Prevention and control of neglected tropical diseases: overview of randomized trials, systematic reviews and meta-analyses

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Objective To analyse evidence from randomized controlled trials (RCTs) on the prevention and control of neglected tropical diseases (NTDs) and to identify areas where evidence is lacking.

Methods The Cochrane Central Register of Controlled Trials and PubMed were searched for RCTs and the Cochrane Database of Systematic Reviews and PubMed were searched for meta-analyses and systematic reviews, both from inception to 31 December 2012.

Findings Overall, 258 RCTs were found on American trypanosomiasis, Buruli ulcer, dengue, geohelminth infection, leishmaniasis, leprosy, lymphatic filariasis, onchocerciasis, rabies, schistosomiasis or trachoma. No RCTs were found on cysticercosis, dracunculiasis, echinococcosis, foodborne trematodes, or human African trypanosomiasis. The most studied diseases were geohelminth infection (51 RCTs) and leishmaniasis (46 RCTs). Vaccines, chemoprophylaxis and interventions targeting insect vectors were evaluated in 113, 99 and 39 RCTs, respectively. Few addressed how best to deliver preventive chemotherapy, such as the choice of dosing interval (10) or target population (4), the population coverage needed to reduce transmission (2) or the method of drug distribution (1). Thirty-one publications containing 32 systematic reviews (16 with and 16 without meta-analyses) were found on American trypanosomiasis, dengue, geohelminths, leishmaniasis, leprosy, lymphatic filariasis, onchocerciasis, schistosomiasis or trachoma. Together, they included only 79 of the 258 published RCTs (30.6%). Of 36 interventions assessed, 8 were judged effective in more than one review.

Conclusion Few RCTs on the prevention or control of the principal NTDs were found. Trials on how best to deliver preventive chemotherapy were particularly rare.

Abstracts in عربي, 中文, Français, Русский and Español at the end of each article.

Introduction

More than one billion of the world's poorest people are affected by neglected tropical diseases (NTDs), which are a group of parasitic, viral and bacterial infections that each year cause an estimated 534 000 deaths and a disease burden of 57 million disability-adjusted life–years (DALYs).[1] The World Health Organization (WHO) advocates five strategies for preventing and controlling NTDs: preventive chemotherapy, intensified case management, control of disease vectors, provision of clean water and sanitation and veterinary public health measures.[2] Historically, the development of drugs for these diseases has been limited by a lack of market incentives.[3] More recently, the formation of public–private partnerships for drug development has increased investment in research and development but the results have been uneven, with some diseases benefiting more than others.[4] For some NTDs, such as geohelminth infection, affordable and effective treatments do exist but their availability for people living in highly endemic areas is often limited.[4] For many others, treatment is inconvenient, poorly tolerated and expensive. A rational and comprehensive approach to disease control may, therefore, involve: (i) prevention strategies, including combined preventive chemotherapy (i.e. the treatment of more than one disease by the mass administration of more than one drug concurrently); (ii) improved access to clean water and sanitation; and (iii) the reduction of disease transmission by insect vectors. In addition, integrating efforts to control several NTDs into a single programme may reduce costs and streamline implementation.[1,5–8]

Evidence from randomized controlled trials (RCTs) can provide valuable information about the relative merits of different preventive interventions. However, the evidence may be scattered across several different trials. Moreover, although several systematic reviews and meta-analyses have been carried out, typically each has considered only one or a few interventions for a single disease, thereby creating a fragmented picture of the evidence available from RCTs. To prioritize research into the control of NTDs and to make evidence-based decisions about prevention, we must know: (i) the extent to which the RCTs available and associated systematic reviews and meta-analyses address the most important questions about control and prevention; (ii) whether these studies leave modest or large gaps in evidence and (iii) whether any interventions have been found to be consistently effective.

To address these issues, we systematically collected evidence from RCTs available in the peer-reviewed literature on the prevention or control of the principal NTDs and from corresponding systematic reviews and meta-analyses. Our aims were to evaluate the evidence from RCTs, to identify interventions that were found to be effective in systematic reviews and meta-analyses, to determine whether different meta-analyses on the same topic yielded similar or conflicting conclusions and to identify gaps in the evidence available.

Methods

Randomized controlled trials

We searched PubMed and the Cochrane Central Register of Controlled Trials for RCTs published on or before 31 December 2012 that addressed the prevention or control of 16 NTDs: American trypanosomiasis (Chagas disease), Buruli ulcer, cysticercosis, dengue, dracunculiasis (guinea-worm

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disease), echinococcosis (hydatid cyst disease), foodborne trematode infection, geohelminth infection, human African trypanosomiasis, leishmaniasis, leprosy, lymphatic filariasis, onchocerciasis, rabies, schistosomiasis and trachoma. We sought additional trials by reviewing our own literature collections, English-language systematic reviews, meta-analyses and Cochrane reviews, and the references of eligible publications we identified. The search strategy is given in detail in Table 1 (available at: http://www.who.int/bulletin/volumes/92/5/13-129601).

For several diseases, prevention, control and treatment overlap. For example, preventive chemotherapy is a disease control strategy that encompasses treatment and prevention: in highly endemic areas, periodic mass drug administration both provides treatment for infected individuals and decreases the burden of disease in the community by reducing transmission and preventing new cases.[9] Currently, preventive chemotherapy is used for schistosomiasis, lymphatic filariasis, geohelminth infection, onchocerciasis and trachoma.[9] Our study included preventive chemotherapy trials, which were defined as trials in which chemotherapy was given to a group of participants regardless of their infection status (i.e. without testing or screening for disease), either by mass drug administration to the whole population or by targeting treatment at a known high-risk group (e.g. schoolchildren). We excluded trials of individual treatment in which only infected participants were randomized. We also excluded trials of diagnostic tests, pharmacokinetic studies in healthy volunteers, trials with nonhuman subjects, non- and pseudo-randomized trials and trials that addressed the prevention of disease complications (e.g. trials of footwear for preventing foot ulcers in leprosy patients). Furthermore, we excluded trials published only as abstracts, descriptions of planned studies, subgroup or secondary analyses of previously published RCTs and trials reported in languages other than Dutch, English, French, German, Portuguese or Spanish. When we found a preliminary report of clinical trial data that were later included in a more complete publication, we included only the final publication. Trials that addressed more than one disease were included in the data set only once, although, for completeness, they are listed in each relevant disease section in Table 2.

Systematic reviews and meta-analyses

We carried out a separate search of PubMed and the Cochrane Database of Systematic Reviews to identify English-language meta-analyses and systematic reviews on the control or prevention of NTDs published on or before 31 December 2012. Eligible reviews had to contain at least one RCT that had been reported in a peer-reviewed publication and had to address the efficacy of any interventions used to prevent or control one of the 16 diseases of interest. We excluded articles on treatment, diagnosis, epidemiology, disease burden or the molecular biology, evolution or ecology of the etiological agent. We also excluded reviews that exclusively addressed animals (for example, vaccines in livestock) and protocols for planned reviews. For Cochrane reviews, we included only the most recent update. Systematic reviews had to include a methods section that described a comprehensive search strategy, with inclusion and exclusion criteria. A subset of systematic reviews included a meta-analysis that provided a formal quantitative synthesis of study results. We excluded three publications that were primarily reviews of reviews rather than of primary research data, though we read these publications to identify any additional suitable RCTs or systematic reviews. The search strategy is described in detail in Table 3 (available at: http://www.who.int/bulletin/volumes/92/5/13-129601).

Data analysis

We extracted the following information from each published RCT: first author, publication year, journal title, study country or site, study design (i.e. cluster, crossover or neither), interventions, sample size and follow-up period. We used the "unit of randomization" for calculating sample sizes: for trials in which individual participants were randomized, the sample size was the total number of individuals randomized and, for cluster randomized trials, the sample size was the total number of clusters (for example, neighbourhoods or villages). For both individually and cluster randomized trials, the sample size was taken to be the total number of individuals or clusters initially randomized rather than the number remaining after accounting for those lost to follow-up. We noted whether the trial report included a funding statement and ascribed funding to one or more of four sources: (i) a government or other public agency, including WHO and national public organizations such as the National Institutes of Health in the United States of America; (ii) industry; (iii) a charity or foundation; and (iv) a university or hospital. For each of the 10 diseases for which data were available, we calculated the Pearson correlation coefficient for the correlation between the number of RCTs performed and the annual global burden of disease, expressed in DALYs, and between the total sample size and the annual global disease burden.[10] We obtained data on the disease burden of American trypanosomiasis,[11] dengue,[11] leishmaniasis,[11] leprosy,[11] lymphatic filariasis,[11] onchocerciasis,[11] rabies,[12] geohelminth infections,[11] schistosomiasis[11] and trachoma.[11] No reliable estimates were available for Buruli ulcer.

For each systematic review, we extracted details of the first author, the publication year and the interventions addressed. Most meta-analyses and systematic reviews included both RCTs and nonrandomized studies. For each RCT, we extracted data on the sample size and the primary outcome. For reviews that included a meta-analysis, we recorded the effect size with 95% confidence intervals and, for all systematic reviews, we recorded the authors' conclusions, including their views on whether the intervention could be classified as: (i) likely to be effective; (ii) likely to be ineffective or (iii) of unknown efficacy due to a lack of sufficient evidence. When two or more reviews were available on the same intervention, we recorded whether they had similar or conflicting conclusions. Finally, we determined which RCTs in our RCT data set had not been included in a systematic review.

Results

Randomized controlled trials

The initial literature search for RCTs identified 2855 publications (Fig. 1, available at: http://www.who.int/bulletin/volumes/92/5/13-129601), of which 223, containing 236 eligible RCTs, were retained for analysis. Five publications were added from our literature collection or from the bibliographies of the publications retained; 18 were added

Table 2. **Randomized controlled trials (RCTs) and annual global disease burden for selected neglected tropical diseases (NTDs), to 2012**

NTD and management	RCTs		Disease burden in DALYs[c] (×1000)
	No.[a]	Total sample size[b]	
Geohelminth infection	51	22 848	3796
Preventive chemotherapy[d]	47	22 101	NA
Non-antihelminthic preventive chemotherapy (e.g. micronutrients or iron)	2	608	NA
Strongyloidiasis prophylaxis in immunocompromised hosts	1	103	NA
Hookworm vaccine	1	36	NA
Leishmaniasis	46	22 758	2090
Leishmaniasis vaccine	29	19 605	NA
Interventions targeting vectors[e]	17	3 153	NA
Rabies	34	5 176	1780
Pre-exposure vaccine	29	4 489	NA
Pre-exposure vaccine administered with other vaccines or schedules	4	621	NA
Pre-exposure vaccine delivery system[f]	1	66	NA
Dengue	31	71 206	616
Dengue vaccine	20	70 539	NA
Interventions targeting vectors[e]	10	658	NA
Education exclusively	1	9	NA
Schistosomiasis	29	14 023	1702
Preventive chemotherapy[d]	13	9 643	NA
Chemoprophylaxis in high-risk individuals who test negative for the disease	9	3 783	NA
Education	4	90	NA
Non-antihelminthic preventive chemotherapy (e.g. micronutrients or iron)	2	491	NA
Vaccine	1	16	NA
Trachoma[g]	27	8 338	2329
Preventive chemotherapy[d]	15	1 114	NA
Trachoma vaccine	8	5 515	NA
Sanitation or fly control	5	77	NA
Facial cleanliness	1	424	NA
Neonatal conjunctivitis	1	2 004	NA
Leprosy	25	736 567	198
Leprosy vaccine	18	730 284	NA
Contact chemoprophylaxis	7	6 283	NA
Lymphatic filariasis	10	5 538	5777
Preventive chemotherapy[d]	10	5 538	NA
Onchocerciasis	8	15 268	484
Preventive chemotherapy[d]	7	15 124	NA
Chemoprophylaxis in high-risk individuals who test negative for the disease	1	144	NA
American trypanosomiasis			
Chemical vector control	8	3 340	667
Buruli ulcer			
BCG vaccine	2	6 769	ND

BCG, Bacillus Calmette–Guérin; DALY, disability-adjusted life–year; NA, not applicable; ND, not determined.

[a] The total number of trials listed exceeds 258 because some addressed more than one disease concurrently: 8 addressed geohelminth infection and schistosomiasis, 2 addressed geohelminth infection and lymphatic filariasis, 1 addressed geohelminth infection and onchocerciasis and 1 addressed geohelminth infection, filariasis and schistosomiasis.

[b] The sample size was the number of "units of randomization" in each trial, including the number of clusters in cluster randomized trials. It underestimates the number of individual participants.

[c] A DALY is a year of life lost due to ill health, disability or early death associated with a disease.[10]

[d] Trials were included in this category if any arm involved preventive chemotherapy.

[e] Includes environmental modification, biological control, insecticide spraying and insecticide-treated bednets, curtains and clothing.

[f] This trial compared four different lengths of intradermal needle for intradermal injection and an epidermal abrasion system with intramuscular delivery of rabies vaccine.

[g] The sum of the number of trials in each intervention category does not add to 27 because several trials contained more than one modality (e.g. sanitation and preventive chemotherapy).

Table 4. **Randomized controlled trials (RCTs) on the prevention and control of selected neglected tropical diseases (NTDs), to 2012**

Characteristic	No. (%)[a] of RCTs (No. = 258)
Location[b]	
WHO African Region	59 (21.2)
WHO Region of the Americas	78 (28.1)
WHO South-East Asia Region	62 (22.3)
WHO European Region	20 (7.2)
WHO Eastern Mediterranean Region	26 (9.4)
WHO Western Pacific Region	33 (11.9)
Number of study sites	
Single centre	248 (96.1)
Multicentre	10 (3.9)
Type of trial	
With individual participants	187 (72.5)
Cluster randomized trial	71 (27.5)
Funding	
Publication explicitly stated funding source	191 (74.0)
Any public funding	144 (55.8)
Any charity or foundation funding	53 (20.5)
Any industry funding	26 (10.1)
Any university or hospital funding	31 (12.0)
Publication did not explicitly state funding source	66 (25.6)
Unable to ascertain	1 (0.4)
Duration of follow-up	
1 year or less	155 (60.1)
Longer than 1 year	103 (39.9)
Sample size[c]	
Mean	3517
Median (interquartile range)	151 (36–553)

WHO, World Health Organization.

[a] All values in the table represent absolute numbers and percentages unless otherwise stated.

[b] The sum of the number of trials in each location exceeds 258 because some were multicentre trials.

[c] The mean and the median were calculated using the "unit of randomization" in each trial, including the number of clusters in cluster randomized trials. Consequently, the number of individual participants was underestimated. When the number of participants in cluster randomized trials was taken into account, when available, rather than the number of clusters, the median sample size was 396 (interquartile range: 123–1425).

from the bibliographies of systematic reviews or meta-analyses. The final analysis included 246 publications containing details of 258 RCTs (Appendix A, available at: https://stanford.box.com/s/nm7ri7xnxq58m744gcl5).

Table 2 shows, for 11 NTDs, the number of RCTs on prevention or control performed, the total sample size and the annual global disease burden. Geohelminth infection was studied most (51 RCTs with a total sample size of 22 848), followed by leishmaniasis (46 RCTs with a total sample size of 22 758) and rabies (34 RCTs with a total sample size of 5176). No RCT had been performed on the prevention or control of five diseases: cysticercosis, dracunculiasis, echinococcosis, foodborne trematode infection and human African trypanosomiasis. There was no significant correlation between disease burden and either the number of RCTs ($\rho = 0.12$, $P = 0.73$) or the total sample size ($\rho = -0.38$; $P = 0.28$). Although the disease burden was greatest for lymphatic filariasis, only 10 RCTs had been performed.

Table 4 shows that most RCTs were conducted in the WHO Region of the Americas, the South-East Asia Region or the African Region. Only 10 RCTs (3.9%) were multicentre trials. There were 71 (27.5%) cluster randomized trials. Most trials were publicly funded (55.8%) or had no reported funding source (25.6%) and only 10.1% were funded by industry. The median sample size was 151 (interquartile range: 36 to 553).

Overall, 113 of the 258 RCTs (43.8%) involved vaccines, 99 (38.4%) involved topical or oral chemoprophylaxis and 39 (15.1%) involved interventions that targeted insect vectors, such as insecticide-treated bednets or indoor residual spraying. In addition, 80 (31.0%) had one or more preventive chemotherapy arms – either mass drug administration or targeted treatment. Few trials addressed the delivery of preventive chemotherapy: only 10 considered dosing intervals, 4 considered the choice of target population, 2 considered the population coverage needed for mass drug administration and 1 considered how best to deliver preventive chemotherapy. The other preventive chemotherapy trials either compared a drug with placebo or compared two or more drugs. Only 12 trials addressed co-treatment of more than one disease by mass drug administration. Preventive chemotherapy is the main intervention for four diseases – lymphatic filariasis, onchocerciasis, schistosomiasis and geohelminth infections – and is a key component in the control of trachoma.[9,13] Although 80 of 112 RCTs on these five diseases had a targeted treatment or mass drug administration arm, again very few addressed how best to deliver preventive chemotherapy: only 10 investigated different time intervals for drug distribution, 2 considered population coverage, 4 considered the target population and 1 considered the method of drug distribution. Moreover, of the 80 RCTs, 27 compared mass treatment and placebo, whereas 24 compared different drugs.

Systematic reviews and meta-analyses

The literature search identified 31 publications that reported one or more systematic reviews, with or without a formal meta-analysis (Fig. 2, available at: http://www.who.int/bulletin/volumes/92/5/13-129601). They addressed 36 different interventions for nine different diseases: American trypanosomiasis, dengue, geohelminths, leishmaniasis, leprosy, lymphatic filariasis, onchocerciasis, schistosomiasis and trachoma. Of the 16 systematic reviews that included a meta-analysis, there were 2 on dengue,[14,15] 1 on leishmaniasis,[16] 5 on leprosy (3 on the bacillus Calmette–Guérin [BCG] vaccine[17–19] and two on chemoprophylaxis[20,21]), 2 on schistosomiasis,[22,23] 1 on onchocerciasis,[24]

4 on lymphatic filariasis[25–28] and 1 on trachoma.[29] Of the 16 systematic reviews that did not include a meta-analysis (reported in 15 publications), there were 4 on trachoma,[30–33] 3 on dengue,[34–36] 1 on leprosy,[37] 2 on leishmaniasis,[38,39] 1 on onchocerciasis,[40] 3 on schistosomiasis,[41–43] 1 on geohelminths[43] and 1 on American trypanosomiasis.[44] Details of the systematic reviews are given in Appendix B (available at: https://stanford.box.com/s/af4co496bynqxlfwnlgc).

Appendix C (available at: https://stanford.box.com/s/ftoxgslppc4d9qzno3j5) lists the RCTs included in each review. Overall, only 79 of the 258 RCTs (30.6%) were included in a systematic review: 31 (12.0%) were included only in a systematic review without a meta-analysis, 40 (15.5%) were included only in a systematic review with a meta-analysis and 8 (3.1%) were included in both a systematic review without a meta-analysis and one with a meta-analysis.

Nineteen interventions had been assessed by a single systematic review (Table 5). Of the 19, 14 were found to be effective, 3 were found to be ineffective and, for 2, there was insufficient evidence to judge efficacy. Another 17 interventions had been assessed by two or more systematic reviews (Table 6). Of the 17, 8 were consistently found to be effective (all had been assessed in a meta-analysis), 1 was consistently found to be ineffective and, for 8, different reviews produced conflicting conclusions. For 4 of the 8 interventions on which conclusions conflicted, different systematic reviews concluded either that the intervention was likely to be effective or that there was insufficient evidence; for 1 other intervention, different systematic reviews concluded either that the intervention was likely to be ineffective or that there was insufficient evidence; and for the remaining 3 interventions, different reviews reported all possible conclusions (i.e. likely to be effective, likely to be ineffective and insufficient evidence). Only interventions for trachoma, leprosy and schistosomiasis were consistently judged to be effective by more than one systematic review. However, interventions for American trypanosomiasis, geohelminth infection, onchocerciasis and lymphatic filariasis were judged effective by the one systematic review in which each had been assessed.

Table 5. **Interventions for the prevention and control of neglected tropical diseases (NTDs) evaluated in only one systematic review, to 2012**

Effectiveness of intervention, NTD and intervention	Systematic review	
	Without meta-analysis	With meta-analysis
Likely to be effective		
American trypanosomiasis		
Chemical vector control	Abad-Franch 2011[44]	NA
Vector surveillance: notification of vector presence by residents compared to active searches by vector control staff plus vector detection devices or active searches alone	Abad-Franch 2011[44]	NA
Schistosomiasis		
Repeated praziquantel doses versus single doses	King 2011[42]	NA
Educational programmes that include videos	Bieri 2012[41]	NA
Praziquantel plus artesunate chemoprophylaxis	NA	Liu 2011[22]
Leprosy		
Rifampin chemoprophylaxis	NA	Reveiz 2009[20]
Onchocerciasis		
Single-dose ivermectin for prevention	NA	Basáñez 2008[24]
Lymphatic filariasis		
Diethylcarbamazine for prevention	NA	Tisch 2005[27]
Ivermectin for prevention	NA	Tisch 2005[27]
Geohelminth infection		
Albendazole for prevention	Uneke 2010[43,a]	NA
Mebendazole for prevention	Uneke 2010[43,a]	NA
Levamisole for prevention	Uneke 2010[43,a]	NA
Mebendazole plus levamisole for prevention	Uneke 2010[43,a]	NA
Pyrantel-oxantel for prevention	Uneke 2010[43,a]	NA
Likely to be ineffective		
Leishmaniasis		
Killed whole parasite *Leishmania* vaccines	NA	Noazin 2009[16]
Insecticide spraying	Romero 2010[39]	NA
Combined insecticide spraying and dog culling	Romero 2010[39]	NA
Insufficient evidence		
Onchocerciasis		
Ivermectin to prevent visual loss in onchocercal eye disease	Ejere 2012[40]	NA
Trachoma		
Health education	Rabiu 2012[31]	NA

NA, not applicable.
[a] All five drugs or drug combinations were judged likely to be effective against *Ascaris lumbricoides* and hookworm but were judged less effective against *Trichuris trichiura*.

For Buruli ulcer and rabies, no systematic review of a prevention or control intervention containing a peer-reviewed RCT had been performed, though RCTs had been carried out. For cysticercosis, dracunculiasis, echinococcosis, foodborne trematode infection and human African trypanosomiasis, neither a systematic review nor an RCT had been performed.

Discussion

Our analysis of 258 RCTs and 32 systematic reviews provides a summary of the evidence available on the prevention and control of NTDs and identifies gaps in that evidence. Although prevention is likely to be more cost-effective than treatment for these diseases,[45,46] far fewer trials of prevention than treatment have been carried out.[47] We found that RCTs

Table 6. **Interventions for the prevention and control of neglected tropical diseases (NTDs) evaluated in more than one systematic review, to 2012**

Effectiveness of intervention, NTD and intervention	Systematic review	
	Without meta-analysis	With meta-analysis
Consistently likely to be effective		
Trachoma		
Topical tetracycline	Kuper 2003[32]	Evans 2011[29]
Azithromycin	Kuper 2003[32]	Evans 2011[29]
Leprosy		
Bacillus Calmette–Guérin vaccine for prevention	Barreto 2006[37]	Setia 2006,[18] Zodpey 2007,[19] Merle 2010[17]
Dapsone chemoprophylaxis	NA	Smith 2000,[21] Reveiz 2009[20]
Acedapsone chemoprophylaxis	NA	Smith 2000,[21] Reveiz 2009[20]
Schistosomiasis		
Artesunate chemoprophylaxis	NA	Liu 2011,[22] Pérez del Villar 2012[23]
Artemether chemoprophylaxis	NA	Liu 2011,[22] Pérez del Villar 2012[23]
Praziquantel chemoprophylaxis	Uneke 2010[43]	Liu 2011[22]
Consistently likely to be ineffective		
Leishmaniasis		
Dog culling	Costa 2011,[38] Romero 2010[39]	NA
Discordant results		
Lymphatic filariasis		
Albendazole	NA	Insufficient evidence: Critchley 2005,[25] Critchley 2005[26] Likely to be ineffective: Tisch 2005[27]
Albendazole plus ivermectin	NA	Insufficient evidence: Critchley 2005,[25] Critchley 2005[26] Likely to be ineffective: Tisch 2005.[27] Likely to be effective: Gyapong 2005[28]
Albendazole plus diethylcarbamazine	NA	Insufficient evidence: Critchley 2005[25] Critchley 2005.[26] Likely to be ineffective: Tisch 2005[27] Likely to be effective: Gyapong 2005[28]
Trachoma		
Face and eye washing, including face washing plus topical tetracycline	Insufficient evidence (for preventing active trachoma): Emerson 2000,[48] Ejere 2012[a,30] Likely to be effective: Kuper 2003[b,32]	NA
Environmental improvements, including fly control with pit latrines or with insecticide spraying and water provision	Insufficient evidence: Emerson 2000,[48] Rabiu 2012[31] Likely to be effective: Kuper 2003[b,32]	NA
Dengue		
Chemical vector control	Insufficient evidence: Ballenger-Browning 2009[34] Likely to be ineffective: Esu 2010[35]	Likely to be effective: Erlanger 2008[14]
Biological control	Insufficient evidence: Ballenger-Browning 2009[34]	Likely to be effective: Erlanger 2008[14]
Community-based or educational interventions or both, including environmental management and integrated vector management	Insufficient evidence: Ballenger-Browning 2009,[34] Heintze 2007[36]	Likely to effective: Al-Muhandis 2011,[15] Erlanger 2008[14]

NA, not applicable; RCT, randomized controlled trial.

[a] This review included two RCTs and concluded: "[There is]… evidence that face washing can be effective in increasing facial cleanliness and in reducing severe trachoma, but its effect in reducing active trachoma is inconclusive. In another trial, there was no evidence of effect of face washing alone or in combination with tetracycline in reducing active trachoma in children with already established disease."

[b] This paper concluded that there was "weak supportive evidence" for the effectiveness of facial cleanliness and environmental modification but the evidence was minimal.

on prevention or control had been performed for only 11 of the 16 principal NTDs and that systematic reviews had been performed for only 9. Most RCTs had not been included in a systematic review. We identified 8 interventions that were consistently found to be effective in two or more systematic reviews: topical tetracycline and oral azithromycin chemotherapy for the prevention of trachoma; BCG vaccination, dapsone and acedapsone chemoprophylaxis for

the prevention of leprosy; and artesunate, artemether and praziquantel chemoprophylaxis for schistosomiasis (Table 6). For another 14 interventions, a single review concluded that they were effective (Table 5). However, for 8 interventions for which two or more reviews were available, conclusions were conflicting (Table 6).

A range of nonpharmacological interventions for disease control was reported. Future meta-analyses would be made easier by standardizing the design of trials on vector control strategies, including habitat modification, the use of insecticide-impregnated materials and spraying for dengue and leishmaniasis. Furthermore, most vector control trials for leishmaniasis and dengue did not consider human disease as an outcome and there is a need for more research on the relationship between vector control and human disease to justify such interventions. In particular, research on leishmaniasis and dengue is very different from that on trachoma: the recent literature on trachoma reports that collaborative, large-scale studies have been carried out, study designs and protocols have been published and efforts have been made to standardize definitions and outcome measures.[13,48,49]

There was either limited evidence that trachoma could be prevented by environmental improvements, such as increased access to sanitation, or conflicting conclusions in meta-analyses and systematic reviews. However, since such interventions may have broader benefits for other conditions, such as childhood diarrhoea[50,51] and geohelminth infection,[52] and may reduce overall childhood mortality,[53] it may not be a good use of resources to carry out further studies into their effect on this one disease.

Publications on the five NTDs for which no systematic review or RCT had been performed – cysticercosis, dracunculiasis, echinococcosis, foodborne trematode infections and human African trypanosomiasis – generally focused on treatment.[47] These diseases all have a focal form of transmission, which means that controlled trials would require the collaboration of veterinary public health experts, clinical researchers and behavioural health experts. For two diseases – rabies and Buruli ulcer – RCTs had been carried out but no systematic review containing an RCT was found in the literature search. For example, the systematic reviews found on rabies prevention did not include RCTs from peer-reviewed publications.[54,55]

Limitations

Our study has several limitations. First, we did not consider unpublished findings or the results of trials that were published only as abstracts because such material is difficult to identify systematically and formal peer-reviews have not been carried out. Consequently, we do not know the extent to which publication or selective reporting bias may have influenced the reliability of the evidence available. However, it is unlikely that such biases would completely invalidate the large preventive effects observed. Second, we did not conduct our own systematic review or meta-analysis because this would have been difficult to achieve for the dozens of different interventions used for 16 diseases. However, the reviews and meta-analyses we identified provide a summary of the evidence available and our analysis highlights those interventions that remain controversial and indicates those that need to be evaluated in systematic reviews and meta-analyses and those that need to be tested in RCTs. Third, we avoided adopting a specific conclusion when different systematic reviews and meta-analyses reached different conclusions. Instead, we registered the discrepancy, which may have reflected differences in eligibility criteria, data analysis or interpretation.[56–58] For example, different eligibility criteria were used in the reviews of chemical vector control for dengue,[14,34,35] different eligibility criteria and different methods for calculating summary effect measures were used in the meta-analyses of albendazole for lymphatic filariasis,[27,28] and mainly the same evidence was interpreted in different ways in the reviews of eye or face washing and environmental improvements for trachoma.[30,32,33]

Although trials of individual treatments can help in selecting drugs for use in mass drug administration programmes, such trials are not usually designed to address rare but serious side-effects or drug resistance, both of which are concerns in large-scale programmes. In addition, these trials rarely include nursing or pregnant women, who could also benefit from preventive chemotherapy.[59–61] Furthermore, while the evidence supporting the use of individual drugs included in mass drug administration programmes may be adequate, there are few reports of prevention or treatment trials involving combinations of drugs for several diseases, which are essential for evaluating integrated preventive chemotherapy.[47]

In conclusion, our study provides an overview of what is and is not known about the effectiveness of prevention and control measures for the principal NTDs. Where strong evidence is available, it can be used to guide the introduction and scale-up of prevention and control programmes; where gaps in evidence have been identified, the result should be new RCTs on prevention and control measures, although carrying out such trials in endemic areas is challenging. Moreover, these trials may have to be large to detect significant effects in the population and the costs may be prohibitive. However, a considerable amount of money has already been invested in, for example, mass drug administration programmes. Such programmes could only become more acceptable and financially viable if the most effective and cost-effective ways of delivering preventive chemotherapy were identified. ■

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ملخص

الوقاية من أمراض المناطق المدارية المهملة ومكافحتها: نظرة عامة على التجارب العشوائية والاستعراضات المنهجية والتحليلات الوصفية

الغرض تحليل البيّنات من التجارب العشوائية المضبوطة حول الوقاية من أمراض المناطق المدارية المهملة ومكافحتها وتحديد المناطق التي تفتقر إلى البيّنات.

الطريقة تم البحث في سجل كوكرين المركزي للتجارب المضبوطة وPubMed للوقوف على التجارب العشوائية المضبوطة وتم البحث في قاعدة بيانات كوكرين عن الاستعراضات المنهجية وتم البحث في PubMed للوقوف على التحليلات الوصفية والاستعراضات المنهجية، من البداية حتى 31 كانون الأول/ ديسمبر 2012.

النتائج بشكل عام، تبين إجراء 258 تجربة عشوائية مضبوطة على داء المثقبيات الأمريكي أو قرحة بورولي أو حمى الضنك أو العدوى الديدانية المنقولة بالتربة أو داء الليشمانيات أو الجزام أو داء الفيلاريات اللمفية أو داء كلابية الذنب أو البلهارسية أو التراخوما. وتبين عدم إجراء تجارب عشوائية مضبوطة على داء الكيسات المذنبة أو داء المشوكات أو داء الديدان المثقوبة المنقولة بالأغذية أو داء التنينات أو داء المثقبيات البشري الأفريقي. وكانت الأمراض التي حظيت بأكبر قدر من الدراسة هي العدوى الديدانية المنقولة بالتربة (51 تجربة عشوائية مضبوطة) وداء الليشمانيات (46 تجربة عشوائية مضبوطة). وتم تقييم اللقاحات والوقاية الكيميائية والتدخلات التي تستهدف نواقل الحشرات في 113 و99 و39 تجربة عشوائية مضبوطة، على التوالي. وتناولت بعض التجارب أفضل الطرق لإيتاء العلاج الكيميائي الوقائي، مثل اختيار الفواصل الزمنية بين الجرعات (10) أو الفئة السكانية المستهدفة (4) أو التغطية السكانية المطلوبة لتقليل السريان (2) أو أسلوب توزيع العقار (1). وتم العثور على واحد وثلاثين نشرة تتضمن 32 استعراضاً منهجياً (يتضمن 16 منها تحليلات وصفية بينما لا يتضمن 16 منها ذلك) على داء المثقبيات الأمريكي أو حمى الضنك أو العدوى الديدانية المنقولة بالتربة أو داء الليشمانيات أو الجزام أو داء الفيلاريات اللمفية أو داء كلابية الذنب أو البلهارسية أو التراخوما. وقد اشتملا معاً على 79 تجربة عشوائية مضبوطة فقط تم نشرها من بين 258 تجربة عشوائية مضبوطة (30.6٪). وتم الحكم على نجاعة 8 تدخلات، من إجمالي 36 تدخلاً تم الوصول إليها، في أكثر من استعراض.

الاستنتاج تبين إجراء بضعة تجارب عشوائية مضبوطة حول الوقاية من أمراض المناطق المدارية المهملة الأساسية ومكافحتها. وكانت التجارب المعنية بأفضل الطرق لإيتاء العلاج الكيميائي الوقائي على وجه الخصوص نادرة.

摘要

被忽视的热带病的预防和控制：随机试验、系统评价和元分析概述

目的 分析来自有关预防和控制被忽视热带疾病（NTD）随机对照试验（RCT）的证据并识别缺少证据的领域。

方法 在科克伦对照试验注册中心和 PubMed 检索 RCT，在科克伦系统评价数据库和 PubMed 搜索元分析和系统评价，二者时间均为最初到 2012 年 12 月 31 日。

结果 总计找到有关美洲锥虫病、布鲁里溃疡、登革热、土源性蠕虫感染、利什曼病、麻风病、淋巴丝虫病、盘尾丝虫病、狂犬病、血吸虫病或沙眼的 258 项 RCT。未发现囊虫病、包虫病、食源性吸虫、麦地那龙线虫病或非洲人类锥虫病的相关 RCT。大多数研究疾病是土源性蠕虫感染（51 项 RCT）和利什曼病（46 项 RCT）。分别在 113、99 和 39 项 RCT 中评估针对昆虫介体的疫苗、化学预防和干预措施。很少谈及如何最好地提供预防性化学疗法，例如选择给药间隔（10）或目标人群（4）、减少传播所需的人群覆盖率（2）或者药物配送方法（1）。发现有关美洲锥虫病、登革热、土源性蠕虫、利什曼病、麻风病、淋巴丝虫病、盘尾丝虫病、血吸虫病或沙眼包含 32 篇系统评价（16 篇有元分析，16 篇没有）的 31 份出版物。在 258 项已发表的 RCT 中加在一起仅有 79 项（30.6%）包括在内。在评估的 36 个干预措施中，不止一份评价判定 8 种干预是有效的。

结论 几乎未发现有关主要 NTD 防控的 RCT。如何最好地提供预防性化学疗法的试验尤其稀少。

Résumé

Prévention et contrôle des maladies tropicales négligées: vue d'ensemble des essais randomisés, des revues systématiques et des méta-analyses

Objectif Analyser les données tirées des essais contrôlés randomisés (ECR) sur la prévention et le contrôle des maladies tropicales négligées (MTN) et identifier les domaines où les données manquent.

Méthodes Des recherches sur les ECR ont été menées dans le registre central de Cochrane des essais contrôlés (*Cochrane Central Register of Controlled Trials*) et PubMed, et des recherches sur les méta-analyses et les revues systématiques ont été effectuées dans la base de données de Cochrane et PubMed, depuis la date de leur création jusqu'au 31 décembre 2012.

Résultats Globalement, 258 ECR ont été trouvés sur la trypanosomiase américaine, l'ulcère de Buruli, la dengue, les infections à géohelminthes, la leishmaniose, la lèpre, la filariose lymphatique, l'onchocercose, la rage, la schistosomiase ou le trachome. Aucun ECR n'a été trouvé sur la cysticercose, l'échinococcose, les trématodes d'origine alimentaire, la dracunculose ou la trypanosomiase humaine africaine. Les maladies les plus étudiées étaient les infections à géohelminthes (51 ECR) et la leishmaniose (46 ECR). Les vaccins, la chimioprophylaxie et les interventions ciblant les insectes vecteurs ont été évalués dans

113, 99 et 39 ECR, respectivement. Un faible nombre s'intéressait à la meilleure manière d'administrer une chimiothérapie préventive, comme le choix de l'intervalle posologique (10) ou de la population cible (4), la couverture de population nécessaire pour réduire la transmission (2) ou la méthode de distribution des médicaments (1). Trente et une publications contenant 32 revues systématiques (16 avec et 16 sans méta-analyses) ont été trouvées sur la trypanosomiase américaine, la dengue, les *géohelminthes,* la leishmaniose, la lèpre, la filariose lymphatique, l'onchocercose, la schistosomiase ou le trachome. Ensemble, ils comptent seulement 79 des 258 ECR publiés (30,6%). Parmi les 36 interventions évaluées, 8 ont été jugées efficaces dans plusieurs revues.

Conclusion Nous avons trouvé peu d'ECR sur la prévention ou le contrôle des principales MTN. Les essais sur la meilleure façon d'administrer une chimiothérapie préventive ont été particulièrement rares.

Резюме

Профилактика и борьба с забытыми тропическими болезнями: обзор рандомизированных исследований, систематических обзоров и мета-анализов

Цель Проанализировать данные рандомизированных контролируемых исследований (РКИ) по профилактике и борьбе с забытыми тропическими болезнями (ЗТБ) и определить области, в которых данные отсутствуют.

Методы Проводился поиск РКИ в Кокрановском центральном регистре контролируемых исследований и базах данных PubMed, а также поиск мета-анализов и систематических обзоров в Кокрановской базе данных систематических обзоров и базах данных PubMed с начала создания баз данных по 31 декабря 2012 года.

Результаты В целом, было найдено 258 РКИ по американскому трипаносомозу, язве Бурули, лихорадке денге, геогельминтной инфекции, лейшманиозу, лепре, лимфатическому филяриатозу, онхоцеркозу, бешенству, шистосомозу или трахоме. Не были найдены РКИ по цистицеркозу, эхинококкозу, трематоде пищевого происхождения, дракункулезу или африканскому трипаносомозу человека. Наиболее изученными заболеваниями являются геогельминтная инфекция (51 РКИ) и лейшманиоз (46 РКИ). Оценка вакцин, химиопрофилактики и мероприятий, направленных на борьбу с насекомыми-переносчиками инфекций, проведена соответственно в 113, 99 и 39 РКИ. Лишь в немногих РКИ рассматривался вопрос о том, как лучше всего проводить профилактическую химиотерапию, например, выбор интервала дозирования (10) или целевой группы населения (4), охвата населения для снижения количества случаев передачи инфекции (2) или методов распространения лекарств (1). Была найдена тридцать одна публикация, содержащая систематические обзоры (16 с мета-анализом и 16 без него) по американскому трипаносомозу, лихорадке денге, геогельминтам, лейшманиозу, лепре, лимфатическому филяриатозу, онхоцеркозу, шистосомозу или трахоме. Все вместе они составили только 79 из 258 опубликованных РКИ (30,6%). Из 36 оцененных мер по исправлению ситуации 8 были признаны эффективными в более чем одном обзоре.

Вывод Было найдено незначительное количество РКИ по профилактике или контролю основных ЗТБ. Особенно редко встречаются исследования, касающиеся поиска наилучших способов проведения профилактической химиотерапии.

Resumen

La prevención y el control de enfermedades tropicales desatendidas: una visión general de ensayos aleatorios, exámenes sistemáticos y metaanálisis

Objetivo Analizar las evidencias procedentes de ensayos controlados aleatorios (RCT, por sus siglas en inglés) sobre la prevención y el control de enfermedades tropicales desatendidas e identificar las áreas en las que se carece de evidencias.

Métodos Se buscaron RCT en el Registro Central Cochrane de Ensayos Controlados y en PubMed, así como metaanálisis y exámenes sistemáticos en la Base de Datos Cochrane de Revisiones Sistemáticas y en PubMed, en ambos casos, desde sus comienzos hasta el 31 de diciembre de 2012.

Resultados En total, se hallaron 258 RCT acerca de la infección por el parásito *Trypanosoma cruzi*, la úlcera de Buruli, el dengue, las infecciones por geohelmintiasis, la leishmaniasis, la lepra, la filariasis linfática, la oncocercosis, las rabias, la esquistosomiasis o el tracoma. No se encontraron RCT sobre la cisticercosis, la equinococosis, las nematodiasis transmitidas por los alimentos, la dracunculosis ni la tripanosomiasis africana humana. Las enfermedades más estudiadas fueron la infección por geohelmiantiasis (51 RCT) y la leishmaniasis (46 RCT). Las vacunas, quimioprofilaxis e intervenciones cuyo objetivo eran los insectos que actúan como vectores quedaron evaluadas en 113, 99 y 39 RCT, respectivamente. Unos pocos ensayos abordaron la mejor manera de administrar quimioterapia preventiva, como la elección del intervalo de dosificación (10) o la población objetivo (4), la cobertura de la población requerida para reducir la transmisión (2) o el método de distribución de medicamentos (1). Se encontraron 31 publicaciones que incluían 32 exámenes sistemáticos (16 con metaanálisis y 16 sin metaanálisis) sobre la infección por el parásito *Trypanosoma cruzi*, el dengue, los geohelmintos, la leishmaniasis, la lepra, la filariasis linfática, la oncocercosis, la esquistosomiasis y el tracoma. En su conjunto, solo incluyeron 79 de los 258 RCT publicados (30,6 %). De las 36 intervenciones evaluadas, 8 se consideraron eficaces en más de un examen.

Conclusión Se hallaron pocos RCT sobre la prevención y el control de las principales enfermedades tropicales desatendidas. Los ensayos sobre la mejor manera de administrar quimioterapia preventiva fueron especialmente escasos.

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Table 1. **Search strategy for randomized controlled trials on neglected tropical diseases (NTDs), to 2012**

NTD	Search terms for PubMed[a,b]	Search terms for Cochrane Central Register of Controlled Trials[b,c]
Leishmaniasis	leishmaniasis[MeSH] or leishman* or kala-azar	leishmaniasis or kala-azar or leishman*
Geohelminthiases	ascariasis[MeSH] or ascari*[tw] or strongyloidiasis[MeSH] or strongyl*[tw] or ancylostomatoidea[MeSH] or hookworm or Ancylostoma[tw] or Necator[tw] or trichuris[MeSH] or trichur*[tw] or whipworm or "soil-transmitted helminths" or geohelminths	ascar* or trichur* or strongyloid* or whipworm or ancylo* or hookworm or Necator or "intestinal nematodes" or "soil-transmitted helminths"
Schistosomiasis	schistosomiasis[MeSH] or schistosomiasis or bilharz*	schistosom* or schistosomiasis or bilharz*
Leprosy	leprosy[MeSH] or leprosy	leprosy or "*Mycobacterium leprae*" or "erythema nodosum leprosum"
Lymphatic filariasis	"Elephantiasis, filarial"[MeSH] or "lymphatic filariasis" or "*Wuchereria bancrofti* " or "*Brugia malayi* " or wucherer*[tw] or brugia*[tw]	"lymphatic filariasis" or Brugia* or Wuchereria or "elephantiasis, filarial"
Onchocerciasis	onchocerciasis[MeSH] or onchocerciasis or onchocerc* or "river blindness"	onchocerciasis or onchocerc* or "river blindness"
Trachoma	trachoma[MeSH] or trichiasis or trachoma	trachoma or trichiasis
Rabies	rabies[MeSH] or rabies	Rabies
Cysticercosis	cysticercosis[MeSH] or cysticercosis or neurocysticercosis or "*Taenia solium*"	cysticercosis or neurocysticercosis or "*Taenia solium*"
Dengue	dengue[MeSH] or dengue or "dengue hemorrhagic fever" or "dengue shock syndrome"	dengue or "dengue hemorrhagic fever" or "dengue shock syndrome"
American trypanosomiasis	"Chaga* disease" or "Chagas disease"[MeSH]	"Chagas disease" or "American trypanosomiasis"
Echinococcosis	echinococcosis[MeSH] or echinococc* or "hydatid cyst" or multilocularis or granulosus or hydatid*	echinococc* or "hydatid cyst" or multilocularis or granulosus
Foodborne trematodiases	trematoda and foodborne[MeSH] or "foodborne trematodes" or clonorch* or opisthorch* or paragonim* or fasciolop* or fasciol* or "intestinal flukes"	Opisthorchis or opisthorch* or clonorch* or clonorchis or paragon* or fasciol* or "intestinal flukes" or "foodborne trematodes"
Human African trypanosomiasis	"trypanosomiasis, African"[MeSH] or "human African trypanosomiasis"	"African trypanosomiasis" or "sleeping sickness"
Dracunculiasis	"dracunculus nematodes"[MeSH] or "Guinea worm" or dracontiasis or dracunculosis	"Guinea worm" or dracunculiasis
Buruli ulcer	"Buruli ulcer"[MeSH] or "Buruli ulcer" or "*Mycobacterium ulcerans*"	"Buruli ulcer" or "*Mycobacterium ulcerans*"

MeSH, medical subject heading; tw, title word.

[a] The PubMed search was done first and was intentionally broad and included redundancies. The medical subject heading (MeSH) term for each disease was used first, followed by additional search terms we thought would capture additional trials. The "randomized controlled trial" limit was used for the PubMed searches.

[b] The asterisk (*) denotes that the preceding search letters (e.g. echinococc) can be followed by any subsequent letters (e.g. echinococcus, echinococcosis or echinococcal).

[c] For the Cochrane Central Register of Controlled Trials search, we used the search terms shown in the table in text word searches.

Table 3. **Search strategy for systematic reviews on neglected tropical diseases (NTDs), to 2012**

NTD	Search terms for PubMed[a,b]	Search terms for Cochrane Central Register of Controlled Trials[b,c]
Leishmaniasis	leishmaniasis[MeSH] or leishman* or kala-azar	leishmaniasis or kala-azar or leishman*
Geohelminthiases	ascariasis[MeSH] or ascari*[tw] or strongyloidiasis[MeSH] or strongyl*[tw] or ancylostomatoidea[MeSH] or hookworm or Ancylostoma[tw] or Necator[tw] or trichuris[MeSH] or trichur*[tw] or whipworm or "soil-transmitted helminths" or geohelminths	ascar* or trichur* or strongyloid* or whipworm or ancylo* or hookworm or Necator or "intestinal nematodes" or "soil-transmitted helminths"
Schistosomiasis	schistosomiasis[MeSH] or schistosomiasis or bilharz*	schistosom* or schistosomiasis or bilharz*
Leprosy	leprosy[MeSH] or leprosy	leprosy or "*Mycobacterium leprae*" or "erythema nodosum leprosum"
Lymphatic filariasis	"Elephantiasis, filarial"[MeSH] or "lymphatic filariasis" or "*Wuchereria bancrofti*" or "*Brugia malayi* " or wucherer*[tw] or brugia*[tw]	"lymphatic filariasis" or Brugia* or Wuchereria or "elephantiasis, filarial"
Onchocerciasis	onchocerciasis[MeSH] or onchocerciasis or onchocerc* or "river blindness"	onchocerciasis or onchocerc* or "river blindness"
Trachoma	trachoma[MeSH] or trichiasis or trachoma	trachoma or trichiasis
Rabies	rabies[MeSH] or rabies	rabies
Cysticercosis	cysticercosis[MeSH] or cysticercosis or neurocysticercosis or "*Taenia solium*"	cysticercosis or neurocysticercosis or "*Taenia solium*"
Dengue	dengue[MeSH] or dengue or "dengue hemorrhagic fever" or "dengue shock syndrome"	dengue or "dengue hemorrhagic fever" or "dengue shock syndrome"
American trypanosomiasis	"trypanosomiasis, American"[MeSH] or "Chaga* disease"	Chagas disease or "American trypanosomiasis"
Echinococcosis	echinococcosis[MeSH] or echinococc* or "hydatid cyst" or multilocularis or granulosus or hydatid*	echinococc* or "hydatid cyst" or multilocularis or granulosus
Foodborne trematodiases	"trematoda and foodborne"[MeSH] or "foodborne trematodes" or clonorch* or opisthorch* or paragonim* or fasciolop* or fasciol* or "intestinal flukes"	Opisthorchis or opisthorch* or clonorch* or clonorchis or paragon* or fasciol* or "intestinal flukes" or "foodborne trematodes"
Human African trypanosomiasis	"trypanosomiasis, African"[MeSH] or "human African trypanosomiasis"	"African trypanosomiasis" or "sleeping sickness"
Dracunculiasis	"dracunculus nematodes"[MeSH] or "Guinea worm" or dracontiasis or dracunculosis	"Guinea worm" or dracunculiasis
Buruli ulcer	"Buruli ulcer"[MeSH] or "Buruli ulcer" or "*Mycobacterium ulcerans*"	"Buruli ulcer" or "*Mycobacterium ulcerans*"

MeSH, medical subject heading; tw, title word.

[a] The PubMed search was done first and was intentionally broad and included redundancies. The medical subject heading (MeSH) term for each disease was used first, followed by additional search terms we thought would capture additional reviews. The "meta-analysis" and "systematic review" limits were used for the PubMed searches.

[b] The asterisk (*) denotes that the preceding search letters (e.g. echinococc) can be followed by any subsequent letters (e.g. echinococcus, echinococcosis or echinococcal).

[c] For the Cochrane Central Register of Controlled Trials search, we used the search terms shown in the table in a search of titles, abstracts and keywords.

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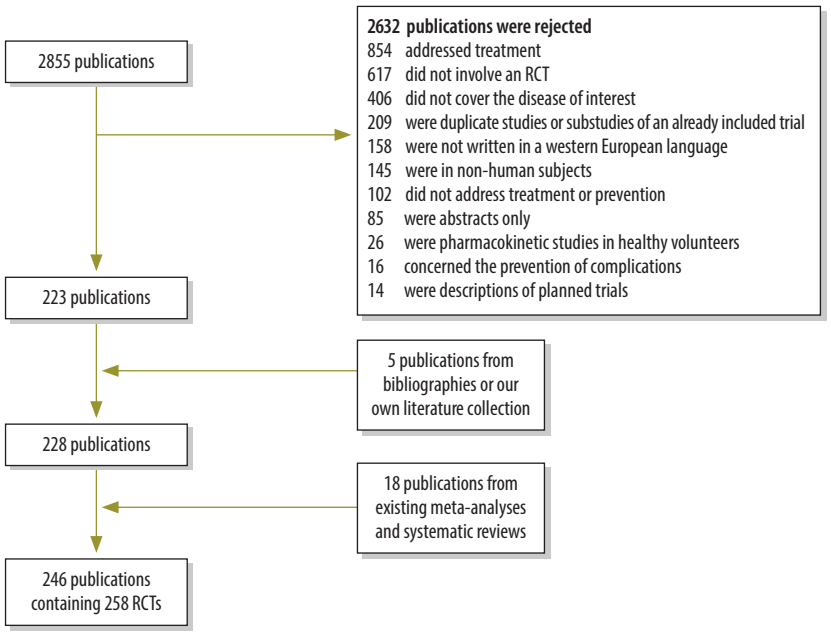
Fig. 1. **Literature search for randomized controlled trials on the prevention and control of neglected tropical diseases, to 2012**



RCT, randomized controlled trial.

Fig. 2. **Literature search for systematic reviews and meta-analyses on the prevention and control of neglected tropical diseases, to 2012**