Clinical interventions for tungiasis (sand flea disease): a systematic review

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Tungiasis (sand flea disease) is an epidermal parasitic skin disease occurring in resource-limited communities. There is no standard treatment for tungiasis, and available treatment options are scarce. To our knowledge, this is the first systematic review aimed to assess randomised controlled trials (RCTs) investigating interventions for tungiasis. We systematically searched databases including MEDLINE (EBSCOhost), CENTRAL, CINAHL, PubMed, Web of Science, SciELO, LILACS and Embase (Scopus) for RCTs in any language, from inception of the databases until June 12, 2021. RCTs exploring preventive and therapeutic interventions for tungiasis were eligible. We used the revised Cochrane Collaboration's risk of bias tool to assess the risk of bias and Jadad scale to quantify the methodological quality of the RCTs. Of the 1839 identified records, only eight RCTs involving 808 participants were included, and several methodological deficiencies were identified in most of the trials. Trial interventions included: oral drugs niridazole and ivermectin and topical interventions of ivermectin lotion, metrifonate lotion, thiabendazole lotion, thiabendazole ointment, dimeticones (NYDA), and a neem seed and coconut oils-based mixture for treatment and coconut oil-based lotion (Zanzarin) for prevention. The coconut oil-based lotion for prevention and dimeticones for treatment of tungiasis have displayed the most promise. Most of the RCTs included in this study had low methodological quality. There is a clear unmet need for high-quality RCTs examining safe and effective prevention and treatment alternatives of tungiasis in endemic settings.

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Introduction

Tungiasis is a parasitic skin disease caused by epidermal penetration of female sand fleas, *Tunga penetrans*, and less commonly by *Tunga trimamillata*.[1,2] These fleas are known by various names worldwide. They are called jigger, chigger, and sand flea in English-speaking countries (eg, Kenya, Uganda, USA, UK, and Australia); puce-chique in French Guiana; nigua in Columbia, Ecuador, Venezuela, and Mexico; kuti in Bolivia; pique in Peru and Argentina; mataquenha in Mozambique; niguá tü in Paraguay; bicho-do-pé in Brazil; chigoe in Trinidad, Guyana, and West Indies; ogri eye in Surinam; and mujale in Ethiopia.[1,3] Tungiasis is classified as a neglected tropical disease within the group of scabies and other parasitic diseases of the skin by WHO, as well as the Pan American Health Organization.[4] It is one of the most widespread epidermal parasitic skin diseases of resource-limited communities in sub-Saharan Africa, Latin America, and the Caribbean, and is considered as probably the most neglected of all neglected tropical diseases.[5,6]

Tungiasis affects humans and other mammals. In endemic communities, children (aged 5–14 years), and older people (≥60 years) are most affected, with prevalences of up to 85% in these groups compared with 50% in the general population.[7–9] However, accurate estimates on the global burden of the disease are not available.[10] According to WHO, 20 million people are estimated to be at risk of developing tungiasis in South America.[3] In 2014, an estimated 1·4 million Kenyans (about 4% of the total population) had the condition, and approximately 10 million were estimated to be at risk.[11] There were 265 deaths reported due to tungiasis, possibly because of complications such as septicaemia and tetanus, in Kenya in 2011 according to the Ahadi Kenya Trust, a local non-governmental organisation.[12] As many cases remain unreported, therefore the actual number of deaths could be higher. In Uganda, the Ministry of Health estimated that tungiasis affected 2·4 million people in 2012 and an additional 6·0 million were at risk.[13] Tungiasis resulted in at least 20 deaths in Uganda in 2010.[14] The condition is also one of the most commonly reported parasitic skin diseases among travellers returning from endemic areas.[15–18]

A person infected with tungiasis can have hundreds of parasites, usually on the feet and hands. Toes, soles, and heels are the sites most frequently affected.[9,19] The infection results in intense inflammation, pain and itching, and frequently leads to secondary bacterial infections, resulting in abscesses and suppuration.[20,21] Bacterial superinfection can cause cellulitis and lymphangitis, and potentially life-threatening complications such as sepsis, tetanus, and poststreptococcal glomerulonephritis.[3,22] Left untreated, tungiasis can lead to deformation or loss of nails, disfigurement of the feet, and ulcers with extended tissue necrosis, causing difficulty in walking, auto-amputation of digits, and immobility in severe cases.[19,20,23]

In addition, tungiasis can cause a substantial decrease in quality of life and effect education, household economy, and wellbeing of the affected community.[3,11,24,25] The disease is also linked to stigmatisation.[11,26] People who are affected are often stigmatised and isolated by their peers and communities, severely affecting their self-esteem and societal participation, and ultimately affecting their health-seeking behaviour and use of health facilities.[11,26]

In endemic settings, a One Health approach, integrating public health, animal health, biological and

See Online for appendix

entomological sciences, and the environment, is likely to be an effective measure to control tungiasis.[27] However, this approach would require a comprehensive process involving (1) integrated preventive and treatment measures for humans who are infected and infected animals; (2) public health education and training, focusing on tungiasis prevention and control; and (3) improving environmental risk factors and reducing the amount of parasites in off-host stages.[3,28,29] In humans, there is evidence that twice-daily application of a plant-based lotion (Zanzarin; containing coconut oil, jojoba oil, and *Aloe vera*) on the hands and feet reduces tungiasis incidence and morbidity.[30–33] Other locally known natural resources (eg, neem, coconut oils, castor oil, palm oil, and *A vera*) have also been used for their repellent properties against tungiasis,[35,36] due to their easy availability, cultural acceptability, and relatively low cost,[29,34] and some of them are included in local government guidelines (eg, in Kenya).[11,37]

There is no standard treatment used for tungiasis.[25] The treatment recommended by WHO in endemic areas is surgical removal of the embedded fleas with a sterile needle followed by disinfection of the skin lesions.[3] However, in resource-poor communities, this method is frequently done using unsafe procedures involving sharing of sharp instruments such as pins, needles, thorns, and sharpened wood pieces to extract the flea,[20] often leading to bacterial superinfections, increased inflammatory response, and potential transmission of viral pathogens such as HIV, hepatitis B, and hepatitis C.[37,38]

Parasiticides such as oral thiabendazole[39] and ivermectin,[40] and topical benzyl benzoate[41] and disinfectant (eg, hydrogen peroxide),[11] have been investigated for treating tungiasis in non-randomised, non-controlled studies with relatively little conclusive information available on their safety or effectiveness. Further, to our knowledge, there has been no systematic synthesis of evidence on randomised controlled trials (RCTs) exploring tungiasis preventive and treatment interventions so far. This systematic review aims to provide a comprehensive, evidence-based critical appraisal of all RCTs investigating preventive and treatment options for tungiasis.

Methods

Study design

Initial searches showed that published RCTs on tungiasis varied considerably in terms of study interventions, duration of treatment, participants, study design, study outcome measures, and follow-up times, making a meta-analysis impossible. Hence, a narrative-style data synthesis was used to systematically organise, present, and appraise the data.

Search strategies and selection criteria

This study is reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement (appendix pp 4–5).[42] Two researchers (SA and Wubshet Tesfaye) independently searched for RCTs exploring prevention and treatment strategies against tungiasis using combinations of terms "tungiasis", "*tunga penetrans*", "sand flea", "jigger flea", "chigoe flea", "nigua", "therap*", "treatment*", "intervention*", "repellen*", and "prevent*". The databases were PubMed, MEDLINE (EBSCOhost), Embase (SCOPUS), Cochrane Central Register of Controlled Trials, Cochrane Library, Cumulative Index to Nursing & Allied Health Literature, ScienceDirect, SciFINDER, Web of Science, The Scientific Electronic Library Online, and Latin America and Caribbean Health Sciences Literature. Databases were searched without language restrictions from inception to June 15, 2020. The full search strategy is summarised in the appendix (pp 2–3).

Grey literature was searched using: The National Research Register, Health Services Research Project database; US National Library of Medicine; NHS national research register; National Institute for Health and Care Excellence; African Index Medicus; OpenGrey; ProQuest Dissertations & Theses Global; Open Access Theses and Dissertations; Directory of Open Access Repositories; Registry of Open Access Repositories; Networked Digital Library of Theses and Dissertations; DART-Europe E-theses Portal; Bielefeld Academic Search Engine; EBSCO Open Dissertations project; International Centre of Insect Physiology and Ecology; WHO International Clinical Trials Registry Platform; International Standard Randomised Controlled Trials Number registry; Australian New Zealand Clinical Trials Registry; EU Clinical Trials register; ClinicalTrials.gov; and controlled-trials.com. Additional searches were undertaken in Google and Google Scholar, and reference lists of included papers were manually searched.

To screen, the records obtained from the search results were exported to Covidence (Veritas Health Innovation, Melbourne, VIC Australia). After duplicates were removed, two researchers (SA and Wubshet Tesfaye) independently screened the titles and abstracts of the records for relevance and reviewed the full-text articles for eligibility. Articles published in languages other than English were translated by Google Translate. Any disagreements were resolved by discussion between the two researchers. Due to the small number of publications on this topic, all RCTs investigating tungiasis interventions were included regardless of study population, intervention type, outcome measures, and duration of follow-up. Although excluded from the systematic assessment, the non-RCT clinical studies were screened and summarised to provide a comprehensive profile on tungiasis prevention and treatment (appendix pp 14–17).

Data extraction and analysis

Two authors (SA and JKC) independently extracted key data from the included studies. Any disagreements regarding information extracted were resolved by

discussion. Data extracted included study origin, type of study, study inclusion and exclusion criteria, patient characteristics, disease diagnoses, intervention details, study outcome measures, and results. All comparisons that were made are narratively described and presented in the appendix (pp 6–9).

Risk of bias and quality assessments

Two authors (SA and JKC) independently assessed the risk of bias of the RCTs using the revised Cochrane Collaboration's risk of bias tool (RoB 2.0)[43] across five domains: bias arising from the randomisation process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result. Disagreements in ratings that could not be resolved through discussion were resolved by a third reviewer (JT). Results were displayed in summary figures generated by Review Manager (version 5.4). The detailed criteria used to determine the risk of bias are listed in the appendix (p 10). We also used Jadad scale,[44] a validated five-point scale, to quantify the methodological quality of the RCTs. The trials were scored on a scale of 0 (low quality) to 5 (high quality) on the basis of the reports of randomisation, blinding, and withdrawals and dropouts (appendix pp 11–12). Trials scoring three or more were considered to have high methodological quality.[45]

Results

The combined search terms yielded a total of 1839 records (figure). After removal of duplicates (n=650) and ineligible articles (n=1157), 32 records were deemed eligible for full-text screening. Finally, eight RCTs[30,31,46–51] involving 808 participants were included in this review (table). Of these, seven studies were published between 2003 and 2019 and one was published much earlier in 1982.[46] All the trials were reported in the English language. Five studies[31,46–48,51] were based in sub-Saharan Africa (Kenya, Uganda, Nigeria, and Madagascar) and the remaining three[30,49,50] were from Brazil. The sizes of the samples of the studies ranged from 47 to 219 participants. Patients' ages ranged from 0 years to 93 years, and in four studies[46–48,51] the participants were children aged 5–16 years.

Diagnostic tools such as a magnifying glass, a handheld digital video microscope, and a digital camera equipped with a macro-objective were used in five studies for lesion staging and flea viability assessment.[31,47–49,51] Except for one,[46] all studies followed the Fortaleza classification for staging of lesions. Three of the studies were placebo-controlled trials,[46,49,50] whereas three trials used active comparators,[47,48,51] and the other two had a no-treatment control group.[30,31]

Prevention trials

Zanzarin repellent lotion was examined for tungiasis prevention in two RCTs, which used infestation intensity (number of lesions present at the time of examination)

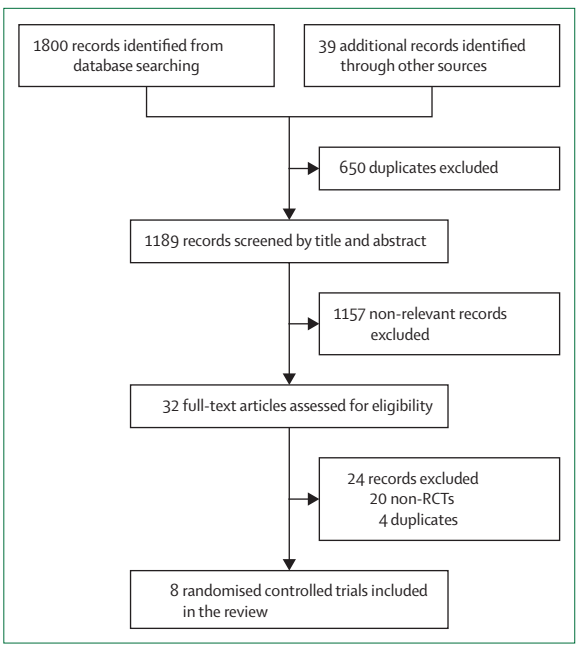

Figure: **Screening and selection of articles**

as the primary outcome measure. Buckendahl and colleagues[30] did a 5 month trial involving intermittent applications of the lotion, aiming at reducing infestation intensity and severity of tungiasis-associated morbidity during a peak season for tungiasis transmission. The 131 patients were randomly assigned to the test group 1, test group 2, or control group 3 (no treatment). All patient groups had received Zanzarin lotion twice daily for 1 month as an initial intervention to bring the median infestation intensity to zero (baseline). Zanzarin lotion was then applied every 2nd week (twice daily for 1 week) in test group 1 and every 4th week (twice daily for 1 week) in test group 2, for 5 months; whereas, the control group received no treatment. The initial intervention (1 month of twice-daily application) resulted in a significant reduction in median infestation intensity from 17 to zero in 98% of the patients, and it was used as a baseline for the subsequent intermittent applications. After 5 months, the median infestation intensities were five in group 1, eight in group 2, and 19 in group 3 (no treatment) and participants in group 1 showed a significant reduction in severity of tungiasis-associated acute pathology ($p<0·001$) compared with group 2 and 3. The authors concluded that the intermittent application of Zanzarin could be used to reduce the infestation intensity and prevent associated tungiasis morbidity in resource-poor settings.

Thielecke and colleagues[31] also aimed to assess the efficacy of Zanzarin lotion and use of protective footwear (shoes) compared with a no treatment control group. The study was done in rural Madagascar, and 219 participants with tungiasis were diagnosed using a digital camera fitted with a macro-objective. The participants were randomly assigned into either Zanzarin, shoe, or control

	Study design	Diagnosis; target lesions	Intervention descriptions		Outcome measures	Treatment outcomes	Quality score
			Test	Comparator			
Prevention trials							
Buckendahl et al (2010,[30] Brazil)	Randomised, unblinded, three-arm, parallel trial	Clinical examination (no diagnostic tool is stated); all target lesions (stage I–IV*)	Phase 1 (n=131), 1 month duration, twice daily (morning and afternoon) application of Zanzarin† lotion (3 mL/person per day) on the feet (up to the ankle); phase 2 (5 months duration), test group I (n=46), twice daily (morning and afternoon) application of Zanzarin lotion (3 mL/person per day) on the feet (up to the ankle) every 2nd week for 1 week; test group II (n=34), twice daily (morning and afternoon) application of Zanzarin lotion (3 mL/person per day) on the feet (up to the ankle) every 4th week for 1 week	Control (n=51); no treatment	Primary outcome of infestation intensity (total number [stage I–IV and manipulated] of lesions presented at the time of examination); secondary outcomes of severity of tungiasis morbidity§ (SSAT: 0–24 points, SSCT: 0–34 points), frequency of adverse events	Phase 1 (after 1 month), MII: 0 in 98% of patients (p<0·001), median SSAT: 0 (IQR 0–1) [baseline 8·5 (6–11)] (p<0·001), median SSCT: 7 (5–10) [baseline 12 (9–15)] (p<0·001); phase 2 (after 5 months), MII: 5 (1–10) [baseline 0 (0–1)] in group I (p<0·001) *vs* 8 (4–16) [baseline 0 (0–1)] in group II (p<0·001) *vs* 19 (week 50‡, 10–34) [baseline 0 (IQR 0–1)] in control group, median SSAT: 2 (IQR 1–4) [baseline 0 (0–1)] in group I (p<0·001) *vs* 5 (3–7) [0 (0–1)] in group II (p<0·001) *vs* 6·5 (4–8) [12 (9–15)] in control group (p<0·001), median SSCT: 4 (IQR 2–6), baseline 12 (9–15) in group I (p<0·001) *vs* 5 (3–8), baseline 12 (9–15) in group II (p<0·001) *vs* 6·5 (5–10), baseline 12 (9–15) in control group (p<0·001); no adverse event was observed	3
Thielecke et al (2013,[31] Madagascar)	Randomised, unblinded, two-arm, parallel trial	Clinical examination using a digital camera equipped with a macro-objective; all viable (*stage I–III), dead (stage IV*), and manipulated lesions	Test group 1 (n=72), twice daily (morning and afternoon) application of Zanzarin† lotion (3 mL/person per day) on the feet (up to the ankle) for 10 weeks; test group 2 (n=77), each participant received a pair of closed and solid shoes that fitted to their size at the start of the study	Control (n=70); no treatment	Primary outcomes of infestation intensity (number of sand flea lesions [viable and dead] on both feet at the time of examination); attack rate (number of newly penetrated sand fleas since the last examination); severity of tungiasis morbidity§ (SSAT: 0–24 points, SSCT: 0–34 points)	After 10 weeks, MII: 3 (IQR 1–13) [baseline 16 (5–31·5)] in Zanzarin group (p<0·001) and 15 (6–36) [baseline 22 (10–35)] in shoes group (p=0·85) *vs* 19 (10–35) [baseline 22 (13–33)] in control group; medium attack rate: 0 in Zanzarin group (p<0·001), 2 (IQR 0–4·5) in shoes group (p=0·049) *vs* 4 (2–8) in control group; median SSAT: 1 (IQR 0–1) [baseline 3 (1–7)] in Zanzarin group (p<0·001), 3 (1–4) [baseline 3 (2–7)] in shoes group (p=0·11) *vs* 4 (2–6) [baseline 4 (3–7)] in control group; median SSCT: 0·5 (IQR 0–2) [baseline 2 (0–3)] in Zanzarin group (p=0·36), 1 (0–3) [baseline 2 (0–3·5)] in shoes group (p=0·43) *vs* 1 (0–2·5) [baseline 1 (0–2)] in control group; adverse events not assessed and reported	2
Treatment trials							
Ade-Serrano et al (1982,[46] Nigeria)	Randomised, double-blinded, placebo-controlled, two-arm, parallel trial	Visual examination; all target lesions	Test group 1 (n=78), single dose of oral niridazole (30 mg/kg, tablet); test group 2 (n=49), two doses of oral niridazole (30 mg/kg, tablet) repeated after 7 days	Control (n=28), single dose of oral ascorbic acid (100 mg, placebo tablet)	Improvement in local pruritus, total lysis of the matured flea, healing of the ulcer, and frequency of adverse events	After 3 weeks, 100% pruritus improvement, 100% flea lysis, 100% ulcer healing in niridazole (I and II) groups *vs* 3·6% (1/28) pruritus improvement, 0% flea lysis, and 0% ulcer healing in control group (no statistics stated in the study); adverse events were: in the niridazole group, 15·6% (20/127), 7 nausea, 4 vomiting, 9 abdominal pain, and in the placebo group, 7·1% (2/28), 1 abdominal pain, 1 dizziness	2
Heukelbach et al (2004,[49] Brazil)	Randomised, double-blinded, placebo-controlled, two-arm, parallel trial	Clinical examination using a magnifying glass; all target lesions (stage II and III) lesions	Test (n=103 lesions); two doses of oral IVM (300 µg/kg, tablets) given 24 h apart	Control (n=89 lesions); two doses of matching oral placebo tablets given 24 h apart	Primary outcome of proportion of lesions with total lysis of the embedded flea; secondary outcomes of itching and pain improvement; frequency of adverse events	After 6 days, total lysis of embedded flea: 40·8% (42/103) in IVM group *vs* 37·1% (33/89) in placebo group (p>0·3); improvement in itching and pain: no difference in IVM group *vs* placebo group (p>0·3); adverse events were: in the IVM group, 22·2% (6/27), 3 headache, 2 abdominal pain, 1 sore throats, and in the placebo group 22·2% (6/27), 3 headache, 3 itching	5

(Table continues on next page)

	Study design	Diagnosis; target lesions	Intervention descriptions		Outcome measures	Treatment outcomes	Quality score
			Test	Comparator			
(Continued from previous page)							
Heukelbach et al (2003,[50] Brazil)	Randomised, single-blinded, placebo-controlled, six-arm, parallel trial	Clinical examination (no diagnostic tool is stated); target lesions of up to 6 viable (stage II and III*) lesions per foot	Treatments applied once for 2 days successively; test group 1 (n=33 feet, 68 lesions); IVM (0·8%, w/v¶) lotion; test group 2 (n=24 feet, 41 lesions); MTF (0·2%, w/v) lotion; test group 3 (n=33 feet, 76 lesions); TBZ lotion (5%, w/v); test group IV (n=27 feet, 64 lesions); TBZ ointment (5%, w/v)	Control (placebo) group (n=26 feet, 58 lesions); placebo lotion control (no-treatment) group (n=26 feet, 78 lesions); no treatment	Primary outcome of proportion of viable lesions remained viable	At day 3: IVM lotion (OR 1·8, p=0·12), MTF lotion (1·3, p=0·6), TBZ lotion (2·0, p=0·06), and TBZ ointment (1·4, p=0·4) *vs* placebo lotion; IVM lotion (2·7, p=0·004), TBZ lotion (3·0, p=0·001) or TBZ ointment (2·1, p=0·04) superior *vs* non-treatment (p<0·05); at day 7: IVM lotion (3·2, p=0·02), MRT lotion (3·5, p=0·03) superior *vs* placebo lotion; IVM lotion (3·8, p=0·004), MTF lotion (4·0, p=0·01), and TBZ lotion (2·2, p<0·05) superior *vs* non-treatment; at day 12: most (>80%) of the embedded fleas being followed were either dying or had died regardless of the trial interventions; adverse events not assessed and reported	2
Thielecke et al (2014,[47] Kenya)	Randomised, unblinded, active-comparator-controlled, two-arm, parallel trial	Clinical examination using a handheld digital video microscope; up to 3 viable lesions (stage II–III*) per foot	Test group (n=88 lesions); dimeticones (NYDA)** on the left foot applied three times within 10 min	Control group (n=82 lesions); applied one-time for 10 min right foot bathing with 0·05% potassium permanganate ($KMnO_4$) solution followed by sun drying and Vaseline application	Primary outcomes of proportion of viable embedded sand fleas that lost their viability signs after 7 days; proportion of embedded sand fleas with abnormal development; secondary outcome of inflammation score‖: 0–27 points	After 7 days, dead fleas: 78% (67/8) in dimeticone group *vs* 39% (28/71) in $KMnO_4$ group (p<0·001); abnormal development 92% (79/86) in dimeticone group *vs* 63% (47/71) in $KMnO_4$ group (p<0·001); inflammation score 4·75 (baseline 6·0) in dimeticone group (p<0·0001) *vs* 5 (baseline 4·5) in $KMnO_4$ group (p=0·009); adverse events not assessed and reported	2
Nordin et al (2017,[48] Uganda)	Randomised, unblinded, active-comparator-controlled, two-arm, parallel trial	Clinical examination with a handheld digital microscope; 3 viable lesions (stage II and III*) per foot	Test (whole-foot, or standard application) group (n=134 lesions); whole foot (up to the ankle) application of dimeticones (NYDA; 2–5 mL)** three times within 10 min	Control (targeted application) group (n=140 lesions); dimeticone (NYDA, 450 µL or 3 drops)** applied three times within 10 min with a 5 mL syringe fitted with tube	Primary outcome of viability of the embedded sand flea; secondary outcome of inflammation (pain and itching) score††: 1–22 points; visual scale (itching, pain, sleep disturbance, and mobility impairment)††	Dead fleas at day 2: 76·6% (105/137) in whole-foot group *vs* 93·0% (132/142) in targeted group (p<0·001); at day 5: 87·5% (105/120) in whole-foot group *vs* 96·1% (122/127) in targeted group (p<0·02); at day 7: 95·5% (122/128) in whole-foot group *vs* 97·9% (134/137) in targeted group (p=0·326); inflammation score after 7 days: 0·5 (IQR 1·5) [baseline 4·3 (3·4)], p<0·001; the median of visual scale (both feet combined): 0 [baseline 3 (1)], p<0·001; adverse events not assessed and reported	1
Elson et al (2019,[51] Kenya)	Randomised, unblinded, active-comparator-controlled, two-arm, parallel trial	Clinical examination with a handheld digital microscope; 1–2 viable lesions (stage II and IIIa*) per individual	Test group (n=56 lesions); two-time (days 1 and 3) targeted application of a drop (0·05 ml) of neem-coconut-oil mixture‡‡ into the abdominal tip of the embedded flea with a 20 mL dropper bottle	Control group (n=63 lesions); one time (day 1) 15 min foot bathing with 2·5 L, 0·05% potassium permanganate ($KMnO_4$) solution followed by Vaseline application	Primary outcome of effect of the treatments on viability of the embedded sand flea by day 7 (OR¶); secondary outcome of proportion of embedded sand fleas with abnormal development proportion of rapid ageing viable lesions; OR of finding non-reproductive flea; change in acute pathology (SSAT§: 1–24 points); proportion with a reduction in pain and itching (visual analogue scale††: 0–3 points)	After 7 days, dead fleas: 30% in neem-coconut-oil group *vs* 40% in $KMnO_4$ group (OR 0·62¶, p=0·253); rapid ageing viable lesions: 67% in neem-coconut-oil group *vs* 37% in $KMnO_4$ group (OR 3·4, p=0·019); OR of non-reproductive flea: no difference in neem-coconut-oil group *vs* $KMnO_4$ group (OR 2, p=0·120; no percentage reported); SSAT score: 3·5 (baseline 6·5) in neem-coconut-oil group (p<0·001) *vs* 5·0 (baseline 5·0) in $KMnO_4$ group (p=0·189); pain reduction: 78% in neem-coconut-oil group *vs* 64% in $KMnO_4$ group (OR 0·37, p<0·001); itching reduction: 67% in neem-coconut-oil group *vs* 60% in $KMnO_4$ group (OR 0·49, p=0·002); adverse events in neem-coconut-oil group, 6·4% (3/47) had an abscess and in $KMnO_4$ group, 4·1% (2/49) had an abscess, 3 malaria, 2 chicken pox (no report on their group)	3

The studies have been summarised based on the pharmaceutical intervention used and mode of application. IVM=ivermectin. MII=median infestation intensity. MTF=metrifonate. OR=odds ratio. RCTs=randomised control trials. SSAT=severity score for acute tungiasis. SSCT=severity score for chronic tungiasis. TBZ=thiabendazole. *Staged according to Fortaleza classification system described by Eisele M et al.[52] †Composed of coconut oil, jojoba oil (ester), *Aloe vera*, tocopheryl acetate, decanoic acid, panthenol, methylparaben, and propylparaben. §SSAT and SSCT morbidities are assessed according to the method described by Kehr et al,[53] lower point is better. ‡MII for control not reported in text at the end of the study (week 52). ¶Weight in volume. ‖Embedded flea: viability signs expulsion of eggs, excretion of a faecal thread, excretion of faecal liquid or the flea pulsations or contractions. **Dimeticones are synthetic oils; according to the chain length they have different physical properties and NYDA is a mixture of dimeticones with different viscosity. ††Assessed using a visual depicting analogue scale, lower point is better. ‡‡A mixture of cold-pressed 20% virgin neem seed oil and 80% virgin coconut oil.

***Table*: Summary of RCTs for prevention and treatment of tungiasis**

(no treatment) groups. For the test group, the repellent was applied on the participants' feet (twice daily for 10 weeks), and the participants in the shoe group received protective footwear at the beginning of the study. The control group received no treatment. Sand flea infestation intensity, attack rate, and severity of acute and chronic pathology were assessed at baseline and every 2 weeks after the treatment. The authors concluded that after 10 weeks, the attack rate, the intensity of infestation, and severity scores for acute tungiasis morbidities were significantly reduced in the Zanzarin group compared with the no treatment group ($p<0·001$). In the shoe group, a significant reduction ($p=0·049$) was observed in only the attack rate compared with the control group.

Treatment trials

For oral treatments, Ade-Serrano and colleagues[46] examined the efficacy of niridazole (30 mg/kg of bodyweight) for tungiasis in a double-blinded RCT. The efficacy of single dose versus double dose regimens (given 1 week apart) was compared with a placebo of a 100 mg ascorbic acid tablet. The 155 participating school children were examined for the total lysis of the embedded flea (confirmed by visual inspection of the slough and necrotic tissue covering the embedded flea), improvement of the local pruritus, and healing of the ulcer over 3 weeks. Both treatment regimens resulted in complete killing of the parasite, resolution of the pruritus, and healing of the ulcer compared with no killing of the parasite and no healing of the ulcer in the placebo group. The double-dose regimen completely healed all the ulcers within 2 weeks, but it took 3 weeks for the single-dose regimen to generate the same outcome. No statistical comparison was reported between the study treatments. Niridazole was associated with side-effects (predominantly nausea, vomiting, and abdominal pain) in 25 (16%) of 155 participants.

A trial by Heukelbach and colleagues[49] examined the efficacy of oral ivermectin (300 µg/kg of bodyweight, repeated after 24 h) compared with a placebo tablet in a double-blinded trial (n=54). The number of lesions with total flea lysis was counted and their ratios (number of lesions with total flea lysis to total number of lesions with viable fleas) were calculated for both test and control groups. Improvements in pain and itching were also assessed throughout the study period. The results showed that there was no statistically significant difference in the proportion of dead fleas between the groups ($p>0·3$). Furthermore, the treatment resulted in no significant improvement in pain and itching compared with the placebo group ($p>0·3$). The study reported that six (22%) of 27 participants who received ivermectin experienced adverse effects, such as headache, abdominal pain, and sore throat.

For topical treatments, an investigator-blinded trial by Heukelbach and colleagues[50] tested two consecutive days of application of topical ivermectin (0·8% weight per volume [w/v]) lotion, metrifonate (0·2% w/v) lotion, thiabendazole (5·0% w/v) lotion, and thiabendazole (5·0% w/v) ointment against placebo lotion and a no treatment control group. Feet of 108 participants were randomly assigned into six groups and received either one of the treatments, placebo, or no treatment. The number of lesions with embedded sand fleas that remained viable in each group was counted and the proportion of lesions with viable sand fleas was calculated on days 3, 7, and 12. After 3 days, there was no significant difference in the reduction in number of lesions with viable sand fleas between each of the topical treatments compared with the placebo lotion ($p>0·05$). However, ivermectin lotion ($p=0·004$), thiabendazole lotion ($p=0·001$), and thiabendazole ointment ($p=0·04$) showed significantly higher efficacy than the no treatment group. After 7 days, the ivermectin ($p=0·004$), metrifonate ($p=0·01$), and thiabendazole ($p<0·05$) lotions significantly reduced the number of lesions with viable sand fleas compared with the no treatment control, but only the ivermectin ($p=0·02$) and metrifonate ($p=0·03$) lotions had significantly higher efficacy compared with the placebo lotion. After 12 days, most (>80%) of the embedded fleas being followed up were either dying or had died regardless of the trial interventions. These results should be interpreted with caution given the variability of the lesions with viable sand fleas reported in the metrifonate group (n=41) compared with the placebo (n=78) and no treatment (n=58) control groups.

Two trials tested topical dimeticones (NYDA, a mixture of dimeticones with different viscosity) for tungiasis treatment. In the first trial, Thielecke and colleagues[47] compared the efficacy of a single topical application of dimeticones with 0·05% (w/v) $KMnO_4$ (potassium permanganate) solution. Feet of 47 children were randomly assigned (left or right foot) to receive either topically applied dimeticones (one-off treatment which included three applications within 10 min) or 0·05% $KMnO_4$ solution (one-off treatment which included foot bathing for 10 min, followed by sun drying and Vaseline application [Vaseline was not part of the treatment but used as a skin soothing agent]). Outcome measures, such as viability of the embedded fleas, their abnormal development (when the lesion size did not change on two consecutive follow-ups and there was discolouration or desiccation of the sand flea's abdominal rear cone), and localised inflammation, were followed up for 7 days. After 7 days, 78% of the embedded fleas in the dimeticones group and 39% in the $KMnO_4$ group were non-viable ($p<0·001$). In the dimeticones group, lesions at an early stage of development (stage 2; 88%) lost their viability signs more often than lesions in later stages (stage 3; 65%) at day 7 ($p=0·01$). In addition, abnormal development in the embedded sand fleas was observed in 92% after dimeticone treatment and in 63% after $KMnO_4$ treatment

(p<0·001). The reduction of local skin inflammation was significant in the dimeticones group (p<0·001).

The second dimeticones trial by Nordin and colleagues[48] investigated the efficacy of two modes of dimeticones application (directly on the abdominal cone of the embedded parasite *vs* whole-foot application) in 60 children affected with tungiasis, and followed up the proportion of the non-viable embedded fleas of both applications on days 2, 5, and 7. Patients' right or left feet were randomly assigned to either group, and the number of viable embedded sand fleas was recorded once at baseline and every 2 days afterwards. Compared with the whole foot application, the targeted application killed a significantly higher percentage of embedded sand fleas at day 2 (93·0% *vs* 76·6%, p<0·01) and day 5 (96·1% *vs* 87·5%, p<0·02). However, at day 7, targeted and whole foot applications showed no difference (97·9% *vs* 95·5%, respectively; p>0·05).

Elson and colleagues[51] evaluated the efficacy of neem and coconut oils treatment, a mixture of 20% virgin neem seed and 80% coconut oils (targeted application on days 1 and 3), compared with 0·05% (w/v) $KMnO_4$ foot bath (one-off treatment; 15 min application on day 1). The 96 participants were followed up for 7 days, with researchers evaluating the embedded flea viability, changes in acute pathology of the treated feet, changes in natural development of lesion morphology, and reduction in the percentage of participants with pain and itching. After 7 days, 30% of the embedded fleas were found dead in the neem and coconut oils group compared with 40% in the $KMnO_4$ group (p=0·253), showing that neem and coconut oils treatment was no different to the comparator. However, the neem and coconut oils treatment group showed significant clinical improvement in acute pathology (p<0·001), and abnormal development of the embedded fleas (p=0·019). Both treatment groups displayed a significant improvement in tungiasis-related pain (78% of people in the neem and coconut oils group *vs* 64% in the $KMnO_4$ group, OR 0·37; p<0·001) and itching (67% in the neem and coconut oils group *vs* 60% in the $KMnO_4$ group, OR 0·49; p=0·002).

A full assessment of results of risk of bias evaluations for the RCTs are provided in the appendix (pp 7–8). There was 90% agreement on 40 (eight RCTs×five) domains assessed. Among the eight RCTs, two were found with some concerns, and the remaining six with high risk of bias for the overall bias. All the trials were randomised, but only one trial[49] provided information on treatment allocation concealment. Three trials[30,49,51] presented a clear description on participant blinding, delivery of interventions, and adherence to the trialled interventions. All trials reported adequate details about the loss of study participants' follow-up. All, except one trial,[46] used appropriate methods to evaluate the outcome measures. Two trials[31,51] showed low risk for the selective outcome reporting domain, with clear study protocols detailing a prespecified data analysis plan.

Regarding Jadad quality score, five of the studies scored less than three points (table) and the mean Jadad score for all studies was 2·5, indicating overall low quality of the studies. All the studies were described as randomised trials. Three studies[30,49,51] reported the numbers of participants and the reasons for withdrawal in each group, and two studies[46,49] had a double-blind design. The full assessment results of the studies are provided in the appendix (pp 8–9).

Discussion

To our knowledge, we report the first systematic review to rigorously assess all RCTs exploring tungiasis preventive and treatment interventions. Our review identified a small number of high-quality prevention and treatment trials, indicating that tungiasis has been largely neglected by the scientific community and stakeholders.

A coconut oil-based lotion (Zanzarin) was explored for the prevention of tungiasis in the trials by Buckendahl and colleagues[30] and Thielecke and colleagues.[31] The product was registered in many European countries as a repellent for mosquitoes, ticks, and other biting insects.[54,33,55] Capric, caprylic, and lauric fatty acids from coconut oil are likely to be the major active components of this product.[56,57] The lotion also contained jojoba oil and *A vera*, which have anti-inflammatory effects.[56,58,59] Regular application of Zanzarin lotion had substantial benefits in preventing tungiasis in both trials compared with its intermittent application.[30,31] A small pilot trial[33] and a cross-over study[32] (which did not meet the inclusion criteria as an RCT in this review) further revealed the protective effect of the regular application of Zanzarin from tungiasis.[32,33] Even though Zanzarin lotion showed an impressive preventive effect against sand fleas in the trials, it has been withdrawn from the market by the producer and it is therefore unavailable.[36] However, other widely available repellents from natural resources such as coconut oil, castor oil, and cassava extracts could potentially be formulated into an optimum skin dosage form and explored for the prevention of tungiasis.[29,34,35] Combining effective repellents with treatments could be a better approach to reduce tungiasis morbidity in the affected population in endemic areas.

The policy guideline released by the Kenyan Ministry of Health recommends applying the locally produced herbal preparations containing neem and coconut oils on the hands and feet, as well as on the surfaces of house floors and outdoor resting areas for the prevention and control of the off-host cycle of sand fleas.[11] At the community level, the multifaceted One Health approach is likely to be an effective strategy to eliminate tungiasis in endemic areas.[3,27–29] However, this approach would require a comprehensive intervention including stakeholders at different levels such as the community, policy makers, veterinarians, and clinicians.

Single-dose and double-dose regimens of niridazole (an antischistosomal agent) showed high efficacy within 3 weeks of treatment in a study done by Ade-Serrano and colleagues .[46] However, the study design had considerable methodological deficiencies. These include no adequate description of the randomisation process, no definition of outcome measures, and limitations related to patient enrolment. This drug can cause severe side-effects, including CNS toxicity and cancer,[60] and is no longer recommended for human use.

Oral ivermectin has been the most commonly used therapy for various blood-sucking ectoparasites over the past three decades.[61–63] Nevertheless, one of the trials (Heukelbach and colleagues)[49] included in this review found that oral ivermectin was not effective against tungiasis-causing parasites. However, two mass drug administration studies[40,64] reported varying efficacies of oral ivermectin for tungiasis. The first study[40] reported a 64% cure rate at the end of a 4 week study period, whereas the second study[64] showed a 20% reduction in tungiasis prevalence at the end of a 9 month follow up period, following the same treatment regimen (two×200 µg/kg doses given 10 days apart). The duration of follow-up periods reported in these studies could have caused this discrepancy. In fact, the embedded sand fleas die naturally within 4–6 weeks after skin penetration, which makes it difficult to draw conclusions about the effectiveness of a drug in uncontrolled studies (including mass drug administration) with longer follow-up periods.[35,52] Recent reports from animal studies[65,66] investigating orally administered single-dose ivermectin (0·6 mg/kg) for dogs infected with fleas (*Ctenocephalides felis felis*), which are classified under the same insect order (Siphonaptera) and have a similar off-host cycle to the sand fleas,[67] also showed no efficacy, corroborating the findings of the Heukelbach and colleagues trial.[49] These data seem to suggest that oral ivermectin is unlikely to be an effective treatment for tungiasis. Poor bioavailability (attributed to its lipophilic nature) and reduced distribution of ivermectin to lower extremities (owing to diminished blood perfusion) are likely to reduce the concentration of the drug below that required to elicit lethal effects against embedded fleas at the target sites.[68]

Topical ivermectin and metrifonate lotions, but not thiabendazole (lotion and ointment), showed significant efficacy against embedded sand fleas compared with the placebo lotion in Heukelbach and colleagues' study.[50] Ivermectin works through disruption of gamma-aminobutyric acid neurotransmission in the nerve endings of the parasites, thereby causing muscle paralysis of the parasite and its eventual death.[69] The lipophilic nature of ivermectin allows the drug to accumulate at the application site and extends its effect; this characteristic is likely to be the main reason for the drug's improved efficacy following topical application compared with oral administration.[65] This observation is consistent with other studies on topical ivermectin against similar ectoparasites. A high (96%) cure rate with topical ivermectin (0·5% w/v) was reported in dogs infected with fleas (*C felis* and *Ctenocephalides canis*).[70] A recent meta-analysis on RCTs of scabies treatments[71] and a comparative study on head lice treatments[72] also reported higher efficacy of topical ivermectin than of its oral counterpart, and topical ivermectin is now approved by the FDA for head lice treatment.[73] Given its broad and notable parasiticidal effects against other ectoparasites of clinical importance,[74] topical ivermectin could have a future role in tungiasis treatment. However, additional large-scale RCTs should investigate topical ivermectin for conclusive safety and clinical outcomes to warrant a broad recommendation for tungiasis treatment. These studies could consider optimising the strength of topical ivermectin (eg, ≥1%) and its formulation-related rheological properties.[75] Such formulations are likely to offer ease of application, better body coverage, and enhanced skin contact time, allowing the drug to permeate more effectively into the parasite. However, metrifonate (a schistosomicidal drug) is no longer commercially available due to its reduced clinical potential[76–78] and concerns with possible risks for human health and the environment,[79,80] limiting its recommendation for future use in tungiasis.

Topical treatment with dimeticones (NYDA) exhibited considerable promise against the tungiasis-causing parasite in the trials by Thielecke and colleagues[47] and Nordin and colleagues.[48] It showed a rapid killing effect when it was applied directly on the embedded sand fleas.[48] A case series published in 2019 in five people[23] also showed a similar trend with three applications (two applications 24 h apart and one after a week) of dimeticones (NYDA), together with systemic antibiotics, in cases of very severe tungiasis.

Dimeticones are an effective treatment for head lice infestation.[81–87] They physically block the respiratory tract of lice thereby causing suffocation and death.[81] Due to their physical mode of action, resistance development to dimeticones seems highly unlikely.[84] In tungiasis, the exact mechanism of action for the product is yet to be fully elucidated, but they might work by occluding the rear abdominal cone of the embedded flea protruding above the skin, which is used by the parasite for breathing, mating, expelling eggs, and defecating.[47] Dimeticones showed impressive outcomes against embedded sand fleas in clinical trials; however, drawing lessons from the head lice studies, further refinement of the dosage form might be required.[82] A gel-based formulation for head lice treatment has been developed to improve the formulation characteristics (such as fluid mobility or dripping) of the previous products (eg, Hedrin 4% lotion),[82,83] and the same could apply for tungiasis treatment; this could facilitate self-application of the product in endemic communities.

Dimeticones are biochemically inert and considered non-toxic,[6] but owing to their flammable nature, they should not be applied near open fires.[36,88] Currently,

dimeticones are only accessible in a few tungiasis endemic areas,[36] limiting treatment options in endemic communities to traditional remedies of poor efficacy or extraction of embedded fleas using non-sterile sharp instruments.

A 2019 RCT by Elson and colleagues[51] examined the clinical efficacy of neem and coconut oil mixture for tungiasis. Neem seed extract-based products have been shown to have a broad range of activity against different insects and blood-sucking ectoparasites including head lice, ticks, and mites.[89–91] Repellent properties of coconut oil containing-products against various ectoparasites including sand fleas have been well documented.[30,31,57] A combination of these oils has been used as a traditional remedy for tungiasis by local communities in Kenya.[36] However, the RCT showed that the neem and coconut oil mixture treatment was not different to the comparator (ie, $KMnO_4$ foot bath) in terms of proportion of dead embedded sand fleas, 7 days after the treatment. However, the neem and coconut oil mixture treatment caused a significant proportion of the embedded fleas to age unnaturally fast and showed a significant reduction in the acute tungiasis pathologies compared with a $KMnO_4$ foot bath. The rapid ageing of the embedded fleas could be due to azadirachtin, which is the main active ingredient responsible for the repellent, insecticidal, and growth-disrupting (growth-regulating) effects of neem seed oil against insects and arthopods.[92,93] Whereas, the improvement in acute pathology is likely attributed to the antibacterial and anti-inflammatory activities of both the neem seed (predominantly) and coconut oils.[90,92–95]

The commercially available neem oil-based insecticidal products contain concentrated neem oil (≥80%) with substantial azadirachtin content (up to 3000 mg/mL).[89,96] Azadirachtin is highly sensitive to ultraviolet light, pH, and temperature, and it requires proper storage conditions.[91,93,97,98] The relatively lower content of azadirachtin (3·96 mg/mL), lower proportion of the neem seed oil (ie, 20%), and the potential degradation of the neem components during the field trial could have contributed towards the poor treatment outcomes observed in the neem and coconut oils treatment group. There are potential opportunities to optimise the neem seed and coconut oils treatment for tungiasis in the future. These include increasing the neem seed oil composition in the product, incorporating pharmaceutical additives such as photoprotectors and stabilisers, and formulating it in an appropriate topical dosage form (eg, gel).[90,98] Even though a $KMnO_4$ foot bath is the locally endorsed treatment for tungiasis in Kenya,[11] trials showed its marginal efficacy against the embedded fleas.[47,51] Considering its toxic (irritant and hazardous) nature, and cumbersome nature of application,[36,47] it is unlikely to be an effective and sustainable treatment for household application in endemic communities.

In summary, among the treatment interventions evaluated, dimeticones, metrifonate, and topical ivermectin showed efficacy against embedded fleas, of which, dimeticones showed a superior efficacy. However, the trialled treatment interventions had little anti-inflammatory properties and are less likely to offer any lethal effect on the secondary bacterial pathogens. In endemic communities, tungiasis often presents with inflammatory skin reactions and secondary bacterial complications, which can lead to substantial human consequences, including disability and life-threatening conditions. Thus, future research priorities should focus on developing treatment options that have the potential to address the morbidities caused by the parasite and treat associated secondary bacterial complications.

According to the Cochrane risk of bias and Jadad quality assessment criteria, several methodological deficiencies were identified in the reviewed trials. Several of the reviewed RCTs did not report the total number of lesions with viable sand fleas before and after treatments. To allow easy comparisons between treatment interventions, it is essential that researchers performing RCTs are consistent in the way they measure and report treatment outcomes. In the case of RCTs on tungiasis, we suggest that investigators should consistently measure and report infestation intensity and attack rates for prevention, and proportional viability of lesions for treatment trials in each intervention group. Overall, we found no RCT with a low overall risk of bias and most studies had low methodological quality. This finding no doubt partly reflects the difficult nature of performing clinical studies on tungiasis, the resource-limited environments, limited funding opportunities, and logistical challenges faced by researchers in this space.

The main limitation of this systematic review is the narrative approach used to review the available data. The small number of trials, heterogeneity in trial designs and outcome measures, and the fact that the trials were conceived as proof-of-principle studies made a meta-analysis impossible. We were also unable to pool the evidence given the heterogeneity of interventions, comparators, and the outcome variables, limiting the judgement of the quality and certainty of evidence using the GRADE approach.

Conclusion

This Review identifies a small number of tungiasis clinical trials exploring prevention and treatment options. Among the trialled interventions, the coconut oil-based lotion (Zanzarin) for prevention, and dimeticones (NYDA) for treatment appear to hold the most promise. However, most of the studies included in this review had low methodological quality. Despite the significant burden of tungiasis, the small number of high-quality RCTs underscores the neglect by scientists, policy makers, entrepreneurial philanthropists, and the pharmaceutical industry. There is a clear unmet need for well-designed studies to investigate new preventive and therapeutic

solutions, which could include repurposing currently available repellent and parasiticidal agents. A topical treatment is most suited to endemic settings, and treatment should be simple, enabling self-administration and started as soon as symptoms appear. An ideal treatment candidate should possess parasiticidal, anti-inflammatory, and antibacterial properties.

Contributors

SA and JT were responsible for project conceptulisation. SA and WT did the literature search and screening. SA, JCK, and JT extracted the data. SA and JT did the first draft preparation and review. JH, GMP, AB, JKC, SC, SK, HF, and JT reviewed and edited this paper. All authors read and approved the final manuscript.

Declaration of interests

We declare no competing interests.

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References

1 Pampiglione S, Fioravanti ML, Gustinelli A, et al. Sand flea (*Tunga spp.*) infections in humans and domestic animals: state of the art. *Med Vet Entomol* 2009; **23:** 172–86.

2 Feldmeier H, Heukelbach J. Epidermal parasitic skin diseases: a neglected category of poverty-associated plagues. *Bull World Health Org* 2009; **87:** 152–59.

3 WHO. Scabies and other ectoparasites. 2020. https://www.who.int/neglected_diseases/diseases/scabies-and-other-ectoparasites/en/index1.html (accessed Feb 6, 2020).

4 WHO Department of Control of Neglected Tropical Diseases. Recognizing neglected tropical diseases through changes on the skin: a training guide for front-line health workers. 2018. http://www.who.int/neglected_diseases/resources/9789241513531/en (accessed Oct 9, 2018).

5 Heukelbach J, de Oliveira FA, Hesse G, Feldmeier H. Tungiasis: a neglected health problem of poor communities. *Trop Med Int Health* 2001; **6:** 267–72.

6 Miller H, Trujillo-Trujillo J, Mutebi F, Feldmeier H. Efficacy and safety of dimeticones in the treatment of epidermal parasitic skin diseases with special emphasis on tungiasis: an evidence-based critical review. *Braz J Infect Dis* 2020; **24:** 170–77.

7 Muehlen M, Heukelbach J, Wilcke T, Winter B, Mehlhorn H, Feldmeier H. Investigations on the biology, epidemiology, pathology and control of *Tunga penetrans* in Brazil: II. Prevalence, parasite load and topographic distribution of lesions in the population of a traditional fishing village. *Parasitol Res* 2003; **90:** 449–55.

8 Wilcke T, Heukelbach J, César Sabóia Moura R, Kerr-Pontes LRS, Feldmeier H. High prevalence of tungiasis in a poor neighbourhood in Fortaleza, Northeast Brazil. *Acta Tropica* 2002; **83:** 255–58.

9 Ugbomoiko US, Ofoezie IE, Heukelbach J. Tungiasis: high prevalence, parasite load, and morbidity in a rural community in Lagos State, Nigeria. *Int J Dermatol* 2007; **46:** 475–81.

10 Feldmeier H, Eisele M, Van Marck E, Mehlhorn H, Ribeiro R, Heukelbach J. Investigations on the biology, epidemiology, pathology and control of *Tunga penetrans* in Brazil: IV. Clinical and histopathology. *Parasitol Res* 2004; **94:** 275–82.

11 Ministry of Health. National policy guidelines on prevention and control of jigger infestations. Kenya. 2014. http://guidelines.health.go.ke/#/category/12/95/meta (accessed Oct 3, 2018).

12 Ahadi Kenya Trust. The jigger menace in Kenya report 2011. http://www.jigger-ahadi.org/index.html (accessed Oct 2, 2018).

13 Ministry of Health. Press statement on new master plan to tackle targeted neglected tropical diseases. 2012. http://www.health.go.ug/docs/Press%20statement%20on%20NTDs.pdf (accessed Oct 2, 2018).

14 Jawoko K. Jiggers outbreak in Uganda. *Can Med Assoc J* 2011; **183:** e33–34.

15 Herbinger KH, Siess C, Nothdurft HD, von Sonnenburg F, Loscher T. Skin disorders among travellers returning from tropical and non-tropical countries consulting a travel medicine clinic. *Trop Med Int Health* 2011; **16:** 1457–64.

16 Heukelbach J, Gomide M, Araújo JF, et al. Cutaneous larva migrans and tungiasis in international travelers exiting Brazil: an airport survey. *J Travel Med* 2007; **14:** 374–80.

17 Grupper M, Potasman I. Outbreak of tungiasis following a trip to Ethiopia. *Trav Med Infect Dis* 2012; **10:** 220–23.

18 Belaz S, Gay E, Robert-Gangneux F, Beaucournu JC, Guiguen C. Tungiasis outbreak in travelers from Madagascar. *J Travel Med* 2015; **22:** 263–66.

19 Feldmeier H, Eisele M, Sabóia-Moura RC, Heukelbach J. Severe tungiasis in underprivileged communities: case series from Brazil. *Emerg Infect Dis* 2003; **9:** 949–55.

20 Feldmeier H, Sentongo E, Krantz I. Tungiasis (sand flea disease): a parasitic disease with particular challenges for public health. *Eur J Clin Microbiol Infect Dis* 2013; **32:** 19–26.

21 Feldmeier H, Heukelbach J, Eisele M, Sousa AQ, Barbosa LMM, Carvalho CBM. Bacterial superinfection in human tungiasis. *Trop Med Int Health* 2002; **7:** 559–64.

22 Veraldi S, Valsecchi M. Imported tungiasis: a report of 19 cases and review of the literature. *Int J Dermatol* 2007; **46:** 1061–66.

23 Miller H, Ocampo J, Ayala A, Trujillo J, Feldmeier H. Very severe tungiasis in Amerindians in the Amazon lowland of Colombia: a case series. *PLoS Negl Trop Dis* 2019; **13:** e0007068-e.

24 Wiese S, Elson L, Feldmeier H. Tungiasis-related life quality impairment in children living in rural Kenya. *PLoS Negl Trop Dis* 2018; **12:** e0005939.

25 Elson L, Fillinger U, Feldmeier H. Tungiasis. In: Tyring SK, Lupi O, Hengge UR, eds. Tropical dermatology. Second edn. UK: Elsevier BV; 2017: 401–04.

26 Kimotho S, Miller AN, Ngure P. Managing communication surrounding tungiasis stigma in Kenya. *Communication* 2015; **41:** 523–42.

27 Centers for Disease Control and Prevention. One health. 2018. https://www.cdc.gov/onehealth/index.html (accessed June 19, 2020).

28 Feldmeier H, Heukelbach J, Ugbomoiko US, et al. Tungiasis—a neglected disease with many challenges for global public health. *PLoS Negl Trop Dis* 2014; **8:** e3133.

29 Heukelbach J. Tungiasis: invited review. *Rev Inst Med Trop Sao Paulo* 2005; **47:** 307–13.

30 Buckendahl J, Heukelbach J, Ariza L, Kehr JD, Seidenschwang M, Feldmeier H. Control of tungiasis through intermittent application of a plant-based repellent: an intervention study in a resource-poor community in Brazil. *PLoS Negl Trop Dis* 2010; **4:** e879.

31 Thielecke M, Raharimanga V, Rogier C, Stauss-Grabo M, Richard V, Feldmeier H. Prevention of tungiasis and tungiasis-associated morbidity using the plant-based repellent Zanzarin: a randomized, controlled field study in rural Madagascar. *PLoS Negl Trop Dis* 2013; **7:** e2426.

32 Feldmeier H, Kehr JD, Heukelbach J. A plant-based repellent protects against *Tunga penetrans* infestation and sand flea disease. *Acta Trop* 2006; **99:** 126–36.

33 Schwalfenberg S, Witt LH, Kehr JD, Feldmeier H, Heukelbach J. Prevention of tungiasis using a biological repellent: a small case series. *Ann Trop Med Parasitol* 2004; **98:** 8994.

34 Karunamoorthi K. Tungiasis: a neglected epidermal parasitic skin disease of marginalized populations—a call for global science and policy. *Parasitol Res* 2013; **112:** 3635–43.

35 Heukelbach J. Revision on tungiasis: treatment options and prevention. *Expert Rev Anti Infect Ther* 2006; **4:** 151–17.

36 Elson L, Wright K, Swift J, Feldmeier H. Control of tungiasis in absence of a roadmap: grassroots and global approaches. *Trop Med Infect Dis* 2017; **2:** 33.

37 Winter B, Oliveira FA, Wilcke T, Heukelbach J, Feldmeier H. Tungiasis-related knowledge and treatment practices in two endemic communities in northeast Brazil. *J Infect Dev Ctries* 2009; **3:** 458–66.

38 Kamau T, House SK. The potential risk of HIV infection and transmission of other blood-borne pathogens through the sharing of needles and pins among people infested with jiggers in Kenya. *Int J Health Sci Res* 2014; **4:** 278–85.

39 Cardoso A. Generalized tungiasis treated with thiabendazole. *Arch Dermatol* 1981; **117:** 127.

40 Heukelbach J, Wilcke T, Winter B, et al. Efficacy of ivermectin in a patient population concomitantly infected with intestinal helminths and ectoparasites. *Arzneimittelforschung* 2004; **54:** 416–21.

41 Mitchell CJ, Stephany P. Infestation of *Tunga penetrans* in villages near Zomba Central Hospital. *Malawi Med J* 2013; **25:** 88–89.

42 Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. 2009; **339:** b2535.

43 Sterne JAC, Savovic J, Page MJ, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ* 2019; **366:** l4898.

44 Jadad AR, Moore RA, Carroll D, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Control Clin Trials* 1996; **17:** 1–12.

45 Moher D, Pham B, Jones A, et al. Does quality of reports of randomised trials affect estimates of intervention efficacy reported in meta-analyses? *Lancet* 1998; **352:** 609–13.

46 Ade-Serrano MA, Olomolehin OG, Adewunmi A. Treatment of human tungiasis with niridazole (ambilhar) a double-blind placebo-controlled trial. *Ann Trop Med Parasitol* 1982; **76:** 89–92.

47 Thielecke M, Nordin P, Ngomi N, Feldmeier H. Treatment of tungiasis with dimeticone: a proof-of-principle study in rural Kenya. *PLoS Negl Trop Dis* 2014; **8:** e3058.

48 Nordin P, Thielecke M, Ngomi N, Mudanga GM, Krantz I, Feldmeier H. Treatment of tungiasis with a two-component dimeticone: a comparison between moistening the whole foot and directly targeting the embedded sand fleas. *Trop Med Health* 2017; **45:** 6.

49 Heukelbach J, Franck S, Feldmeier H. Therapy of tungiasis: a double-blinded randomized controlled trial with oral ivermectin. *Mem Inst Oswaldo Cruz* 2004; **99:** 873–76.

50 Heukelbach J, Eisele M, Jackson A, Feldmeier H. Topical treatment of tungiasis: a randomized, controlled trial. *Ann Trop Med Parasitol* 2003; **97:** 743–49.

51 Elson L, Randu K, Feldmeier H, Fillinger U. Efficacy of a mixture of neem seed oil (*Azadirachta indica*) and coconut oil (*Cocos nucifera*) for topical treatment of tungiasis. A randomized controlled, proof-of-principle study. *PLoS Negl Trop Dis* 2019; **13:** e0007822-e.

52 Eisele M, Heukelbach J, Van Marck E, *et al*. Investigations on the biology, epidemiology, pathology and control of *Tunga penetrans* in Brazil: I. Natural history of tungiasis in man. *Parasitol Res* 2003; **90:** 87–99.

53 Kehr JD, Heukelbach J, Mehlhorn H, Feldmeier H. Morbidity assessment in sand flea disease (tungiasis). *Parasitol Res* 2007; **100:** 413–21.

54 Codecheck. Zanzarin mosquito repellent organic lotion. Jun 6, 2016. https://www.codecheck.info/kosmetik_koerperpflege/koerper_sonnenschutz/insektenschutz/ean_2001040115899/id_538123/Zanzarin_Muecken_Schutz_Bio_Lotion.pro (accessed Oct 29, 2018).

55 Medpex. Zanzarine ticks protection organic lotion. 2016. https://www.medpex.de/insektenabwehr-schutz-vor-insekten-urlaub-sonne/zanzarin-zecken-schutz-bio-lotion-p3913907/erfahrungen (accessed Nov 2, 2018).

56 Thielecke M, Raharimanga V, Stauss-Grabo M, Rogier C, Richard V, Feldmeier H. Regression of severe tungiasis-associated morbidity after prevention of re-infestation: a case series from rural Madagascar. *Am J Trop Med Hyg* 2013; **89:** 932–36.

57 Zhu JJ, Cermak SC, Kenar JA, et al. Better than DEET repellent compounds derived from coconut Oil. *Sci Rep* 2018; **8:** 14053.

58 Lin T-K, Zhong L, Santiago JL. Anti-inflammatory and skin barrier repair effects of topical application of some plant oils. *Int J Mol Sci* 2017; **19:** 70.

59 Surjushe A, Vasani R, Saple DG. *Aloe vera*: a short review. *Indian J Dermatol* 2008; **53:** 163–66.

60 WHO. Model prescribing information: drugs used in parasitic diseases—Second Edition. 1995. https://apps.who.int/iris/handle/10665/41765 (accessed Oct 5, 2018).

61 Sanchezruiz WL, Nuzum DS, Kouzi S. Oral ivermectin for the treatment of head lice infestation. *Bull Am Soc Hosp Pharm* 2018; **75:** 937–43.

62 Holzchuh FG, Hida RY, Moscovici BK, et al. Clinical treatment of ocular *Demodex folliculorum* by systemic ivermectin. *Am J Ophthalmol* 2011; **151:** 1030–4.e1.

63 Elmogy M, Fayed H, Marzok H, Rashad A. Oral ivermectin in the treatment of scabies. *Int J Dermatol* 1999; **38:** 926–8.

64 Heukelbach J, Winter B, Wilcke T, et al. Selective mass treatment with ivermectin to control intestinal helminthiases and parasitic skin diseases in a severely affected population. *Bull World Health Organ* 2004; **82:** 563–71.

65 Magalhães VS, Cid YP, Ferreira TP, et al. Evaluation of pharmacokinetics and efficacy of ivermectin following oral administration in dogs against experimental infection of *Ctenocephalides felis felis* and *Rhipicephalus sanguineus*. *Vet Parasitol* 2016; **228:** 167–71.

66 Zakson-Aiken M, Gregory LM, Meinke PT, Shoop WL. Systemic activity of the avermectins against the cat flea (Siphonaptera: Pulicidae). *J Med Entomol* 2001; **38:** 576–80.

67 Rozendaal JA, WHO. Vector control: methods for use by individuals and communities/prepared by Jan A Rozendaal. 1997. https://apps.who.int/iris/handle/10665/41968 (accessed July 12, 2019).

68 González Canga A, Sahagún Prieto AM, Diez Liébana MJ, Fernández Martínez N, Sierra Vega M, García Vieitez JJ. The pharmacokinetics and interactions of ivermectin in humans—a mini-review. *AAPS J* 2008; **10:** 42–46.

69 Crump A, Ōmura S. Ivermectin, 'wonder drug' from Japan: the human use perspective. *Proc Jpn Acad Ser B Phys Biol Sci* 2011; **87:** 13–28.

70 Ibarra-Velarde F, Vera-Montenegro Y, Ambía Medina J, Sánchez-Peralta K, Ochoa Galván P. Comparison of two pour-on formulations of ivermectin against gastrointestinal worms, fleas and lice in naturally infected stray Dogs. *Pharmacol Pharm* 2015; **6:** 177–84.

71 Dhana A, Yen H, Okhovat J-P, Cho E, Keum N, Khumalo NP. Ivermectin versus permethrin in the treatment of scabies: a systematic review and meta-analysis of randomized controlled trials. *J Am Acad Dermatol* 2018; **78:** 194–98.

72 Ahmad HM, Abdel-Azim ES, Abdel-Aziz RT. Assessment of topical versus oral ivermectin as a treatment for head lice. *Dermatol Ther* 2014; **27:** 307–10.

73 US Food and Drug Administration. Sklice (ivermectin) Lotion, 0.5% drug approval package 2012. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2012/202736_sklice_toc.cfm (accessed Jan 28, 2020).

74 Victoria J, Trujillo R. Topical ivermectin: a new successful treatment for scabies. *Pediatr Dermatol* 2001; **18:** 63–65.

75 Dumortier G, Grossiord JL, Agnely F, Chaumeil JC. A review of poloxamer 407 pharmaceutical and pharmacological characteristics. *Pharm Res* 2006; **23:** 2709–28.

76 Trainor-Moss S, Mutapi F. Schistosomiasis therapeutics: whats in the pipeline? *Expert Rev Clin Pharmacol* 2016; **9:** 157–60.

77 Kramer CV, Zhang F, Sinclair D, Olliaro PL. Drugs for treating urinary schistosomiasis. *Cochrane Database Syst Rev* 2014; **8:** CD000053.

78 López-Arrieta J, Schneider L. Metrifonate for Alzheimer's disease. *Cochrane Database Syst Rev* 2006; **2:** CD003155.

79 Okoroiwu HU, Iwara IA. Dichlorvos toxicity: a public health perspective. *Interdiscip Toxicol* 2018; **11:** 129–37.

80 United Nations Environment Programme, the Food and Agriculture Organization of the United Nations. Rotterdam Convention on operation of the prior informed consent procedure for banned or severely restricted chemicals: decision guidance document for trichlorfon. In: Secretariat of the Rotterdam Convention on the prior informed consent procedure for certain hazardous chemicals and pesticides in international trade. Geneva: Secretariat of the Rotterdam Convention on the Prior Informed Consent Procedure for Certain Hazardous Chemicals and Pesticides in International Trade, 2017.

81 Heukelbach J, Pilger D, Oliveira FA, Khakban A, Ariza L, Feldmeier H. A highly efficacious pediculicide based on dimeticone: randomized observer blinded comparative trial. *BMC Infect Dis* 2008; **8:** 115.

82 Burgess IF, Brunton ER, Burgess NA. Single application of 4% dimeticone liquid gel versus two applications of 1% permethrin creme rinse for treatment of head louse infestation: a randomised controlled trial. *BMC Dermatol* 2013; **13:** 5.

83 Burgess IF, Burgess NA. Dimeticone 4% liquid gel found to kill all lice and eggs with a single 15 minute application. *BMC Res Notes* 2011; **4:** 15.

84 Heukelbach J, Wolf D, Clark JM, Dautel H, Roeschmann K. High efficacy of a dimeticone-based pediculicide following a brief application: in vitro assays and randomized controlled investigator-blinded clinical trial. *BMC Dermatol* 2019; **19:** 14.

85 Burgess IF, Brown CM, Lee PN. Treatment of head louse infestation with 4% dimeticone lotion: randomised controlled equivalence trial. *BMJ* 2005; **330:** 1423.

86 Burgess IF, Lee PN, Matlock G. Randomised, controlled, assessor blind trial comparing 4% dimeticone lotion with 0.5% malathion liquid for head louse infestation. *PLoS One* 2007; **2:** e1127.

87 Kurt O, Balcioglu IC, Burgess IF, et al. Treatment of head lice with dimeticone 4% lotion: comparison of two formulations in a randomised controlled trial in rural Turkey. *BMC Pub Health* 2009; **9:** 441.

88 Abdel-Ghaffar F, Semmler M, Al-Rasheid K, Klimpel S, Mehlhorn H. Comparative in vitro tests on the efficacy and safety of 13 anti-head-lice products. *Parasitol Res* 2010; **106:** 423–29.

89 Schmahl G, Al-Rasheid KA, Abdel-Ghaffar F, Klimpel S, Mehlhorn H. The efficacy of neem seed extracts (Tre-san, MiteStop) on a broad spectrum of pests and parasites. *Parasitol Res* 2010; **107:** 261–69.

90 Saleem S, Muhammad G, Hussain MA, Bukhari SNA. A comprehensive review of phytochemical profile, bioactives for pharmaceuticals, and pharmacological attributes of *Azadirachta indica*. *Phytother Res* 2018; **32:** 1241–72.

91 Schmutterer H. Properties and potential of natural pesticides from the neem tree, *Azadirachta indica*. *Annu Rev Entomol* 1990; **35:** 271–97.

92 Alzohairy MA. Therapeutics role of *Azadirachta indica* (Neem) and their active constituents in diseases prevention and treatment. *Evid Based Complement Alternat Med* 2016; **2016:** 7382506.

93 Chaudhary S, Kanwar RK, Sehgal A, *et al*. Progress on *Azadirachta indica* based biopesticides in replacing synthetic toxic pesticides. *Front Plant Sci* 2017; **8:** 610.

94 Verallo-Rowell VM, Dillague KM, Syah-Tjundawan BS. Novel antibacterial and emollient effects of coconut and virgin olive oils in adult atopic dermatitis. *Dermatitis* 2008; **19:** 308–15.

95 Dayrit FM. The properties of lauric acid and their significance in coconut oil. *J Am Oil Chem Soc* 2015; **92:** 1–15.

96 US Environmental Protection Agency. Cold pressed neem oil PC Code 0250062012. USA: US Environmental Protection Agency.

97 Barrek S, Paisse O, Grenier-Loustalot M-F. Analysis of neem oils by LC–MS and degradation kinetics of azadirachtin-A in a controlled environment. *Anal Bioanal Chem* 2004; **378:** 753–63.

98 Zuleta-Castro C, Rios D, Hoyos R, Orozco-Sánchez F. First formulation of a botanical active substance extracted from neem cell culture for controlling the armyworm. *AGRON Sustain Dev* 2017; **37:** 40.