Definition and evaluation
Abdel-Raheem 2016	Complete cure	• Negative parasitological examination with complete absence of new lesions • residual and all new lesions were scraped for detection of mites • if only one mite was detected, this was considered as treatment failure
Ahmad 2016	Cure	• Clinical assessment by 1 researcher • 4-point scale for lesion count: 0 = no skin lesions; 1 = ≤ 10 lesions; 2 = 11 to 49 lesions; 3 ≥ 50 lesions) • 4-point scale for pruritus: 0 = no pruritus; 1 = mild pruritus; 2 = moderate pruritus; 3 = marked pruritus • cure = 0 • laboratory diagnosis: demonstration of mites and/or mite products (eggs, larva, or faecal pellets) in scrapings from skin lesions (burrows or scabetic papules from classical sites: finger webs, flexural aspect of wrist, or penile shaft) using light microscopy after incubation in 15% potassium hydroxide
Bachewar 2009	Cure	• No new lesions papules, vesicles, and classical burrows • examined by dermatologist and principal investigator to standardize clinical evaluation
Chhaiya 2012	Clinical cure of scabietic lesions	• No definition
Das 2006	Improvement clinically	• No definition
Macotela-Ruiz 1996	Cure	• Considerable improvement of dermatosis, no pruritus, no new lesions
Manjhi 2014	Complete improvement	• Based on severity of pruritus or lesions • lesion count: < 10: mild, 11 to 49: moderate, > 50: severe • pruritus on 10-centimetre visual analogue scale: 0 - no pruritus, 1 to 3 - mild, 4 to 6 - moderate, 7 to 10 - severe • complete improvement not defined
Meenakshi 2014	Complete clinical cure	• Reduction in clinical grading score up to grade 0 or 1 and reduction in itching grading score up to grade 0, 1, or 2; "moderate or good improvement" • clinical grading score: 0 = free of lesions (no lesions), 1 = 10 or fewer lesions (mild), 2 = 11 to 49 lesions (moderate), 3 = 50 or more lesions (severe) • itching grading score: participant was asked for reduction in pruritus, grading was done on given scale by the observer: 0 = 0% (no pruritus), 1 = 1% to 25% (mild pruritus), 2 = 26% to 50% (moderate pruritus), 3 = 51% to 75% (severe pruritus), 4 = 76% to 100% (very severe pruritus)

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(*Continued*)

Mushtaq 2010	Cure of disease	• No lesions
Rohatgi 2013	Cure	• Absence of clinical lesions and no new lesions like papules, vesicles, and classical burrows suggestive of live parasite
Saqib 2012	Cure	• No itching, cutaneous lesions/burrows, and negative microscopy
Sharma 2011	Complete clinical cure	• Reduction in both the number of lesions and the grade of pruritus by more than or equal to 50% (that is, moderate and good improvement) and negative microscopy
Usha 2000	Complete clearance	• Good improvement
Wankhade 2013	Cure rate	• No definition
Wankhade 2016	Cure	• No new clinical lesions and improvement in pruritus, no new lesions like papules, vesicles, and classical burrows suggestive of live parasite seen

CONTRIBUTIONS OF AUTHORS

SR was the contact person with the editorial base, co-ordinating the contributions from the co-authors; sought additional information about papers; entered data into RevMan 5 (RevMan 2014); worked on the Methods section; updated the clinical sections of the Background based on the Cochrane Review 'Interventions for treating scabies' by Mark Strong and Paul Johnstone (Strong 2007). SR screened all hits using the inclusion/exclusion criteria; screened reference lists of included studies for additional randomized controlled trials; independently extracted data using the standardized form; performed the 'Risk of bias' evaluation for all included trials; analysed and interpreted data; wrote the final draft of the review.

CD screened all hits using the inclusion/exclusion criteria and independently extracted data using the standardized form; performed the 'Risk of bias' evaluation for all included trials. CD discussed data analysis strategies with SR and checked the data entered into Review Manager 5. CD also contributed substantially to writing the Cochrane Review.

SR and CD performed the GRADE assessment of all comparisons.

SR, CD, and AN jointly finalized the review. AN was solely responsible for the medical input and the 'Implications for practice' section.

DECLARATIONS OF INTEREST

SR and CD have no conflicts of interest. CD, SR, and AN previously published a systematic review on scabies treatments (Dressler 2016a).

CD is a member of the Cochrane Scientific Committee.

AN is a member of the expert panel of the German consensus-based guideline for the diagnosis and treatment of scabies published in January 2016 (AWMF (Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften e.V.), Association of the Scientific Medical Societies in Germany; register number: 013-052).

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Internal sources

- Liverpool School of Tropical Medicine, UK.

External sources

- Department for International Development (DFID), UK.

Grant: 5242

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We have changed the secondary outcome 'number of patients requiring re-treatment' to 'number of participants re-treated'. We found this to be a more suitable outcome measure considering our research question.

In case of inconsistent or implausible outcome data within a publication, we asked the corresponding author for clarification, irrespective of the date of publication.

We clarified in the Types of participants section that we only included studies investigating people with classical scabies.

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6 Lebenslauf

Mein Lebenslauf wird aus datenschutzrechtlichen Gründen in der elektronischen Version meiner Arbeit nicht veröffentlicht.

7 Publikationsliste

2018	Impact Factor
Dressler C, **Rosumeck S**, Werner RN, Magerl M, Metz M, Maurer M, Nast A, Zuberbier T. Executive summary of the methods report for , The EAACI/GA(2) LEN/EDF/WAO Guideline for the Definition, Classification, Diagnosis and Management of Urticaria. The 2017 Revision and Update'. Allergy. 2018 Jan 16. [Epub ahead of print]	7.361 (2016)
Zuberbier T, Aberer W, Asero R, Abdul Latiff AH, Baker D, Ballmer-Weber B, Bernstein JA, Bindslev-Jensen C, Brzoza Z, Buense Bedrikow R, Canonica GW, Church MK, Craig T, Danilycheva IV, Dressler C, Ensina LF, Gimenez-Arnau A, Godse K, Goncalo M, Grattan C, Hebert J, Hide M, Kaplan A, Kapp A, Katelaris CH, Kocaturk E, Kulthanan K, Larenas-Linnemann D, Leslie TA, Magerl M, Mathelier-Fusade P, Meshkova RY, Metz M, Nast A, Nettis E, Oude-Elberink H, **Rosumeck S**, Saini SS, Sanchez-Borges M, Schmid-Grendelmeier P, Staubach P, Sussman G, Toubi E, Vena GA, Vestergaard C, Wedi B, Werner RN, Zhao Z, Maurer M. The EAACI/GA(2)LEN/EDF/WAO Guideline for the Definition, Classification, Diagnosis and Management of Urticaria. The 2017 Revision and Update. Allergy. 2018 Jan 15. [Epub ahead of print]	7.361 (2016)
Rosumeck S, Nast A, Dressler C. Ivermectin and permethrin for treating scabies. Cochrane Database Syst Rev. 2018 Apr 2;4:CD012994.	6.124 (2016)

2017	Impact Factor
Nast A, Spuls PI, van der Kraaij G, Gisondi P, Paul C, Ormerod AD, Saiag P, Smith CH, Dauden E, de Jong EM, Feist E, Jobling R, Maccarone M, Mrowietz U, Papp KA, Reich K, **Rosumeck S**, Talme T, Thio HB, van de Kerkhof P, Werner RN, Dressler C. European S3-Guideline on the systemic treatment of psoriasis vulgaris - Update Apremilast and Secukinumab - EDF in cooperation with EADV and IPC. J Eur Acad Dermatol Venereol. 2017 Dec;31(12):1951-63.	3.528 (2016)

Dressler C, **Rosumeck S**, Werner RN, van der Kraaij G, van Lumig P, Wakkee M, Spuls P, Nast A. Methods report: European S3-Guideline on the systemic treatment of psoriasis vulgaris - Update Apremilast and Secukinumab - EDF in cooperation with EADV and IPC. J Eur Acad Dermatol Venereol. 2017 Dec;31(12):1964-77.	3.528 (2016)
Heppt MV, Steeb T, Schlager JG, **Rosumeck S**, Dressler C, Ruzicka T, Nast A, Berking C. Immune checkpoint blockade for unresectable or metastatic uveal melanoma: A systematic review. Cancer Treat Rev. 2017 Nov;60:44-52.	8.589 (2016)
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Schlager JG, **Rosumeck S**, Werner RN, Jacobs A, Schmitt J, Schlager C, Nast A. Topical treatments for scalp psoriasis: summary of a Cochrane Systematic Review. Br J Dermatol. 2017 Mar;176(3):604-14.	4.706 (2016)
Werner RN, Nikkels AF, Marinovic B, Schafer M, Czarnecka-Operacz M, Agius AM, Bata-Csorgo Z, Breuer J, Girolomoni G, Gross GE, Langan S, Lapid-Gortzak R, Lesser TH, Pleyer U, Sellner J, Verjans GM, Wutzler P, Dressler C, Erdmann R, **Rosumeck S**, Nast A. European consensus-based (S2k) Guideline on the Management of Herpes Zoster - guided by the European Dermatology Forum (EDF) in cooperation with the European Academy of Dermatology and Venereology, Part 2: Treatment. J Eur Acad Dermatol Venereol. 2017 Jan;31(1):20-9.	3.528 (2016)
Werner RN, Nikkels AF, Marinovic B, Schafer M, Czarnecka-Operacz M, Agius AM, Bata-Csorgo Z, Breuer J, Girolomoni G, Gross GE, Langan S, Lapid-Gortzak R, Lesser TH, Pleyer U, Sellner J, Verjans GM, Wutzler P, Dressler C, Erdmann R, **Rosumeck S**, Nast A. European consensus-based (S2k) Guideline on the Management of Herpes Zoster - guided by the European Dermatology Forum (EDF) in cooperation with the European Academy of Dermatology and Venereology, Part 1: Diagnosis. J Eur Acad Dermatol Venereol. 2017 Jan;31(1):9-19.	3.528 (2016)

Dressler C, **Rosumeck S**, Nast A. Which treatment options do acne patients prefer? J Dtsch Dermatol Ges. 2017 Jan;15(1):77-81.	2.865 (2016)

2016	Impact Factor
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