RESEARCH

Neglected tropical diseases: survey and geometry of randomised evidence

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Abstract

Objective To assess the quantity and distribution of evidence from randomised controlled trials for the treatment of the major neglected tropical diseases and to identify gaps in the evidence with network analysis.

Design Systematic review and network analysis.

Data sources Cochrane Central Register of Controlled Trials and PubMed from inception to 31 August 2011.

Study selection Randomised controlled trials that examined treatment of 16 neglected tropical diseases or complications thereof published in English, French, Spanish, Portuguese, German, or Dutch.

Results We identified 971 eligible randomised trials. Leishmaniasis (184 trials, 23 039 participants) and geohelminth infections; 160 trials, 46 887 participants) were the most studied, while dracunculiasis (nine trials, 798 participants) and Buruli ulcer (five trials, 337 participants) were least studied. Relative to its global burden of disease, lymphatic filariasis had the fewest trials and participants. Only 11% of trials were industry funded. Either a single trial or trials with fewer than 100 participants comprised the randomised evidence for first or second line treatments for Buruli ulcer, human African trypanosomiasis, American trypanosomiasis, cysticercosis, rabies, echinococcosis, New World cutaneous leishmaniasis, and each of the foodborne trematode infections. Among the 10 disease categories with more than 40 trials, five lacked sufficient head to head comparisons between first or second line treatments.

Conclusions There is considerable variation in the amount of evidence from randomised controlled trials for each of the 16 major neglected tropical diseases. Even in diseases with substantial evidence, such as leishmaniasis and geohelminth infections, some recommended treatments have limited supporting data and lack head to head comparisons.

Introduction

The neglected tropical diseases comprise parasitic, viral, and bacterial infections that cause substantial morbidity among the world's poorest people but have historically not been targeted for intensive drug development because of limited financial incentives in the private sector.^{1 2} These diseases are both a cause and an effect of poverty. Some cause chronic disability (such as lymphatic filariasis and leprosy) and blindness (such as trachoma and onchocerciasis), which impair adults' ability to work, while others (such as geohelminth infections) are associated with decreased educational achievements in children.³ More than one billion people worldwide have one or more neglected tropical disease, causing an estimated 534 000 deaths and a loss of 57 million disability adjusted life years (DALYs) annually.⁴ Estimates of their global burden of disease might undervalue the importance of neglected tropical diseases to public health, particularly in areas where they co-occur with HIV and malaria. For instance, schistosomiasis infection might enhance HIV transmission^{5 6} and both schistosomiasis and geohelminth infections might be associated with more rapid progression of HIV disease.⁵⁻⁷ Geohelminth infections and schistosomiasis are also associated with increased susceptibility to and severity of malaria.⁸⁻¹¹

Although some neglected tropical diseases have affordable and effective treatments, many require treatments that are expensive, toxic, and difficult to administer. In addition, some treatment regimens—unchanged for decades—might be declining in efficacy because of drug resistance.¹²⁻¹⁴ Historically, drug development for these diseases has been limited. A review of drug development in the United States and Europe found that of 1393 new drugs developed and marketed between 1975 and 1999, only 1.1% were for tropical diseases.¹⁵ In the past several years, new public-private partnerships, such as the Drugs for

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Appendix: Supplementary figures and tables

Neglected Diseases Initiative, have provided a framework to accelerate drug development.¹⁶

We compiled the evidence from randomised controlled trials for treatment of 16 neglected tropical diseases. We used treatment networks to illustrate the types and numbers of treatments compared (so called “geometry” of evidence).^{17 18} These networks provide a visual and quantitative synopsis of the treatments studied and the amount of randomised evidence supporting current treatment guidelines and indicate whether some treatments or comparisons have been studied disproportionately.

Methods

Search strategy and eligibility criteria

We searched PubMed and Cochrane Central Register of Controlled Trials for randomised controlled trials published up to 31 August 2011 that examined treatment of 16 neglected tropical diseases: American trypanosomiasis (Chagas disease), Buruli ulcer, cysticercosis, dengue, dracunculiasis (Guinea worm), echinococcosis (hydatid cyst disease), foodborne trematode infections, geohelminth infections, human African trypanosomiasis, leishmaniasis, leprosy, lymphatic filariasis, onchocerciasis, rabies (prophylaxis after exposure), schistosomiasis, and trachoma. We also reviewed our own literature collections, relevant Cochrane reviews, and references of identified eligible trials to identify additional trials. Appendix table 1 shows the search strategy in detail.

We excluded trials with non-human participants, non-randomised and pseudo randomised trials, and non-treatment trials (such as trials of diagnostic tests, prevention interventions, and pharmacokinetic studies in healthy volunteers). We excluded abstracts, descriptions of planned studies, and subgroup or secondary analyses of previously published randomised controlled trials. We also excluded trials published in languages other than English, French, Spanish, Portuguese, German, or Dutch. Trials were eligible regardless of phase. For preliminary reports of clinical trial data that were later included in a more complete publication, we included only the final publication. For duplicate publications of the same trial we included the publication that appeared first; if both appeared in the same year, we included the publication from the journal with the higher impact factor. Studies that examined more than one of the 16 diseases (such as combination treatment for schistosomiasis and geohelminth infections) were included as a separate randomised controlled trial for each disease.

Data extraction

For each trial we read the first page, the methods, and the acknowledgments (to identify funding source) and extracted information on first author, publication year, journal, country/site(s), whether the study examined the primary disease or a complication, study design (crossover, cluster, or neither), interventions, number of participants per arm, and follow-up period. The trials were classified as either primary disease trials in which the tested treatments were aimed at eliminating or neutralising (as in rabies post-exposure prophylaxis) the aetiological agent of the infection, regardless of whether the infection was symptomatic, or complication trials in which patients with a specific complication of the primary infection (for example, anaemia, nutritional deficiency, growth impairment, portal hypertension, or cardiomyopathy) were enrolled. The treatments tested in complication trials generally did not target the infectious agent but aimed to modify the pathophysiology of the complication—for example, use of

angiotensin converting enzyme (ACE) inhibitors for cardiomyopathy associated with Chagas disease. We recorded whether the trial had a funding statement and all funding sources (industry, government, or other public agency (including the World Health Organization), charity or foundation, and hospital or university).

Descriptive analyses and correlation with disease burden

We present descriptive statistics for eligible trials and show the cumulative sample size and number of trials over time. To provide an estimate of how the evidence from randomised controlled trials has changed over time for different diseases, we divided the trials into those published before 2000 (n=609) and those published in 2000–12 (n=362). We chose 2000 as a watershed date as several initiatives to promote drug development for the neglected tropical diseases were started after 2000.¹⁶

For cluster randomised controlled trials, we used the number of clusters in the sample size calculations. For each disease, we separated trials targeting the primary infection from trials examining disease complications. We examined the correlations between the global burden of disease and the number of trials and total sample size for each disease. We obtained data on the burden of disease in DALYs for American trypanosomiasis,¹⁹ dengue,¹⁹ echinococcosis,²⁰ foodborne trematode infections,²¹ human African trypanosomiasis,¹⁹ leishmaniasis,¹⁹ leprosy,¹⁹ lymphatic filariasis,¹⁹ onchocerciasis,¹⁹ rabies,²² geohelminth infections,¹⁹ schistosomiasis,¹⁹ and trachoma.¹⁹ For three diseases (dracunculiasis, Buruli ulcer, and cysticercosis) we did not have reliable estimates of global burden of disease. DALYs are a measure of the years of life lost from ill health, disability, or early death from disease in a population and are calculated as the years of life lost plus the years lived with disability.²³ They can be used to compare the burden of disease across diseases that have disparate clinical courses—for example, a short lived disease with high mortality such as rabies and a chronically disabling disease with low mortality such as lymphatic filariasis.

Evidence for first and second line treatments

For each disease, we recorded the number of trials and total sample size for each treatment. We present these data only for currently recommended first or second line treatments. When available (for Buruli ulcer,²⁴ dengue,²⁵ echinococcosis,²⁶ leprosy,²⁷ rabies,²⁸ and trachoma²⁹) we used WHO guidelines published in the past six years to identify first and second line treatments. We used published consensus guidelines for cysticercosis.³⁰ For the nine remaining diseases, we reviewed the first and second line treatments and the primary references cited in UpToDate and *Medical Letter: Drugs for Parasitic Infections*.³¹ When these sources differed or for diseases for which influential randomised controlled trials have changed clinical practice pending clinical guideline revisions, we used our own judgment, additional recent randomised controlled trials, and review articles to designate first and second line treatments. This strategy was used for geohelminth infections (ascariasis,^{32–37} trichuriasis,^{32 38–43} hookworm,^{37 44–46} strongyloidiasis,^{41 47 48} onchocerciasis,⁴⁹ schistosomiasis,⁵⁰ lymphatic filariasis,^{49 51} visceral,^{52–56} cutaneous,^{57–60} and mucocutaneous⁶¹ leishmaniasis, American trypanosomiasis,^{62–64} foodborne trematode infections (clonorchiasis,^{65 66} opisthorchiasis,^{66 67} fascioliasis,^{68–70} fasciolopsiasis,⁷¹ paragonimiasis^{72–74}), human African trypanosomiasis,^{75–77} and dracunculiasis. When there was any uncertainty, we erred on the side of including more rather than fewer recommended

treatments. Appendix table 2 shows the designation of first and second line regimens for each of these nine diseases.

Treatment networks

The networks include only primary disease trials, omitting disease complication trials. Each node in a network (circle) represents a treatment and the connecting lines represent randomised comparisons. The node size is proportional to the total sample size for each treatment and the thickness of the connecting line is proportional to the number of comparisons. “Self loops” on the same node are comparisons within drugs—for example, comparisons of the same drug at different doses. We analysed in depth networks for diseases with over 40 randomised controlled trials.

We used methods described elsewhere¹⁷ to calculate network diversity and co-occurrence metrics. Diversity is a measure of the number of treatments in a network and whether the treatments are equally represented. A network with few treatments will have low diversity. A network where one or two treatments are repeatedly tested while others are tested rarely will have lower diversity than one where treatments are more evenly represented. We used the probability of interspecific encounter (PIE)—probability that two treatments sampled at random without replacement from all possible treatments in a network will be different—to estimate diversity. When there are N different treatments tested in a total of S clinical trial arms, the maximum value that the probability of interspecific encounter can take is $S(N-1)/(N(S-1))$ and the minimum is $(N-1)(2S-N)/(S(S-1))$, thus it cannot be greater than 1 or less than 0 under any circumstances. When there are many trials (for example, over 40, as in our analysis) and a modest number of different treatments, the maximum potential value of the probability of interspecific encounter is close to 1 and values above 0.8 represent high diversity.

We used the co-occurrence score (or C score) to assess whether some pairs of treatments are compared more or less often than would be expected by chance—that is, whether specific comparisons are preferred and/or others are avoided. To generate the C score, a symmetrical matrix of all the possible treatments is made by listing all the treatments in the dataset as row and column headings and entering a 1 or 0 in the matrix depending on whether a particular pairwise comparison is represented in the data or not. The row and column totals are then kept constant and multiple (5000) permutations are run to generate multiple possible sets of pairwise comparisons that can be made with the dataset. The observed matrix is then compared with the expected or average value of matrix over multiple permutations to test the null hypothesis that there is no co-occurrence. A permutation based P value of <0.05 for the C score represents significant co-occurrence. The P value can be non-significant, even if there is substantial co-occurrence, when the number of trials is small; for this reason, we limited analyses to networks with more than 40 trials.

Software

We used SAS Enterprise Guide 4.3 (SAS Institute, Cary, NC) for descriptive statistics and Ucinet for Windows Software for Social Network Analysis and NetDraw: Graph Visualization Software (Analytic Technologies, Harvard, MA) for network diagrams. For diversity and co-occurrence calculations, we used EcoSim Professional: Null Modelling Software for Ecologists, version 1 (Acquired Intelligence, Kesey-Bear, and Pinyon Publishing, Montrose, CO).

Results

Search results

The initial searches of PubMed and Cochrane Central Register of Controlled Trials generated 2857 publications (fig 1). We retained 927 publications containing 966 eligible randomised controlled trials. Five publications were added from our literature collection or bibliographies of included publications eventually yielding 971 randomised controlled trials in 932 publications.

Trial characteristics

Of the 971 trials, 854 dealt with one of the 16 primary diseases and 117 with a complication of one of the diseases (table 1). The most common study sites were Africa (27.6%) and Southeast Asia (26.9%). Only 26 (2.7%) of the trials were multicentre. Less than 3% and 2% of the trials had cluster or crossover designs, respectively. Most trials were either publicly funded or had no funding statement; only 11% reported industry funding. The median number of randomised participants per trial was 89 (interquartile range 42–184).

Randomised evidence and correlation with burden of disease

Figure 2 shows the cumulative number of randomised participants and trials over time. There is an inflection point in the pace of evidence accumulation around 1980 when the growth of evidence accelerates, but growth has remained steady since then. Table 2 shows that for six diseases—Buruli ulcer, cysticercosis, dengue, echinococcosis, human African trypanosomiasis, and leishmaniasis—there were more randomised controlled trials published in the past 12 years than in the preceding 50. For the 10 remaining diseases there have been fewer trials published in the past 12 years than in the preceding 50. The correlation coefficient between the two series was 0.66, indicating there was a modest correlation between the number of trials published before and after 2000 for each of the diseases. Table 3 shows the number of trials, total sample size, and annual global burden for each disease. Leishmaniasis was the most studied disease (184 trials, total sample size 23 039), followed by geohelminth infections (160 trials, total sample size 46 887), and schistosomiasis (142 trials, total sample size 35 026). The least studied diseases were dracunculiasis (nine trials, total sample size 798) and Buruli ulcer (five trials, total sample size 337). There was no strong correlation (Pearson correlation coefficient 0.33, $P=0.27$ for both analyses) between the global burden of disease and total sample size or number of clinical trials (appendix figure 1) for 13 diseases with available burden of disease estimates. Relative to its global burden of disease (5 777 000 DALYs), lymphatic filariasis was the least studied disease (73 trials, total sample size 9996). Leprosy was the best studied (120 trials, total sample size 14 772) relative to its fairly low global burden of disease (198 000 DALYs).

Dengue, American trypanosomiasis, the five major foodborne trematode infections, human African trypanosomiasis, dracunculiasis, mucocutaneous leishmaniasis, and Buruli ulcer each had 10 or fewer randomised controlled trials. Few treatment regimens were tested: six for dengue, five for American trypanosomiasis, seven or fewer for each of the foodborne trematode infections, six for dracunculiasis, seven for human African trypanosomiasis and mucocutaneous leishmaniasis, and eight for Buruli ulcer. Diseases with 11–40 randomised controlled trials examining the primary disease included rabies ($n=13$), strongyloidiasis ($n=14$), echinococcosis ($n=15$),

tuberculoid/paucibacillary leprosy (n=21), trachoma (n=29), and cysticercosis (n=32). As table 4¹ shows the evidence for one of the first or second line treatments for Buruli ulcer (all recommended treatments), human African trypanosomiasis (pentamidine), chronic American trypanosomiasis (nifurtimox), cysticercosis (praziquantel plus corticosteroids), rabies (several intramuscular post-exposure vaccine regimens), echinococcosis (percutaneous drainage plus albendazole and watchful waiting/no treatment), New World cutaneous leishmaniasis (pentamidine), and foodborne trematode infections (nitazoxanide for fascioliasis and praziquantel for clonorchiasis, paragonimiasis, and fasciolopsiasis) comes from either a single trial or a total of less than 100 randomised participants. Dengue and dracunculiasis have been investigated in few and primarily small randomised controlled trials, but do not have currently recommended pharmacological treatments. Appendix table 3 shows the amount of evidence for each treatment for each disease and disease complication.

Treatment networks

Figure 3¹ shows network diagrams of the tested regimens and comparisons for the 10 disease entities with more than 40 randomised controlled trials—schistosomiasis, ascariasis, hookworm, trichuriasis, lymphatic filariasis, visceral leishmaniasis, Old World cutaneous leishmaniasis, New World cutaneous leishmaniasis, onchocerciasis, and multibacillary leprosy. Appendix figure 2 shows networks for diseases that had 11–40 randomised controlled trials. Figure 3 omits a few trials that used regimens that were not compared with any of those shown in the connected network. This included one trial for Old World cutaneous leishmaniasis, three for visceral leishmaniasis, one for ascariasis, one for schistosomiasis, four for multibacillary leprosy, and one for lymphatic filariasis. Data from these trials are included in tables 3 and 4, but were not used to calculate the probability of interspecific encounter and C scores.

The typical geometry resembled a star or several stars, where star centres were usually first line treatments, sometimes second line treatments, and often placebo. There were some cases where treatments that are not accepted first or second line treatments were star centres, meaning a drug that is not a current first or second line drug has been compared against multiple other treatments. In most cases, this just reflects changes in clinical practice over time. These star centres are either treatments that were recommended treatments at the time of the trial—such as DEC (diethylcarbamazine) for onchocerciasis,^{78 79} bephenium for hookworm,⁸⁰ and dapsone monotherapy for leprosy⁸¹—or a standard of care in the country where the trial was conducted at the time of the trial—such as dapsone-rifampin dual treatment for multibacillary leprosy in Asia.^{82 83} Other drugs such as ivermectin and albendazole monotherapy for lymphatic filariasis were shown to be effective in small randomised controlled trials and were used as comparators (often with combination treatment) in subsequent larger trials.^{84 85}

For nine of the 10 disease networks in figure 3, there was more than one first or second line treatment. In seven of these nine, one or two treatments were most often studied while the other recommended treatments had limited evidence. For example, recommended treatments were compared in fewer than seven clinical trial arms and/or fewer than 1000 patients in onchocerciasis (combination ivermectin-doxycycline), trichuriasis (ivermectin), New World cutaneous leishmaniasis (pentamidine and miltefosine), and visceral leishmaniasis (miltefosine, paromomycin, amphotericin B lipid complex, and liposomal amphotericin).

In many networks, there were few data from head to head comparisons for first and second line treatments, despite them being tested in many trials against multiple comparators. The most extreme examples of this are in the networks for New World cutaneous leishmaniasis, for which there were no head to head comparisons between second line treatments miltefosine and pentamidine, and in visceral leishmaniasis, for which there were few or no head to head comparisons between miltefosine and paromomycin and between miltefosine and either amphotericin B lipid complex or liposomal amphotericin. To a lesser extent, this lack of head to head comparisons between recommended treatments is shown in the geohelminth networks. Trichuriasis and ascariasis networks have few or no comparisons of mebendazole and ivermectin, and the hookworm network shows few comparisons of pyrantel pamoate with albendazole or mebendazole.

All 10 networks had high diversity, with probability of interspecific encounter scores ≥ 0.82 (table 5¹). In seven of the 10 networks (Old World leishmaniasis, visceral leishmaniasis, the three geohelminth infections, multibacillary leprosy, and lymphatic filariasis) there was significant co-occurrence, meaning there was a tendency to compare specific pairs of treatments more often and to avoid other comparisons. This could reflect the fact that these networks have multiple star centres and each star centre is compared against a largely non-overlapping set of comparators. Conversely, the networks for New World cutaneous leishmaniasis and schistosomiasis, which mostly have a single star centre (systematic pentavalent antimonials and praziquantel, respectively), do not exhibit significant co-occurrence.

Discussion

In this systematic review, we identified almost a thousand randomised controlled trials examining the 16 neglected tropical diseases, although the distribution of the evidence across diseases was uneven. Six diseases had ≤ 10 randomised controlled trials, and for eight diseases either a single trial or fewer than 100 participants comprised the randomised evidence for a first or second line regimen. Even for diseases with numerous randomised controlled trials, such as leishmaniasis and geohelminth infections, evidence was limited for some of the recommended treatments, and there were few head to head comparisons for diseases with more than one recommended treatment. As expected, trials funded by the pharmaceutical industry were uncommon.

Several reasons could explain the lack of randomised evidence for some recommended treatments. For some diseases, a recommended treatment might not be available in all endemic areas—for example, the schistosomiasis drug oxamniquine is mainly used and available in Brazil.⁸⁶ Oxamniquine is effective only against *S. mansoni*, which limits its utility in areas of Africa where more than one species of *Schistosoma* co-occur. Other recommended treatments are unaffordable relative to standard treatment—for example, miltefosine and lipid formulations of amphotericin for visceral leishmaniasis. Despite cost and despite limited clinical evidence, however, newer treatments might rapidly supplant previously recommended drugs when they have seemingly much better side effect profiles, ease of administration, or drug resistance profiles than standard treatment (for example, miltefosine compared with pentavalent antimonials in visceral leishmaniasis). The relative lack of evidence from randomised controlled trials for certain diseases might also reflect the geographical distribution of the disease and whether there is capacity for clinical trial research in

endemic sites—for example, through links with institutions in developed countries.

Trials with inactive controls are typically less expensive and require smaller sample sizes than head to head comparisons. This could explain the popularity of placebo controlled trials in resource poor settings. The choice of placebo or “strawman” comparators leading to a lack of head to head comparisons of appropriately dosed recommended treatments has been noted in other diseases⁸⁷⁻⁹⁰ and has often been attributed to the goals of industry sponsors.⁸⁷⁻⁹¹ In our data, however, where industry funding was uncommon, lack of head to head comparisons could be explained by the cost and availability constraints noted above as well as unwillingness to use older, more toxic drugs as comparators with newer, seemingly safer agents. This might explain the lack of head to head comparisons between newer drugs and pentamidine in New World leishmaniasis. Finally, placebo controlled trials can sometimes still be appropriate in self limited diseases such as Old World cutaneous leishmaniasis. In general, however, head to head comparisons are essential to understand the relative effectiveness and harms of currently recommended regimens. Such comparisons of active agents are not lacking in general for neglected tropical diseases; it is specifically head to head comparisons of the most promising recommended agents that are sparse. Our networks show that often each recommended treatment forms the centre of a star whose points represent a cadre of several inferior regimens. There is little overlap between the comparators of each recommended treatment, and trials are rarely designed to establish which recommended regimen is best. Lastly, as the field of neglected tropical disease control moves towards integrated programmes of combined preventive chemotherapy,^{1 3 92} it is notable how few published randomised controlled trials examined concurrent treatment of more than one disease with combination chemotherapy—just 13 trials in our dataset (mostly geohelminth infections and schistosomiasis or geohelminth infections and lymphatic filariasis).

Limitations

Our work has several limitations. Exclusion of unpublished trials and trials published only in abstract underestimates the amount of randomised evidence. The published evidence, however, already gives us a wide view of the topic. While publication bias can affect estimates of treatment effects, it is unclear whether and how it would affect network geometries. Testing for co-occurrence is subject to power considerations, but our networks had a sufficiently large number of trials to make these estimates robust. The number of nodes in each network has some subjectivity; other investigators might have combined more treatments into single categories, which would have yielded simpler network patterns and lower estimates of network diversity. The correlations between the DALY based global burden of disease estimates and the amount of data from randomised controlled trials should be interpreted with caution. The established disability weights that go into the DALY estimates for the different neglected tropical diseases might not be nuanced enough to capture the effects of the wide range of different acute and chronic disease manifestations caused by the diseases, and inappropriate disability weights can considerably underestimate disease burden.⁹³ In addition, for several diseases there is a paucity of literature on which to base accurate estimates of disease specific mortality.

Finally, we did not perform a quantitative synthesis of treatment effects. This would have been impractical for a body of evidence including almost 1000 trials. Instead, we mapped the current perceptions about recommended treatments and the amount of

evidence supporting them. Network meta-analyses would benefit from our collected evidence to estimate precise treatment effects for these multiple different treatments.

Conclusions

Our systematic overview depicts the randomised evidence for the treatment of neglected tropical diseases and highlights where opportunities and needs exist for future trials. Clearly, there is not a direct inverse correlation between the amount of evidence available for each disease and the need for new drug development. Our findings must be interpreted in light of the safety and efficacy of existing treatments and other disease control efforts. For example, dracunculiasis is currently the target of a successful prevention oriented eradication programme⁹⁴; initiation of treatment focused research and development is unlikely to be a good use of resources. This situation contrasts with human African trypanosomiasis and visceral leishmaniasis, for which data on the safety and efficacy of existing drugs are limited, and with the foodborne trematode infections, for which well tolerated drugs are available but the evidence supporting their use and head to head comparisons among recommended treatments is minimal. Box 1 lists disease attributes—in addition to “relative neglect” and burden of disease—that could be used to determine priorities in drug development for neglected tropical diseases. Network analyses can provide a way to see not only which diseases are most and least studied but also which direct comparisons are absent or under-represented in the evidence from randomised controlled trials (box 2). Our systematic presentation of the randomised evidence for 16 neglected tropical diseases might help to prioritise research and advocacy efforts and provide a way to measure whether public-private partnerships and incentive programmes for research and development are succeeding in expanding the treatment options for these diseases.

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Ethical approval: Not required.

Data sharing: Dataset of the primary raw data is available on request from the corresponding author.

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Box 1: Considerations in setting priorities for drug development*Diseases with drug resistance or potential for emerging drug resistance*

- Leishmaniasis: pentavalent antimonials, miltefosine
- African trypanosomiasis: melarsoprol, eflornithine
- Onchocerciasis: ivermectin

Diseases with poorly tolerated, difficult to administer, or expensive drugs

- Human African trypanosomiasis: melarsoprol
- Visceral leishmaniasis: amphotericin deoxycholate, pentamidine, miltefosine
- Leprosy: clofazimine

Diseases with only a single drug available

- Schistosomiasis: praziquantel (oxamniquine has limited availability)
- Foodborne trematode infections: praziquantel or triclabendazole

Box 2: Examples of head to head comparisons among first and/or second line treatments that have been conducted only once or not at all in published randomised trials*Cutaneous leishmaniasis*

- Liposomal amphotericin/amphotericin B lipid complex v miltefosine
- Combination of miltefosine with parenteral treatments v amphotericin B lipid complex/liposomal amphotericin alone
- Heat treatment v topical aminoglycosides (Old World cutaneous leishmaniasis only)

Mucocutaneous leishmaniasis

- Miltefosine v amphotericin deoxycholate/liposomal amphotericin/paromomycin

Visceral leishmaniasis

- Miltefosine v liposomal amphotericin/paromomycin

Trichuriasis

- Mebendazole v ivermectin

Echinococcosis

- Percutaneous drainage v drainage plus albendazole/mebendazole

Buruli ulcer

- Shorter durations of streptomycin plus rifampin v standard duration

What is already known on this topic

Diseases described as "neglected" have historically not been targeted for research and drug development

These diseases carry a high cumulative global burden of disease

What this study adds

We identified 971 randomised trials pertinent to the treatment of neglected tropical diseases and found large variability, with some diseases being far more understudied than others

For several neglected diseases evidence for at least one first or second line treatment was scant and head to head comparisons were uncommon

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Tables

Table 1 | Characteristics of included randomised controlled trials

Characteristic	No (%)
Examines primary disease	854 (88.0)
Examines complication of disease	117 (12.0)
Location of study sites (WHO Regions)*:	
Africa	283 (27.6)
Southeast Asia	276 (26.9)
Americas	201 (19.6)
Eastern Mediterranean	132 (12.9)
Western Pacific	96 (9.4)
Europe	38 (3.7)
No of sites:	
Single centre	945 (97.3)
Multicentre	26 (2.7)
Cluster randomised trials	27 (2.8)
Crossover trials	15 (1.5)
Funding:	
Contains explicit statement	565 (58.2)
Any industry funding	107 (11.0)
Any public funding	388 (40.0)
Any charity or foundation funding	184 (18.9)
Any university or hospital funding	79 (8.1)
No explicit statement of funding	404 (41.6)
Unable to ascertain	2 (<1)
Trial size (total No randomised participants)†:	
Mean	191.0
Median (IQR)	89 (42-184)
Follow-up (years):	
≤1	772 (79.5)
>1	199 (20.5)

IQR=interquartile range.

*Total number of study sites is more than 971 because of multicentre trials.

†Calculated with "units of randomisation" in each trial, including number of clusters in cluster randomised trials and number of randomised units in trials in which unit of randomisation was not individual (for example, skin lesions in leishmaniasis or eyes in trachoma). It slightly underestimates number of individual participants.

Table 2| Number of randomised controlled trials published before and after 2000 for each disease

Disease	Published 1949-99 (n=609)	Published 2000-12 (n=362)
Buruli ulcer	1	4
Chagas disease	15	7
Cysticercosis	12	20
Dengue	9	15
Dracunculiasis	9	0
Echinococcosis	6	9
Foodborne trematode infections	9	5
Geohelminth infections	113	47
Human African trypanosomiasis	1	9
Leishmaniasis	82	102
Leprosy	93	27
Lymphatic filariasis	40	33
Onchocerciasis	52	10
Rabies	24	21
Schistosomiasis	109	33
Trachoma	34	20

Table 3| Number of trials, total sample size and annual global burden of disease for each disease

	No of trials*	No exclusively examining primary disease	Total sample size†	Annual global burden of disease in 1000s of DALYs
Leishmaniasis	184	179	23 039	2090
Geohelminth infections	160	133	46 887	3796
Ascariasis	—	79‡	—	—
Hookworm	—	77‡	—	—
Trichuriasis	—	66‡	—	—
Strongyloidiasis	—	14‡	—	—
Schistosomiasis	142	114	35 026	1702
Leprosy	120	77	14 772	198
Lymphatic filariasis	73	73	9996	5777
Onchocerciasis	62	53	25 182	484
Trachoma	54	29	10 420	2329
Rabies§	45	13	6756	1780
Cysticercosis	32	32	2872	—
Dengue	24	4	2374	616
American trypanosomiasis	22	8	1772	667
Echinococcosis	15	15	1064	666
Foodborne trematode infections	14	14	1306	665
Fascioliasis	—	5‡	—	—
Opisthorchiasis	—	4‡	—	—
Clonorchiasis	—	3‡	—	—
Paragonimiasis	—	2‡	—	—
Fasciolopsiasis	—	1‡	—	—
Human African trypanosomiasis¶	10	10	2840	1525
Dracunculiasis	9	9	798	—
Buruli ulcer	5	5	337	—

*Includes both primary disease and its complications.

†Calculated with "units of randomisation" in each trial, including number of clusters in cluster randomised trials and number of randomised units in trials in which unit of randomisation was not individual (for example, skin lesions in leishmaniasis or eyes in trachoma). It slightly underestimates number of individual participants.

‡Sum of individual categories is greater than total number of trials because of trials that examined more than disease.

§Thirteen trials examined post-exposure prophylaxis after appropriate exposure, 32 others were simulated prophylaxis trials

¶Early and late stage *Trypanosoma brucei gambiense*.

Table 4| Number of trials examining primary disease, number of regimens tested, and amount of evidence from randomised clinical trials supporting first and second line treatments in 16 neglected tropical diseases

	Trials	Regimens	No of trials/sample size supporting first and second line treatments
Schistosomiasis	114	34	Praziquantel (76/14488); oxamniquine (23/2419)
Ascariasis	79	37	mebendazole (24/5865); albendazole (33/7526); pyrantel pamoate (16/1838); levamisole (12/1254); ivermectin (5/1432); piperazine citrate (5/223); nitazoxanide (1/35)
Hookworm	77	29	Albendazole (40/7106); mebendazole (27/5790); pyrantel pamoate (16/1429); levamisole (3/400)
Trichuriasis	66	24	Mebendazole (25/6321); albendazole (41/8739); ivermectin (5/1432)
Strongyloidiasis	14	6	Ivermectin (6/803); albendazole (11/1066)
Lymphatic filariasis	73	17	Diethylcarbamazine plus albendazole (15/1953); diethylcarbamazine (44/2901)
Visceral leishmaniasis	67	29	Pentavalent antimonials (28/3026); liposomal amphotericin (7/758); miltefosine (5/754); amphotericin B deoxycholate (23/3999); paromomycin (5/1098); amphotericin B colloidal dispersion (1/405); amphotericin B lipid complex (5/284)
Old World cutaneous leishmaniasis	61	35	Pentavalent antimonials (16/863); heat treatment (3/224)
New World cutaneous leishmaniasis	44	22	Pentavalent antimonials (39/1589); miltefosine (5/398); pentamidine (2/55)
Mucocutaneous leishmaniasis	7	7	Pentavalent antimonials (5/157); amphotericin B deoxycholate (1/10)
Onchocerciasis	53	26	Ivermectin (27/5398); doxycycline plus ivermectin (2/150)
Multibacillary leprosy	56	55	Rifampin, dapsone plus clofazimine (16/846)
Paucibacillary leprosy	21	16	Rifampin plus dapsone (14/2299)
Trachoma	29	22	Oral azithromycin (8/871); ophthalmic tetracyclines (14/1849)
Rabies	13	17	PVCV IM (3/399); PCECV ID (4/171); PCECV IM (4/134); CPVCV IM (1/200); PDEV IM (1/52); HDCV IM (1/10); CPVCV IM plus rabies Ig (2/255); PCECV IM plus rabies Ig (2/159); PVCV ID (2/374); HDCV ID rabies Ig (1/78); HDCV IM plus rabies Ig (1/39); PVCV IM plus rabies Ig (1/47)
Cysticercosis	32	7	Albendazole plus corticosteroids (12/690); praziquantel plus corticosteroids (2/64)
American trypanosomiasis	8	5	Benznidazole (5/429); nifurtimox (1/27)
Echinococcosis	15	8	Surgery alone (8/279); surgery plus albendazole (5/209); albendazole (4/224); percutaneous drainage plus albendazole (2/37); placebo or no treatment (2/64); mebendazole (3/204)
Human African trypanosomiasis*	10	7	Melarsoprol (5/1865); nifurtimox plus eflornithine (3/211); eflornithine (4/536); pentamidine (1/52)
Dracunculiasis	9	6	No recommended first line treatment against disease among tested agents
Buruli ulcer	5	8	Streptomycin plus rifampin (1/76); streptomycin, rifampin plus clarithromycin (1/75); streptomycin plus rifampin followed by excision (1/16)
Dengue or dengue hemorrhagic fever	4	6	No recommended first line treatment against disease among tested agents
Foodborne trematode infections:			
Fascioliasis	5	4	Triclabendazole (4/399); nitazoxanide (1/80)
Opisthorchiasis	4	7	Praziquantel (3/140)
Clonorchiasis	3	5	Praziquantel (3/63)
Paragonimiasis	2	2	Praziquantel (1/15); triclabendazole (2/201)
Fasciolopsiasis	1	1	Praziquantel (1/85)

ID=intradermal; IM=intramuscular; PVCV=purified Vero cell vaccine; PCECV=purified chick embryo cell vaccine; CPVCV=chromatographically purified Vero cell vaccine; HDCV=human diploid cell rabies vaccine; PDEV=purified duck embryo vaccine; Ig=immunoglobulin.

*Early and late stage *Trypanosoma brucei gambiense*.

Table 5| Network metrics for 10 disease networks shown in figure 3

	C score	P value	Diversity (PIE) score
New World cutaneous leishmaniasis	0.13		0.82
Old World cutaneous leishmaniasis	0.031		0.92
Visceral leishmaniasis	0.039		0.88
Ascariasis	<0.001		0.90
Trichuriasis	0.003		0.86
Hookworm	0.013		0.94
Schistosomiasis	0.38		0.83
Multibacillary leprosy	<0.001		0.94
Lymphatic filariasis	0.014		0.82
Onchocerciasis	0.07		0.82

Figures

Fig 1 Schematic of literature search

Fig 2 Total sample size and number of clinical trials over time

Fig 3 Network diagrams for diseases with more than 40 randomised controlled trials. Node size is proportional to total sample size and line thickness is proportional to number of comparisons. Scale of nodes is different between different networks; see appendix table 3 for exact information on number of participants on each regimen. ABLC=amphotericin B lipid complex; ACT=artesunate combination treatment (includes artesunate+sulfalene, artesunate+mefloquine, artesunate+sulfadoxine-pyrimethamine, artesunate+sulfamethoxypyrazine-pyrimethamine, artesunate-amodiaquine and artesunate-praziquantel); ALB=albendazole; AM=antigen marianum; Azithro=azithromycin; Clarithro=clarithromycin; CLO=clofazimine; DAP=dapsone; DEC=diethylcarbamazine; Doxy=doxycycline; FLUB=flubendazole; GM-CSF=granulocyte-macrophage colony-stimulating factor; IFN=interferon; INH=isoniazid; Itra=itraconazole; IVM=ivermectin; LEV=levamisole; MEB=mebendazole; Metro=metronidazole; MINO=minocycline; MVT=multivitamin; NIC=nicotinamide;

NT=no treatment; OxPyrPam=oxantel-pyrantel pamoate; PAs=pentavalent antimonials; PIP=piperazine; PRO=prothionamide; PyrPam=pyrantel pamoate; PZA=pyrazinamide; PZQ=praziquantel; RIF=rifampin; RIF+CLO+DAP=rifampin, clofazimine, and dapsone; SDM=sulfadimethoxine; SMP=sulfamethoxypyridazine; SODM=sulforhodimethoxine; TCE=tetrachloroethylene; TAC=thiacetazone; Topical AG=topical aminoglycoside