Br J Dermatol 2024; **190**:163–173
https://doi.org/10.1093/bjd/ljad308
Advance access publication date: 25 August 2023

BJD
British Journal of Dermatology
Systematic Review

Failure of scabies treatment: a systematic review and meta-analysis

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Abstract

Background Treatment failure is considered to be an important factor in relation to the increase in scabies incidence over the last decade. However, the regional and temporal differences, in addition to the predictors of therapy failure, are unclear.

Objectives We aimed to conduct a systematic review of the prevalence of treatment failure in patients with scabies and investigation of associated factors.

Methods We searched MEDLINE, EMBASE, CINAHL, Web of Science, Scopus, Global Health and the Cochrane Central Register of Controlled Trials from inception to August 2021 for randomized and quasi-randomized trials, in addition to observational studies that enrolled children or adults diagnosed with confirmed or clinical scabies treated with permethrin, ivermectin, crotamiton, benzyl benzoate, malathion, sulfur or lindane, and measured treatment failure or factors associated with treatment failure. We performed a random effects meta-analysis for all outcomes reported by at least two studies.

Results A total of 147 studies were eligible for inclusion in the systematic review. The overall prevalence of treatment failure was 15.2% [95% confidence interval (CI) 12.9–17.6; I^2=95.3%, moderate-certainty evidence] with regional differences between World Health Organization regions (P=0.003) being highest in the Western Pacific region (26.9%, 95% CI 14.5–41.2). Oral ivermectin (11.8%, 95% CI 8.4–15.4), topical ivermectin (9.3%, 95% CI 5.1–14.3) and permethrin (10.8%, 95% CI 7.5–14.5) had relatively lower failure prevalence compared with the overall prevalence. Failure prevalence was lower in patients treated with two doses of oral ivermectin (7.1%, 95% CI 3.1–12.3) compared with those treated with one dose (15.2%, 95% CI 10.8–20.2; P=0.021). Overall and permethrin treatment failure prevalence in the included studies (1983–2021) increased by 0.27% and 0.58% per year, respectively. Only three studies conducted a multivariable risk factor analysis; no studies assessed resistance.

Conclusions A second dose of ivermectin showed lower failure prevalence than single-dose ivermectin, which should be considered in all guidelines. The increase in treatment failure over time hints at decreasing mite susceptibility for several drugs, but reasons for failure are rarely assessed. Ideally, scabicide susceptibility testing should be implemented in future studies.

What is already known about this topic?

- Several drug treatments are available for the management of scabies infestation; however, treatment failure is considered to be an important factor in the increasing incidence of scabies infestations.
- Reduced susceptibility *in vitro* and case reports on clinical resistance have been reported for both main scabicides, permethrin and ivermectin.
- There is limited evidence on the reasons for treatment failure.

Accepted: 20 August 2023

What does this study add?

- We performed a comprehensive systematic review on the prevalence of treatment failure and associated factors.
- Treatment failure was lower with two oral doses of ivermectin compared with one dose. Treatment failure with permethrin increased significantly over time, which might indicate decreasing mite susceptibility.
- We identified the need to assess the reasons for treatment failure in future studies, as only three studies conducted a multivariable risk factor analysis and none assessed resistance.

Scabies is a pruritic contagious dermatosis caused by the *Sarcoptes scabiei* mite.[1] It spreads mostly via direct skin contact. Scabies was added to the World Health Organization (WHO) portfolio of neglected tropical diseases in 2017. It continues to be a common skin disorder, affecting approximately 130 million people globally.[2] While the majority of cases occur in developing countries,[3,4] outbreaks in developed countries account for a significant proportion of the global scabies burden.[5] Treatment failure, which can occur in up to 30% of cases, is considered a major factor in the increasing incidence of scabies that has recently been reported in developed countries.[6–9]

There are a variety of scabicidal drugs, which can be broadly divided into topical and oral agents, and include oral or topical ivermectin, topical permethrin, lindane, benzyl benzoate and crotamiton. There are several systematic reviews and meta-analyses on the benefits and harms of scabies treatments,[10–13] but these reviews lack an assessment of the reasons for failure and do not consider differences between regions or differences over time.

It has been suggested that predictors of treatment failure are associated with the immune status of the host, choice of treatment, exposure to future transmission events and drug resistance.[14,15] However, studies are very heterogeneous and have never been assessed systematically. Treatment failure resulting from drug resistance is difficult to ascertain without excluding inadequate treatment or reinfestation.[1]

There is limited evidence on the prevalence of treatment-resistant scabies for various drugs. Furthermore, there has been no comprehensive review on the factors associated with treatment failure. Therefore, we conducted a systematic review and meta-analysis of randomized clinical trials and observational studies to determine the prevalence of treatment failure and investigate the associated factors in children and adults diagnosed with scabies treated with permethrin, ivermectin, crotamiton, benzyl benzoate, malathion, sulfur or lindane.

Materials and methods

We registered our protocol on the international prospective register of systematic reviews (PROSPERO) (CRD42021274639) and reported the review findings according to the PRISMA guidelines.[16]

Eligibility criteria

We included randomized and quasi-randomized trials, prospective or retrospective cohorts, case–control studies, and longitudinal (one-arm) observational studies (time-series and before–after studies), and case-series with more than five patients that enrolled children or adults with a diagnosis of confirmed or clinical scabies (all forms, including crusted scabies) treated with permethrin, ivermectin, crotamiton, benzyl benzoate, malathion, sulfur or lindane, and measured at least one of our outcomes of interest (i.e. treatment failure, reinfestation, retreatment/recurrence, persistent itching, susceptibility of scabies mites, or risk factors for treatment failure).

Information sources

A medical librarian (R.C.) developed search strategies specific to individual databases for the review questions listed above. We searched MEDLINE, EMBASE, CINAHL, Cochrane Central Register of Controlled Trials (CENTRAL), Scopus, Global Health and Web of Science without language or publication status restrictions. We reviewed the reference lists of included studies and relevant reviews for additional eligible studies. Our search strategy included terms for scabies, the mite and treatments, and further details of this strategy are provided in Appendix S1 (see Supporting Information). All databases were searched from inception until 13 August 2021.

Study selection

Pairs of trained reviewers screened titles and abstracts of identified citations independently, using a standardized, pilot-tested form. Subsequently, reviewers assessed eligibility of full texts of potentially eligible studies. Reviewers resolved disagreements by discussion or adjudication with a third reviewer (B.S. or L.M.). We used DistillerSR online systematic review software (Evidence Partners, Ottawa, ON, Canada; http://systematic-review.net) for screening titles and abstracts and full-text articles.

Data abstraction and risk of bias assessment

Using standardized, pilot-tested forms, trained reviewers, independently and in duplicate, extracted the following information from eligible studies: (i) study characteristics [author's name, publication year, study design (observational, quasi-randomized and randomized), country of origin, and funding source], (ii) population-related information [age, percentage of female patients, setting (i.e. hospitalized or outpatient), disease severity, diagnosis method, type of scabies], (iii) details of the intervention/exposure and comparison [e.g. scabicidal drug(s) used, doses, and formulations (e.g. oral, topical), duration of treatment, level of assessment (i.e. confirmed scabies, clinically diagnosed scabies, mite

susceptibility)], and details of any additional instructions given, and (iv) outcomes of interest (treatment failure, reinfestation, retreatment/recurrence, persistent itching, susceptibility of scabies mites) and their definitions. Data were collected from all intervention or control arms of studies, provided the participants received a scabicide of interest.

Risk of bias in the studies that reported the frequency of treatment failure was assessed using the tool developed by Hoy *et al*.[17] This tool has the following 10 domains: (i) representativeness of the sample, (ii) the sampling frame, (iii) sampling technique, (iv) response bias, (v) the use of proxies, (vi) case definition, (vii) validity of measurements, (viii) uniformity of data collection, (ix) the prevalence period and (x) the appropriateness of the numerator and denominator. A judgement of high or low risk of bias can be assigned to each of these domains. An overall judgement of low, moderate or high risk of bias was made for each study based on the rater's appraisal of the 10 items, as recommended by Hoy *et al*.[17]

Reviewers resolved disagreements about data extraction and risk of bias assessment by discussion and, if needed, adjudication by a third reviewer (B.S. or L.M.). The results of these assessments were plotted as bar charts using Microsoft Excel.

Data synthesis

In the studies that reported treatment success, we estimated treatment failure as the number of participants who did not have treatment success but were not lost to follow-up. All listed definitions of our outcome of interest were analysed as treatment failure. We pooled any outcome reported in two or more studies using the DerSimonian–Laird random effects model for meta-analysis.[18] For meta-analysis of the prevalence of treatment failure, we used the Freeman–Tukey double arcsine transformation to stabilize the variances.[19] Heterogeneity was determined by visual inspection of forest plots and I^2-values. The results of the studies were narratively described when the number of eligible studies was not sufficient for meta-analysis or when studies were conceptually heterogeneous and did not warrant pooling. We used STATA (StataCorp, Release 16.0, College Station, TX, USA) for all statistical analyses.

Subgroup analyses

Regardless of the observed statistical heterogeneity, when two or more studies were available in each subgroup, we conducted the following subgroup analyses: (i) level of assessment (diagnosis), (ii) type of scabicides used and route of administration and (iii) region/country. We used meta-regression to investigate whether the prevalence of treatment failure changed over time. For subgroup analysis, we tested for interaction using a χ^2 test for significance.[20]

To investigate treatment failure that was unlikely, owing to lack of compliance or mistakes in drug application but possibly hinting towards drug resistance, we selected studies for subgroup analyses in which precautions were described and taken in order to ascertain whether treatments were applied appropriately and/or reinfestation was unlikely. These were studies that had at least 14 days of follow-up and in which additional instructions were given, e.g. treat and wash clothes, beddings and belongings, or treat close contacts. For these analyses, we focused on ivermectin and permethrin.

Certainty of evidence assessment

We assessed the certainty in our pooled estimates using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach. GRADE evaluates the following five domains: risk of bias, inconsistency, imprecision of pooled estimates, indirectness and evidence of publication bias. Based on these domains, the certainty of evidence can be graded as very low, low, moderate or high.[21]

Results

Our search yielded 3536 unique records, from which 401 articles (11.3%) were retrieved for full-text screening. Of those, 254 articles (63.3%) were excluded for the following reasons: not including adults or children with confirmed or clinical scabies treated with scabicides (134 articles, 52.7%), nor reporting treatment failure (37 articles, 14.6%) or factors associated with scabies treatment failure/success (83 articles, 32.7%). Figure 1 provides details of the study selection process and the list of excluded studies is available in Appendix S2 (see Supporting Information).

Characteristics of included studies

We included 147 studies, the majority of which were randomized trials (63 studies, 42.9%) and observational studies (58 studies, 39.5%). Almost 30% were conducted in high-income countries (46 studies), one-third in upper middle-income countries (47 studies) and another third in lower middle-income countries (48 studies). Most of the studies were conducted in the Eastern Mediterranean region (40 studies, 27.2%), Europe (29 studies, 19.7%) and South East Asia (32 studies, 21.8%). Included studies were published between 1983 and 2021, with a median publication year of 2010 [interquartile range (IQR) 1999–2015]. Most studies enrolled both adults and children (65 studies, 44.2%), 52 studies enrolled only adults (35.4%) and 17 studies enrolled only children (11.6%). Characteristics of the included studies are provided in Table S1 (see Supporting Information), and the list of included studies is available in Appendix S3 (see Supporting Information).

Treatment characteristics

The most common treatments given to patients with scabies were ivermectin (83 studies, 34.7%) and permethrin (62 studies, 25.9%) followed by lindane (33 studies, 13.8%) and benzyl benzoate (32 studies, 13.4%). In eight studies (5.4%) patients were treated with two or more drugs as a combination therapy or sequentially. In addition to the pharmacotherapy, one or more additional treatment instructions (e.g. treatment of contacts and environmental control measures) were given to participants in 87 studies (59.2%). Further information on the treatment characteristics is provided in Tables S1 and S2 (see Supporting Information).

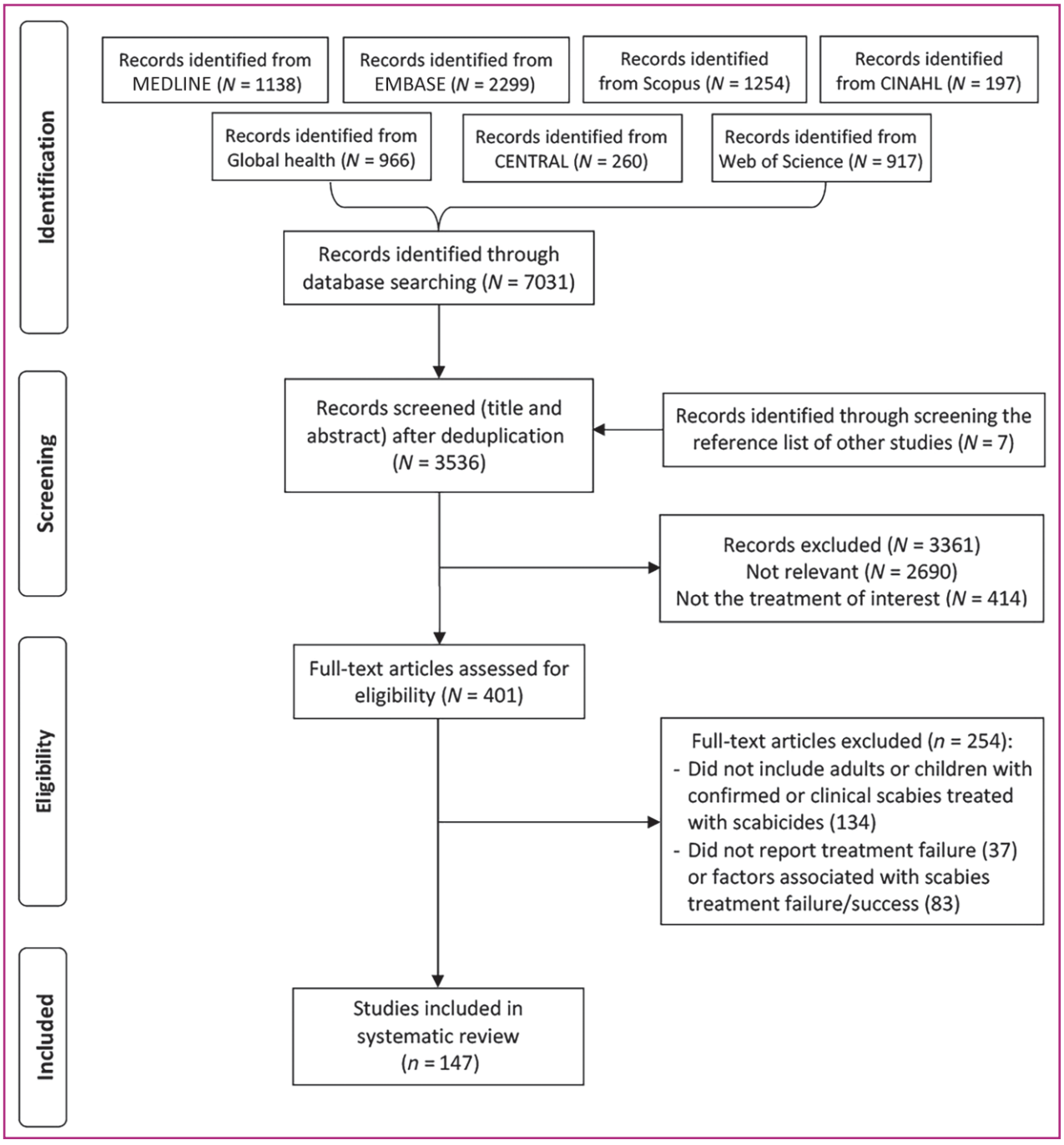

Figure 1 PRISMA flow diagram.

Outcomes

Most studies expressed their outcomes as treatment success (124 studies, 84.4%); the remaining 23 studies (15.7%) reported treatment failure (Table S1). In these studies, treatment failure was not clearly defined, or defined as reinfestation, retreatment, recurrence of scabies, persistent itching or lack of scabies mite susceptibility. The assessment of the outcome of treatment was performed using one or more of the following: clinical examination (121 studies, 82.3%), microscopic examination (52 studies, 35.4%), patient history (27 studies, 18.4%) and dermatoscopy (12 studies, 8.2%). The median time for outcome assessment was 14 days (IQR 7–28). Additional details are outlined in Table S3 (see Supporting Information).

Risk of bias

The overall risk of bias for the majority of included studies was judged to be moderate (76 studies, 51.7%) or high (46 studies, 31.3%). The domains with the most concerns were the nonrandom nature of the sample, the representativeness of the sample, the sampling frame and the follow-up time (prevalence period). Details of risk of bias assessments are summarized in Figure 2.

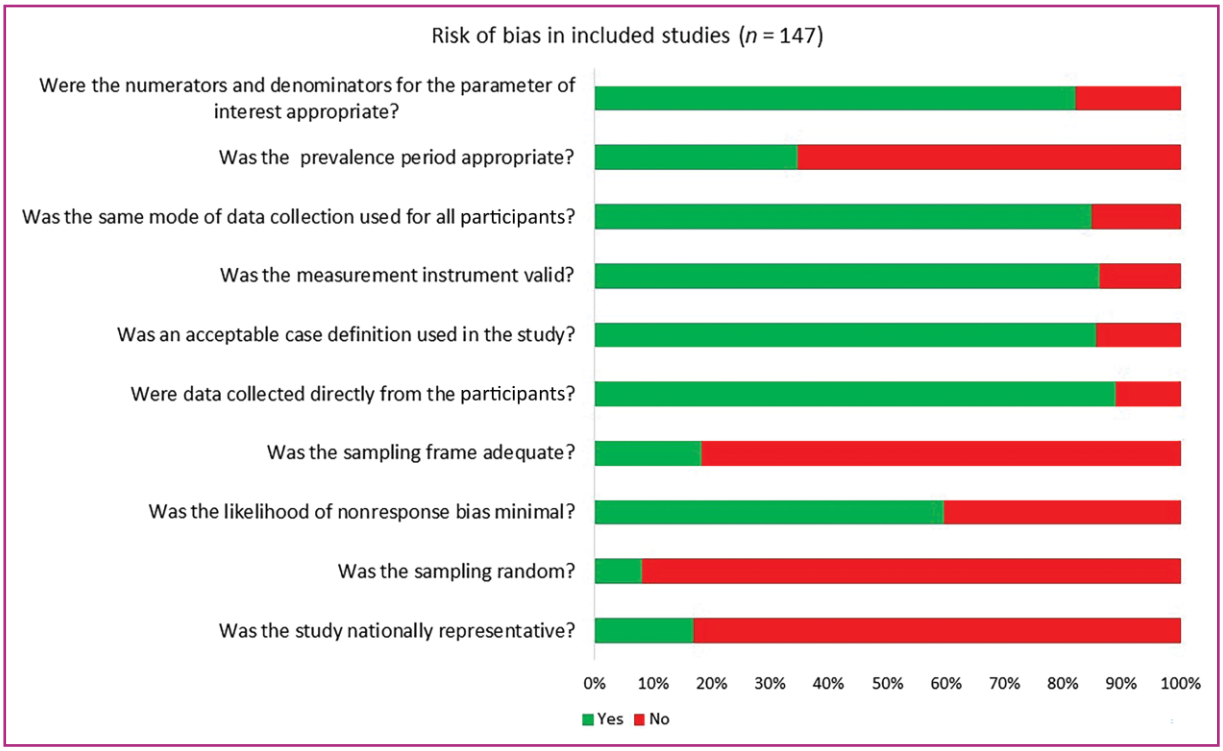

Figure 2 Risk of bias in included studies.

Overall treatment failure

The overall prevalence of treatment failure across treatments was 15.2% (95% CI 12.9–17.6; I^2 = 95.3%, moderate-certainty evidence). The prevalence of treatment failure was numerically higher in children (18.6%, 95% CI 13.3–24.5) compared with adults (14.1%, 95% CI 10.4–18.2), but the difference was not statistically significant (*P*-value for test of interaction = 0.196).

Specific treatment regimens

Pooled prevalence of treatment failure for topical ivermectin was 9.3% (95% CI 5.1–14.3; I^2 = 82.1), 11.8% (95% CI 8.4–15.4; I^2 = 92.5%) for oral ivermectin, 10.8% (95% CI 7.5–14.5; I^2 = 93.5%) for permethrin, 18.1% (95% CI 12.5–24.3; I^2 = 92.8%) for lindane, 25.3% (95% CI 16.4–35.3; I^2 = 97.7%) for benzyl benzoate, 27.7% (95% CI 17.9–38.7; I^2 = 90.6%) for crotamiton. Few studies reported on combination therapies with heterogeneous results. Table 1 provides the results of meta-analysis for therapy failure.

Oral ivermectin when used in two doses was associated with lower treatment failure prevalence (7.1%, 95% CI 3.1–12.3) compared with a single dose (15.2%, 95% CI 10.8–20.2; *P* = 0.021). The difference in treatment failure between a single and a second application of permethrin was not statistically significant (single dose: 8.5%, 95% CI 3.6–15.1; second dose: 7.3%, 95% CI 3.3–12.5; *P*-value for the test for subgroup effects = 0.757).

Subgroup analyses

The lowest levels of treatment failure were in the studies conducted in Europe (6.0%, 95% CI 1.5–12.4; I^2 = 95.3) and the highest levels of treatment failure were from the studies conducted in the Western Pacific region (26.9%, 95% CI 14.5–41.2; I^2 = 94.1) (Figure S1; see Supporting Information). The test for subgroup effects between WHO regions was significant (*P* = 0.003). However, studies that used objective methods (microscopy or dermatoscopy) to confirm scabies infestation were more likely to report treatment failure (19.5%, 95% CI 16.0–23.3; I^2 = 95.2%) compared with studies that used clinical examination and/or patient history (12.2%, 95% CI 9.7–14.9; *P*-value for test of interaction = 0.001). This was the case for most treatments (Table 1).

In studies with additional precautions implemented to minimize mistakes in drug application, compliance or reinfestation, hence possibly hinting at drug resistance, the overall prevalence of failure was 9.2% (95% CI 5.4–13.8; I^2 = 91.3%) in patients treated with ivermectin. This was lower in patients treated with two doses of oral ivermectin (4.2%, 95% CI 0.7–9.5; I^2 = 86.0%) compared with those treated with one dose (13.1%, 95% CI 7.4–20.0; I^2 = 85.5%) or with topical ivermectin (13.7%, 95% CI 9.4–18.8; I^2 = 66.4) (*P* = 0.023) (Figure 3). For permethrin, prevalence of failure in such studies was 9.9% (95% CI 5.4–15.3, I^2 = 90.1%).

Treatment failure over time

Overall treatment failure was more likely in recent studies (17.4%, 95% CI 14.4–20.5; I^2 = 93.8%) compared with studies published before 2011 (12.8%, 95% CI 10.0–15.8]; I^2 = 93.9%). This is also the case for oral ivermectin. Our findings were limited for topical ivermectin owing to the low number of studies that examined this treatment (Table 1).

Table 1 Results of the meta-analysis and subgroup analysis of therapy failure for different scabicidal agents

Drug/treatment regimen	Subgroup[a]	Number of studies	Number of patients analysed	Failure rate (95% CI)	I^2	Interaction *P*-value
Oral ivermectin	Objective assessment	34	1814	18.6 (12.9–25.0)	88.2	< 0.001
	Clinical exam/patient history	45	4083	7.7 (4.7–11.4)	91.3	
	Published before 2011	37	2636	8.2 (4.9–12.2)	92.4	0.031
	Published 2011 or later	42	3264	15.3 (9.9–21.5)	94.1	
	Eastern Mediterranean	19	1516	17.1 (11.1–23.9)	89.6	0.073
	South East Asia	22	1255	12.0 (6.6–18.6)	89.9	
	Europe	15	943	2.1 (0.0–8.2)	87.4	
	Africa	6	1359	11.6 (2.0–26.0)	91.9	
	America	9	350	8.6 (3.5–15.4)	66.3	
	Western Pacific	8	470	24.5 (6.2–49.0)	95.9	
	Overall	79	5893	11.8 (8.4–15.4)	92.5	NA
Topical ivermectin	Objective assessment	5	562	15.0 (12.0–18.2)	0.0	0.037
	Clinical exam/patient history	5	535	5.7 (0.7–14.3)	89.7	
	Published before 2011	2	39	0.0 (0.0–4.2)	0.0	0.005
	Published 2011 or later	8	1058	11.6 (7.2–16.8)	81.9	
	Eastern Mediterranean	6	902	16.2 (13.8–18.7)	0.0	< 0.001
	South East Asia	2	156	2.0 (0.2–5.0)	0.0	
	Europe	1	10	0.0 (0.0–27.8)	–	
	Africa	–	–	–	–	
	America	1	29	0.0 (0.0–11.7)	–	
	Western Pacific	–	–	–	–	
	Overall	10	1097	9.3 (5.1–14.3)	82.1	NA
Permethrin 5%	Objective assessment	23	1459	13.3 (6.7–21.9)	93.2	0.355
	Clinical exam/patient history	34	3658	9.0 (5.8–12.7)	93.8	
	Published before 2011	22	2046	6.7 (3.2–11.3)	89.3	0.048
	Published 2011 or later	35	3071	13.7 (9.5–18.5)	91.7	
	Eastern Mediterranean	19	1336	13.3 (7.2–20.6)	90.3	< 0.001
	South East Asia	18	966	8.6 (5.4–12.3)	69.2	
	Europe	9	406	9.7 (0.0–30.2)	94.6	
	Africa	–	–	–	–	
	America	10	1888	8.0 (2.7–15.3)	93.6	
	Western Pacific	1	546	50.0 (33.2–66.8)	NA	
	Overall	57	5142	10.8 (7.5–14.5)	93.5	NA
Lindane	Objective assessment	15	1121	20.0 (12.4–28.7)	90.5	0.604
	Clinical exam/patient history	19	1518	16.7 (9.2–25.6)	93.9	
	Published before 2011	22	1645	18.1 (11.1–26.3)	93.1	0.973
	Published 2011 or later	12	994	18.2 (10.1–28.0)	91.6	
	Eastern Mediterranean	14	1006	19.9 (11.6–29.5)	90.9	< 0.001
	South East Asia	7	524	30.0 (16.4–45.6)	92.7	
	Europe	2	61	8.0 (2.0–16.7)	–	
	Africa	1	117	0.0 (0.0–3.2)	–	
	America	9	881	13.9 (7.9–21.1)	83.6	
	Western Pacific	1	50	2.0 (0.4–10.5)	NA	
	Overall	34	2639	18.1 (12.5–24.3)	92.8	NA
Benzyl benzoate	Objective assessment	13	841	34.8 (23.3–47.3)	91.3	0.054
	Clinical exam/patient history	21	5797	20.0 (11.6–30.0)	97.1	
	Published before 2011	19	5435	26.2 (15.1–39.0)	97.3	0.809
	Published 2011 or later	15	1203	24.6 (16.1–34.1)	91.7	
	Eastern Mediterranean	6	667	34.4 (20.4–49.8)	92.8	< 0.001
	South East Asia	9	4948	19.4 (6.7–36.3)	98.0	
	Europe	7	369	3.1 (0.0–9.9)	77.2	
	Africa	8	411	36.6 (23.2–51.2)	87.5	
	America	1	20	90.0 (69.9–97.2)	–	
	Western Pacific	3	223	39.7 (20.1–61.0)	NA	
	Overall	34	6638	25.3 (16.4–35.3)	97.7	NA
Crotamiton	Objective assessment	8	743	20.6 (9.8–34.0)	93.2	0.029
	Clinical exam/patient history	5	182	41.1 (27.9–55.0)	63.3	
	Published before 2011	6	227	21.9 (4.1–46.7)	92.6	0.281
	Published 2011 or later	7	698	35.7 (31.6–39.8)	15.1	
	Eastern Mediterranean	8	740	32.1 (25.5–39.1)	68.1	< 0.001
	South East Asia	–	–	–	–	
	Europe	2	81	2.1 (0.0–7.2)	100.0	
	Africa	–	–	–	–	
	America	3	104	37.4 (4.1–78.9)	99.9	
	Western Pacific	–	–	–	–	
	Overall	13	925	27.7 (17.9–38.7)	90.6	NA
Malathion	–	2	247	53.9 (47.6–60.1)	0.0	NA
Sulfur	–	2	230	52.2 (45.6–58.8)	0.0	NA

(*Continued*)

Table 1 (*Continued*)

Drug/treatment regimen	Subgroup[a]	Number of studies	Number of patients analysed	Failure rate (95% CI)	I^2	Interaction *P*-value
Permethrin 2%	–	4	448	14.6 (2.1–34.4)	94.1	NA
Permethrin – ivermectin	–	2	61	3.8 (0.0 –11.3)	0.0	NA
Permethrin – crotamiton	–	2	45	5.1 (0.1–14.5)	0.0	NA
Permethrin – sulfur	–	1	30	13.3 (0.0–11.3)	–	NA
Crotamiton – benzyl benzoate	–	1	10	10.0 (1.8–40.4)	–	NA
Crotamiton – lindane	–	2	15	4.8 (0.0–25.4)	0.0	NA
Crotamiton – sulfur	–	1	15	0.0 (0.0–20.4)	–	NA
Ivermectin – lindane	–	1	2	–	–	
Ivermectin – benzyl benzoate	–	2	250	53.2 (46.9–59.4)	0.0	

CI, confidence interval; NA, not applicable. [a]Some studies reported failure rates using both objective and clinical exam/patient history.

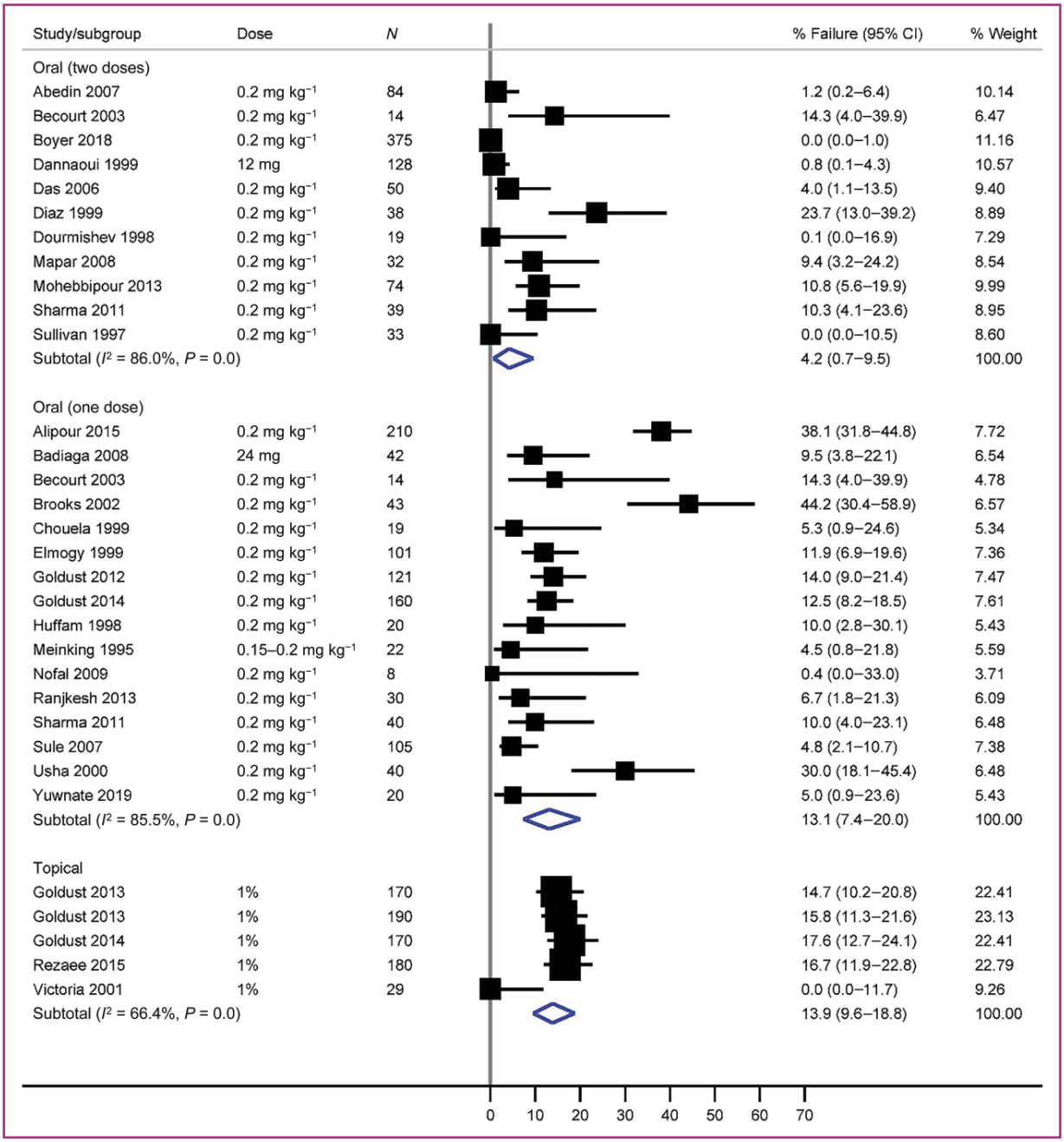

Figure 3 Treatment failure possibly resulting from drug resistance in patients treated with ivermectin.CI, confidence interval. The subgroups include studies in which precautions against mistakes in drug application, compliance or reinfestation were taken (treatment of contacts, washing and sealing of bedding and clothing, clear instructions on medication use).

In a meta-regression, year of publication was a significant predictor of treatment failure, with a 0.27% (95% CI 0.01–0.50; $P=0.017$) increase in treatment failure for every 1-year increase in publication year. We found a similar trend for permethrin (increase in failure prevalence per publication year = 0.58%, 95% CI 0.18–0.98; $P=0.005$), while the trend for ivermectin was not significant (0.41%, 95% CI −0.08–0.89; $P=0.097$) (Figure 4a,b).

Factors associated with treatment failure

A total of 20 studies reported factors assumed to be associated with treatment failure (Table 2). Three of these studies used multivariable regression analysis (Table 3).[14,15,36] Owing to considerable variability among these studies, we were not able to perform meta-analysis. One study explicitly listed resistance as a reason for treatment failure but justified this only by the fact that the treatments were applied by the investigators.[25]

Discussion

Treatment failure varied greatly across the drugs used to treat scabies, with permethrin and ivermectin showing the lowest prevalence of treatment failure. Oral ivermectin

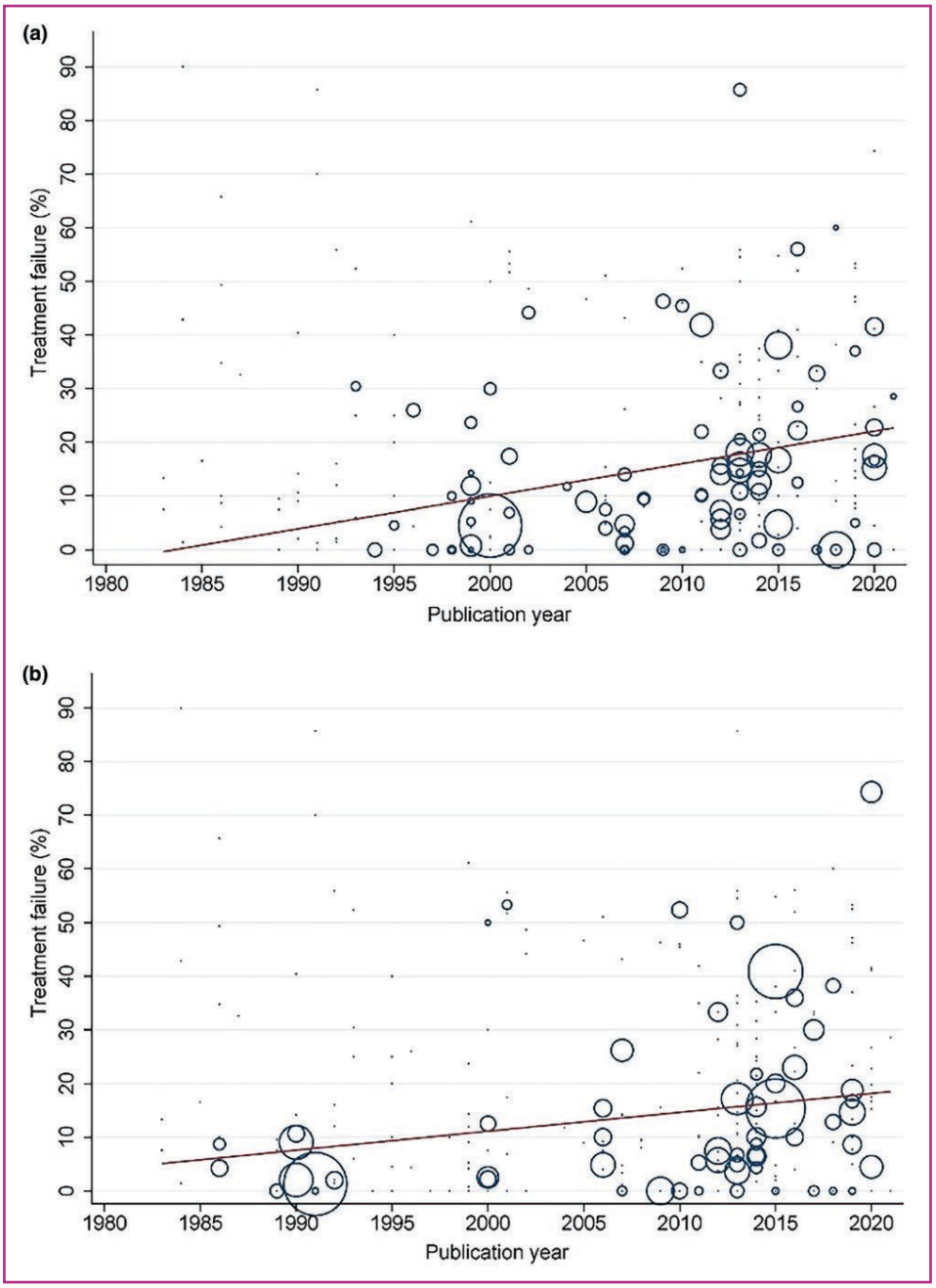

Figure 4 Trends in treatment failure (%) over time based on publication year of included studies for (a) permethrin and (b) ivermectin.The red line represents the linear prediction. The blue circles represent studies, and the size of a circle is proportional to weight (inverse variance).

Table 2 Putative factors assumed to be associated with treatment failure in included studies

Drug characteristics
Limited drug potency[22–24]
Taking only one type of treatment (oral or topical)[14]
Single-dose treatments[14]
Resistance[25]
Lower doses of medication[26]
Longer delay between administration of treatments[26]
Disease characteristics
Severity of scabies[27]
Treatment implementation issues
Delay between onset of pruritus and first treatment[14]
Contact with untreated[25,28–32]
Inappropriate application[33,34]
No decontamination[14]
Taking treatment with food[14]
Lack of water for bathing[29]
Use of corticosteroids during treatment[14,35]
Failure to reach/treat contacts[14,22,25]
Patient characteristics
Being a nurse[36]
Being female[36]
Cognitive, behavioural or mobility impairments (owing to ageing or other factors)[35,37]
Impaired surface lipid content on ageing skin[37]

administered in two doses was associated with a significant reduction in treatment failure compared with a single dose. Treatment failure has increased progressively over time at a rate of 0.2% per year. In the included studies, treatment failure was assumed to be linked to the characteristics of the drug administration, the disease severity, treatment implementation issues and patient characteristics. Drug resistance has never been assessed.

Our findings on the levels of treatment failure of ivermectin and permethrin are mostly similar to the findings from other studies.[11,13] In contrast to one trial,[38] this systematic review presents evidence that two doses of oral ivermectin are associated with a lower prevalence of treatment failure compared with one dose. This may reflect both the fact that ivermectin has limited ovicidal activity and a short half-life.[39–41] Several current guidelines, such as the European or UK National guidelines, already recommend two rounds of oral ivermectin treatment.[42] Other guidelines, such as the German and Japanese guidelines, do not generally recommend a second dose of ivermectin, but the findings of this systematic review support doing so in the future.[43,44]

Our analysis revealed a significant increase over time in overall and permethrin treatment failure, and we also found higher rates of ivermectin treatment failure in studies published in 2011 or later. This correlates with the dramatic increase in scabies incidence observed in several European countries since 2011, especially in adolescents and young adults with presumed lower treatment compliance.[6–9]

Resistance phenomena were reported for ivermectin-refractory cases[45,46] and suggested for treatment with permethrin in recent case reports.[37–49] Possible resistance mechanisms are known for most commonly used scabicides.[50] Moreover, subtle changes in drug formulation cannot be ruled out, leading to less effective treatment. This possibility would be consistent with recent work[51] that assessed mites isolated from permethrin-refractory cases that did not yield an *in vitro* correlate for loss of permethrin susceptibility. While promising novel treatments are being tested,[52,53] our finding of a significant increase in treatment failure over the last decade and the ongoing surge in incident cases provides justification for taking swift action. Thus, combinations of current treatments may be an option as suggested by a recent network meta-analysis.[11]

Few studies investigated the reasons for treatment failure, and none assessed the susceptibility of mites. Information on the latter would be required to differentiate treatment resistance from other reasons for failure such as compliance errors. While methods to assess resistance phenotypically were developed many years ago, they are applicable only in specific settings.[45,46,54] In larger studies, susceptibility of mites is not determined, which is likely to reflect the lack of suitable methods. It would be highly desirable to fill this methodological gap. Genetic typing of mites with typing schemes exceeding single-gene assessments would be a feasible approach going forward.[55–57] For a start, typing schemes combining variable gene markers with *S. scabiei* orthologues of genes predicted to encode target proteins of

Table 3 Predictors of treatment failures from the multivariable logistic regression analysis

Study (year), design	Population/treatment(s)	Predictor of therapy failure	Adjusted odds ratio (95% CI)
Aussy (2019), prospective cohort[14]	Ambulatory patients with clinical diagnosis of scabies from 14 private dermatology practices in France treated with any scabicide regimen	Delay between onset of pruritus and first scabies treatment > 1 month	2.95 (1.38–6.32)
		Other known case(s) of scabies in the patient's contacts	2.13 (1.07–4.24)
		Absence of decontamination of furniture with acaricide	5.81 (1.96–16.7)
		One dose of oral ivermectin vs. two doses (with or without benzyl benzoate)	6.62 (2.71–16.2)
		Topical benzyl benzoate alone vs. two doses of ivermectin	3.51 (1.55–7.95)
Leistner (2017), one-arm longitudinal study[36]	Healthcare workers in one acute care hospital in Germany treated with 5% permethrin ointment	Disposable gloves rarely used when examining the patient	9.79 (1.16–82.42)
		Holding the patient often	8.15 (1.12–59.27)
Makigami (2011), retrospective chart review[15]	Inpatients from a long-term care hospital for the elderly with confirmed diagnosis of scabies treated with any scabicide regimen	Higher serum total lymphocyte count[a]	0.57 (0.38–0.84)
		Treatment with lindane[a]	0.21 (0.08–0.54)

CI, confidence interval. [a]Predictors are reported as in the original study. As the reported odds ratio is below 1, these factors are considered predictors for treatment success and factors with an odds ratio greater than 1 would be considered a predictor of treatment failure.

ivermectin and permethrin may be derived from the recently expanded *S. scabiei* genomic information. Genotyping of mites from treatment-responsive vs. refractory groups may eventually become informative in relation to resistance-associated genotypes. This approach has been successful for other classes of pathogens.[58]

The strengths of this work lie in the breadth of the search, the examination of trends over time (1983–2021) and the narrative synthesis of factors associated with treatment failure. Most limitations of our review originate from the underlying evidence. The risk of bias was moderate to high in most of the studies. Despite our subgroup analyses, there is some considerable unexplained heterogeneity. This may be due to study design, differences in dosing, duration of treatments, timing of outcome assessment, and other clinical aspects of the studies. Topical synergized pyrethrins were not included in the search and analysis. Furthermore, our search was completed in 2021 and therefore more recent studies have not been included in this analysis. We used a random effects model, which appropriately incorporated heterogeneity, but we advise caution in the interpretation of these findings. Owing to the lack of statistical power, we could not adjust the temporal trend analysis for overall treatment failure by type of treatment. Therefore, we cannot rule out that the overall increasing trend can be attributed to permethrin only or that this trend is influenced by a change of treatment over time. In addition, the reporting of dosages, frequency of administration and treatment instructions in general was poor and precluded in-depth investigation into these issues. These items should be standard in reporting in order to improve comparability of treatment regimens and understanding of treatment failure.

We made two modifications to our protocol. Firstly, we used one adapted search strategy, rather than two, for both research questions. Secondly, we used the tool designed by Hoy *et al.*[17] to assess and report risk of bias, given that we were extracting proportion data from studies of different designs.

Our study is the most comprehensive review on the prevalence of scabies treatment failure and failure possibly resulting from the development of treatment resistance. In contrast to previous reviews, our findings show evidence of lower treatment failure for two doses of ivermectin compared with one dose. There is a trend of increasing overall and permethrin treatment failure, which may hint towards reduced mite susceptibility. Approaches to enable investigation of reduced mite susceptibility in trials are needed and should be a high research priority. Guidelines should be harmonized with respect to two treatment courses and consideration may be given to combinatorial treatments.

Funding sources

This work was supported by the Robert Koch Institute, Berlin, Germany through grant funding (TFS_221). The Robert Koch Institute contributed to the study design, data extraction and interpretation, and the writing of the manuscript.

Conflicts of interest

B.S. and L.M. received funding from Robert Koch Institute to perform this review.

Additional statements

L.M. and B.S. contributed equally to this work.

Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

Ethics statement

Not applicable.

Supporting information

Additional Supporting Information may be found in the online version of this article at the publisher's website.

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