

REVIEW

Open Access



The pipeline for drugs for control and elimination of neglected tropical diseases: 2. Oral anti-infective drugs and drug combinations for off-label use

Kenneth M. Pfarr^{1,2}, Anna K. Krome^{1,2,3}, Issraa Al-Obaidi⁴, Hannah Batchelor⁴, Michel Vaillant⁵, Achim Hoerauf^{1,2}, Nicholas O. Opoku⁶ and Annette C. Kuesel^{7*}

Abstract

In its 'Road map for neglected tropical diseases 2021–2030', the World Health Organization outlined its targets for control and elimination of neglected tropical diseases (NTDs) and research needed to achieve them. For many NTDs, this includes research for new treatment options for case management and/or preventive chemotherapy. Our review of small-molecule anti-infective drugs recently approved by a stringent regulatory authority (SRA) or in at least Phase 2 clinical development for regulatory approval showed that this pipeline cannot deliver all new treatments needed. WHO guidelines and country policies show that drugs may be recommended for control and elimination for NTDs for which they are not SRA approved (i.e. for 'off-label' use) if efficacy and safety data for the relevant NTD are considered sufficient by WHO and country authorities. Here, we are providing an overview of clinical research in the past 10 years evaluating the anti-infective efficacy of oral small-molecule drugs for NTD(s) for which they are neither SRA approved, nor included in current WHO strategies nor, considering the research sponsors, likely to be registered with a SRA for that NTD, if found to be effective and safe. No such research has been done for yaws, guinea worm, *Trypanosoma brucei gambiense* human African trypanosomiasis (HAT), rabies, trachoma, visceral leishmaniasis, mycetoma, *T. b. rhodesiense* HAT, echinococcosis, taeniasis/cysticercosis or scabies. Oral drugs evaluated include sparfloxacin and acedapsone for leprosy; rifampicin, rifapentin and moxifloxacin for onchocerciasis; imatinib and levamisole for loiasis; itraconazole, fluconazole, ketoconazole, posaconazole, ravuconazole and disulfiram for Chagas disease, doxycycline and rifampicin for lymphatic filariasis; arterolane, piperazine, artesunate, artemether, lumefantrine and mefloquine for schistosomiasis; ivermectin, tribendimidine, pyrantel, oxantel and nitazoxanide for soil-transmitted helminths including strongyloidiasis; chloroquine, ivermectin, balapiravir, ribavirin, ceftriaxone, UV-4B, ivermectin and doxycycline for dengue; streptomycin, amoxicillin, clavulanate for Buruli ulcer; fluconazole and isavuconazole for mycoses; clarithromycin and dapsona for cutaneous leishmaniasis; and tribendimidine, albendazole, mebendazole and nitazoxanide for foodborne trematodiasis. Additional paths to identification of new treatment options are needed. One promising path is exploitation of the worldwide experience with 'off-label' treatment of diseases with insufficient treatment options as pursued by the 'CURE ID' initiative.

*Correspondence:

Annette C. Kuesel

kuesela@who.int; annette.kuesel@mailbox.org

Full list of author information is available at the end of the article



© World Health Organization 2023. **Open Access** This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit <http://creativecommons.org/licenses/by/4.0/>. The Creative Commons Public Domain Dedication waiver (<http://creativecommons.org/publicdomain/zero/1.0/>) applies to the data made available in this article, unless otherwise stated in a credit line to the data.

Keywords Neglected tropical diseases, Drug repurposing, Drug reprofiling, Off-label use, Acedapsone, Albendazole, Amoxicillin, Artemether, Artemisinins, Artesunate, Arterolane, Azithromycin, Azoles, Balapiravir, Celgosivir, Chloroquine, Clarithromycin, Clavulanate, Disulfiram, Dapsone, Diethylcarbamazine, Disulfiram, Doxycycline, Fluconazole, Imatinib, Ivermectin, Isavuconazonium, Itraconazole, Ketoconazole, Levamisole, Lumefantrine, Mebendazole, Mefloquine, Moxidectin, Moxifloxacin, Nitazoxanide, Oxamniquine, Oxantel, Piperaquine, Posaconazole, Praziquantel, Pyrantel pamoate, Ravuconazole, Ribavirin, Rifampicin, Rifapentine, Sparfloxacin, Streptomycin, Tribendimidine, UV-4B, CURE ID

Background

Around 1 billion people, primarily in low- and middle-income countries (LMIC), are affected by Neglected Tropical Diseases (NTDs) [1]. In 2020, WHO provided an overview of current strategic interventions and new tools and approaches needed to achieve the targets laid out in its 2021–2030 roadmap for NTDs (the ‘Roadmap’) [1]. New tools needed include, but are not limited to, new drugs, optimized drug regimens and/or new formulations.

We have previously provided an overview of new small-molecule anti-infective molecular entities (drugs) in the pipeline for NTD control and elimination strategies which have recently been approved by a regulatory authority for treatment of an NTD or are in at least Phase 2 clinical development for regulatory approval for an NTD [2]. Research and development (R&D) of new drugs comes with a significant risk of failure and it takes many years even from initiation of Phase 2 clinical development to the first regulatory agency approval (registration). R&D for new drugs also requires significant financial resources to achieve regulatory registration and further resources to maintain the registration [3]. Furthermore, studies beyond those that supported regulatory approval may be needed to provide the basis for inclusion of the new drug in WHO guidelines, country policies and practice [2].

Repurposing (also referred to as ‘reprofiling’ or ‘repositioning’) drugs already registered provides a cheaper, less risky and faster path to new treatment options. Repurposing of registered veterinary drugs for human use led to a number of drugs used today for NTDs [2]. Repurposing of drugs registered for one indication in humans for another indication can provide an even cheaper, less risky and faster pathway to new treatment options: the pre-clinical toxicology profile is known, a formulation for human use is available, the pharmacokinetics (PK) and safety of the drug in healthy volunteers and the potential for drug-drug interactions have been characterized and data are available on the safety profile of the drug in the approved indication(s) with the approved formulation(s) and dosing regimen(s). Therefore, repurposing drugs approved

for indication(s) in humans can, in most cases, be initiated with Phase 2 studies with the available formulation to obtain proof of concept for efficacy in the new indication and identify a dose regimen to be evaluated in Phase 3 studies. The Phase 3 studies will be designed to establish the efficacy with acceptable statistical significance and to better characterize the safety profile of the chosen regimen in the targeted indication. Depending on the intended use context, these studies may have to be followed by additional larger scale studies to support guidelines and policies and by implementation research as is often necessary for new drugs [2].

Availability of efficacy and safety data for an indication may qualify the drug for inclusion in guidelines and policies even if the drug is not registered for the new indication, i.e. will be used ‘off-label’. Some WHO guidelines for ‘Preventive Chemotherapy’ (PC, i.e. drug administration to specified populations irrespective of the presence of symptoms or infection; for an overview of WHO guidelines see supplementary information in [2]) include drugs and drug combinations which have not been registered for the disease for which WHO recommends their use during PC. An example is PC for elimination of LF as a public health problem: in onchocerciasis co-endemic countries albendazole combined with ivermectin is recommended, in countries where onchocerciasis is not co-endemic albendazole combined with diethylcarbamazine or with diethylcarbamazine and ivermectin is recommended and in *Loa loa* co-endemic areas PC with albendazole alone is recommended [1, 2, 4, 5]. The basis for the introduction of albendazole + ivermectin and albendazole + diethylcarbamazine for PC of LF was studies on the effect of ivermectin on LF microfilaraemia as well as large-scale studies on the safety of the combination treatments conducted to support a potential WHO guideline as per WHO expert consultations [6–8]. LF is an indication for ivermectin (under the brand name Mectizan) in the prescribing information (label) authorized by the French Regulatory Authority (Agence nationale de sécurité du médicament et des produits de santé) [9] but not in the prescribing information authorized for ivermectin (under the brandname Stromectol) by

the US FDA. To our knowledge, indications for albendazole by national regulatory authorities may include strongyloidiasis, ascariasis, trichuriasis and infections with *Echinococcus granulosus*, *Enterobius vermicularis*, *Giardia intestinalis*, *G. duodenalis*, *Taenia solium*, *T. saginata*, *Trichinella spiralis* or hookworm infections but not LF. LF was recently included among ivermectin and albendazole indications for products prequalified by the WHO Prequalification Programme [10, 11]. For another ivermectin product, prequalified via the abbreviated prequalification process for products approved by stringent regulatory authorities (SRA [12]) in this case the US FDA [13, 14]), the prescribing information is that approved by the US FDA, i.e. does not include LF. However, the WHO Prequalification Programme specifies in Part 1 of the documentation that WHO recommended uses include LF, scabies, strongyloidiasis and, when administered with albendazole, soil-transmitted intestinal worm infections [15].

Here, we provide an overview of clinical studies for repurposing small-molecule anti-infective drugs, as mono- or combination treatment, for an NTD. This research is driven primarily by two concerns: (1) potential development of resistance when current strategies are based on the use of a single drug and (2) inadequate efficacy or safety of available drugs/drug combinations. Both could be addressed by new treatment options with repurposed drugs including combination treatment.

We included clinical research which meets the following criteria:

- The drugs evaluated are approved for human use and administered orally;
- The drugs have not received regulatory approval for the NTD for which they are being clinically evaluated and/or are not included in current NTD control and elimination strategies as per the Roadmap for the NTD for which their efficacy was evaluated [1, 2];
- Based on the study sponsors, submission of an application for regulatory registration for the NTD should the research show that the drug is efficacious and safe for the new NTD indication appears unlikely, i.e. potential use would be off-label;
- The anti-infective effect was evaluated.

We did not consider co-administration of different drugs in view of integration of current strategies for different diseases as 'combination treatment'; consequently, relevant studies are not included. Unless previously provided by us [2] or in recent reviews by others, we are summarizing basic information on the drugs, prior research that motivated repurposing and the main conclusions to date.

For information on regulatory approval, we searched first for registration in the US for the following reasons: (1) given the characteristics of the US market, the probability of registration for indications present in the US population is highest, and even drugs for indications not endemic in the US may be registered in the US (e.g. ivermectin for onchocerciasis), (2) the US FDA website provides an excellent, easy-to-search data base on approved drugs [16]. The data base includes current US FDA approved labelling (prescribing information), past labelling and for many drugs the very informative assessment of the US FDA reviewers at the time of the original registration. When needed, we also searched the websites of other SRAs that provide detailed product information with reviewer assessment (European Medicines Agency, the United Kingdom Medicines and Healthcare products Regulatory Agency). Search of the websites of other SRAs (Ministry of Health, Labour and Welfare of Japan, Swissmedic, Health Canada, Australia, Iceland, Liechtenstein, Norway [12]) was not necessary.

Clinical studies were identified through search of the WHO International Clinical Trials Registry Platform (ICTRP) for studies registered in a clinical trials platform in the past approximately 10 years. Additional file 1: Table S1 shows the ICTRP source registries and last data file import date into the ICTRP as of the search date of 8 February 2023. For studies for which the literature search identified no publications, we accessed the source registry file for any update on the study status. We excluded studies with records that had not been updated for 2 years after the study completion date (as provided in the record or estimated based on recruitment start and study duration) or for 3 years if the information in the record was insufficient to estimate the study completion date. Studies completed as per the source registry but for which we could not identify a publication as well as ongoing and planned studies are included in Table 1. Table 2 provides an overview of the drugs meeting our inclusion for this manuscript combined with those we reviewed previously [2] together with the drugs in current WHO-recommended strategies and the needs for improved treatment options WHO identified in the Roadmap.

The literature review and review of the studies in the ICTRP showed that for some NTDs plant extracts/traditional medicines which do not meet our 'inclusion criteria' were evaluated. Given the contribution of traditional medicines to drugs in use today (e.g. the artemisinins for malaria [17]) and WHO initiatives to harness such knowledge [18, 19], following the literature for results of these studies will be interesting. For some plant extracts/traditional medicines being evaluated, we included information in Additional file 1.

Table 1 Planned, ongoing or unpublished completed studies in the ICTRP as of 8 February 2023 evaluating small-molecule anti-infective drugs approved for human use but not included in current WHO recommended NTD strategies

WHO target NTD Source registry trial ID	Scientific title	Country of conduct	Registration date ^a Status ^b
Elimination			
Onchocerciasis			
NCT02078024 ISRCTN50035143	Comparison of ivermectin alone with albendazole (ALB) plus ivermectin (IVM) in their efficacy against onchocerciasis in the Volta Region, Ghana	Ghana	20140228 (completed)
NCT04188301 PACTR 201906665550709	Safety and efficacy of combination therapy with ivermectin, diethylcarbamazine, and albendazole (IDA) for individuals with onchocerciasis	Ghana	20191202 20190624 Active, not recruiting
ISRCTN43697583	The efficacy of rifapentine 900 mg/d plus moxifloxacin 400 mg/d given for 14 or 7 days against onchocerciasis: a randomized, parallel-group, open-label, phase II pilot trial	Ghana	20150417 (completed)
PACTR202212910949177	Exploiting the synergy of registered drugs rifampicin and albendazole to shorten the treatment duration of macrofilaricide for the cure of onchocerciasis in areas co-endemic with loiasis: an exploratory pilot phase II clinical trial study	Cameroon	20221219 (not yet recruiting, last follow-up December 2025)
ISRCTN38954299	Assessment of the efficacy of 7-14 days treatment with either high dose rifampicin 35 mg/kg/day plus albendazole (400 mg/day), rifampicin 10 mg/kg/day plus albendazole (400 mg/d) or doxycycline 200 mg/day plus albendazole (400 mg/day) in the treatment of onchocerciasis: a randomized, controlled, parallel-group, open-label, phase II pilot trial Cameroon	Cameroon	20210604 Active, not recruiting, last follow-up May 2023)
PACTR 202009704006025	The efficacy of rifampicin 35mg/kg/d plus albendazole 400mg/d given for 7 or 14 days against lymphatic filariasis and onchocerciasis: a randomized, controlled, parallel-group, open-label, phase II pilot trial	Ghana	20200713 Recruiting (last follow-up Dec. 2024)
Loiasis			
ISRCTN14889921	Pre-treatment of loiasis caused by the parasitic African eye worm <i>Loa loa</i> in Gabon with the antiparasitic medication albendazole among patients with a high risk of adverse events after another antiparasitic administration, ivermectin	Gabon	20221129 (retrospectively) Projected completion February 2023

Table 1 (continued)

WHO target NTD Source registry trial ID	Scientific title	Country of conduct	Registration date ^a Status ^b
PACTR201807197019027	Safety and efficacy of different albendazole-based treatment regimens to reduce microfilaraemia in subjects infected by <i>Loa loa</i> in an endemic area of Gabon: a randomised controlled open-label pilot study [3 weeks albendazole 400mg bid vs. 3 weeks albendazole followed by 2 weeks albendazole vs. 3 weeks albendazole followed by a single dose of 150 µg/kg ivermectin as soon as microfilarial loads have dropped to < 4000 mf/ml in > 90% of subjects vs. no treatment	Gabon	20180607 (retrospectively) Completed
Elimination as public health problem Chagas disease			
Registro Brasileira de Ensaios Clínicos ID: RBR-5n4htp	Disulfiram repurposing in the combined chemotherapy of Chagas disease—phase I/II clinical trial	Brazil	20200217 Recruiting
Lymphatic filariasis			
PACTR202009704006025	The efficacy of rifampicin 35mg/kg/d plus albendazole 400mg/d given for 7 or 14 days against lymphatic filariasis and onchocerciasis a randomized, controlled, parallel-group, open-label, phase II pilot trial	Ghana	20200713 Recruiting (last follow-up Dec. 2024)
ISRCTN15320064	Comparing the effectiveness of test and treat approaches with doxycycline or the triple-drug therapy with ivermectin/diethylcarbamazine/albendazole vs. ivermectin/albendazole for targeted elimination of lymphatic filariasis in a phase III clinical trial	Ghana	20220,329 Not yet recruiting (last update August 2022)
Schistosomiasis			
NCT03893097	A proof-of-concept trial to evaluate artesunate-mefloquine as a novel alternative treatment for schistosomiasis in African children	Senegal	20190328 Completed
STH including strongyloidiasis			
PACTR202011642671155	An adaptive phase II/III single-blinded, randomized, multi-centre, parallel-group, active-controlled, superiority study to evaluate the safety and efficacy of a single day or 3-day single dose of an albendazole-ivermectin coformulation vs. albendazole for the treatment of soil-transmitted helminth infections (<i>Trichuris trichiura</i> , hookworm, <i>Strongyloides stercoralis</i>) in paediatric and young adult population	Kenya, Mozambique, Ethiopia	20201015 Recruiting Last follow-up 31 July 2023
Control Dengue			
NCT03432442	Pharmacokinetics and pharmacodynamics of ivermectin in pediatric dengue patients	Thailand	20180214 Completed (last update February 2021)

Table 1 (continued)

WHO target NTD Source registry trial ID	Scientific title	Country of conduct	Registration date ^a Status ^b
CTRI/2021/09/036661	Role of doxycycline in the treatment of dengue infection	India	20210920 Not yet recruiting (last update September 2021)
Buruli ulcer PACTR202209521256638	Shortening Buruli ulcer treatment: WHO recommended vs. a novel beta-lactam-containing therapy—phase III evaluation in West Africa [rifampicin plus clarithromycin (RC) for 8 weeks vs. RC plus amoxicillin/clavulanate for 4 weeks]	Ghana, Côte d'Ivoire, Togo	20220912 Planned start December 2022, planned final follow-up November 2023 Not yet recruiting
NCT05169554	Beta-lactam containing regimen for the shortening of Buruli ulcer disease therapy: comparison of 8 weeks standard therapy (rifampicin plus clarithromycin) vs. 4 weeks standard plus amoxicillin/clavulanate therapy (RC8 vs. RCA4)	Benin	20211227 Recruiting, Primary outcome data November 2024
Cutaneous leishmaniasis IRCT20140211016554N4	Evaluation of the effectiveness of oral dapsone with intralesional antimoniate in treatment of cutaneous leishmaniasis in comparison with intralesional antimoniate alone	Islamic Republic of Iran	20190428 Completed

^a Registration date provided as year month day. ^b Status as of source registry, accuracy of the status information depends on the timeliness with which sponsors update the source registry. If a study was registered in more than one registry, the most up-to-date status information at the time of writing of the manuscript is provided

CTRI Clinical Trials Registry India, ICTRP WHO International Clinical Trials Registry Platform, ISRCTN registry managed by BMC, Springer Nature, NCT Clinical Trials.gov, PACTR Pan African Clinical Trial Registry, RBR Registro Brasileiro de Ensaios Clinicos

As for our previous review of drugs in the pipeline for regulatory approval [2], we wanted to ensure to the best of our ability that readers in LMIC can access all references. Therefore, all references are either openly accessible (open access or accessible as author manuscripts e.g. via the US National Institutes of Health's National Library of Medicine platform (Pubmed Central, PMC), the European Molecular Biology Laboratory European Bioinformatics Institute platform (Europe PMC) or institutional websites, or publications in the WHO Institutional Repository for Information Sharing (WHO IRIS)) or were accessible via HINARI to the WHO staff co-author (ACK). HINARI is a WHO initiative through which not-for-profit institutions in LMIC can obtain free or low cost online access to major journals in the biomedical and related social sciences [20]. Publishers do not provide the same access to the publications in HINARI to all eligible institutions. WHO has a relatively limited level of access and we used WHO staff (ACK) access as the criterion for 'accessible via HINARI'. Our objective to minimize differences in access to references between readers

from rich institutions in high income countries and all other readers has resulted in some relevant literature not being referenced. Hopefully, in the context of increasing attention to Open Access, all journals will, at a minimum, make all content more than 2 years old accessible to all HINARI eligible institutions.

NTDs targeted for eradication

In the Roadmap, WHO defines eradication as: 'Permanent reduction to zero of the worldwide incidence of infection caused by a specific pathogen, as a result of deliberate efforts, with no risk of reintroduction'. Documentation of eradication is termed certification [1].

Yaws

The current strategy is based on PC with azithromycin. For case management, azithromycin is the preferred treatment and benzathine benzylpenicillin the treatment

Table 2 Overview of small-molecule anti-infective drugs evaluated alone or in combination in the past 10 years for NTDs for which they are not registered or included in current WHO NTD strategies

WHO objective NTD [Drugs included in WHO strategies] [1, 2]	Gaps in/actions required for anti-infective drugs as per 2030 roadmap [1, 2]	1. In at least Phase 2 development for regulatory approval or recently approved [2] 2. Evaluated in the past 10 years for off-label use as per ICTRP records
Eradication		
Yaws [azithromycin, benzathine benzylpenicillin]	–	1. None 2. None
Guinea worm [–]	Drugs for case management	1. None 2. None
Elimination of transmission		
Leprosy [rifampicin, dapson, clofazimine, clarithromycin, minocycline or a quinolone (ofloxacin, levofloxacin or moxifloxacin)]	New drugs or combinations	1. Bedaquiline 2. Sparfloxacin, acedapsone [21]
Human African trypanosomiasis (<i>gambiense</i>) [fexinidazole, eflornithine-nifurtimox, pentamidine]	Safe and efficient single oral dose for both stages to help integration of treatment into primary health system Oral formulation for children < 6 years	1. Acoziborole 2. None
Onchocerciasis [ivermectin]	Macrofilaricide Efficacy and safety of moxidectin in children and community settings Safe drugs safe in <i>Loa loa</i> co-endemic areas	1. Moxidectin, emodepside, flubentylosin (TyAMac, ABBV-4083), oxantel pamoate, Oxfendazole 2. Albendazole in combination with ivermectin, albendazole and diethylcarbamazine in combination with ivermectin, antibiotics (rifampicin, rifapentin, moxifloxacin); Loiasis focussed: imatinib (discontinued), levamisole
Elimination as a public health problem		
Rabies [none]	Monoclonal antibodies Anti-virals and agents promoting entry of drugs, antibodies and immune effectors cells across the blood-brain barrier	1. None 2. None
Trachoma [azithromycin, tetracycline]	–	1. None 2. None
Chagas disease [benznidazole, nifurtimox]	Dosage and duration of benznidazole and nifurtimox treatment Combination treatment, new drugs	1. Fexinidazole, fosravuconazole (discontinued) 2. Azoles (itraconazole, fluconazole, ketoconazole, posaconazole and ravuconazole) disulfram
Human African Trypanosomiasis (<i>rhodesiense</i>) [suramin, melarsoprol]	Safe, efficient treatments to replace toxic arsenic-based melarsoprol New, safe, cheap oral drugs not requiring cold chain Shorter first line regimens in East Africa More treatment options including combination treatments to mitigate risk of resistance	1. Fexinidazole 2. None 1. LXE408 2. None
Visceral leishmaniasis [pentavalent antimonials, liposomal amphotericin B, paromomycin, miltefosine]	Macrofilaricide, drug safe in <i>Loa loa</i> -infected individuals	1. Moxidectin 2. Antibiotics: doxycycline [22], rifampicin
Lymphatic filariasis [albendazole, ivermectin, diethylcarbamazine]		

Table 2 (continued)

Schistosomiasis [praziquantel]	Improved praziquantel and pediatric formulation New drugs to complement praziquantel in case of resistance	1.None 2.Antimalarial drugs (arterolane, piperazine, artesunate, artemether, lumefantrine, mefloquine)
Soil transmitted helminths including strongyloidiasis [albendazole, mebendazole]	More effective medicines and drug combinations against <i>T. trichiura</i> and hookworm infections Drugs and drug combinations to be used in case of emergence of drug resistance	1.Moxidectin, emodepside, oxantel pamoate, oxfendazole 2.Ivermectin, ivermectin-albendazole combination, tribendimidine, pyrantel pamoate (monotherapy or in combination with albendazole, mebendazole, oxantel), nitazoxanide
Control		
Dengue and chikungunya [none]	Anti-viral drugs	1.JNJ-64281802 2.Chloroquine, ivermectin, balapiravir, ribavirin, celgosivir, UV-4B [23], ivermectin, doxycycline
Buruli ulcer [rifampicin, clarithromycin, moxifloxacin]	New treatment options with reduced treatment duration and lower toxicity, especially for children	1.None 2.Streptomycin, amoxicillin/ clavulanate
Mycetoma [antibiotics for actinomycetoma, antifungals for eumycetoma]	Better treatment regimens (shorter duration, higher efficacy)	1.Fosravuconazole 2.None
Chromoblastomycosis and other deep mycoses [itraconazole, amphotericin B]	Prospectively obtained effectiveness of itraconazole and other antifungals; Improved treatment regimens (shorter duration and increased efficacy)	1.None 2.Fluconazole, isavuconazonium
<i>Cutaneous leishmaniasis</i> [pentavalent antimoniate (with or without allopurinol), liposomal amphotericin B, amphotericin B deoxycholate, paromomycin, miltefosine, pentamidine, fluconazole, ketoconazole]	Oral/topical treatment suitable for health center and community level use	1.Potentially LX408 2.Clarithromycin, dapsone (for others see [24–27])
Echinococcosis [albendazole, mebendazole]	Identification of optimal albendazole treatment courses (indicates that drugs with improved efficacy would add value)	1.Oxfendazole, oxantel pamoate 2.None
Foodborne trematodiasis [praziquantel, triclabendazole]	–	1.Oxantel pamoate 2.Tribendimidine, albendazole, mebendazole [28], nitazoxanide
Taeniasis and cysticercosis [albendazole, praziquantel, niclosamide]	Efficacy of current treatment strategies	1.Oxfendazole 2.None
Scabies [ivermectin, topical permethrin, benzyl benzoate, malathion, sulphur]	Determine efficacy of single dose IVM for programmatic use and safe dose in children < 15 kg, < 90 cm or < 5 years Identify alternative strategies for ivermectin MDA including for Ioliasis co-endemic areas Evaluate moxidectin	1.Moxidectin 2.None

for patients who are suspected to have failed azithromycin treatment and those who cannot be treated with azithromycin [1, 2].

No drugs not already part of current strategies have been evaluated for efficacy against yaws in the past 10 years, and no trials are ongoing or planned as of the records in the ICTRP on 8 February 2023.

Guinea worm

The current strategy for guinea worm eradication is based on safe drinking water, sanitation and hygiene (WASH) [1, 2].

No drugs have been clinically evaluated for guinea worm in the past 10 years and no trials are planned as per the records in the ICTRP on 8 February 2023.

NTDs targeted for elimination (interruption of transmission)

In the Roadmap, WHO defines 'Elimination (interruption of transmission)' as 'Reduction to zero of the incidence of infection caused by a specific pathogen in a defined geographical area, with minimal risk of reintroduction, as a result of deliberate efforts; continued action to prevent re-establishment of transmission may be required.' Documentation of elimination of transmission is termed verification [1].

Leprosy

Drugs currently recommended for case management include rifampicin, dapson, clofazimine, clarithromycin, minocycline or a quinolone (ofloxacin, levofloxacin or moxifloxacin). Rifampicin is recommended for chemoprophylaxis [1, 2].

A recent systematic review identified no regimens better than the WHO recommended regimens. With the exception of regimens including sparfloxacin or acedapson, all regimens evaluated were based on drugs already recommended by WHO [21]. Our ICTRP search on 8 February 2023 did not identify studies with other drugs for potential off-label use.

Human African trypanosomiasis due to *Trypanosoma brucei gambiense*

The drugs currently recommended for case management include fexinidazole, eflornithine-nifurtimox combination and pentamidine [1, 2].

No trials with other drugs or not conducted in view of regulatory registration [2] have been conducted in the past 10 years, are currently ongoing or planned as per the records in the ICTRP on 8 February 2023.

Onchocerciasis

The current strategy for elimination of transmission of *Onchocerca volvulus* is based on PC with ivermectin [1, 2].

Ivermectin-albendazole and ivermectin-diethylcarbamazine-albendazole combination

Addition of albendazole to bi-annual or annual single-dose ivermectin treatment did not significantly affect the proportion of adult female worms with normal embryogenesis, dead macrofilariae or of individuals with detectable skin microfilariae levels (ISRCTN50035143, Clinicaltrials.gov identifier NCT03238131) [29].

The superiority of ivermectin-diethylcarbamazine-albendazole over diethylcarbamazine-albendazole for LF resulted in a conditional WHO recommendation for use of this combination for LF elimination in specified situations and where neither onchocerciasis nor loiasis is endemic [4]. A pilot-study evaluating ivermectin-diethylcarbamazine-albendazole treatment of *O. volvulus*-infected individuals completed collection of the data for the primary outcome (rates of severe adverse events (AEs) and percentage of worms killed/sterilized) in January 2022. Macrofilariae evaluation is ongoing (NCT04188301, Pan African Clinical Trials Registry identifier (PACTRI) PACTR201906665550709) [30]. Eligible individuals were treated 6 months earlier with ivermectin to reduce microfilariae levels and thus the probability of adverse reactions to diethylcarbamazine [31]. The severity of such reactions is a function of pre-treatment microfilaria levels and diethylcarbamazine dose [32–34].

Antibiotics targeting the *O. volvulus* *Wolbachia* symbiont

Research into the role of endosymbiotic *Wolbachia* bacteria in development of filarial parasites (*O. volvulus*, *Wuchereria bancrofti*, *Brugia malayi*, *B. timori*, *Mansonella perstans*) and the effect of antibiotics on their fertility and viability dates back to the 1990s [35]. Clinical proof of concept for the utility of targeting *Wolbachia* for treatment of filarial infections was obtained with doxycycline for *O. volvulus*: *Wolbachia* depletion 6 months after 4 or 6 weeks of treatment with 200 mg or 100 mg doxycycline/day was a predictor of female *O. volvulus* worm death or sterility [36–41].

The long doxycycline treatment duration required is a challenge for large-scale use outside clinical or pilot implementation studies. Furthermore, neither onchocerciasis nor LF meets current doxycycline labelling criteria for use in children < 9 years, pregnant or breastfeeding women which have been questioned for young children

and pregnant women [42]. These factors continue to drive evaluation of other antibiotics already approved for human use including minocycline [43, 44] and rifapentine-moxifloxacin combination treatment [45] as well as discovery of new antibiotics and preclinical and clinical development of emerging drug candidates. This research has recently been reviewed [2, 22].

Rifampicin and rifapentine are rifamycins and ansamycins developed in the 1960s. They are active against gram-positive and, to a lesser extent, gram-negative bacteria and are an important element of multi-drug tuberculosis treatment. Rifamycins block the early stages of DNA-dependent RNA synthesis [46].

Rifapentine-moxifloxacin combination: Based on animal model results [47], an open label, proof-of-concept phase 2 trial evaluated the *Wolbachia* depleting effect of 7 or 14 days of moxifloxacin 400 mg/day + rifapentine 900 mg/day in Ghana (ISRCTN43697583).

Rifampicin: In a proof-of-concept study, 10 mg/kg/day rifampicin for 2 ($n=12$) or 4 ($n=16$) weeks resulted in 0% (0/23) and 18% (2/11) live macrofilariae without *Wolbachia* 18 months after treatment compared to 1% (1/88) in the concurrent untreated control and 82% (9/11) in a historical 6-week 100 mg/day doxycycline control [48]. Considering the dose-response relationship in animal models [49] and the tolerability of rifampicin up to 35 mg/kg [50], two trials evaluating the efficacy of rifampicin in combination with albendazole for both onchocerciasis and lymphatic filariasis were initiated (Table 1).

Drugs for safe reduction of *Loa loa* microfilaraemia in onchocerciasis and LF co-endemic areas

Ivermectin mass drug administration is currently the main strategy for control and elimination of onchocerciasis and ivermectin is also a component of the strategy for control and elimination of LF. Since ivermectin can result in severe and potentially deadly adverse reactions in individuals with high *Loa loa* microfilaraemia [51], loiasis co-endemicity is a significant obstacle to elimination of *O. volvulus* transmission and elimination of LF as a public health problem in loiasis co-endemic areas in Africa [52]. Alternative strategies are required in *L. loa* co-endemic areas [53, 54]. These could include treatments which target *Wolbachia* (*L. loa* does not harbour *Wolbachia* symbionts [55]) as well as treatment with drugs which reduce *L. loa* microfilaraemia safely before ivermectin treatment.

Imatinib is a protein-tyrosine kinase inhibitor registered in the US since 2001 for treatment of leukaemia [56]. Non-clinical studies identified imatinib as a micro- and macrofilaricidal candidate drug [57, 58]. A case report suggested safe *L. loa* microfilaraemia reduction [59]. A pilot study comparing the effect of a single dose

of 200 mg, 400 mg, 600 mg or placebo on *L. loa* microfilaraemia was terminated based on a planned interim analysis demonstrating futility of the intervention (NCT02644525). Protein kinase inhibitors are in non-clinical evaluation for *Fasciola hepatica* [60] and schistosomiasis [61].

Levamisole is an imidazothiazole and a nicotinic acetylcholine receptor (nAChR) receptor agonist [62] with a mechanism of action not fully understood and a long history of use for intestinal helminth control [63, 64]. It is on the WHO Essential Medicines List (EML) for ascariasis. The safe but only transient *L. loa* microfilaraemia reduction after a single 2.5 mg/kg levamisole dose should motivate studies of higher doses and longer treatment [65]. Table 1 shows studies completed but not yet published.

NTDs targeted for elimination as a public health problem

In the Roadmap WHO defines 'Elimination as a public health problem' as 'Reduction to zero of the incidence of infection caused by a specific pathogen in a defined geographical area, with minimal risk of reintroduction, as a result of deliberate efforts; continued action to prevent re-establishment of transmission may be required'. Documentation of elimination as a public health problem is termed validation [1].

Rabies

Anti-infectives are not part of the current strategy [1, 2]. No anti-infectives have been trialed or studies registered in the past 10 years.

Trachoma

The current core strategic intervention is PC with azithromycin [1, 2]. No other drugs have been clinically evaluated in the past 10 years, and no trials are currently ongoing or planned as per the records in the ICTRP on 8 February 2023.

Chagas disease

The drugs currently recommended for case management are benznidazole and nifurtimox [1, 2].

The history and current pipeline for Chagas disease treatment have been recently reviewed [66–68]. The current pipeline for off-label use includes azoles (itraconazole, fluconazole, ketoconazole, posaconazole and ravuconazole) and allopurinol, primarily as combination treatment with nifurtimox or benznidazole. A detailed description of these and other compounds that have been or are being evaluated and the rationale for their evaluation for Chagas disease has been provided recently [66].

Disulfiram (tetraethylthiuram disulphide) is a carbamoyl derivative, approved for alcohol aversion therapy: it inhibits acetaldehyde dehydrogenase resulting in accumulation of the ethanol metabolite acetaldehyde, which causes a range of unpleasant symptoms (Disulfiram | C10H20N2S4—PubChem (nih.gov), accessed 12 March 2022). Disulfiram inhibits 20S proteasome activity [69] and is a candidate for repurposing as a cancer drug [70], antibiotic [71, 72] and anti-leishmanial drug [73]. Its anti-trypanosomal activity was reported in 1996 [74]. The ongoing study in Brazil is evaluating its safety and anti-trypanosomal efficacy in combination with benznidazole in chronic Chagas disease (Table 1).

Human African trypanosomiasis caused by *Trypanosoma brucei rhodesiense*

The drugs currently recommended for case management are suramin for first-stage and melarsoprol for second-stage *Trypanosoma brucei rhodesiense* human African trypanosomiasis (HAT) [1, 2].

No trials with other drugs or not conducted in view of regulatory registration [2] have been conducted in the past 10 years, are currently ongoing or planned as per the records in the ICTRP on 8 February 2023.

Visceral leishmaniasis

Drugs recommended for management of cases of visceral leishmaniasis include pentavalent antimonials, liposomal amphotericin B, paromomycin and miltefosine [1, 2].

No studies evaluating the efficacy and safety of drugs not already included in current strategies and not conducted in view of regulatory registration [2] for the treatment of visceral leishmaniasis have been published or conducted over the past 10 years, are currently being conducted or planned as per the records in the ICTRP on 8 February 2023.

Lymphatic filariasis

The current strategy for control of LF as a public health problem is PC with albendazole alone or in combination with ivermectin and/or diethylcarbamazine depending on co-endemicity of onchocerciasis and/or loiasis and PC history [1, 2].

Wuchereria bancrofti, *B. malayi* and *B. timori* harbour Wolbachia. The status of research into antibiotics to treat filarial diseases has been recently reviewed [22]. Two studies evaluating antibiotics are currently ongoing or in preparation (Table 1).

Schistosomiasis

Both strategies recommended by WHO to eliminate schistosomiasis as a public health problem (PC and 'test

and treat approaches', depending on endemicity and PC history) use praziquantel [1, 2].

Artemisinin (artemisinin derivatives)

Research into the effect of artemisinins on schistosomes was initiated in China in the 1980s and identified activity against juvenile stages of *Schistosoma japonicum* [75–78].

Evaluation of the effect of treatment of malaria patients on co-infection with schistosomiasis suggested that treatment with artemisinin-based combination therapy for malaria provides benefits for infection with *Schistosoma mansoni* [79] and *S. haematobium* [80]. Systematic reviews and meta-analyses concluded that the combination of artemisinins with praziquantel, but not artemisinins alone, can lead to higher cure rates (CR) than praziquantel alone but that studies with less risk of bias are needed for definitive conclusions [81–84]. A higher effect of artemisinins and praziquantel combination treatment may be due to the fact that artemisinins have activity against juvenile stages while praziquantel affects adult worms with little activity against the juvenile stages [76, 85–87].

Randomized studies conducted since these reviews include a single-blinded (participant and laboratory staff) exploratory study in Côte d'Ivoire (ISRCTN 63657086) [87] and an open-label non-inferiority study in Tanzania (PACTR201612001914353) [87]. In Côte d'Ivoire, 12–17-year-old adolescents infected with *S. haematobium* or *S. mansoni* were randomized to three daily doses of Synriam (150 mg arterolane plus 750 mg piperaquine), a single dose of praziquantel 40 mg/kg plus three daily doses of Synriam or a single dose of 40 mg/kg praziquantel (or to a single dose of moxidectin). The number of children included in the analysis ranged from 26 to 30. CRs (95% confidence interval) 3 weeks after the last dose of the combination vs. praziquantel treatment for *S. haematobium* were 60.0% (40–80%) vs. 38.5% (20–60%) and for *S. mansoni* 27.0% (10–50%) vs. 27.6% (10–50%). Egg reduction rates (ERR), considered a more suitable indicator for drugs for PC for schistosomiasis and STH [88], calculated based on the geometric mean egg counts, were 96% (80–100%) vs. 93.5% (80–100%) for *S. haematobium* and 77.6% (50–110%) vs. 87.5% (80–100%) for *S. mansoni* after combination vs. praziquantel treatment. Treatment with Synriam alone or with moxidectin was not efficacious. Further studies are needed before definitive conclusions can be drawn, including follow-up on the CR in the praziquantel monotreatment arms [87]. In Tanzania, *S. mansoni*-infected 7–17-year-old children were randomized to a single dose of 40 mg/kg praziquantel plus 4 mg/kg dihydroartemisinin per day and 18 mg/kg piperaquine per day for 3 days (as per WHO guidelines for

treatment of uncomplicated malaria [89]) or a single dose of 40 mg/kg praziquantel (PACTR201612001914353). CRs (95% confidence interval) in the combination ($n=298$) vs. praziquantel treatment group ($n=341$) were 88.3% (84.1–91.4%) vs. 81.2% (76.7–85.0%), respectively, 3 weeks after treatment and 81.9% (77.1–85.8%) vs. 63.9% (58.7–68.8%), respectively, 8 weeks after treatment. ERRs, calculated based on arithmetic mean egg counts, also showed a smaller treatment difference between the combination vs. praziquantel treatment groups 3 weeks after treatment [95.3% (92.9–97.7%) vs. 95.0% (92.7–97.3%)] than 8 weeks after treatment [93.6% (90.8–96.4%) vs. 87.9% (84.4–91.4%)] [90].

The effect of treatment of *S. haematobium* co-infected 7–18-year-old patients for uncomplicated malaria on egg excretion and cure rates was evaluated in Gabon (NCT04264130). Median (interquartile range) egg excretion rates 4 and 6 weeks after treatment, respectively, were 100% (17–100%) and 65% (– 133–100%) after artesunate-pyriminidone treatment ($n=21$) and 35% (– 250–70%) and 65% (– 65–79%) after artemether-lumefantrine treatment ($n=18$). Cure was only observed after artesunate-pyriminidone treatment (56% and 37% at 4 and 6 weeks after treatment, respectively). [91].

A trial evaluating the effect of artesunate-mefloquine combination on schistosomiasis [92] has completed recruitment in Senegal (NCT03893097) but results have not yet been published.

Any decisions to include artemisinins or other anti-malarial drugs in strategies for elimination of schistosomiasis as a public health problem will have to consider the risk to malaria programmes.

Soil-transmitted helminthiasis (STH) including strongyloidiasis

The WHO recommended strategy to eliminate STH and strongyloidiasis as a public health problem is based on PC with albendazole or mebendazole targeting children from 12 months through school age, non-pregnant adolescent girls and women of reproductive age, pregnant women in second and third trimester and lactating women [1, 2]. Table 1 shows the currently ongoing study.

Ivermectin and ivermectin combinations

WHO is preparing new guidelines for PC for STH and strongyloidiasis. Systematic review of all available evidence, a standard element of guideline preparation [93], is currently expected to result in addition of ivermectin to PC with albendazole or mebendazole in areas where prevalence of *Strongyloides stercoralis* exceeds 10% and in areas with high prevalence of *Trichuris trichiura* infection [1]. The results of the systematic review will be appended to the guideline.

Strongyloidiasis is one of the two indications for which oral ivermectin has regulatory approval (single dose of 200 µg/kg), but only for children weighing at least 15 kg. This is also the lower weight limit for the other US FDA-approved indication, onchocerciasis (single dose of 150 µg/kg) [94]. Minimum weight and height for which ivermectin is approved for onchocerciasis and LF by the French Agence nationale de sécurité du médicament et des produits de santé are 15 kg and 90 cm [9].

This weight or height limit drives exclusion of smaller children from PC including ivermectin as well as from ivermectin treatment in most trials evaluating ivermectin for its efficacy against STH and strongyloidiasis (and e.g. scabies) either completely (e.g. ongoing studies NCT03605758, TCTR20190111001) or inclusion with treatments other than ivermectin (e.g. albendazole for STH and strongyloidiasis [95], permethrin for scabies [96]). Given the burden of disease, an important consideration during WHO guideline development will be the lower age limit (based on age, height, or weight) of eligibility for ivermectin treatment and the relevant dose. Identification of a safe and efficacious dose for smaller children is also important for use of ivermectin for other infections, notably scabies [97], and may impact eligibility criteria for trials of new drugs in which ivermectin is a comparator.

Reviews to date of safety data for children < 5 years or weighing < 15 kg treated with ivermectin for a variety of infections with doses around 200 µg/kg identified no safety concerns [98, 99]. A dose-finding PK, safety and efficacy study (ISRCTN15871729) in Côte d'Ivoire in *T. trichiura*-infected children 2–5 years ($n=80$, 100 or 200 µg/kg) and 6–12 years ($n=120$, 200, 400 or 600 µg/kg) old and adults ($n=11$, 200 µg/kg) showed lower dose-dependent dose-adjusted exposures in children than adults. AE data collected to 72 h and indicators of hepatic and renal function 72 h after treatment identified no safety concerns [100, 101]. A randomized controlled trial in Honduras investigated the PK, efficacy and safety of high-dose ivermectin in *T. trichiuria*-infected children 2–14 years old weighing at least 15 kg. Fifty-six and 58 children, respectively, received 600 µg/kg ivermectin with 400 mg albendazole once or for 3 days. No safety concerns and no differences in IVM blood concentrations between children with and without AEs were identified [102]. Two population PK modelling studies of ivermectin concentration data obtained in *T. trichiura* [101] and scabies-infected children [103] proposed a 3 mg dose of ivermectin for children 75–90 cm [104] or children 2–4 years old weighing 10–15 kg [103]. The currently available formulation is a 3 mg tablet. Two studies

evaluating ivermectin PK and safety in smaller children with scabies infection are planned (NCT04332068, NCT05500326). A trial evaluating the pharmacokinetics and pharmacodynamics of three daily doses of ivermectin in paediatric dengue patients (400 µg/kg/day or 600 µg/kg/day, minimum participant weight 15 kg) has been completed (NCT03432442) but has not yet been published (Table 1).

In the ivermectin paediatric dose-finding PK, safety and efficacy study (ISRCTN15871729), *T. trichiura* CR and ERR 14–21 days after treatment were not different after up to 400 µg/kg ivermectin compared with after placebo and were low or moderate even after 600 µg/kg. CR and ERR for co-incident *Ascaris lumbricoides* (between 8 and 14 participants) were around 90–100% and 100%, respectively [101].

Better results were obtained when ivermectin was added to albendazole treatment. In a double-blind randomized trial in Côte d'Ivoire, Laos and Pemba Island, Tanzania, 6–60-year-old individuals with at least 100 *T. trichiura* eggs/g stool were treated with a single dose of 200 µg/kg ivermectin plus 400 mg albendazole or 400 mg albendazole. CRs after ivermectin + albendazole were significantly higher than after albendazole alone in Laos (66% vs. 8%) and on Pemba Island (49% vs. 6%) but similar in Côte d'Ivoire (14% vs. 10%). The same was true for the effect of the combination vs. monotherapy on geometric mean-based ERRs, which were 99% vs. 69% in Laos, 98% vs. 57% in Pemba Island and 70% vs. 64% in Côte d'Ivoire. The reason for the difference in efficacy observed in Laos and on Pemba Island vs. Côte d'Ivoire remains to be investigated. No safety concerns were identified [105]. In the study in Honduras, the efficacy data obtained from 117 children showed *T. trichiura* CR of 88.6% and 100% and ERR of 96.7% and 100%, respectively, 14–21 days after treatment with 600 µg/kg ivermectin plus 400 mg albendazole once or for 3 consecutive days compared to CR of 4.2% and 33.3% and ERR of 47.7% and 72.1% after a single or three daily doses of 400 mg albendazole, respectively. The AE profile in all four treatment arms indicated acceptable tolerability [102].

Tribendimidine

Tribendimidine is a symmetrical diamidine and, like levamisole, oxantel and pyrantel pamoate, a nAChR agonist [106]. The mechanism of action may depend on the nematode, trematode or cestode species [107, 108].

Tribendimidine is a broad-spectrum anthelmintic and was registered for STH treatment in China in 2004 [107, 109, 110]. This motivated work towards registration elsewhere, including in the USA [111], spearheaded by

the collaboration between the Swiss Tropical and Public Health Institute and the Chinese Center for Diseases Control and Prevention. Non-clinical pharmacology and clinical studies against a wide range of helminths were reviewed in 2013 [107]. Additional file 1: Table S2 provides the CRs and ERRs for *T. trichuris*, hookworm and *A. lumbricoides* reported for tribendimidine mono- and combination treatment since 2013 together with the results for other treatment arms included in the studies [111–114]. Tribendimidine should be further evaluated as a useful addition to the limited number of drugs available for PC, in particular for *S. stercoralis* [115] and in combination treatment against hookworm [116, 117]. None of the studies identified AEs precluding further evaluation.

Pyrantel pamoate and pyrantel pamoate combinations

Pyrantel is a tetrahydropyrimidine, introduced to the small animal market for the control of hookworm and roundworm in the 1970s [118]. Like oxantel, tribendimidine and levamisole, pyrantel is a nAChR agonist. Pyrantel and levamisole activate the L-subtype [62]. Pyrantel pamoate (also known as embonate, see [2]) is on the 2021 WHO EML for ascariasis, trichuriasis, enterobiasis and hookworm and on the EML for children for intestinal helminths [119].

The few placebo- or active-controlled studies available suggest that the efficacy of a single 10 mg/kg dose pyrantel pamoate dose is comparable to that of single albendazole or mebendazole doses for *A. lumbricoides* but unsatisfactory for hookworm and very low for *T. trichiura* [111, 120], consistent with veterinary experience [118]. Combination with albendazole did not increase CR or ERR [121]. Combination of pyrantel pamoate with albendazole and oxantel pamoate resulted in CR and ERR for *A. lumbricoides*, *T. trichiura* and hookworm superior to those of albendazole-oxantel, pyrantel-oxantel and mebendazole-pyrantel-oxantel combinations [122].

Nitazoxanide

Nitazoxanide is a nitrothiazole benzamide first described in 1975 and available in some Latin American countries since 1996 [123]. Nitazoxanide was approved by the US FDA in 2002 for use in children 1–11 years old with diarrhoea due to *Cryptosporidium parvum* and *Giardia lamblia* [124, 125]. Nitazoxanide is a pro-drug with high oral bioavailability that is metabolized to the active drug tizoxanide, which is active against a broad spectrum of intestinal protozoa, helminths and anaerobic bacteria. Studies in *Caenorhabditis elegans* showed that nitazoxanide affects a subunit of the glutamate-gated chloride

channels through which ivermectin acts, that other mechanisms are likely involved and that nitazoxanide acts synergistically with albendazole and pyrantel Somvanshi et al. [126]. Thiazolides, including nitazoxanide, have activity against many DNA and RNA viruses [127–129]. Nitazoxanide has been evaluated in vitro against mycobacteria [130–132] and is being investigated as a cancer drug (as are other antiparasitic drugs [133]).

Pharmacology and early studies of efficacy in approved indications (cryptosporidiosis, giardiasis) and off-label uses (including *A. lumbricoides*, *T. trichiura*, *S. stercoralis*, *F. hepatica*, *Taenia saginata*, *Enterobius vermicularis*, *Hymenolepis nana*, *Ancylostoma duodenale*) have been reviewed [123, 134]. In a double-blind, randomized trial (ISRCTN83836427) in 533 Tanzanian children, 1000 mg nitazoxanide alone or in combination with 400 mg albendazole did not increase *T. trichiura* or hookworm CR and ERR beyond that achieved with 400 mg albendazole alone. Children receiving nitazoxanide had significantly more adverse events than children receiving placebo, but most adverse events were transient and mild [135].

NTDs targeted for control

WHO defines 'Control' as 'Reduction of disease incidence, prevalence, morbidity and/or mortality to a locally acceptable level as a result of deliberate efforts; continued interventions are required to maintain the reduction. Control may or may not be related to global targets set by WHO [1].

Dengue and chikungunya

In the absence of antiviral drugs, WHO recommends symptomatic treatment for case management and vaccination for people with previous laboratory-confirmed dengue infection [1, 2].

A review of drugs in clinical development for dengue, identified through search of the clinical trials in the ICTRP as of 2015 (including the anti-parasitic drugs chloroquine and ivermectin, anti-inflammatory agents corticosteroids and statins, anti-viral drugs balapiravir and ribavirin, iminosugars celgosivir and UV-4B, and traditional medicines *Cissampelos pareira* extracts and *Carica papaya* extracts) concluded that promising treatments are yet to be identified and that significant investment is required to identify safe, effective and inexpensive drugs [23]. An update on anti-dengue drug discovery has been provided recently [136].

The vast majority of clinical trials do not evaluate anti-infective drugs registered for human use for an indication other than the NTD for which they are trialed and thus do not meet our inclusion criteria. Given the extent of research with traditional medicines which does not meet

our inclusion criteria (*Cocculus hirsutus* extracts [137, 138], *C. papaya* extracts [139–141], Ganghuo Kanggan decoction (GHKGD) [142], *Eupatorium perfoliatum* [143, 144]) we provided short summaries in Additional file 1.

Ivermectin has been shown to inhibit the replication of all four DENV serotypes in vitro [145]. The rationale for its evaluation for dengue has been provided previously [23]. A randomized, placebo-controlled trial of three daily dose of 400 µg/kg of ivermectin in adult dengue patients showed that the incidence of adverse events was comparable in the placebo and ivermectin treatment group. There was no difference in viraemia clearance time but ivermectin accelerated plasma nonstructural protein1 clearance [146]. A trial evaluating the pharmacokinetics and pharmacodynamics of three daily doses of ivermectin in paediatric dengue patients (400 µg/kg/day or 600 µg/kg/day, minimum participant weight 15 kg) has been completed (NCT03432442) but has not yet been published.

Doxycycline antiviral activity has been shown against flaviviruses [147]. Evaluation of the efficacy of doxycycline treatment for dengue is planned (Table 1, CTRI/2021/09/036661).

Buruli ulcer

The current core strategic intervention is case management with rifampicin and clarithromycin or moxifloxacin [1, 2].

A randomized controlled trial in Ghana in 297 participants at least 5 years of age with PCR-confirmed *Mycobacterium ulcerans* infection and lesions of < 10 cm diameter did not identify a significant difference in the percentage of participants with healed lesions between 8 weeks of daily treatment with extended-release clarithromycin (15 mg/kg oral) and rifampicin (10 mg/kg oral) and 8 weeks of daily streptomycin (intramuscular 15 mg/kg) and rifampicin (10 mg/kg oral) treatment [148]. Two studies evaluating the effect of adding amoxicillin/clavulanate to the standard regimen are ongoing or planned (Table 1).

Actinomycetoma and eumycetoma

The current case management strategy for actinomycetoma is long-term treatment with antibiotic combinations and wound cleaning/dressing. The types of antibiotics are not specified in the Roadmap. For eumycetoma, case management with antifungals (mainly itraconazole) and surgery combined with wound cleaning/dressing is recommended [1, 2].

Early detection and treatment are critical, but rare given that mycetoma affects primarily poor communities in remote areas in the LMICs of the 'mycetoma belt' (latitudes of 15° South and 30° North) [149, 150]. Available treatment options are ineffective and have an unfavourable safety profile and required treatment duration is unsuitable for the health system context [151]. Approaches to mycetoma management have been reviewed recently and the need for improved tools emphasized [151–156].

No clinical trials to assess the safety and efficacy of drugs in actinomycetoma have been registered in the past 10 years as per records in the ICTRP as of 8 February 2023.

Beyond the proof-of-concept study comparing fosravuconazole vs. itraconazole for eumycetoma in Sudan (NCT03086226) [2, 151], no other drug trials have been registered in the past 10 years.

The challenges clinical trials for mycetoma face have been outlined recently [157].

Chromoblastomycosis and other deep mycoses

For management of chromoblastomycosis and other deep mycoses, the Roadmap specifies that there is no gold standard and lists a number of treatment options, including physical therapies, immune adjuvants, and surgery of minor lesions and treatment with the antifungal drug itraconazole [1, 2]. Itraconazole is included in the WHO EML and the WHO EML for children for chromoblastomycosis and paracoccidioidomycosis [119].

In the last 10 years the drugs fluconazole and isavuconazonium sulphate have been evaluated in clinical trials against deep mycosis.

Fluconazole is a synthetic triazole antifungal agent registered in the US for vaginal, oropharyngeal and oesophageal candidiasis and for cryptococcal meningitis [158]. The Committee for Medicinal Products for Human Use of the European Medicines agency recommended use in the European Union for mucosal and invasive candidiasis, genital candidiasis (trush), cryptococcal meningitis, dermatomycosis, coccidioidomycosis and onychomycosis [159]. Fluconazole is a highly selective inhibitor of the fungal cytochrome P450-dependent enzyme lanosterol 14- α -demethylase, which converts lanosterol to ergosterol. The subsequent loss of normal sterols results in accumulation of 14- α -methyl sterols in fungi and may be responsible for the fungistatic activity of fluconazole. Mammalian cell demethylation is much less sensitive to fluconazole inhibition [158]. Given that fluconazole is only fungistatic, efforts are underway to identify whether it can be combined with other agents to achieve a fungicidal effect [160, 161]. In 2014, a Pfizer-sponsored observational prospective case-only

study ($N=27$) (NCT01680458) evaluated the safety and efficacy of fluconazole in the treatment ($n=2$) and prophylaxis ($n=25$) of deep mycoses in children < 4 weeks to 7 years. The results have been posted on the clinicaltrials.gov website record, but we were unable to identify a peer-reviewed publication as of December 2022.

Isavuconazonium is a prodrug of the active drug isavuconazole, a triazole with a broad spectrum of activity against yeasts, moulds and dimorphic fungi [162]. It has been registered since 2015 in the US and Europe for treatment of invasive aspergillosis and invasive mucormycosis in adults. Like fluconazole, isavuconazole inhibits the cytochrome P450-dependent lanosterol 14- α -demethylase and thus the synthesis of ergosterol, a critical component of the fungal cell membrane [162–164]. Isavuconazole has also been evaluated for other invasive fungal infections including cryptococcosis, paracoccidiosis and chronic pulmonary aspergillosis [165, 166].

Given that these studies were sponsored by pharmaceutical companies, it is possible that ultimately regulatory registration for additional indications will be sought.

Cutaneous leishmaniasis

The cutaneous leishmaniasis (CL) case management strategy depends on factors including the disease, concomitant pathologies, parasite species, location and national guidelines. Topical/intralesional treatment approaches include pentavalent antimonials, paromomycin/methylbenzethonium chloride, cryotherapy and thermotherapy. Drugs for systemic treatment include fluconazole, ketoconazole, liposomal amphotericin B, amphotericin B deoxycholate, pentamidine, pentavalent antimonials (with or without allopurinol), paromomycin and miltefosine [1, 2].

Most studies evaluating new treatment options identified in the ICTRP are outside the scope of our manuscript since they evaluate the effect of intralesional and topical treatments. Treatment for CL overall and CL in the Americas has been reviewed recently including experimental treatments [24–27]. Oral treatments with recent publications not covered in these reviews are included here.

Around 1990, oral dapsone (2 mg/kg for 6 weeks) was shown to have efficacy in the treatment of CL in India [167–169]. Oral dapsone is used in Indian hospitals (see e.g. [170]). Evaluation of a case series ($N=11$) in Colombia resulted in the conclusion that dapsone efficacy was not satisfactory against *Leishmania (V) panamensis* [171]. A study comparing the effect of intralesional injection of glucantime without and with oral dapsone in Iran has been completed, but we were unable to identify a

publication (IRCT20140211016554N4). In Pakistan, a randomized trial compared intramuscular meglumine antimoniate (15 mg/kg/day, total \leq 15 ml) to healing or for 40 days and oral dapsons (2.5 mg /kg/body weight/day, \leq 200 mg/day) to healing or for 80 days in patients with biopsy-confirmed CL. Post-treatment blinded efficacy evaluation showed 51–75% reduction and 76–100% reduction in lesion size in 21/50 and 21/50 patients, respectively, after meglumine antimoniate and in 7/50 and 33/50 patients, respectively, after oral dapsons treatment [172].

Clarithromycin is a semi-synthetic macrolide with in vitro activity shown against *Leishmania major* [173]. In a pilot study in Iran, previously untreated patients were randomly assigned to clarithromycin ($N=10$, 500 mg twice a day for 2 months, mean \pm standard deviation of lesion number 5 ± 4.3 and induration size 15.47 ± 15.6 mm) or three injections of glucantime ($N=10$, 20 mg/kg/day for 20 days; $N=10$, lesion number 3 ± 2.8 , induration size 19.81 ± 13 mm). Three, 6 and 12 months after treatment, lesions had disappeared in all patients in the clarithromycin group and the mean number of lesions in the glucantime group was 0.17 ± 0.04 with a mean induration size of 1.59 ± 6.8 mm [174].

Given the number of studies in the ICTRP evaluating traditional medicines, information on plant extracts with anti-leishmanial activity or activity against other infectious agents demonstrated in in vitro or in vivo studies is included in Additional file 1.

Echinococcosis

Albendazole and mebendazole are the drugs currently recommended for case management of echinococcosis [1, 2].

No studies of other drugs have been published or conducted over the past 10 years, are ongoing or planned as per the records in the ICTRP on 8 February 2023.

Foodborne trematodiasis

The current strategies for PC and case management are based on praziquantel and triclabendazole [1, 2].

Clonorchiasis and opisthorchiasis (small liver flukes)

Comparative trials evaluating the effect of tribendimidine, albendazole, mebendazole and praziquantel alone or in combination on *Clonorchis sinensis*, *Opisthorchis viverrini* and *O. felinus* have recently been reviewed. The review found that praziquantel is highly efficacious, recommended further evaluation of tribendimidine as a potential alternative treatment option and concluded that too few high quality studies are available to support

definitive conclusions about the benefit of 5–7 days of treatment with albendazole [28].

Fascioliasis

Nitazoxanide at a dose of 500 mg orally every 12 h for 7 days was partially effective in 30% of patients with clinical manifestations of acute fascioliasis who had failed triclabendazole treatment suggesting that further clinical evaluation of nitazoxanide for fascioliasis should be conducted [175].

Paragonimiasis

No trials focussed on paragonimiasis were identified.

Taeniasis and cysticercosis

The current strategies for PC and case management are based on praziquantel, niclosamide and albendazole [1, 2]. No studies of other drugs have been published or conducted over the past 10 years, are ongoing or planned as per the records in the ICTRP on 8 February 2023.

Scabies

Core elements of current strategies for control of scabies include PC and case management with ivermectin and with topical scabicides for children too small to be eligible for ivermectin [1, 2]. Identification of an efficacious and safe dose of ivermectin for small children is a priority, as are evaluation of moxidectin and identification of an alternative treatment strategy for loiasis co-endemic areas [1, 2]. The current status of research for a safe ivermectin dose for children has been provided in the context of clinical studies drugs against STH and strongyloidiasis.

Conclusions

Considering both the small anti-infective drugs in at least Phase 2 clinical development for regulatory approval [2] and the small anti-infective drugs/drug combinations being evaluated for repurposing, the pipeline for drugs and drug combinations for NTDs is, unsurprisingly but still disappointingly, small (Table 2).

Given the factors that impact the feasibility of advances in discovery of new drugs, their pre-clinical characterization to qualify them for clinical development and funding and other challenges clinical trials for NTDs face, whether with new molecular entities or drugs that could be repurposed, not only increased advocacy for research into new treatment options but also additional paths to new treatment options are needed.

One promising path is 'CURE ID', initiated by the US FDA in collaboration with the US National Institutes of

Health's National Center for Advancing Translational Sciences. WHO joined the collaboration [176] as did the Infectious Diseases Society of America, the Critical Path Institute and the Drugs for Neglected Diseases initiative. CURE-ID is a web-based platform, accessible on the computer or via a mobile app, in which healthcare providers can share their experience with repurposing drugs for diseases that lack effective and safe treatments via succinct easy to fill deidentified case report forms. In addition, users can view and participate in discussions and stay up to date through a newsfeed that is updated daily providing information on case reports submitted, discussion posts, clinical trials, the latest infectious disease journal articles and events. The platform is searchable by disease/infectious agent. Analysis of the pooled experience reported may identify treatments that can advance into clinical trials. Additional file 1: Table S4 includes links to further information.

Abbreviations

ADME	Absorption, distribution, metabolism, elimination
APOC	African Programme for Onchocerciasis Research
CR	Cure rate
CTRI	Clinical Trials Registry India
DNDi	Drugs for Neglected Diseases initiative
EDCTP	European & Developing Countries Clinical Trials Partnership
EMA	European Medicines Agency
EML	WHO Essential Medicines list
ERR	Egg reduction rate
HAT	Human African trypanosomiasis
ICTRP	WHO International Clinical Trials Registry Platform
ISRCTN	Clinical study registry managed by Biomed Central, Part of Springer Nature
LMIC	Low- and middle-income countries
LF	Lymphatic filariasis
MDGH	Medicines Development for Global Health
NCT	Prefix of clinical trial numbers in the data base of privately and publicly funded clinical studies conducted around the world by the US National Institute of Health
NDA	New Drug Application
NTD	Neglected Tropical Disease
PACTRI	Pan African Clinical Trials Registry identifier
PC	Preventive chemotherapy
PK	Pharmacokinetics
RBR	Registro Brasileiro de Ensaios Clinicos
R&D	Research and development
SRA	Stringent regulatory authority (for definition see https://extranet.who.int/pqweb/content/glossary)
STH	Soil transmitted helminths/helminthiasis
STPH	Swiss Tropical and Public Health Institute
TDR	UNICEF/UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases
US FDA	United States of America Food and Drug Administration
WASH	Safe drinking water, sanitation and hygiene
WHO	World Health Organization

Supplementary Information

The online version contains supplementary material available at <https://doi.org/10.1186/s13071-023-05909-8>.

Additional file 1: Table S1. Source registries and last data file import into the WHO Clinical Trials Registry Platform as of 8 February 2023. **Table S2.** Cure and egg reduction rates in studies of the efficacy of tribendimidine alone and in combination and in comparator treatment arms against intestinal helminths. Background information on traditional medicines evaluated for Dengue, Background information on traditional medicines evaluated for cutaneous leishmaniasis, **Table S3.** Resources on CURE ID.

Acknowledgements

We thank Rebecca Smith from Medicines Development for Global Health for early drafts of some subsections. The views and opinions presented in this article are solely those of the authors and should not be attributed to the institutions they are affiliated with or the funders. Annette C. Kuesel—Retired.

Author contributions

ACK and KMP conceptualized the manuscript. Each co-author drafted the section for between one and seven diseases or drugs. ACK reviewed and edited all draft sections and wrote the remaining sections. All authors read and approved submission of the manuscript.

Funding

This review is part of the MiniMox project for development of a paediatric moxidectin formulation (<https://minimox.squarespace.com/>). That project is part of the EDCTP2 programme supported by the European Union (RIA2019PD-2880) and co-funded by Medicines Development for Global Health and the Luxembourg National Research Fund Fonds National de la Recherche Luxembourg (FNR n° INTER/EDCTP/19/14338294/MiniMox/Vaillant).

Availability of data and materials

Not applicable.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

KMP and AH are leading research on repurposing antibiotics for control and elimination of diseases caused by parasites harbouring Wolbachia endosymbionts.

Author details

¹Institute of Medical Microbiology, Immunology and Parasitology, University Hospital Bonn, Bonn, Germany. ²German Center for Infection Research (DZIF), Partner Site Bonn-Cologne, Bonn, Germany. ³Department of Pharmaceutical Technology and Biopharmaceutics, University of Bonn, Bonn, Germany. ⁴Strathclyde Institute of Pharmacy and Biomedical Sciences, University of Strathclyde, Glasgow, UK. ⁵Competence Center for Methodology and Statistics, Luxembourg Institute of Health, Strassen, Grand Duchy of Luxembourg. ⁶Department of Epidemiology and Biostatistics School of Public Health, University of Health and Allied Sciences, Hohoe, Ghana. ⁷UNICEF/UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases (WHO/TDR), World Health Organization, Geneva, Switzerland.

Received: 27 March 2023 Accepted: 31 July 2023

Published online: 31 October 2023

References

1. World Health Organization. Ending the neglect to attain the sustainable development goals: a road map for neglected tropical diseases 2021–2030. Geneva: World Health Organization; 2020.

2. Pfarr KM, Krome AK, Al-Obaidi I, Batchelor H, Vaillant M, Hoerauf A, et al. The pipeline for drugs for control and elimination of neglected tropical diseases: 1. Anti-infective drugs for regulatory registration. *Parasites Vectors*. 2023;16:82. <https://doi.org/10.1186/s13071-022-05581-4>.
3. Kuesel AC. Research for new drugs for elimination of onchocerciasis in Africa. *Int J Parasitol Drugs Drug Resist*. 2016;6:272–86. <https://doi.org/10.1016/j.ijpddr.2016.04.002>.
4. World Health Organization. Guideline: alternative mass drug administration regimens to eliminate lymphatic filariasis. Geneva: World Health Organization; 2017.
5. World Health Organization. Provisional strategy for interrupting lymphatic filariasis transmission in loiasis-endemic countries: report of the meeting on lymphatic filariasis, malaria and integrated vector management, Accra, Ghana, 5–9 March 2012. Geneva: World Health Organization; 2012.
6. World Health Organization. Report from Informal consultation on albendazole research findings in lymphatic filariasis: 13–14 October 1998. Geneva: World Health Organization; 1998.
7. Horton J, Witt C, Ottesen EA, Lazdins JK, Addiss DG, Awadzi K, et al. An analysis of the safety of the single dose, two drug regimens used in programmes to eliminate lymphatic filariasis. *Parasitology*. 2000;121:S147–60.
8. Brown KR, Ricci FM, Ottesen EA. Ivermectin: effectiveness in lymphatic filariasis. *Parasitology*. 2000;121:S133–46. <https://doi.org/10.1017/S003118200006570>.
9. Agence nationale de sécurité du médicament et des produits de santé (ansm): Résumé des caractéristiques du produit (Mectizan). 2022. <http://agence-prd.ansm.sante.fr/php/ecodex/frames.php?specid=65817014&typedoc=R&ref=R0388687.htm>. Accessed 16 Feb 2023.
10. World Health Organization Prequalification Programme: Ivermectin WHO Public Assessment Report (NT007). 2021. <https://extranet.who.int/pqweb/medicine/4359>. Accessed 8 Nov 2022.
11. World Health Organization Prequalification Programme: Albendazole WHO Public Assessment Reports (NT005). 2021. <https://extranet.who.int/pqweb/medicine/4338>. Accessed 05 Nov 2022.
12. World Health Organization, WHO Expert Committee on Specifications for Pharmaceutical Preparations: Fifty-first report of the WHO Expert Committee on Specifications for Pharmaceutical Preparations. In: WHO technical report series 1003 2017.
13. World Health Organization: Forty-fifth report of the WHO Expert Committee on specifications for pharmaceutical preparations. 2011. <https://apps.who.int/iris/handle/10665/44079>.
14. World Health Organization: Forty-eighth report of the WHO Expert Committee on specifications for pharmaceutical preparations. 2014. <https://apps.who.int/iris/handle/10665/112733>.
15. World Health Organization Prequalification Programme: Ivermectin WHO Public Assessment Report (NT009(a)). 2020. <https://extranet.who.int/pqweb/medicine/4279>. Accessed 8 Nov 2022.
16. Not applicable. <https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm>.
17. Tambo E, Khater El, Chen JH, Bergquist R, Zhou XN. Nobel prize for the artemisinin and ivermectin discoveries: a great boost towards elimination of the global infectious diseases of poverty. *Infect Dis Poverty*. 2015;4:58. <https://doi.org/10.1186/s40249-015-0091-8>.
18. World Health Assembly: Traditional medicine. 2014.
19. World Health Organization Regional Office for the Western Pacific: Regional framework for harnessing traditional and complementary medicine for achieving health and well-being in the Western Pacific. Manila: WHO Regional Office for the Western Pacific; 2022.
20. Robertson F. HINARI: Opening access in biomedicine and health. *Appl Transl Genom*. 2014;3:384–5. <https://doi.org/10.1016/j.atg.2014.07.003>.
21. Lazo-Porras M, Prutsky GJ, Barrionuevo P, Tapia JC, Ugarte-Gil C, Ponce OJ, et al. World Health Organization (WHO) antibiotic regimen against other regimens for the treatment of leprosy: a systematic review and meta-analysis. *BMC Infect Dis*. 2020;20:62. <https://doi.org/10.1186/s12879-019-4665-0>.
22. Ehrens A, Hoerauf A, Hubner MP. Current perspective of new anti-Wolbachial and direct-acting macrofilaricidal drugs as treatment strategies for human filariasis. *GMS Infect Dis*. 2022. <https://doi.org/10.3205/id000079>.
23. Beesetti H, Khanna N, Swaminathan S. Investigational drugs in early development for treating dengue infection. *Expert Opin Investig Drugs*. 2016;25:1059–69. <https://doi.org/10.1080/13543784.2016.1201063>.
24. Pinart M, Rueda JR, Romero GA, Pinzon-Florez CE, Osorio-Arango K, Silveira Maia-Elkhoury AN, et al. Interventions for American cutaneous and mucocutaneous leishmaniasis. *Cochrane Database Syst Rev*. 2020;8:CD004834. <https://doi.org/10.1002/14651858.CD004834.pub3>.
25. de Vries HJ, Reedijk SH, Schallig HD. Cutaneous leishmaniasis: recent developments in diagnosis and management. *Am J Clin Dermatol*. 2015;16:99–109. <https://doi.org/10.1007/s40257-015-0114-z>.
26. de Vries HJ, Schallig HD. Cutaneous leishmaniasis: a 2022 updated narrative review into diagnosis and management developments. *Am J Clin Dermatol*. 2022;23:823–40. <https://doi.org/10.1007/s40257-022-00726-8>.
27. Azim M, Khan SA, Ullah S, Ullah S, Anjum SI. Therapeutic advances in the topical treatment of cutaneous leishmaniasis: a review. *PLoS Negl Trop Dis*. 2021;15:e0009099. <https://doi.org/10.1371/journal.pntd.0009099>.
28. Qian MB, Patel C, Palmeirim MS, Wang X, Schindler C, Utzinger J, et al. Efficacy of drugs against Clonorchiasis and Opisthorchiasis: a systematic review and network meta-analysis. *Lancet Microbe*. 2022;3:e616–24. [https://doi.org/10.1016/S2666-5247\(22\)00026-X](https://doi.org/10.1016/S2666-5247(22)00026-X).
29. Batsa DL, Klarmann-Schulz U, Osei-Mensah J, Dubben B, Fischer K, Mubarik Y, et al. Comparison of repeated doses of ivermectin versus ivermectin plus albendazole for the treatment of onchocerciasis: a randomized, open-label, clinical trial. *Clin Infect Dis*. 2020;71:933–43.
30. Hong AR, Opoku NO, Weil GJ, Kanza EM, Gyasi ME. New research aims to optimize therapy against onchocerciasis. *Mo Med*. 2022;119:55–9.
31. Opoku NO, Gyasi ME, Doe F, Lew D, Hong AR, Chithenga S, et al. A re-evaluation of the tolerability and effects of single-dose ivermectin treatment on *Onchocerca volvulus* microfilariae in the skin and eyes in eastern Ghana. *Am J Trop Med Hyg*. 2021;106:740–5. <https://doi.org/10.4269/ajtmh.21-0859>.
32. Francis H, Awadzi K, Ottesen EA. The Mazzotti reaction following treatment of onchocerciasis with diethylcarbamazine: clinical severity as a function of infection intensity. *Am J Trop Med Hyg*. 1985;34:529–36.
33. Awadzi K, Gilles HM. Diethylcarbamazine in the treatment of patients with onchocerciasis. *Br J Clin Pharmacol*. 1992;34:281–8.
34. Fischer PU, King CL, Jacobson JA, Weil GJ. Potential value of triple drug therapy with ivermectin, diethylcarbamazine, and albendazole (IDA) to accelerate elimination of lymphatic filariasis and onchocerciasis in Africa. *PLoS Negl Trop Dis*. 2017;11:e0005163. <https://doi.org/10.1371/journal.pntd.0005163>.
35. Bosshardt SC, McCall JW, Coleman SU, Jones KL, Petit TA, Klei TR. Prophylactic activity of tetracycline against *Brugia pahangi* infection in jirds (*Meriones unguiculatus*). *J Parasitol*. 1993;79:775–7.
36. Hoerauf A, Mand S, Adjei O, Fleischer B, Buttner DW. Depletion of Wolbachia endobacteria in *Onchocerca volvulus* by doxycycline and microfilaridermia after ivermectin treatment. *Lancet*. 2001;357:1415–6.
37. Hoerauf A, Mand S, Volkmann L, Buttner M, Marfo-Debrekvei Y, Taylor M, et al. Doxycycline in the treatment of human onchocerciasis: Kinetics of Wolbachia endobacteria reduction and of inhibition of embryogenesis in female *Onchocerca* worms. *Microbes Infect*. 2003;5:261–73.
38. Hoerauf A, Marfo-Debrekvei Y, Buttner M, Debrah AY, Konadu P, Mand S, et al. Effects of 6-week azithromycin treatment on the Wolbachia endobacteria of *Onchocerca volvulus*. *Parasitol Res*. 2008;103:279–86.
39. Hoerauf A, Specht S, Buttner M, Pfarr K, Mand S, Fimmers R, et al. Wolbachia endobacteria depletion by doxycycline as antifilarial therapy has macrofilaricidal activity in onchocerciasis: a randomized placebo-controlled study. *Med Microbiol Immunol*. 2008;197:295–311.
40. Specht S, Hoerauf A, Adjei O, Debrah A, Buttner DW. Newly acquired *Onchocerca volvulus* filariae after doxycycline treatment. *Parasitol Res*. 2009;106:23–31. <https://doi.org/10.1007/s00436-009-1624-5>.
41. Hoerauf A, Volkmann L, Hamelmann C, Adjei O, Autenrieth IB, Fleischer B, et al. Endosymbiotic bacteria in worms as targets for a novel chemotherapy in filariasis. *Lancet*. 2000;355:1242–3.
42. Cross R, Ling C, Day NP, McGready R, Paris DH. Revisiting doxycycline in pregnancy and early childhood—time to rebuild its reputation? *Expert Opin Drug Saf*. 2016;15:367–82. <https://doi.org/10.1517/14740338.2016.1133584>.

43. Klarmann-Schulz U, Specht S, Debrah AY, Batsa L, Ayisi-Boateng NK, Osei-Mensah J, et al. Comparison of doxycycline, minocycline, doxycycline plus albendazole and albendazole alone in their efficacy against onchocerciasis in a randomized, open-label, pilot trial. *PLoS Negl Trop Dis*. 2017;11:e0005156. <https://doi.org/10.1371/journal.pntd.0005156>.
44. Sharma R, Jayoussi GA, Tyrer HE, Gamble J, Hayward L, Guimaraes AF, et al. Minocycline as a re-purposed anti-Wolbachia macrofilaricide: superiority compared with doxycycline regimens in a murine infection model of human lymphatic filariasis. *Sci Rep*. 2016;6:23458. <https://doi.org/10.1038/srep23458>.
45. Specht S, Pfarr KM, Arriens S, Hubner MP, Klarmann-Schulz U, Koschel M, et al. Combinations of registered drugs reduce treatment times required to deplete Wolbachia in the *Litomosoides sigmodontis* mouse model. *PLoS Negl Trop Dis*. 2018;12:e0006116. <https://doi.org/10.1371/journal.pntd.0006116>.
46. Aristoff PA, Garcia GA, Kirchoff PD, Showalter HD. Rifamycins—obstacles and opportunities. *Tuberculosis (Edinb)*. 2010;90:94–118.
47. Specht S, Pfarr KM, Arriens S, Hübner MP, Klarmann-Schulz U, Koschel M, et al. Combinations of registered drugs reduce treatment times required to deplete *Wolbachia* in the *Litomosoides sigmodontis* mouse model. *PLoS Negl Trop Dis*. 2018;12:e0006116. <https://doi.org/10.1371/journal.pntd.0006116>.
48. Specht S, Mand S, Marfo-Debrekyei Y, Debrah AY, Konadu P, Adjei O, et al. Efficacy of 2- and 4-week rifampicin treatment on the Wolbachia of *Onchocerca volvulus*. *Parasitol Res*. 2008;103:1303–9. <https://doi.org/10.1007/s00436-008-1133-y>.
49. Aljayoussi G, Tyrer HE, Ford L, Sjöberg H, Pionnier N, Waterhouse D, et al. Short-course, high-dose rifampicin achieves Wolbachia depletion predictive of curative outcomes in preclinical models of lymphatic filariasis and onchocerciasis. *Sci Rep*. 2017;7:210. <https://doi.org/10.1038/s41598-017-00322-5>.
50. Boeree MJ, Diacon AH, Dawson R, Narunsky K, Du BJ, Venter A, et al. A dose-ranging trial to optimize the dose of rifampin in the treatment of tuberculosis. *Am J Respir Crit Care Med*. 2015;191:1058–65. <https://doi.org/10.1164/rccm.201407-1264OC>.
51. Gardon J, Gardon-Wendel N, Demanga N, Kamgno J, Chippaux JP, Boussinesq M. Serious reactions after mass treatment of onchocerciasis with ivermectin in an area endemic for Loa loa infection. *Lancet*. 1997;350:18–22. [https://doi.org/10.1016/S0140-6736\(96\)11094-1](https://doi.org/10.1016/S0140-6736(96)11094-1).
52. Zoure HG, Wanji S, Noma M, Amazigo UV, Diggle PJ, Tekle AH, et al. The geographic distribution of Loa loa in Africa: results of large-scale implementation of the Rapid Assessment Procedure for Loiasis (RAPLOA). *PLoS Negl Trop Dis*. 2011;5:e1210.
53. Boussinesq M, Fobi G, Kuesel AC. Alternative treatment strategies to accelerate the elimination of onchocerciasis. *Int Health*. 2018;10:140–8. <https://doi.org/10.1093/inthealth/ihx054>.
54. World Health Organization, African Programme for Onchocerciasis Control (APOC): report of the consultative meetings on strategic options and alternative treatment strategies for accelerating onchocerciasis elimination in Africa. Ouagadougou 2015.
55. Büttner D, Wanji S, Bazzocchi C, Bain O, Fischer P. Obligatory symbiotic Wolbachia endobacteria are absent from Loa loa. *Filaria J*. 2003;2:10.
56. Food and Drug Administration of the United States of America (US FDA): Drug Approval Package Gleevec (Imatinib Mesylate) Capsules. 2001.
57. O'Connell EM, Bennuru S, Steel C, Dolan MA, Nutman TB. Targeting filarial Abl-like kinases: orally available, food and drug administration-approved tyrosine kinase inhibitors are microfilaricidal and macrofilaricidal. *J Infect Dis*. 2015;212:684–93. <https://doi.org/10.1093/infdis/jiv065>.
58. O'Connell EM, Kamenyeva O, Lustigman S, Bell A, Nutman TB. Defining the target and the effect of imatinib on the filarial c-Abl homologue. *PLoS Negl Trop Dis*. 2017;11:e0005690. <https://doi.org/10.1371/journal.pntd.0005690>.
59. O'Connell EM, Nutman TB. Reduction of Loa loa microfilaremia with imatinib—a case report. *N Engl J Med*. 2017;377:2095–6. <https://doi.org/10.1056/NEJMc1712990>.
60. Morawietz CM, Houhou H, Puckelwaldt O, Hehr L, Dreisbach D, Mokosch A, et al. Targeting kinases in *Fasciola hepatica*: anthelmintic effects and tissue distribution of selected kinase inhibitors. *Front Vet Sci*. 2020;7:611270. <https://doi.org/10.3389/fvets.2020.611270>.
61. Pereira MB, Weber MHW, Haeblerlein S, Mokosch AS, Spengler B, Grevelding CG, et al. Drug repurposing and de novo drug discovery of protein kinase inhibitors as new drugs against schistosomiasis. *Molecules*. 2022. <https://doi.org/10.3390/molecules27041414>.
62. Martin RJ, Robertson AP. Mode of action of levamisole and pyrantel, anthelmintic resistance, E153 and Q57. *Parasitology*. 2007;134:1093–104. <https://doi.org/10.1017/S0031182007000029>.
63. Moser W, Schindler C, Keiser J. Efficacy of recommended drugs against soil transmitted helminths: systematic review and network meta-analysis. *BMJ*. 2017;358:4307. <https://doi.org/10.1136/bmj.j4307>.
64. Campillo JT, Eiden C, Boussinesq M, Pion SDS, Faillie JL, Chesnais CB. Adverse reactions with levamisole vary according to its indications and misuse: A systematic pharmacovigilance study. *Br J Clin Pharmacol*. 2022;88:1094–106. <https://doi.org/10.1111/bcp.15037>.
65. Campillo JT, Bikita P, Hemilembolo M, Louya F, Missamou F, Pion SDS, et al. Safety and efficacy of levamisole in loiasis: a randomized, placebo-controlled, double-blind clinical trial. *Clin Infect Dis*. 2021. <https://doi.org/10.1093/cid/ciab906>.
66. Sales Junior PA, Molina I, Fonseca Murta SM, Sanchez-Montalva A, Salvador F, Correa-Oliveira R, et al. Experimental and clinical treatment of chagas disease: a review. *Am J Trop Med Hyg*. 2017;97:1289–303. <https://doi.org/10.4269/ajtmh.16-0761>.
67. Martinez-Peinado N, Cortes-Serra N, Losada-Galvan I, Alonso-Vega C, Urbina JA, Rodriguez A, et al. Emerging agents for the treatment of Chagas disease: what is in the preclinical and clinical development pipeline? *Expert Opin Investig Drugs*. 2020;29:947–59. <https://doi.org/10.1080/13543784.2020.1793955>.
68. Maguire BJ, Dahal P, Rashan S, Ngu R, Boon A, Forsyth C, et al. The Chagas disease study landscape: A systematic review of clinical and observational antiparasitic treatment studies to assess the potential for establishing an individual participant-level data platform. *PLoS Negl Trop Dis*. 2021;15:e0009697. <https://doi.org/10.1371/journal.pntd.0009697>.
69. Hasinoff BB, Patel D. Disulfiram is a slow-binding partial noncompetitive inhibitor of 20S proteasome activity. *Arch Biochem Biophys*. 2017;633:23–8. <https://doi.org/10.1016/j.abb.2017.09.003>.
70. Kannappan V, Ali M, Small B, Rajendran G, Elzhenni S, Taj H, et al. Recent advances in repurposing disulfiram and disulfiram derivatives as copper-dependent anticancer agents. *Front Mol Biosci*. 2021;8:741316. <https://doi.org/10.3389/fmolb.2021.741316>.
71. Sheppard JG, Frazier KR, Saralkar P, Hossain MF, Geldenhuys WJ, Long TE. Disulfiram-based disulfides as narrow-spectrum antibacterial agents. *Bioorg Med Chem Lett*. 2018;28:1298–302. <https://doi.org/10.1016/j.bmcl.2018.03.023>.
72. Frazier KR, Moore JA, Long TE. Antibacterial activity of disulfiram and its metabolites. *J Appl Microbiol*. 2019;126:79–86. <https://doi.org/10.1111/jam.14094>.
73. Peniche AG, Renslo AR, Melby PC, Travi BL. Antileishmanial activity of disulfiram and thiuram disulfide analogs in an ex vivo model system is selectively enhanced by the addition of divalent metal ions. *Antimicrob Agents Chemother*. 2015;59:6463–70.
74. Lane JE, Ribeiro-Rodrigues R, Suarez CC, Bogitsh BJ, Jones MM, Singh PK, et al. In vitro trypanocidal activity of tetraethylthiuram disulfide and sodium diethylamine-N-carbodithioate on *Trypanosoma cruzi*. *Am J Trop Med Hyg*. 1996;55:263–6. <https://doi.org/10.4269/ajtmh.1996.55.263>.
75. Xiao SH. Development of antischistosomal drugs in China, with particular consideration to praziquantel and the artemisinins. *Acta Trop*. 2005;96:153–67. <https://doi.org/10.1016/j.actatropica.2005.07.010>.
76. Bergquist R, Elmorshedy H. Artemether and praziquantel: origin, mode of action, impact, and suggested application for effective control of human schistosomiasis. *Trop Med Infect Dis*. 2018. <https://doi.org/10.3390/tropicalmed3040125>.
77. Shuhua X, Chollet J, Weiss NA, Bergquist RN, Tanner M. Preventive effect of artemether in experimental animals infected with *Schistosoma mansoni*. *Parasitol Int*. 2000;49:19–24. [https://doi.org/10.1016/S1383-5769\(00\)00028-3](https://doi.org/10.1016/S1383-5769(00)00028-3).
78. Utzinger J, Tanner M, Keiser J. ACTs for schistosomiasis: do they act? *Lancet Infect Dis*. 2010;10:579–81. [https://doi.org/10.1016/S1473-3099\(10\)70169-9](https://doi.org/10.1016/S1473-3099(10)70169-9).

79. Abay SM, Tilahun M, Fikrie N, Habtewold A. *Plasmodium falciparum* and *Schistosoma mansoni* coinfection and the side benefit of artemether-lumefantrine in malaria patients. *J Infect Dev Count.* 2013;7:468–74. <https://doi.org/10.3855/jidc.2658>.
80. Adedija AA, Akanbi AA, Oshodi AJ. Effect of artemether-lumefantrine treatment of *falciparum* malaria on urogenital schistosomiasis in co-infected School Aged Children in North Central of Nigeria. *Int J Biol Chem Sci.* 2015. <https://doi.org/10.4314/ijbcs.v9i1.13>.
81. Liu R, Dong H-F, Guo Y, Zhao Q-P, Jiang M-S. Efficacy of praziquantel and artemisinin derivatives for the treatment and prevention of human schistosomiasis: a systematic review and meta-analysis. *Parasites Vectors.* 2011;4:201. <https://doi.org/10.1186/1756-3305-4-201>.
82. Pérez del Villar L, Burguillo FJ, López-Abán J, Muro A. Systematic review and meta-analysis of artemisinin based therapies for the treatment and prevention of schistosomiasis. *PLOS ONE.* 2012;7:e45867; <https://doi.org/10.1371/journal.pone.0045867>.
83. Kramer CV, Zhang F, Sinclair D, Olliaro PL. Drugs for treating urinary schistosomiasis. *Cochrane Database Syst Rev.* 2014;8:CD000053.
84. Saeed MEM, Krishna S, Greten HJ, Kremsner PG, Efferth T. Antischistosomal activity of artemisinin derivatives in vivo and in patients. *Pharmacol Res.* 2016;110:216–26. <https://doi.org/10.1016/j.phrs.2016.02.017>.
85. Utzinger J, N'Goran EK, Caffrey CR, Keiser J. From innovation to application: social-ecological context, diagnostics, drugs and integrated control of schistosomiasis. *Acta Trop.* 2011;120:S121–37. <https://doi.org/10.1016/j.actatropica.2010.08.020>.
86. Keiser J, Silue KD, Adioassan LK, N'Guessan NA, Monsan N, Utzinger J, et al. Praziquantel, mefloquine-praziquantel, and mefloquine-artesunate-praziquantel against *Schistosoma haematobium*: a randomized, exploratory, open-label trial. *PLoS Negl Trop Dis.* 2014;8:e2975. <https://doi.org/10.1371/journal.pntd.0002975>.
87. Barda B, Coulibaly JT, Puchkov M, Huwyler J, Hattendorf J, Keiser J. Efficacy and safety of moxidectin, synriam, synriam-praziquantel versus praziquantel against *Schistosoma haematobium* and *S. mansoni* infections: a randomized, exploratory phase 2 trial. *PLoS Negl Trop Dis.* 2016;10:e0005008. <https://doi.org/10.1371/journal.pntd.0005008>.
88. Montresor A. Cure rate is not a valid indicator for assessing drug efficacy and impact of preventive chemotherapy interventions against schistosomiasis and soil-transmitted helminthiasis. *Trans R Soc Trop Med Hyg.* 2011;105:361–3. <https://doi.org/10.1016/j.trstmh.2011.04.003>.
89. World Health Organization. Guidelines for the treatment of malaria. 3rd ed. Geneva: World Health Organization; 2015.
90. Mnkugwe RH, Minzi O, Kinung'hi S, Kamuhabwa A, Aklillu E. Efficacy and safety of praziquantel and dihydroartemisinin piperazine combination for treatment and control of intestinal schistosomiasis: a randomized, non-inferiority clinical trial. *PLOS Negl Trop Dis.* 2020;14:e0008619. <https://doi.org/10.1371/journal.pntd.0008619>.
91. Zoleko-Manego R, Okwu DG, Handrich C, Dimessa-Mbadinga LB, Akinosho MA, Ndzebe-Ndoumba WF, et al. Effectiveness of antimalarial drug combinations in treating concomitant urogenital schistosomiasis in malaria patients in Lambaréné, Gabon: a non-randomised event-monitoring study. *PLOS Negl Trop Dis.* 2022;16:e0010899. <https://doi.org/10.1371/journal.pntd.0010899>.
92. Roucher C, Brosius I, Mbow M, Faye BT, De Hondt A, Smekens B, et al. Evaluation of artesunate-mefloquine as a novel alternative treatment for schistosomiasis in African children (SchistoSAM): protocol of a proof-of-concept, open-label, two-arm, individually-randomised controlled trial. *BMJ Open.* 2021;11:e047147. <https://doi.org/10.1136/bmjopen-2020-047147>.
93. World Health Organization. WHO handbook for guideline development. 2nd ed. Geneva: World Health Organization; 2014.
94. Food and Drug Administration of the United States of America (US FDA) MSDC: Stromectol (ivermectin) prescribing information. 2022. https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/050742s030lbl.pdf. Accessed 7 Nov 2022.
95. Kearns TM, Currie BJ, Cheng AC, McCarthy J, Carapetis JR, Holt DC, et al. Strongyloides seroprevalence before and after an ivermectin mass drug administration in a remote Australian Aboriginal community. *PLoS Negl Trop Dis.* 2017;11:e0005607. <https://doi.org/10.1371/journal.pntd.0005607>.
96. Kearns TM, Speare R, Cheng AC, McCarthy J, Carapetis JR, Holt DC, et al. Impact of an ivermectin mass drug administration on scabies prevalence in a remote Australian aboriginal community. *PLoS Negl Trop Dis.* 2015;9:e0004151. <https://doi.org/10.1371/journal.pntd.0004151>.
97. World Health Organization. WHO informal consultation on a framework for scabies control: World Health Organization Regional Office for the Western Pacific: Manila, Philippines, 19–21 February 2019: meeting report. Geneva: World Health Organization; 2020.
98. Wilkins AL, Steer AC, Cranswick N, Gwee A. Question 1: Is it safe to use ivermectin in children less than five years of age and weighing less than 15 kg? *Arch Dis Child.* 2018;103:514. <https://doi.org/10.1136/archdischild-2017-314505>.
99. Jittamala P, Monteiro W, Smit MR, Pedrique B, Specht S, Chaccour CJ, et al. A systematic review and an individual patient data meta-analysis of ivermectin use in children weighing less than fifteen kilograms: Is it time to reconsider the current contraindication? *PLoS Negl Trop Dis.* 2021;15:e0009144. <https://doi.org/10.1371/journal.pntd.0009144>.
100. Schulz JD, Coulibaly JT, Schindler C, Wimmersberger D, Keiser J. Pharmacokinetics of ascending doses of ivermectin in *Trichuris trichiura*-infected children aged 2–12 years. *J Antimicrob Chemother.* 2019;74:1642–7. <https://doi.org/10.1093/jac/dkz083>.
101. Wimmersberger D, Coulibaly JT, Schulz JD, Puchkov M, Huwyler J, Ngbesso Y, et al. Efficacy and safety of ivermectin against *Trichuris trichiura* in preschool-aged and school-aged children: a randomized controlled dose-finding trial. *Clin Infect Dis.* 2018;67:1247–55. <https://doi.org/10.1093/cid/ciy246>.
102. Matamoros G, Sanchez A, Gabrie JA, Juarez M, Ceballos L, Escalada A, et al. Efficacy and safety of albendazole and high-dose ivermectin coadministration in school-aged children infected with *Trichuris trichiura* in honduras: a randomized controlled trial. *Clin Infect Dis.* 2021;73:1203–10. <https://doi.org/10.1093/cid/ciab365>.
103. Gwee A, Duffull S, Zhu X, Tong SYC, Cranswick N, McWhinney B, et al. Population pharmacokinetics of ivermectin for the treatment of scabies in Indigenous Australian children. *PLoS Negl Trop Dis.* 2020;14:e0008886. <https://doi.org/10.1371/journal.pntd.0008886>.
104. Brussee JM, Schulz JD, Coulibaly JT, Keiser J, Pfister M. O24 Ivermectin in children: what is the right dose to achieve equivalent exposure coverage in children and adults? *Arch Dis Child.* 2019;104:e10. <https://doi.org/10.1136/archdischild-2019-esdppp.24>.
105. Hurlimann E, Keller L, Patel C, Welsche S, Hattendorf J, Ali SM, et al. Efficacy and safety of co-administered ivermectin and albendazole in school-aged children and adults infected with *Trichuris trichiura* in Cote d'Ivoire, Laos, and Pemba Island, Tanzania: a double-blind, parallel-group, phase 3, randomised controlled trial. *Lancet Infect Dis.* 2022;22:123–35. [https://doi.org/10.1016/S1473-3099\(21\)00421-7](https://doi.org/10.1016/S1473-3099(21)00421-7).
106. Hu Y, Xiao SH, Aroian RV. The new anthelmintic tribendimidine is an L-type (levamisole and pyrantel) nicotinic acetylcholine receptor agonist. *PLoS Negl Trop Dis.* 2009;3:e499. <https://doi.org/10.1371/journal.pntd.0000499>.
107. Xiao SH, Utzinger J, Tanner M, Keiser J, Xue J. Advances with the Chinese anthelmintic drug tribendimidine in clinical trials and laboratory investigations. *Acta Trop.* 2013;126:115–26. <https://doi.org/10.1016/j.actatropica.2013.01.009>.
108. Robertson AP, Puttachary S, Buxton SK, Martin RJ. Tribendimidine: mode of action and nAChR subtype selectivity in *Ascaris* and *Oesophagostomum*. *PLoS Negl Trop Dis.* 2015;9:e0003495. <https://doi.org/10.1371/journal.pntd.0003495>.
109. Xiao SH, Hui-Ming W, Tanner M, Utzinger J, Chong W. Tribendimidine: a promising, safe and broad-spectrum anthelmintic agent from China. *Acta Trop.* 2005;94:1–14. <https://doi.org/10.1016/j.actatropica.2005.01.013>.
110. Zhang H, Liu C, Zheng Q. Development and application of anthelmintic drugs in China. *Acta Trop.* 2019;200:105181. <https://doi.org/10.1016/j.actatropica.2019.105181>.
111. Moser W, Coulibaly JT, Ali SM, Amour AK, Yapi RB, et al. Efficacy and safety of tribendimidine, tribendimidine plus ivermectin, tribendimidine plus oxantel pamoate, and albendazole plus oxantel pamoate against hookworm and concomitant soil-transmitted helminth infections in Tanzania and Cote d'Ivoire: a randomised, controlled, single-blinded, non-inferiority trial. *Lancet Infect Dis.* 2017;17:1162–71. [https://doi.org/10.1016/S1473-3099\(17\)30487-5](https://doi.org/10.1016/S1473-3099(17)30487-5).

112. Xu LL, Jiang B, Duan JH, Zhuang SF, Liu YC, Zhu SQ, et al. Efficacy and safety of praziquantel, tribendimidine and mebendazole in patients with co-infection of *Clonorchis sinensis* and other helminths. *PLoS Negl Trop Dis*. 2014;8:e3046. <https://doi.org/10.1371/journal.pntd.0003046>.
113. Barda B, Ame SM, Ali SM, Albonico M, Puchkov M, Huwyler J, et al. Efficacy and tolerability of moxidectin alone and in co-administration with albendazole and tribendimidine versus albendazole plus oxantel pamoate against *Trichuris trichiura* infections: a randomised, non-inferiority, single-blind trial. *Lancet Infect Dis*. 2018;18:864–73. [https://doi.org/10.1016/S1473-3099\(18\)30233-0](https://doi.org/10.1016/S1473-3099(18)30233-0).
114. Coulibaly JT, Hiroshige N, N'Gbesso YK, Hattendorf J, Keiser J. Efficacy and safety of ascending dosages of tribendimidine against hookworm infections in children: a randomized controlled trial. *Clin Infect Dis*. 2019;69:845–52. <https://doi.org/10.1093/cid/ciy999>.
115. Steinmann P, Zhou XN, Du ZW, Jiang JY, Xiao SH, Wu ZX, et al. Tribendimidine and albendazole for treating soil-transmitted helminths, *Strongyloides stercoralis* and *Taenia* spp.: open-label randomized trial. *PLoS Negl Trop Dis*. 2008;2:e322.
116. Brussee JM, Hiroshige N, Neodo A, Coulibaly JT, Pfister M, Keiser J. Population pharmacokinetics and exposure-response analysis of tribendimidine to improve treatment for children with hookworm infection. *Antimicrob Agents Chemother*. 2021. <https://doi.org/10.1128/AAC.01778-20>.
117. Brussee JM, Neodo A, Schulz JD, Coulibaly JT, Pfister M, Keiser J. Pharmacometric analysis of tribendimidine monotherapy and combination therapies to achieve high cure rates in patients with hookworm infections. *Antimicrob Agents Chemother*. 2021. <https://doi.org/10.1128/AAC.00714-20>.
118. Kopp SR, Koltze AC, McCarthy JS, Traub RJ, Coleman GT. Pyrantel in small animal medicine: 30 years on. *Vet J*. 2008;178:177–84. <https://doi.org/10.1016/j.tvjl.2007.06.021>.
119. World Health Organization. The selection and use of essential medicines: report of the WHO Expert Committee on Selection and Use of Essential Medicines, 2021 (including the 22nd WHO model list of essential medicines and the 8th WHO model list of essential medicines for children). Geneva: World Health Organization; 2021.
120. Keiser J, Utzinger J. Efficacy of current drugs against soil-transmitted helminth infections: systematic review and meta-analysis. *JAMA*. 2008;299:1937–48.
121. Sapulete EJJ, Sanjaya Putra IGN, Kanya WD, Arimbawa IM, Gustawan IW. Efficacy of albendazole-pyrantel pamoate compared to albendazole alone for *Trichuris trichiura* infection in children: a double blind randomised controlled trial. *Malays J Med Sci*. 2020;27:67–74. <https://doi.org/10.21315/mjms2020.27.3.7>.
122. Moser W, Sayasone S, Xayavong S, Bounheuang B, Puchkov M, Huwyler J, et al. *Lancet Infect Dis*. 2018;18:729–37. [https://doi.org/10.1016/S1473-3099\(18\)30220-2](https://doi.org/10.1016/S1473-3099(18)30220-2).
123. Fox LM, Saravolatz LD. Nitazoxanide: a new thiazolide antiparasitic agent. *Clin Infect Dis*. 2005;40:1173–80.
124. Food and Drug Administration of the United States of America (US FDA): Drug Approval Package Alinia (Nitazoxanide) oral suspension (application number 21-498). Edited by Center for drug evaluation and research (CDER)2003.
125. Food and Drug Administration of the United States of America (US FDA): Drug approval package Alinia (Nitazoxanide) Tablets and Oral Suspension (Application number 21-497, 21-498/5001). Edited by (CDER) Cfdear2004.
126. Vishal S. Somvanshi¹, Brian L. Ellis², Yan Hu, and Raffi V. Aroian Nitazoxanide: Nematicidal Mode of Action and Drug Combination Studies, Published in final edited form as: *Mol Biochem Parasitol*. 2014 January; 193(1): 1–8. <https://doi.org/10.1016/j.molbiopara.2013.12.002>
127. US: Food and Drug Administration: The Paediatric Exclusivity Provision: January 2001 Status Report to Congress. 2001. <http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM049915.pdf>. Accessed 12 Aug 2016.
128. Rossignol J-F. Nitazoxanide: a first-in-class broad-spectrum antiviral agent. *Antiviral Res*. 2014;110:94–103. <https://doi.org/10.1016/j.antiviral.2014.07.014>.
129. Rossignol JF. Thiazolides: a new class of antiviral drugs. *Expert Opin Drug Metab Toxicol*. 2009;5:667–74.
130. Bailey MA, Na H, Duthie MS, Gillis TP, Lahiri R, Parish T. Nitazoxanide is active against *Mycobacterium leprae*. *PLoS ONE*. 2017;12:e0184107. <https://doi.org/10.1371/journal.pone.0184107>.
131. Lam KK, Zheng X, Forestieri R, Balgi AD, Nodwell M, Vollett S, et al. Nitazoxanide stimulates autophagy and inhibits mTORC1 signaling and intracellular proliferation of *Mycobacterium tuberculosis*. *PLoS Pathog*. 2012;8:e1002691. <https://doi.org/10.1371/journal.ppat.1002691>.
132. Iacobino A, Giannoni F, Pardini M, Piccaro G, Fattorini L. The combination Rifampin-nitazoxanide, but not rifampin-isoniazid-pyrazinamide-ethambutol, kills dormant *Mycobacterium tuberculosis* in hypoxia at neutral pH. *Antimicrob Agents Chemother*. 2019. <https://doi.org/10.1128/AAC.00273-19>.
133. Huang H, He Q, Guo B, Xu X, Wu Y, Li X. Progress in redirecting antiparasitic drugs for cancer treatment. *Drug Des Devel Ther*. 2021;15:2747–67. <https://doi.org/10.2147/DDDT.S308973>.
134. Van den Enden E. Pharmacotherapy of helminth infection. *Expert Opin Pharmacother*. 2009;10:435–51. <https://doi.org/10.1517/14656560902722463>.
135. Speich B, Ame SM, Ali SM, Alles R, Hattendorf J, Utzinger J, et al. Efficacy and safety of nitazoxanide, albendazole, and nitazoxanide-albendazole against *Trichuris trichiura* infection: a randomized controlled trial. *PLoS Negl Trop Dis*. 2012;6:e1685. <https://doi.org/10.1371/journal.pntd.0001685>.
136. Dighe SN, Ekwudu OM, Dua K, Chellappan DK, Katavic PL, Collet TA. Recent update on anti-dengue drug discovery. *Eur J Med Chem*. 2019;176:431–55. <https://doi.org/10.1016/j.ejmech.2019.05.010>.
137. Logesh R, Das N, Adhikari-Devkota A, Devkota HP. *Cocculus hirsutus* (L.) W.Theob (Menispermaceae): a review on traditional uses, phytochemistry and pharmacological activities. *Medicines (Basel)*. 2020. <https://doi.org/10.3390/medicines7110069>.
138. Dar SK, Kumar S, Maiti S, Dhawan S, Joglekar S, Arora U, et al. Clinical safety and pharmacokinetic evaluation of aqueous extract of *Cocculus hirsutus*, an anti-viral phytopharmaceutical drug as a potential for the treatment of dengue and COVID-19. *Heliyon*. 2022;8:e09416. <https://doi.org/10.1016/j.heliyon.2022.e09416>.
139. Sarker MMR, Khan F, Mohamed IN. Dengue fever: therapeutic potential of *Carica papaya* L. Leaves. *Front Pharmacol*. 2021. <https://doi.org/10.3389/fphar.2021.610912>.
140. Pambhar V, Mathur N, Mehta A, Mathur M, Kumawat DC, Mangalia R, et al. Effect of doxycycline and doxycycline with *Carica papaya* on thrombocytopenia and leucopenia in acute dengue fever patients. *J Family Med Prim Care*. 2022;11:3270–5.
141. Charan J, Saxena D, Goyal JP, Yasobant S. Efficacy and safety of *Carica papaya* leaf extract in the dengue: a systematic review and meta-analysis. *Int J Appl Basic Med Res*. 2016;6:249–54. <https://doi.org/10.4103/2229-516X.192596>.
142. Lai Y, Zhang Q, Long H, Han T, Li G, Zhan S, et al. Ganghuo Kanggan decoction in influenza: integrating network pharmacology and in vivo pharmacological evaluation. *Front Pharmacol*. 2020. <https://doi.org/10.3389/fphar.2020.607027>.
143. Derksen A, Kühn J, Hafezi W, Sendker J, Ehrhardt C, Ludwig S, et al. Antiviral activity of hydroalcoholic extract from *Eupatorium perfoliatum* L. against the attachment of influenza A virus. *J Ethnopharmacol*. 2016;188:144–52. <https://doi.org/10.1016/j.jep.2016.05.016>.
144. Sinha M, Chakraborty U, Kool A, Chakravarti M, Das S, Ghosh S, et al. In-vitro antiviral action of *Eupatorium perfoliatum* against dengue virus infection: modulation of mTOR signaling and autophagy. *J Ethnopharmacol*. 2022;282:114627. <https://doi.org/10.1016/j.jep.2021.114627>.
145. Tay MYF, Fraser JE, Chan WKK, Moreland NJ, Rathore AP, Wang C, et al. Nuclear localization of dengue virus (DENV) 1–4 non-structural protein 5; protection against all 4 DENV serotypes by the inhibitor Ivermectin. *Antiviral Res*. 2013;99:301–6. <https://doi.org/10.1016/j.antiviral.2013.06.002>.
146. Suputtamongkol Y, Avirutnan P, Mairiang D, Angkasekwinai N, Niwattayakul K, Yamasmith E, et al. Ivermectin accelerates circulating nonstructural protein 1 (NS1) clearance in adult dengue patients: a combined phase 2/3 randomized double-blinded placebo controlled trial. *Clin Infect Dis*. 2021;72:e586–93. <https://doi.org/10.1093/cid/ciaa1332>.
147. Yang JM, Chen YF, Tu YY, Yen KR, Yang YL. Combinatorial computational approaches to identify tetracycline derivatives as flavivirus inhibitors. *PLoS ONE*. 2007;2:e428. <https://doi.org/10.1371/journal.pone.0000428>.

148. Phillips RO, Robert J, Abass KM, Thompson W, Sarfo FS, Wilson T, et al. Rifampicin and clarithromycin (extended release) versus rifampicin and streptomycin for limited Buruli ulcer lesions: a randomised, open-label, non-inferiority phase 3 trial. *Lancet*. 2020;395:1259–67. [https://doi.org/10.1016/S0140-6736\(20\)30047-7](https://doi.org/10.1016/S0140-6736(20)30047-7).
149. Fahal AH. Mycetoma: a thorn in the flesh. *Trans R Soc Trop Med Hyg*. 2004;98:3–11. [https://doi.org/10.1016/S0035-9203\(03\)00009-9](https://doi.org/10.1016/S0035-9203(03)00009-9).
150. Emery D, Denning DW. The global distribution of actinomycetoma and eumycetoma. *PLOS Negl Trop Dis*. 2020;14:e0008397. <https://doi.org/10.1371/journal.pntd.0008397>.
151. Fahal AH, Ahmed KO, Saeed AA, Elkhawad AO, Bakhiet SM. Why the mycetoma patients are still neglected. *PLOS Negl Trop Dis*. 2022;16:e0010945. <https://doi.org/10.1371/journal.pntd.0010945>.
152. Agarwal P, Jagati A, Rathod SP, Kalra K, Patel S, Chaudhari M. Clinical features of mycetoma and the appropriate treatment options. *Res Rep Trop Med*. 2021;12:173–9. <https://doi.org/10.2147/rrtm.S282266>.
153. Bakhiet SM, Fahal AH, Musa AM, Mohamed ESW, Omer RF, Ahmed ES, et al. A holistic approach to the mycetoma management. *PLOS Negl Trop Dis*. 2018;12:e0006391. <https://doi.org/10.1371/journal.pntd.0006391>.
154. Kunna E, Yamamoto T, Fahal A. The use of traditional medicines among mycetoma patients. *Trans R Soc Trop Med Hyg*. 2020;115:297–306. <https://doi.org/10.1093/trstmh/traa135>.
155. Verma P, Jha A. Mycetoma: reviewing a neglected disease. *Clin Exp Dermatol*. 2019;44:123–9. <https://doi.org/10.1111/ced.13642>.
156. Zijlstra EE, van de Sande WWJ, Welsh O, Mahgoub ES, Goodfellow M, Fahal AH. Mycetoma: a unique neglected tropical disease. *Lancet Infect Dis*. 2016;16:100–12. [https://doi.org/10.1016/S1473-3099\(15\)00359-X](https://doi.org/10.1016/S1473-3099(15)00359-X).
157. Omer RF, Ahmed ES, Ali BM, Alhaj HE, Bakhiet SM, Mohamed ESW, et al. The challenges of recruitment in clinical trials in developing countries: the Mycetoma Research Centre experience. *Trans R Soc Trop Med Hyg*. 2021;115:397–405.
158. United States Food and Drug Administration, 2023. Accessed Jan2023.
159. Unknown.
160. Lu H, Li W, Whiteway M, Wang H, Zhu S, Ji Z, et al. A small molecule inhibitor of Erg251 makes fluconazole fungicidal by inhibiting the synthesis of the 14 α -methylsterols. *MBio*. 2022. <https://doi.org/10.1128/mbio.02639-22>.
161. Li WW, Feng YY, Lu HH, Jiang YY. S3.4a The repurposing approach identifies Pitavastatin (calcium) making fluconazole fungicidal by inhibiting ergosterol synthesis. *Med Mycol*. 2022. <https://doi.org/10.1093/mmy/072.S3.4a>.
162. Miceli MH, Kauffman CA. Isavuconazole: a new broad-spectrum triazole antifungal agent. *Clin Infect Dis*. 2015;61:1558–65. <https://doi.org/10.1093/cid/civ571>.
163. Food and Drug Administration of the United States of America (US FDA), 2015.
164. European Medicines Agency, 2015.
165. Thompson GR, Rendon A, RibeiroDosSantos R, Queiroz-Telles F, Ostrosky-Zeichner L, Azie N, et al. Isavuconazole treatment of cryptococcosis and dimorphic mycoses. *Clin Infect Dis*. 2016;63:356–62. <https://doi.org/10.1093/cid/ciw305>.
166. Kohno S, Izumikawa K, Takazono T, Miyazaki T, Yoshida M, Kamei K, et al. Efficacy and safety of Isavuconazole against deep-seated mycoses: a phase 3, randomized, open-label study in Japan. *J Infect Chemother*. 2023;29:163–70. <https://doi.org/10.1016/j.jiac.2022.10.010>.
167. Dogra J, Lal BB, Misra SN. Cutaneous leishmaniasis: therapeutic efficacy of dapsone in the commonly existing sub-types. *Indian J Dermatol Venereol Leprol*. 1989;55:375–7.
168. Mahajan VK, Sharma NL. Therapeutic options for cutaneous leishmaniasis. *J Dermatolog Treat*. 2007;18:97–104. <https://doi.org/10.1080/0954630601159474>.
169. Moreno E, Calvo A, Schwartz J, Navarro-Blasco I, Gonzalez-Penas E, Sanmartin C, et al. Evaluation of skin permeation and retention of topical dapsone in murine cutaneous leishmaniasis lesions. *Pharmaceutics*. 2019. <https://doi.org/10.3390/pharmaceutics11110607>.
170. Agrawal S, Khandelwal K, Bumb RA, Oghumu S, Salotra P, Satoskar AR. Pediatric cutaneous leishmaniasis in an endemic region in India. *Am J Trop Med Hyg*. 2014;91:901–4. <https://doi.org/10.4269/ajtmh.13-0737>.
171. Osorio LE, Palacios R, Chica ME, Ochoa MT. Treatment of cutaneous leishmaniasis in Colombia with dapsone. *Lancet*. 1998;351:498–9. [https://doi.org/10.1016/S0140-6736\(05\)78687-6](https://doi.org/10.1016/S0140-6736(05)78687-6).
172. Ahmed N, Malik S, Tahir M, Rahman A, Fayyaz I, Raza N, et al. Comparison of oral dapsone with intramuscular meglumine antimoniate in cutaneous leishmaniasis. *J Ayub Med Coll Abbottabad*. 2022;34:802–6. <https://doi.org/10.55519/jamc-04-10265>.
173. Sazgarnia A, Zabolinejad N, Layegh P, Rajabi O, Berenji F, Javidi Z, et al. Antileishmanial activity of liposomal clarithromycin against leishmania major promastigotes. *Iran J Basic Med Sci*. 2012;15:1210–4.
174. Zabolinejad N, Layegh P, Abbasi Shaye Z, Salehi M, Ghanizadeh S. Evaluating the effect of oral clarithromycin on acute cutaneous leishmaniasis lesions compared with systemic glucantime. *J Dermatol Treat*. 2022;33:1418–23. <https://doi.org/10.1080/09546634.2020.1825612>.
175. Ramadan HK, Hassan WA, Elossily NA, Ahmad AA, Mohamed AA, Abd-Elkader AS, et al. Evaluation of nitazoxanide treatment following triclabendazole failure in an outbreak of human fascioliasis in Upper Egypt. *PLoS Negl Trop Dis*. 2019;13:e0007779. <https://doi.org/10.1371/journal.pntd.0007779>.
176. World Health Organization: WHO to support the review and use of online repository to improve treatment of difficult-to-treat infections. 2020. <https://www.who.int/news/item/30-03-2020-who-to-support-the-review-and-use-of-online-repository-to-improve-treatment-of-difficult-to-treat-infections>. Accessed 14 Feb 2023.

Publisher's Note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Ready to submit your research? Choose BMC and benefit from:

- fast, convenient online submission
- thorough peer review by experienced researchers in your field
- rapid publication on acceptance
- support for research data, including large and complex data types
- gold Open Access which fosters wider collaboration and increased citations
- maximum visibility for your research: over 100M website views per year

At BMC, research is always in progress.

Learn more biomedcentral.com/submissions

