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SUMMARY WITH CRITICAL APPRAISAL

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

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Authors: Calvin Young, Charlene Argáez

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Abbreviations

AGREE II	Appraisal of Guidelines for Research & Evaluation 2
CRD	Centre for Reviews and Dissemination
GRADE	Grading of Recommendations Assessment, Development and Evaluation
IUSTI	International Union against Sexually Transmitted Infections
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses

Context and Policy Issues

Pediculosis refers to a group of conditions that result from parasitic skin infestations of lice.[1] Three species of lice typically infest humans: *Pediculus humanus capitis* (i.e., head lice), *Pediculus humanus corporis* (i.e., body lice), and *Pthirus pubis* (i.e., pubic lice).[2] Lice are wingless, blood-sucking, obligate parasites that have no free-living stage in their life cycle.[1,3] Adult lice are between 1 to 3 mm in length and can lay up to 300 eggs, or nits, during a lifecycle.[4,5] Nymphs are hatched from eggs, and become full-sized adults approximately 10 days after hatching.[1,6] Transmission between individuals typically occurs through head-to-head or body-to-body contact, contact with infested linen, brushes, or clothes, and in the case of pubic lice, sexual contact.[2,7]

Infestation with lice may result in discomfort, pruritus (i.e., itchy skin), substantial social distress, anxiety, embarrassment, and unnecessary absence from school and work.[2,8] Although parasitic skin infestations of lice affect all socioeconomic groups, head lice predominantly infests schoolchildren between the ages of 3 and 14 in industrialized countries.[4,7] Reliable data on the prevalence rates of lice infestation are not often available due to large regional variance (both between and within countries).[4] However, it is estimated that there are between 6 million and 12 million head lice infestations among children every year in the United States, with an annual cost of treatment exceeding US$500 million.[2,3,9,10]

Many options for the treatment of lice infestation are available.[1] These include both topical (e.g., shampoos, creams, oils) and oral agents.[2] Historically, pediculocides have been used as a first-line treatment option; however, their extensive use has led to the development and spread of resistant lice.[6,8,11] Ivermectin, a broad-spectrum antiparasitic agent available in both topical and oral forms, has been used as an alternative option for the treatment of lice infestation, especially in individuals who have experienced a treatment failure.[12]

The purpose of the current report is to evaluate the comparative clinical and cost-effectiveness of oral ivermectin, topical ivermectin, and pediculicides for the treatment of parasitic skin infections of lice. Additionally, evidence-based guidelines regarding the use of ivermectin for parasitic skin infections of lice will be reviewed.

Research Questions

1. What is the comparative clinical effectiveness of oral versus topical ivermectin for parasitic skin infections of lice?
2. What is the comparative clinical effectiveness of oral ivermectin versus pediculicides for parasitic skin infections of lice?

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

Key Findings

One relevant non-randomized study was identified regarding the comparative clinical effectiveness of oral versus topical ivermectin for parasitic skin infections of lice. This evidence of limited quality suggested that both oral and topical ivermectin were effective for the treatment of patients with pediculosis capitis. The study found that the cure rates of lice infestation and pruritus were significantly higher among those receiving topical ivermectin compared to oral ivermectin one week after initial treatment; however, after a second treatment for nonresponders in both groups the cure rates improved to 100% (topical) and 97% (oral), a difference that was not statistically significant. Both treatments were reported as having favourable safety profiles.

No evidence regarding the comparative clinical effectiveness of ivermectin versus pediculicides for parasitic skin infections of lice was identified. Additionally, no evidence regarding the comparative cost-effectiveness of oral ivermectin or topical ivermectin versus pediculicides for parasitic skin infections of lice was identified.

One evidence-based guideline was identified regarding the use of ivermectin for parasitic skin infections of lice. The guideline provides weak recommendations (based on evidence of limited quality) for the use of oral or topical ivermectin for the treatment of individuals with pediculosis pubis. Oral ivermectin should be considered as a second-line therapy or as an option for individuals with infestation in the eyelashes (with the exception of children weighing < 15 kg, a group who should not use ivermectin). Topical ivermectin is listed as treatment option that is effective and generally well-tolerated, although it is not recommended as a first- or second-line therapy.

Methods

Literature Search Methods

A limited literature search was conducted on key resources including Medline, EMBASE, The Cochrane Library, University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. No methodological filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2014 and April 18, 2019.

Selection Criteria and Methods

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

Table 1: Selection Criteria

Population	People of all ages, in any setting, having any species of lice (i.e., *Pediculus humanus capitis*, *Pediculus humanus corporis*, or *Pthirus pubis*)
Intervention	Q1, Q2, Q4: Oral ivermectin Q3, Q5: Topical ivermectin Q6: Ivermectin
Comparator	Q1: Topical ivermectin Q2-5: Pediculicides (e.g., dimethicone; isopropyl myristate; isopropyl myristate/cyclomethicone; permethrin; pyrethrins/piperonyl butoxide)
Outcomes	Q1-Q3: Clinical effectiveness (e.g., extermination of lice, nits; complete clearance of skin lesions [e.g., papules, pustules]; relief of pruritus; need for re-treatment); safety (e.g., side effects; number of participants with at least one adverse event) Q4, Q5: Cost-effectiveness outcomes (e.g., cost per health benefit gained, ICER, QALY) Q6: Guidelines on appropriate use, place in therapy, and its use in treatment resistant settings
Study Designs	Health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, non-randomized studies, economic evaluations, and evidence-based guidelines

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

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, they were duplicate publications, or were published prior to 2014. Guidelines with unclear methodology were also excluded.

Critical Appraisal of Individual Studies

One reviewer critically appraised the clinical study using the Downs and Black checklist[13] and the guideline with the AGREE II instrument.[14] Summary scores were not calculated for the included studies; rather, a review of the strengths and limitations of each included study were described narratively.

Summary of Evidence

Quantity of Research Available

A total of 110 citations were identified in the literature search. Following screening of titles and abstracts, 98 citations were excluded and 12 potentially relevant reports from the electronic search were retrieved for full-text review. In addition, two potentially relevant publications were retrieved from the grey literature search for full-text review. Of these 14 potentially relevant articles, 12 publications were excluded for various reasons, while two publications met the inclusion criteria and were included in this report. These comprised one non-randomized study[15] and one evidence-based guideline.[16] Appendix 1 presents the

PRISMA[17] flowchart of the study selection. Additional references of potential interest are provided in Appendix 5.

Summary of Study Characteristics

One non-randomized study[15] and one evidence-based guideline[16] were identified and included in this review. No relevant health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, or economic evaluations were identified. Detailed characteristics are available in Appendix 2, Table 2 and Table 3.

Study Design

One non-randomized study[15] was identified regarding the comparative clinical effectiveness of oral versus topical ivermectin for parasitic skin infections of lice. The study was a single-centre, open-label, prospective cohort study. Dates of patient recruitment were not reported.

One evidence-based guideline was identified regarding the use of ivermectin for parasitic skin infections of lice.[16] This guideline, published in 2017 from the International Union against Sexually Transmitted Infections (IUSTI), was informed by a review of three existing guidelines (i.e., the 2010 European Guideline for the Management of Pediculosis pubis, the 2011 Centers for Disease Control and Prevention guideline, and the 2007 British Association for Sexual Health and HIV guideline) and a literature search of key databases performed between January and May, 2016. A modified GRADE (Grading of Recommendations Assessment, Development and Evaluation) system, as operationalised by the British HIV Association Guidelines Group, was used to rate the quality of evidence and strength of recommendations. The methods for formulating the recommendations were not described.

Country of Origin

The non-randomized study was conducted in Egypt.[15]

The guideline was developed by a group of authors based in Romania and France, with recommendations that are intended to apply across Europe.[16]

Patient Population

The non-randomized study[15] recruited individuals with proven head lice infestation (pediculosis capitis) from a single dermatology outpatient clinic at Al-Mania University Hospital in Al-Mania, Egypt. Individuals were excluded if they were pregnant or lactating, were less than five years of age or less than 15 kg in weight, or had a history of epileptic fits, immunodeficiency, secondary bacterial infection, known hypersensitivity to ivermectin, or any recent anti-pediculosis treatment. A total of 62 participants were included in the study. The mean age of participants was 14.1 years (ranged between 5 and 47 years) and the proportion of female participants was 88.7%.

The evidence-based guideline[16] provides information relating to the treatment of individuals (of all ages) who are suspected to have pediculosis pubis. The intended users of this guideline appear to be those who provide medical care for these individuals.

Interventions and Comparators

The non-randomized study[15] compared oral ivermectin, given as a single dose (200 mcg/kg), to a single application of topical 1% ivermectin solution for the treatment of head

lice. All study participants who had evidence of persistent lice infestation after one week received a second dose of their assigned treatment.

The guideline[16] considered numerous interventions for the treatment of pediculosis pubis, including permethrin cream, pyrethrins with piperonyl butoxide, phenothrin lotion, malathion lotion, oral ivermectin, topical ivermectin, benzyl benzoate lotion, and lindane shampoo.

Outcomes

The outcomes examined in the non-randomized study[15] were the presence or absence of pruritus and of visible signs of head lice infestation (i.e., viable nits, nymphs, or live lice). Additionally, cutaneous and systematic adverse events were recorded. Outcomes were assessed at pre-treatment and at each of the follow-up visits.

The outcome of interest in the guideline[16] was the presence of absence of lice or nits, as assessed at one week following treatment.

Summary of Critical Appraisal

Additional details regarding the strengths and limitations of the included publications are provided in Appendix 3, Table 4 and Table 5.

Non-Randomized Studies

The included non-randomized study[15] had clearly described objectives, interventions, controls, main outcomes, inclusion/exclusion criteria, and patient recruitment methodology. Some details on baseline patient characteristics were included (e.g., age, sex, number of cases with pruritus); however, several relevant patient characteristics, such as treatment history or severity of pruritus or head lice infestation, were not reported. Without providing these key characteristics it can be difficult to gauge the level of balance between the non-randomized cohorts, increasing the risk of confounding. Additionally, because this was an open-label study there is a risk for bias in either direction depending on the perceptions and expectations of participants and outcome assessors, although this risk is partially mitigated for outcomes of an objective nature (e.g., the presence of visible nits, nymphs, and live lice). The study included no mention of sample size calculations and recruited a total of 62 participants. Due to the single-dose nature of the interventions, compliance with the assigned treatment appears to be reliable. The length of follow-up was consistent between the treatment and control groups (one, two, and four weeks after treatment initiation) and no patients were lost to follow-up. Actual probability values (*P*-values) were reported for all monitored outcomes, increasing the strength of reporting.

Study participants, care providers, and health care settings appear to be representative of the "real-world", increasing the external validity of the study. However, this study was conducted at a single centre in Egypt, and the generalizability of the findings to other centres or countries is not clear. A final limitation to consider is that the authors did not disclose conflicts of interest or the sources of funding for the study.

Evidence-Based Guidelines

A number of strengths and limitations of the guidelines[16] were identified. As for the strengths, the guideline provided a clear description of its scope and purpose, including objectives, health questions, intended users, and target population. There were explicit links between the supporting evidence, which was identified using a systematic approach, and the recommendations. Additionally, the guideline was externally reviewed by experts prior

to its publication. The recommendations were well presented and unambiguous, and included information on the quality of the evidence and strength of the recommendations. The guideline incorporated several monitoring and auditing criteria, which may be useful to clinicians aiming to implement the recommendations into practice. Finally, the authors disclosed their sources of funding and potential conflicts of interest, none of which were considered likely to have influenced the content of the guidelines.

Moving on to the guideline's limitations, the views and preferences of the target population (e.g., patients, the public) do not appear to have been sought throughout the development of the guideline. In addition, details on the methodology for evidence selection and recommendation formulation were not provided. There was no mention of a procedure for updating the guideline in the future, no discussion of the facilitators or barriers to implementation, and no consideration for the resource implications of applying the recommendations. Finally, it should be noted that these guidelines were developed for use in European countries; therefore, the generalizability of the recommendations to the Canadian context is unclear.

Summary of Findings

A detailed summary of findings and recommendations are provided in Appendix 4, Table 6 and Table 7.

Clinical Effectiveness of Oral versus Topical Ivermectin

Extermination of Lice

Information regarding the comparative clinical effectiveness of oral versus topical ivermectin for the extermination of lice was available from one non-randomized study.[15] Patients were treated with either a single application of topical 1% ivermectin solution or a single dose of oral ivermectin (200 mcg/kg). The results suggested that patients treated with topical ivermectin were significantly more likely to have their lice infestation resolved after one week (P = 0.0002). The proportion of patients with visible signs of head lice infestation following one week were 55% and 12% in the oral and topical ivermectin groups, respectively. Those who had evidence of persistent infestation after one week (i.e., 55% and 12% in oral and topical ivermectin groups, respectively) received a second dose of their assigned treatment. The two groups did not significantly differ with respect to the number of cases with visible head lice infestation at two week and four week follow-ups. All but one patient (who received treatment with oral ivermectin) no longer showed visible signs of head lice infestation after they received a second dosage of their assigned treatment.

Pruritus

Evidence regarding the comparative clinical effectiveness of oral versus topical ivermectin with respect to the resolution of pruritus was available from one non-randomized study.[15] The findings demonstrated that patients who were treated with topical ivermectin were more likely to no longer have pruritus compared to those who received oral ivermectin at one week follow-up (10% versus 45%, respectively; P = 0.002). Patients who had evidence of persistent lice infestation after one week received a second dose of their assigned treatment. All patients in both treatment groups were pruritus-free at two week and four week follow-ups.

Safety

Information regarding the safety of oral and topical ivermectin was available from one non-randomized study.[15] Individuals with a parasite head lice infestation were assigned to one of two treatment groups: 1) a single application of topical 1% ivermectin solution, or 2) a single dose of oral ivermectin (200 mcg/kg). The publication did not include numerical data on the frequency or severity of adverse events; however, the authors noted that cutaneous (e.g., topical irritation or dermatitis) and systemic (e.g., headache, dizziness, diarrhea, vomiting, muscle pain) adverse events were mild and rare in both treatment groups and that no study participants stopped treatment due to side effects.[15]

Clinical Effectiveness of Oral Ivermectin versus Pediculicides

No relevant evidence regarding the comparative clinical effectiveness of oral ivermectin versus pediculicides for the treatment of parasitic skin infections of lice was identified; therefore, no summary can be provided.

Clinical Effectiveness of Topical Ivermectin versus Pediculicides

No relevant evidence regarding the comparative clinical effectiveness of topical ivermectin versus pediculicides for the treatment of parasitic skin infections of lice was identified; therefore, no summary can be provided.

Cost-Effectiveness of Oral Ivermectin versus Pediculicides

No relevant evidence regarding the comparative cost-effectiveness of oral ivermectin versus pediculicides for the treatment of parasitic skin infections of lice was identified; therefore, no summary can be provided.

Cost-Effectiveness of Topical Ivermectin versus Pediculicides

No relevant evidence regarding the comparative cost-effectiveness of topical ivermectin versus pediculicides for the treatment of parasitic skin infections of lice was identified; therefore, no summary can be provided.

Evidence-Based Guidelines Regarding the Use of Ivermectin

One evidence-based guideline[16] was identified regarding the use of ivermectin for the treatment of parasitic skin infections of lice.

The guideline[16] recommends oral ivermectin as a second-line therapy for the treatment of patients with pediculosis pubis (with the exception of children weighing < 15 kg, a group who should not use ivermectin). The authors further recommend oral ivermectin as an option for the treatment of lice in the eyelashes.[16] A third recommendation suggests that topical ivermectin can be used as an alternative therapy for the treatment of pediculosis pubis.[16] All three of these recommendations were scored as a grade C recommendation, indicating that they are based on evidence obtained from expert committee reports or opinions and/or clinical experience of respected authorities (indicating an absence of directly applicable studies of good quality). These guidelines also include a number of additional recommendations on other treatment options for patients with pediculosis pubis, including information on dosing and considerations to make for special populations (e.g., individuals who are pregnant or who are lactating).[16]

Limitations

A number of limitations were identified in the critical appraisal (Appendix 3, Table 4 and Table 5), however, additional limitations exist.

The quantity of identified relevant literature was relatively low. The clinical effectiveness findings were drawn from a single, open-label, non-randomized study[15] that included 62 individuals. This study may be subject to selection bias or bias due to confounding because participants were not randomized to treatment groups and it is possible that the clinician perceptions and expectations may have played a role in patient allocation.

No evidence regarding the comparative clinical effectiveness of ivermectin versus pediculicides for parasitic skin infections of lice was identified. Additionally, no economic evaluations studying the comparative cost-effectiveness of oral ivermectin, topical ivermectin, and pediculicides for parasitic skin infections of lice were identified.

The applicability of the evidence to Canadian settings is unclear as the clinical study[15] was conducted in Egypt and the evidence-based guideline[16] is intended for use in Europe. This is particularly important given the potential for geographic variability in ivermectin-resistance.[12,18] The non-randomized study[15] recruited both children and adults but did not include separate analyses for these groups; therefore, it is unclear how the effectiveness of these treatment options may vary by patient age. Furthermore, it may be difficult to generalize the results to males since the non-randomized study[15] enrolled a disproportionately higher number of females (88.7%).

Conclusions and Implications for Decision or Policy Making

This review was comprised of one non-randomized study[15] regarding the comparative clinical effectiveness of oral versus topical ivermectin for the treatment of head lice and one evidence-based guideline[16] regarding the use of ivermectin for the management of pediculosis pubis. No evidence was identified for the cost-effectiveness of oral ivermectin, topical ivermectin, and pediculicides for parasitic skin infections of lice.

Evidence from the non-randomized-study[15] suggested that both oral and topical ivermectin were effective and tolerable for the elimination of lice and resolution of pruritus; however, a single treatment with topical ivermectin was more effective than a single dose of oral ivermectin at one week following treatment. This difference was not sustained after a second dose of treatment, which was required in many cases (4/31 patients in the topical ivermectin group; 17/31 patients in the oral ivermectin group) to ensure complete eradication of head lice. The identified guideline[16] provides weak recommendations (based on evidence of limited quality) for the use of oral and topical ivermectin as treatment options for individuals with pediculosis pubis.

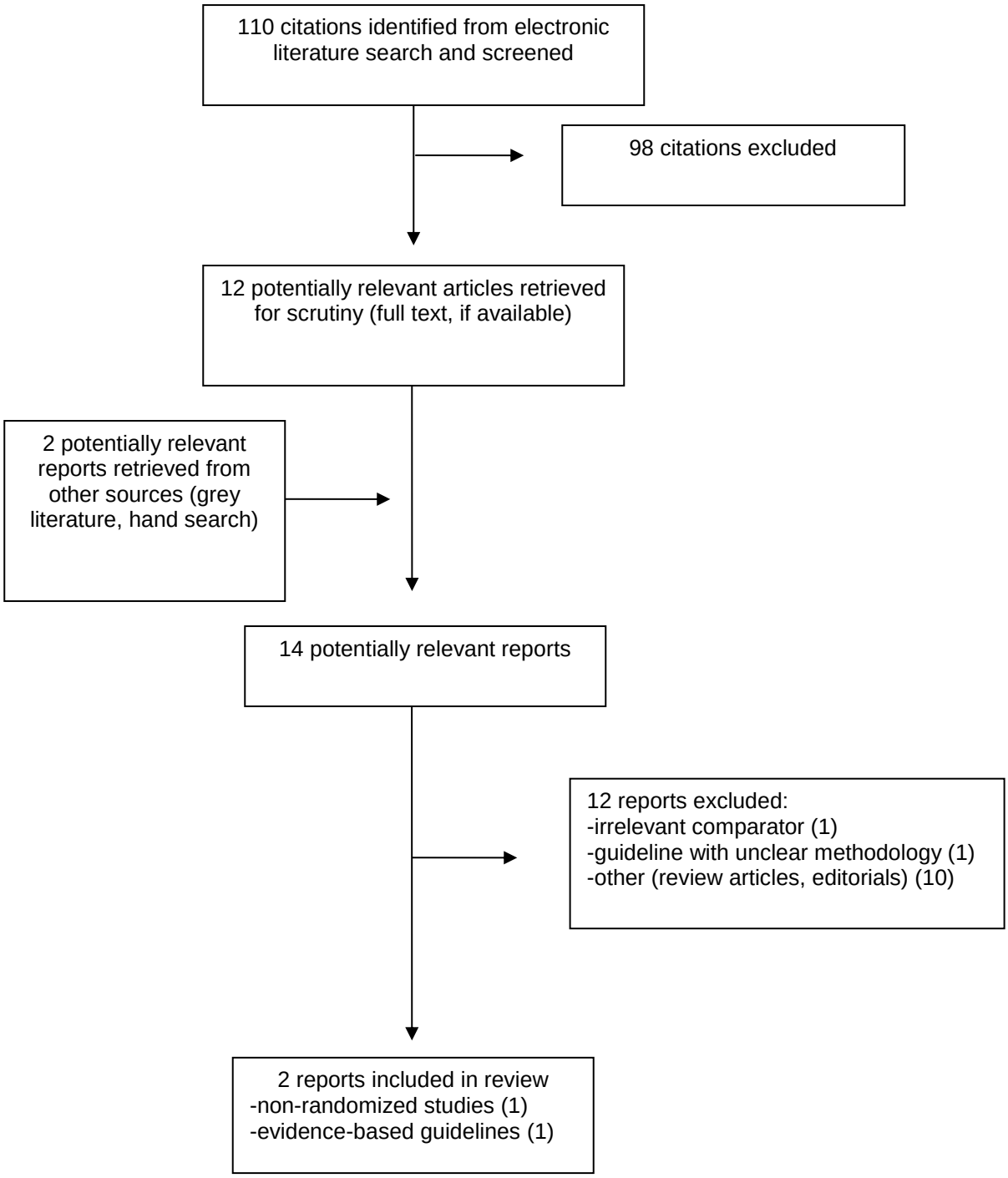
The scarcity of comparative evidence found in this report is consistent with a narrative review[12] article published in 2018. Although this review[12] was not systematic, it discussed the findings of five clinical trials that evaluated the use of oral ivermectin monotherapy for the treatment of head lice infestation (including the non-randomized study[15] included in our report). The four additional studies identified in the review[12] were not relevant under our inclusion criteria due to study design or date of publication; however, the findings may be of interest to those who are seeking evidence regarding the effectiveness of oral ivermectin. The authors concluded that oral ivermectin is an option for the treatment of head lice infestation.[12]

The limitations of the included studies[15,16] and of this report should be considered when interpreting the results. The findings highlighted in this review come with a high degree of uncertainty. Further research investigating the comparative clinical and cost-effectiveness of oral ivermectin, topical ivermectin, and pediculicides for the treatment of parasitic skin infections of lice, especially through the use of large, methodologically-sound randomized controlled trials, would help reduce this uncertainty.

References

1. Do-Pham G, Monsel G, Chosidow O. Lice. *Semin Cutan Med Surg.* 2014;33(3):116-118.
2. Sangare AK, Doumbo OK, Raoult D. Management and treatment of human lice. *Biomed Res Int.* 2016;2016:8962685.
3. Cummings C, Finlay JC, MacDonald NE. Head lice infestations: A clinical update. *Paediatr Child Health.* 2018;23(1):e18-e24.
4. Devore CD, Schutze GE, Okamoto J, et al. Head lice. *Pediatrics.* 2015;135(5):e1355-e1365.
5. Dietrich A, Joshi K, Sayed C. Infestations in the geriatric patient. *Curr Geriatr Rep.* 2018;7(4):210-215.
6. Koch E, Clark JM, Cohen B, et al. Management of head louse infestations in the United States-a literature review. *Pediatr Dermatol.* 2016;33(5):466-472.
7. Feldmeier H. Treatment of pediculosis capitis: a critical appraisal of the current literature. *Am J Clin Dermatol.* 2014;15(5):401-412.
8. Verma P, Namdeo C. Treatment of pediculosis capitis. *Indian J Dermatol.* 2015;60(3):238-247.
9. Center for Disease Control. Head lice: epidemiology & risk factors. 2013 Sep; https://www.cdc.gov/parasites/lice/head/epi.html.
10. Meister L, Ochsendorf F. Head lice. *Deutsches Arzteblatt Int,.* 2016;113(45):763-772.
11. Elston DM. Drug-resistant lice. *Arch Dermatol.* 2003;139(8):1061-1064.
12. Sanchezruiz WL, Nuzum DS, Kouzi SA. Oral ivermectin for the treatment of head lice infestation. *Am J Health Syst Pharm.* 2018;75(13):937-943.
13. Downs SH, Black N. The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. *J Epidemiol Community Health,.* 1998;52(6):377-384. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1756728/pdf/v052p00377.pdf. Accessed 2019 May 13.
14. Agree Next Steps Consortium. The AGREE II Instrument. [Hamilton, ON]: AGREE Enterprise; 2017: https://www.agreetrust.org/wp-content/uploads/2017/12/AGREE-II-Users-Manual-and-23-item-Instrument-2009-Update-2017.pdf. Accessed 2019 May 13.
15. Ahmad HM, Abdel-Azim ES, Abdel-Aziz RT. Assessment of topical versus oral ivermectin as a treatment for head lice. *Dermatol Ther.* 2014;27(5):307-310.
16. Salavastru CM, Chosidow O, Janier M, Tiplica GS. European guideline for the management of pediculosis pubis. *J Eur Acad Dermatol Venereol.* 2017;31(9):1425-1428.
17. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *J Clin Epidemiol.* 2009;62(10):e1-e34.
18. Amanzougaghene N, Fenollar F, Nappez C, et al. Complexin in ivermectin resistance in body lice. *PLoS Genet.* 2018;14(8):e1007569-e1007569.

Appendix 1: Selection of Included Studies



Appendix 2: Characteristics of Included Publications

Table 2: Characteristics of Included Primary Clinical Studies

First Author, Publication Year, Country	Study Design, Setting, and Objective	Patient Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
Ahmad, 2014[15] Egypt	**Study design**: Single-centre, open-label, prospective cohort study **Setting**: Participants were recruited from a single dermatology outpatient clinic at Al-Mania University Hospital in Al-Mania, Egypt. Dates of recruitment were not mentioned. **Objective**: To investigate the efficacy and safety of topical ivermectin (1% solution) versus oral ivermectin (200 µg/kg) for the treatment of head lice	**Inclusion criteria**: Patients with proven head lice infestation (pediculosis capitis) confirmed by the presence of visible nits, nymphs, and live lice **Excluded**: Those who were pregnant or lactating, were less than 5 years of age or less than 15 kg in weight, or had a history of epileptic fits, immunodeficiency, secondary bacterial infection, or any recent anti-pediculosis treatment. Patients with a known hypersensitivity to ivermectin were also excluded **Number of patients**: 62 (31 in the topical ivermectin group; 31 in the oral ivermectin group) **Mean age (SD)**: 11.4 (4.6) in the topical ivermectin group (range = 5 to 23); 16.7 (9.8) in the oral ivermectin group (range = 7 to 47) **Sex**: 87.1% female in the topical ivermectin group; 90.3% female in the oral ivermectin group	**Intervention**: A single application of topical 1% ivermectin solution **Comparator**: A single dose of oral ivermectin (200 mcg/kg) All participants with evidence of persistent infestation after 1 week received a second dose of their assigned treatment.	**Outcomes**: - Eradication of head lice (week 1, 2, and 4) - Presence of puritus - Adverse events **Follow-up**: 1, 2, and 4 weeks after initiation of treatment

SD = standard deviation.

Table 3: Characteristics of Included Guideline

First Author, Publication Year, Country	Scope, Interventions, Intended Users, Target Population	Evidence Collection, Selection, and Synthesis	Recommendations Development and Evaluation	Levels of Evidence, Recommendation Grading System, Guideline Validation
Salavastru, 2017[16] Romania	**Scope**: Guideline for the management of pediculosis pubis **Interventions**: Various treatment options for pediculosis pubis, including permethrin cream, pyrethrins, phenothrin lotion, malathion lotion, oral ivermectin, topical ivermectin, benzyl benzoate lotion, and lindane shampoo **Intended users**: Assumed to be those providing medical care for individuals with pediculosis pubis **Target population**: Individuals (of all ages) who are suspected to have pediculosis pubis	The guideline was updated by reviewing three existing guidelines (the 2010 European Guideline for the Management of Pediculosis pubis, the 2011 CDC guideline, and the 2007 BASHH guideline) and a comprehensive literature search for articles published between 2010 and April 2016 in PubMed, Biomedical Reference Collection, and Medline. The processes for article selection and data synthesis were unclear.	Details regarding the methods used for recommendation development and evaluation were not provided in the guideline.	The levels of evidence were categorized as follows: Ia Evidence obtained from MA of RCTs. Ib Evidence obtained from at least one RCT. IIa Evidence obtained from at least one well-designed study without randomization. IIb Evidence obtained from at least one other type of well-designed quasi-experimental study. III Evidence obtained from well-designed non-experimental descriptive studies such as comparative studies, correlation studies, and case control studies. IV Evidence obtained from expert committee reports or opinions and/or clinical experience of respected authorities. Recommendations were graded as follows: A Requires at least one RCT as part of the body of literature of overall good quality and consistency addressing the specific recommendation. B Requires availability of well conducted clinical studies but no RCTs on the topic of recommendation. C Requires evidence from expert committee reports or opinions and/or clinical experience of respected authorities. Indicates absence of directly applicable studies of good quality. **Guideline validation**: There was no mention of guideline validation

BASHH = British Association for Sexual Health and HIV; CDC = Centers for Disease Control and Prevention; MA = meta-analysis; RCT = randomized controlled trial.

Appendix 3: Critical Appraisal of Included Publications

Table 4: Strengths and Limitations of Clinical Studies using the Downs and Black Checklist[13]

Strengths	Limitations
Ahmad, 2014[15]	
• The objectives, interventions, controls, and main outcomes were clearly described • Detailed methodology on patient recruitment and assessment of inclusion/exclusion criteria were included • Population characteristics were clearly described • Compliance with the assigned treatment appears to be reliable • The main outcome measures used were valid and reliable • The major findings of the study were presented in tabular form and clearly described • Actual probability values (*P*-values) were reported • Adverse events were recorded as part of the study (no patients stopped treatment because of side effects) • Length of follow-up was consistent between the treatment and control groups • No patients were lost to follow-up in either treatment group • Study participants, care providers, and setting appear to be representative of the population and care setting of interest	• Intervention assignment was not done at random • This was an open-label study with no blinding of study participants or outcome assessors • Baseline patient characteristics were not tested for statistically significant differences • The severity of head lice infestation at baseline was not discussed or adjusted for; between-group differences in baseline severity may have affected the findings • The two cohorts under study were of different age ranges (topical ivermectin group: 5 to 23 years; oral ivermectin group: 7 to 47 years) and may be susceptible to inherent differences • No power calculation performed • The source of funding for the study is unclear • Conflicts of interest were not disclosed by the authors • Single-centre study (conducted in Egypt), may not be generalizable to other centres

Table 5: Strengths and Limitations of Guidelines using AGREE II[14]

Item	Guideline Salavastru, 2017[16]
Domain 1: Scope and Purpose	
1. The overall objective(s) of the guideline is (are) specifically described.	Yes
2. The health question(s) covered by the guideline is (are) specifically described.	Yes
3. The population (patients, public, etc.) to whom the guideline is meant to apply is specifically described.	Yes
Domain 2: Stakeholder Involvement	
4. The guideline development group includes individuals from all relevant professional groups.	No
5. The views and preferences of the target population (patients, public, etc.) have been sought.	No
6. The target users of the guideline are clearly defined.	Yes
Domain 3: Rigour of Development	
7. Systematic methods were used to search for evidence.	Yes
8. The criteria for selecting the evidence are clearly described.	No
9. The strengths and limitations of the body of evidence are clearly described.	No
10. The methods for formulating the recommendations are clearly described.	No

Item	Guideline
	Salavastru, 2017[16]
11. The health benefits, side effects, and risks have been considered in formulating the recommendations.	Yes
12. There is an explicit link between the recommendations and the supporting evidence.	Yes
13. The guideline has been externally reviewed by experts prior to its publication.	Yes
14. A procedure for updating the guideline is provided.	No
Domain 4: Clarity of Presentation	
15. The recommendations are specific and unambiguous.	Yes
16. The different options for management of the condition or health issue are clearly presented.	Yes
17. Key recommendations are easily identifiable.	Yes
Domain 5: Applicability	
18. The guideline describes facilitators and barriers to its application.	No
19. The guideline provides advice and/or tools on how the recommendations can be put into practice.	No
20. The potential resource implications of applying the recommendations have been considered.	No
21. The guideline presents monitoring and/or auditing criteria.	Yes
Domain 6: Editorial Independence	
22. The views of the funding body have not influenced the content of the guideline.	Yes
23. Competing interests of guideline development group members have been recorded and addressed.	Yes

Appendix 4: Main Study Findings and Authors' Conclusions

Table 6: Summary of Findings of Included Primary Clinical Study

<table>
<tr><th>Main Study Findings</th><th>Authors' Conclusion</th></tr>
<tr><td colspan="2">Ahmad, 2014[15]</td></tr>
<tr><td>A single-centre, open-label, prospective cohort study assessing the efficacy and safety of topical ivermectin (1% solution) versus oral ivermectin (200 mcg/kg) for the treatment of head lice.

Comparison of topical ivermectin (TI) and oral ivermectin (OI) with respect to several outcomes
<table>
<tr><th rowspan="2">Outcome measure</th><th colspan="2">Treatment group</th><th rowspan="2">Statistical significance (P-value)</th></tr>
<tr><th>TI (N = 31)</th><th>OI (N = 31)</th></tr>
<tr><td>Number of pruritus positive cases (%)</td><td></td><td></td><td></td></tr>
<tr><td>Pre-treatment</td><td>30 (97%)</td><td>31 (100%)</td><td>NR</td></tr>
<tr><td>1 week follow-up*</td><td>3 (10%)</td><td>14 (45%)</td><td>0.002</td></tr>
<tr><td>2 week follow-up</td><td>0</td><td>0</td><td>0.3</td></tr>
<tr><td>4 week follow-up</td><td>0</td><td>0</td><td>0.3</td></tr>
<tr><td>Number of cases with visible signs of head lice infestation (%)</td><td></td><td></td><td></td></tr>
<tr><td>Pre-treatment</td><td>31 (100%)</td><td>31 (100%)</td><td>NR</td></tr>
<tr><td>1 week follow-up*</td><td>4 (12%)</td><td>17 (55%)</td><td>0.0002</td></tr>
<tr><td>2 week follow-up</td><td>0</td><td>1 (3%)</td><td>0.3</td></tr>
<tr><td>4 week follow-up</td><td>0</td><td>1 (3%)</td><td>0.3</td></tr>
</table>
*The treatment was repeated after 1 week only for those with evidence of persistent infestation.
N = number of patients; NR = not reported; OI = oral ivermectin; TI = topical ivermectin.

Adverse events: "Both topical and oral ivermectin treatments were well tolerated. Adverse events, whether cutaneous (e.g., topical irritation or dermatitis) or systemic (e.g., headache, dizziness, diarrhea, vomiting, muscle pain) were mild and rare among both groups. Furthermore, none of the patients stopped treatment because of side effects."[15] (p309)</td><td>"In conclusion, this study suggests that both topical and oral ivermectin demonstrate high efficacy and tolerability in the treatment of pediculosis capitis. However, a single treatment with topical ivermectin provides significantly higher cure of infestation and faster relief of pruritus than oral ivermectin. In addition, whether topical or oral ivermectin is used to treat head lice infestation, a second dose is required in some cases to ensure complete eradication."[15] (p310)</td></tr>
</table>

OI = oral ivermectin; TI = topical ivermectin.

Table 7: Summary of Recommendations in Included Guidelines

<table>
<tr><th>Recommendations</th><th>Strength of Evidence and Recommendations</th></tr>
<tr><td colspan="2">Salavastru, 2017[16]</td></tr>
<tr><td>Evidence-based guideline regarding the management of patients with pediculosis pubis.

Oral ivermectin was recommended as a second-line therapy for the treatment of patients with pediculosis pubis:
• "Ivermectin was reported as efficient but different dosages are used. In a series of pediculus pubis cases, the dosage used was 250 µg/kg orally, repeated after 1 week [level of evidence IV; grade C]. A randomized clinical trial demonstrated that in difficult-to-treat head lice the effective dosage of Ivermectin was 400 µg/kg orally, repeated after 1 week. Ivermectin should not be used in children weighing <15 kg."[16] (p1427)

Oral ivermection was also recommended for the treatment of lice in the eyelashes:</td><td>The levels of evidence were categorized as follows:[16]
Ia Evidence obtained from meta-analysis of RCTs.
Ib Evidence obtained from at least one RCT.
IIa Evidence obtained from at least one well-designed study without randomization.
IIb Evidence obtained from at least one other type of well-designed quasi-experimental study.
III Evidence obtained from well-designed non-experimental descriptive studies such as comparative studies, correlation studies, and case control studies.
IV Evidence obtained from expert committee reports or opinions and/or clinical experience of respected authorities.

Recommendations were graded as follows:[16]
A Requires at least one RCT as part of the body of literature of overall good quality and consistency addressing the</td></tr>
</table>

Recommendations	Strength of Evidence and Recommendations
• "Ivermectin oral 200 µg/kg as two doses 1 week apart [level of evidence IV; grade C recommendation]."[16] (*p1427*) Topical ivermectin was not mentioned as a first- or second-line therapy; however, it was mentioned under other therapies for the treatment of patients with pediculosis pubis: • "Ivermectin topical was reported as effective and generally well-tolerated for pediculosis pubis [level of evidence IV; grade C recommendation]."[16] (*p1427*)	specific recommendation. B Requires availability of well conducted clinical studies but no RCTs on the topic of recommendation. C Requires evidence from expert committee reports or opinions and/or clinical experience of respected authorities. Indicates absence of directly applicable studies of good quality.

RCT = randomized controlled trial

Appendix 5: Additional References of Potential Interest

Previous CADTH Reports

Common Drug Review: Ivermectin (Rosiver): final recommendations. Ottawa (ON): CADTH; 2015 Nov. https://www.cadth.ca/sites/default/files/cdr/complete/SR0429_complete_Rosiver_Nov-23-15_e.pdf Accessed 2019 May 13

Lindane and other treatments for lice and scabies: a review of clinical effectiveness and safety. Ottawa (ON): 2010 Jun. https://www.cadth.ca/sites/default/files/pdf/l0186_treatments_for_lice_scabies_htis-2.pdf Accessed 2019 May 13.

Non-Randomized Studies

Alternative Comparator - Uncontrolled Before-and-After Study

Coscione S, Esau T, Kekeubata E, et al. Impact of ivermectin administered for scabies treatment on the prevalence of head lice in Atoifi, Solomon Islands. *PLoS Neglected Tropical Diseases [electronic resource]*. 2018 09;12(9):e0006825. PubMed: PM30252856

Guidelines and Recommendations

Clinical Practice Guidelines – Unclear Methodology

Cummings C, Finlay JC, MacDonald NE, Canadian Paediatric Society, Community Paediatrics Committee. Head lice infestations: a clinical update. Paediatr Child Health. 2018;23(1):e18–e24:https://www.cps.ca/en/documents/position/head-lice Accessed 2019 May 13.

State of California, Health and Human Services Agency. Guidance on head lice prevention and control for school districts and child care facilities. Sacramento (CA): Vector-Borne Disease Section , California Department of Public Health; 2018 Mar (updated). https://www.cdph.ca.gov/Programs/CID/DCDC/CDPH%20Document%20Library/SchoolGuidanceonHeadLice2018.pdf Accessed 2019 May 13.

Bohl B, Evetts J, McClain K, Rosenauer A, Stellitano E. Clinical practice update: pediculosis capitis. *Pediatr Nurs*. 2015 Sep-Oct;41(5):227-234. PubMed: PM26665422

Federal Bureau of Prisons. Lice protocol: clinical practice guidelines. Washington (DC): Federal Bureau of Prisons; 2014 Oct. https://www.bop.gov/resources/pdfs/lice.pdf Accessed 2019 May 13.