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The pipeline for drugs for control and elimination of Neglected Tropical Diseases: 1. Anti-infective drugs for regulatory registration

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Abstract

Background: The World Health Organization 'Ending the neglect to attain the Sustainable Development Goals: A road map for neglected tropical diseases 2021-2030' outlines the targets for control and elimination of neglected tropical diseases (NTDs). New drugs are needed to achieve some of them. We are providing an overview of the pipeline for new anti-infective drugs for regulatory registration and steps to effective use for NTD control and elimination.

Drugs approved for an NTD by at least one stringent regulatory authority: Fexinidazole, included in WHO guidelines for *Trypanosoma brucei gambiense* African Trypanosomiasis, is in development for Chagas Disease. Moxidectin, registered in 2018 for treatment of individuals ≥12 years old with onchocerciasis, is undergoing studies to extend the indication to 4-11 year old children and obtain additional data to inform WHO and endemic countries decisions on moxidectin inclusion in guidelines and policies. Moxidectin is also being evaluated for other NTDs.

Drugs in at least Phase 2 clinical development: A submission is being prepared for registration of acoziborole as an oral treatment for first and second stage *T. b. gambiense* African Trypanosomiasis. Bedaquiline, registered for tuberculosis, is being evaluated for multibacillary leprosy. Phase 2 studies of emodepside and flubentylosin in *O. volvulus* infected individuals are ongoing; studies for *Trichuris trichuria* and hookworm are planned. A trial of fosravuconazole in *Madurella mycetomatis* infected patients is ongoing. JNJ-64281802 is undergoing Phase 2 trials for reducing dengue viral load. Studies are ongoing or planned to evaluate oxantel pamoate for onchocerciasis and soil transmitted helminths, including *Trichuris*; and oxfendazole for onchocerciasis, *Fasciola hepatica*, *Taenia solium* cysticercosis, *Echinococcus granulosus*, and soil-transmitted helminths, including *Trichuris*.

From first registration to effective use for NTD control and elimination: Additional steps include country registrations, possibly additional studies to inform WHO guidelines and country policies, and implementation research to address barriers to effective use of new drugs.

Conclusions: Relative to the number of people suffering from NTDs, the pipeline is small. Close collaboration and exchange of experience between all stakeholders developing drugs for NTDs may increase the probability that the current pipeline will translate into new drugs effectively implemented in affected countries.

Keywords: neglected topical diseases, drug development, acoziborole, bedaquiline, emodepside, flubentylosin, fexinidazole, fosravuconazole, JNJ-64281802, moxidectin, oxantel pamoate, oxfendazole, implementation research

Background

Neglected Tropical Diseases (NTDs) are infectious diseases affecting more than one billion people in low- and middle-income countries (LMIC) [1]. The diseases considered 'NTDs' differ slightly between different organizations. We consider here the infectious diseases included in the World Health Organization (WHO) 'Ending the neglect to attain the Sustainable Development Goals: A road map for neglected tropical diseases 2021-2030 (subsequently referred to as 'Roadmap' [1]) (Fig. 1). The Roadmap was endorsed by the 73rd World Health Assembly (WHA) in 2020 [2].
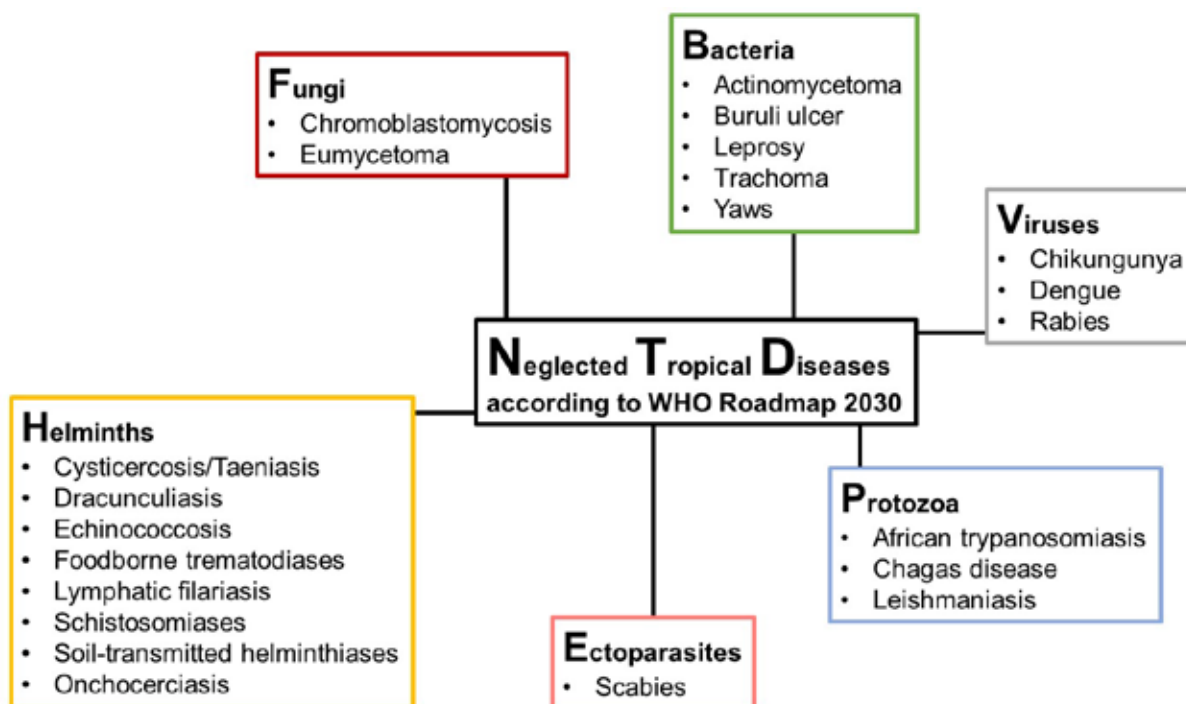
Fig. 1: Infectious NTDs included in the Roadmap

The Roadmap summarizes current core strategic interventions and invokes or specifies the need for new drugs, optimized drug regimens and/or new formulations to achieve the Roadmap targets for many NTDs [1].

We are providing an overview of new small molecule anti-infective drugs in at least Phase 2 clinical development for regulatory registration for NTDs, summarizing information as available and as we considered it of interest to NTD researchers and public health managers for a particular drug. Vaccines, monoclonal antibodies, and drugs to treat signs and symptoms or secondary infections are not covered.

We identified the drugs through search of the WHO International Clinical Trials Registry for studies initiated from 2009 onward. The source registries, last import date as of the search date 8 October 2021 (Additional File 1 Table S1) and last source registry update by the sponsors/investigators determined the trials included in the registry at that time and thus the drugs we considered. At the time of writing, the source registry record was accessed for updates. On 3 July 2022, we searched the WHO International Clinical Trials Registry again for any relevant updates (last import date from all source registries 30 or 31 May 2022).

We based our categorization of drugs as in 'development for regulatory registration' on information available on study sponsor websites and in publications. In the absence of specific information, we used sponsor track record in bringing drugs to regulatory approval.

As new drugs progress through the stages of 'Clinical Development' [3], the probability of success, i.e. achieving regulatory registration (also referred to as 'regulatory approval' or 'marketing authorization'), increases. We are therefore presenting separately drugs which have already received regulatory approval in at least one country for at least one NTD indication and those that have not yet received regulatory approval for an NTD in any country.

NTDs are prevalent primarily in LMIC. To ensure, to the extent possible, that readers in LMIC can access the references, all references are either open access, accessible as author manuscripts in the US National Institutes of Health's National Library of Medicine (Pubmed Central, PMC), on the European Molecular Biology Laboratory European Bioinformatics Institute platform (Europe PMC), on institutional websites, or were accessible via HINARI to the WHO staff co-author (ACK). HINARI is a WHO initiative through which local, not-for-profit institutions in LMIC can obtain free or very low-cost online access to the major journals in biomedical and related social sciences [4]. Currently, institutions in 125 LMIC are eligible for HINARI. 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 access as the criterion for 'accessible via HINARI'. In the absence of publications, the websites of the United States of America Food and Drug Administration (US FDA) and the European Medicines Agency (EMA), as well as trial sponsor websites were searched. For context, the Additional File 1 includes an overview of current core strategic interventions and WHO perspectives on the need for new drugs, combinations or formulations as per the Roadmap (Additional File 1 Table S2), as well as information on the drugs used in these strategies we consider of interest (Additional File 1 Sections 1 and 2).

Drugs approved for an NTD by at least one stringent regulatory authority

Fexinidazole

Fexinidazole is a nitroimidazole, which entered preclinical development in the 1970s as a possible broad-spectrum antimicrobial. Investigation of its activity against *Trypanosoma cruzei* and *Trypanosoma brucei* dates back to the early 1980s. Further research into the anti-trypanosomal activity of fexinidazole [5] and pre-clinical development of fexinidazole as an oral drug candidate for human African Trypanosomiasis (HAT) was initiated by the Drugs for Neglected Diseases initiative (DND*i*). The results motivated initiation of Phase 1 pharmacokinetic and safety studies [6] and a legal agreement between DND*i* and Sanofi for manufacturing, regulatory registration and distribution in 2009 [7, 8]. The Phase 2/3 study in individuals with stage 1 or early stage 2 *T. b. gambiense* HAT was initiated in 2012 [9]**.** The results provided the pivotal clinical data supporting a European Medicines Agency (EMA) positive 'scientific opinion' through the Article 58 of Regulation (EC) No 726/2004 procedure in the context of cooperation with WHO (now referred to as EU-M4all) in 2018 for treatment of individuals ≥6 years and weighing ≥20 kg with stage 1 and stage 2 *T. b. gambiense* HAT [10, 11]. For a 'Scientific Opinion', the EMA assesses drugs not intended for marketing in the European Union according to the same criteria used for drugs for the European market. Since WHO considers the EMA a 'stringent regulatory authority' [12], a positive 'Scientific Opinion' facilitates WHO prequalification [13]and registration in endemic countries. In 2019, fexinidazole was added to the WHO Model List of Essential Medicines List (EML) for adults and children [14] and included in the 'WHO interim guidelines for the treatment of gambiense human African trypanosomiasis' [15] (for more information, see Additional File 1).

A study evaluating the efficacy and safety of fexinidazole in patients ≥ 6 years old with *T. b. rhodesiense* HAT (Clinical Trials.gov study identifier (CTI): NCT03974178; Pan African Clinical Trials Registry identifier (PACTRI):

PACTR202011638938739) is expected to complete primary data collection in June 2022.

DND*i* also initiated clinical development for Chagas disease. A Phase 2 study of fexinidazole in Chagas Disease, initiated in 2014 in Bolivia, was discontinued due to safety and tolerability issues with high doses tested for more than 14 days. Based on the safety and efficacy data obtained with the lower doses, a second Phase 2 study was initiated in 2022 (CTI: NCT NCT03587766). The data supported the conclusion that low doses have high efficacy with acceptable safety and tolerability and that continuation of development of fexinidazole for Chagas Disease is indicated [16].

Moxidectin

Moxidectin is, like ivermectin, a macrocyclic lactone, but is a milbemycin, not an avermectin. Macrocyclic lactones have activity against a broad spectrum of endo- and ecto-parasites. They are agonists of the glutamate-gated chloride channels, present in the neurons and pharyngeal muscles of nematodes and arthropods, but not of humans. Activation of the channels inhibits movement and pharyngeal pumping, leading to paralysis and ultimately death [17, 18, 19]. While the major mode of action of both molecules is through binding to glutamate-gated chloride channels, the difference in chemical structure results in different physico-chemical, and thus pharmacokinetic and pharmacodynamic properties which are reflected in different efficacy and safety profiles [19, 20].

Onchocerciasis: The UNICEF/UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases (WHO/TDR) initiated research on moxidectin in the late 1990s, in consultation and with the support of the Onchocerciasis Control Programme in West Africa (OCP) and the African Programme for Onchocerciasis Control (APOC). Clinical development for onchocerciasis and lymphatic filariasis (LF) was supported by the WHO/TDR-funded in vitro and animal pharmacology studies, as well as the non-clinical safety studies for veterinary use registration provided by Fort Dodge Animal Health to WHO/TDR for external expert assessment. Clinical development for onchocerciasis was initiated in collaboration with Wyeth Pharmaceuticals. The development plan was informed by 'scientific advice' from the EMA in view of obtaining an EMA positive 'scientific opinion' through the Article 58 of Regulation (EC) No 726/2004 procedure in the context of cooperation with WHO (now referred to as EU-M4all). For a 'Scientific Opinion', the EMA assesses drugs not intended for marketing in the European Union according to the same criteria used for drugs for the European market. A positive 'Scientific Opinion' facilitates WHO prequalification and registration in endemic countries. Following acquisition of Wyeth by Pfizer and Pfizer's withdrawal from the collaboration agreement WHO and Wyeth had concluded, TDR completed the Phase 3 study on its own (last participant visit May 2012, database lock and unblinding December 2013). In 2014, WHO licensed all moxidectin-related data at its disposal to Medicines Development for Global Health (MDGH), a not-for-profit Australian Health Charity. MDGH raised funding for all activities required for a 'New Drug Application' (NDA) to the US FDA by leveraging the prospect of a 'Priority Review Voucher'[21]. The US FDA approved an 8 mg moxidectin dose for treatment of onchocerciasis in individuals ≥12 years old. US FDA review summaries and the moxidectin label are available [22].

Eight single dose clinical studies supported the registration. The six pharmacokinetic and safety studies in healthy adult male and female volunteers showed that moxidectin is safe and without clinically significant effect on the QT interval at the highest dose of 36 mg tested, its absorption is not affected in a clinically significant way by administration with or without food, that clinically significant drug interactions are unlikely, and that 0.7% of a single 8 mg maternal dose is excreted into breast milk [23, 24, 25, 26, 27]. The Phase 2 and 3 studies in *O. volvulus* infected individuals in Ghana, Liberia and the Democratic Republic of the Congo (DRC) showed that a single 8 mg dose results in higher and more sustained reduction in skin microfilariae levels than the standard ivermectin dose (150 µg/kg) with a comparable safety profile [28, 29, 30].

Modelling using the data from the Phase 2 study suggests that inclusion of moxidectin mass drug administration (MDA) in national onchocerciasis control and elimination policies could accelerate progress towards onchocerciasis elimination [31, 32]. Three ongoing studies are designed to provide additional data for WHO and countries to decide on inclusion of moxidectin in guidelines and policies for onchocerciasis control and elimination: A study to increase the safety database in individuals with and without measurable *O. volvulus* skin microfilariae levels (CTI: NCT04311671) and a study to compare the safety and efficacy of three annual and five biannual doses of 8 mg moxidectin or 150 µg/kg ivermectin (CTI: NCT03876262) are ongoing in DRC. A study to identify a dose for 4-11 year old children (CTI: NCT03962062) is being conducted in Ghana using the US FDA approved 2 mg tablet, whose size was chosen in view of potential use down to the age of 4 years. The studies are co-funded by MDGH, the Luxembourg National Research Fund and an EDCTP grant [33]. The repeat dose study will provide the first data on the relative effect of repeat dosing with moxidectin or ivermectin on the reproductive capacity of *O. volvulus*, i.e. skin repopulation with microfilariae, the *O. volvulus* life stage which is transmitted. Repeat dosing with ivermectin has a cumulative effect on macrofilariae reproductive capacity [34, 35]. For the impact on parasite transmission, the mechanism through which skin repopulation with microfilariae is reduced or eliminated (permanent sterilization of macrofilariae, reduction of their reproductive life span or reduction of their life span/cidal effect) is irrelevant.

In an *in vitro* model in which worms were incubated for 6 days, moxidectin, like ivermectin, inhibited *O. volvulus* L3 moulting and L4 motility, but with lower IC50 and IC90, absolutely and relative to the maximum serum concentrations and the half-life of moxidectin and ivermectin. Thus, moxidectin could have a 'prophylactic effect' against new infections [36]. Should moxidectin have such an effect in humans, this effect could reduce the negative impact of 'non-compliers' (those who do not take the drug) on elimination goals by reducing new infections due to transmission of skin microfilariae from the non-compliers.

The MDGH pipeline for moxidectin includes scabies, lymphatic filariasis, soil-transmitted helminths and strongyloidiases (in clinical development) and head lice (in preclinical development).

Scabies: Pre-clinical studies suggest that moxidectin could advance scabies control and clinical trials have been identified as a priority [37, 38, 39, 40, 41]. A Phase 2 dose finding study in Australia, Austria and France was completed in February 2022 (CTI: NCT03905265). A study planning to compare a single topically administered dose of moxidectin (cydectin, an animal formulation) and 3 daily topically administered doses of ivermectin (iverzine) in Egypt was registered in 2019

in the Iranian Registry of Clinical Trials (identifier: IRCT20191030045275N). The record has not been updated since February 2020 and shows that the study is not yet recruiting.

LF: A study in adults comparing the effect of three annual administrations of 200 µg/kg ivermectin or 8 mg moxidectin in combination with 400 mg albendazole or 400 mg albendazole plus 6 mg/kg diethylcarbamazine on *Wuchereria bancrofti* microfilaremia was initiated in Côte d'Ivoire in August 2020 (CTI: NCT04410406).

Soil-transmitted helminthiases (STH) including strongyloidiasis: The Phase 3 study in *O. volvulus* infected individuals was not designed to compare efficacy of 8 mg moxidectin and 150 µg/kg ivermectin on STH. The data collected supported the hypothesis that moxidectin has better efficacy against hookworms. There were too few individuals with *Ascaris* and *Trichuris* infection at baseline to allow conclusions (supplemental information to [30]).

The Swiss Tropical and Public Health Institute (STPH) conducted studies evaluating the efficacy of a single moxidectin dose using the veterinary formulation cydectin [42] or tablets manufactured at the University of Basel, Switzerland [42, 43, 44, 45] alone or in combination with other anthelminthics against *Strongyloides stercoralis*, *Trichuris trichiura* and concomitant other helminths and against schistosomiasis (See Additional File 1 Table S3 for tabulation of results). All studies found that moxidectin was well tolerated.

Strongyloides stercoralis: The cure rate (CR) of a single 8 mg moxidectin dose was inferior to that of a single 200 µg/kg ivermectin dose [42]. The dose response showed similar CR for 4, 8 and 12 mg moxidectin [44]. A population pharmacokinetic model supports further exploration of fixed-dose rather than weight-based dosing [46]. A Phase 3 study comparing 8 mg moxidectin to 200 µg/kg ivermectin is planned for 2022 (CTI: NCT04848688). Pharmacometric modelling suggests that a two-dose regimen (for example two 8 mg moxidectin doses, three weeks apart) should be evaluated to achieve high CR in individuals with moderate to high infection intensity [47].

Trichuris trichiura: A single 8 mg moxidectin dose co-administered with 400 mg albendazole was highly efficacious [43]. A dose ranging study confirmed this and showed that 16 mg or 24 mg moxidectin do not increase efficacy as monotherapy or in combination with albendazole [45]. Between study efficacy differences might be due to differences in pre-study egg counts. A study in adolescents and adults comparing 8 mg moxidectin+400 mg albendazole, 400 mg albendazole and 200 µg/kg ivermectin+400 mg albendazole [48] was completed in October 2021 (CTI: NCT04726969).

Hookworm: CR after 8 mg moxidectin or 200 µg/kg ivermectin were moderate [42]. Combination of 8 mg moxidectin with tribendimidine or albendazole improved CR [43]. Increasing the moxidectin dose to 16 mg or 24 mg did not increase egg reduction rates (ERR) or CR either for monotherapy or albendazole combination treatment [45].

Ascaris lumbricoides: CR after 8 mg moxidectin were > 95% [43, 45].

Foodborne trematodiasis: Neither moxidectin nor ivermectin were effective against *Opisthorchis viverrini* [42].

Schistosomiasis: The results to date suggest that potential treatment programmes with 8 mg moxidectin for other infections will have no co-benefit for schistosomiasis control [49].

Paediatric formulation. The size of the approved 2 mg tablet (8.13mm x 4.55mm x 2.50 mm average thickness) was chosen to accommodate children ≥ 4 years of age. To facilitate dosing of younger children and in view of the moxidectin development program for scabies, development of a paediatric formulation is ongoing, co-funded by MDGH, the Luxembourg National Research Fund (FNR n° INTER/EDCTP/19/14338294/MiniMox/Vaillant) and an EDCTP grant (RIA2019PD-2880, MiniMox – Treatment for all: a paediatric formulation of moxidectin for neglected infectious diseases).

Drugs in at least Phase 2 clinical development for first regulatory registration for an NTD

Acoziborole

Acoziborole (SCYX-7158, AN5568) is a benzoxaborole. Discovery of novel benzoxaboroles with anti-trypanosomal activity [50, 51] resulted in a lead-optimization program. Acoziborole emerged from this as a compound with an *in vitro* and *in vivo* absorption, distribution, metabolism, elimination (ADME), toxicology and efficacy profile that met the criteria for initiation of preclinical studies intended to qualify acoziborole for clinical development for stage 2 human African trypanosomiasis (HAT) [52, 53]. Research into the mode of action currently points to the RNA cleavage and polyadenylation specificity factor submit 3 (CPSF3) as a target of benzoxaboroles in trypanosomes (as also in *Plasmodium* spp. and *Toxoplasma gondii*) reducing the amount of mRNA and stopping protein synthesis [54, 55].

A Phase 1 study in France in healthy volunteers of sub-Saharan origin showed a half-life of 17 days and no issues preventing further clinical development [55]. The Phase 2/3 study of the efficacy and safety of a single oral 960 mg dose in 208 patients with first or second stage *Trypanosoma brucei gambiense* HAT to 18 months post-treatment (CTI: NCT03087955) was analysed in 2021. The data to date, including those of a Phase 1 study to improve the understanding of acoziborole ADME (CTI: NCT04270981) sponsored by DND*i*, will be complemented by non-clinical studies required by the US FDA and the EMA for registration of new chemical entities [56]. A study of the safety and tolerability of acoziborole in *T. b. gambiense* HAT seropositive individuals without parasitological confirmation of infection (CTI: NCT05256017) was initiated by DND*i* in 2021.

Sanofi will be the regulatory sponsor and has committed to manufacturing and providing acoziborole free of charge to HAT endemic countries within its collaboration with WHO [57], now extended to 2025 [58].

Bedaquiline

Bedaquiline (TMC207, JNJ-16175328-AAA, R207910) is a diarylchinoline which inhibits mycobacterial ATP synthase, a mode of action different from that of other anti-mycobacterial drugs [59]. Bedaquiline was approved as part of combination treatment of pulmonary multi-drug resistant tuberculosis in adults by the US FDA in 2012 [60] and in adults and adolescents by the EMA in 2014 [61]. In 2019, the US FDA approval was extended to 12-17 year old adolescents [62] and has been included in WHO guidelines on treatment of drug-resistant tuberculosis [63, 64].

Based on data from murine models of leprosy [59], Janssen Research & Development is developing bedaquiline for *Mycobacterium leprae* infections. An open-label study is ongoing in Brazil to evaluate the efficacy and safety of

bedaquiline monotherapy in individuals with multibacillary leprosy (CTI: NCT03384641).

Emodepside

Emodepside is an N-methylated cyclic octadepsipeptide authorized in 2005 by the EMA as a spot-on solution combination product with praziquantel for treatment of dogs and cats with or at risk of infection with nematodes (*Toxocara cati, Toxascaris leonina, Ancylostoma tubaeforme*) and cestodes (*Dipylidium caninum, Taenia taeniaeformis, Echinococcus multilocularis*) (sponsor Bayer HealthCare AG) [65]. Since then, modified release tablets have been authorized as well as a combination product with toltrazirul [66].

Cyclic octadepsipeptides have a novel mechanism of action that was recently reviewed together with the majority of pre-clinical pharmacology studies supporting clinical studies for onchocerciasis as well as LF [67, 68].

Emodepside emerged as a drug candidate for human use from the WHO/TDR drug discovery programme [69, 70]. The last step funded by WHO/TDR was an *ex vivo* study by Drs K Awadzi, S. Tagboto and S. Townson at the Onchocerciasis Chemotherapy Research Center in Ghana in 2006-2007. It examined the effect of emodepside, provided by Bayer, on motility and viability of male and female *O. volvulus* macrofilariae obtained via nodulectomy. The data (unpublished, report from Dr Townson to TDR available from the corresponding author), together with the pharmacology and safety data from the veterinary registration identified emodepside not only as a candidate for onchocerciasis but also for soil-transmitted helminths [65].

Onchocerciasis: In 2014, DNDi and Bayer agreed to develop emodepside. Two safety and tolerability studies in healthy male volunteers showed that single and multiple doses of a liquid formulation and single doses of immediate release tablets (5 or 20 mg emodepside) are well tolerated. Emodepside was rapidly absorbed after administration of the liquid in the fasted state and somewhat slower in the fed state [71]. A Phase 2 safety, tolerability, pharmacodynamics, pharmacokinetics and efficacy study in *O. volvulus* infected individuals in Ghana has started recruitment (PACTRI: PACTR202010898529928). The study is sponsored by DNDi and conducted by researchers at the University of Health and Allied Sciences, Ghana.

In an *in vitro* model in which worms were exposed to emodepside for 6 days, emodepside inhibited *O. volvulus* L3 moulting and L4 motility with both IC_{50} and IC_{90} around a factor 100 lower than those for moxidectin. Considering the pharmacokinetic profile of emodepside in humans available to date, emodepside might have a prophylactic effect against new infection [36].

***Trichuris trichiura* and hookworm**: In 2021, the STPH sponsored a study in Tanzania evaluating efficacy and safety of single doses of 5 mg to 30 mg (CTI: NCT05017194). STPH has obtained a European Research Council grant (Grant agreement ID: 101019223, DOI 10.3030/101019223), which includes funding for two dose-selection phase 2a trials and a phase 2b trial comparing efficacy and safety of the selected dose with that of albendazole.

Flubentylosin (TylAMac, ABBV-4083)

Flubentylosin (TylAMac, ABBV-4083) is a derivative of tylosin A, an antibiotic of the macrolide class approved for veterinary use since the 1990ies. Research into the role of the endosymbiotic *Wolbachia* bacteria for filarial development and how

antibiotics affect filariae fertility and viability was initiated in the 1990ies [72, 73, 74, 75, 76]. Studies evaluating the effect of 6 weeks of daily doxycycline treatment provided clinical proof-of-concept of the macrofilariae sterilizing and -cidal effect of anti-*Wolbachia* treatment for onchocerciasis and LF [77, 78, 79, 80]. Doxycycline-induced *Wolbachia* depletion killed up to 70% of *O. volvulus* adult female worms within 2 years and rendered the remaining worms sterile [81, 82]. Drugs with a virtually 100% macrofilariae sterilizing or macrofilaricidal effect after a single treatment course could significantly accelerate elimination of *O. volvulus* transmission [83] compared to ivermectin which has only a partial macrofilaricidal and modest sterilizing effect after at least four annual treatments [35].

Anti-*Wolbachia* drugs will not be effective against *Loa loa,* which does not contain *Wolbachia* [84, 85]. The efficacy of ivermectin against *L. loa* can lead to serious adverse reactions in individuals with high *L. loa* microfilariaemia [86, 87]. In areas which are at least onchocerciasis meso-endemic, this element of ivermectin's safety profile requires that MDA including ivermectin is implemented with special provisions to ensure prompt identification and management of serious adverse reactions [88]. In other *L. loa* co-endemic areas, alternative strategies for control and elimination of onchocerciasis and lymphatic filariasis are required [89].

The clinical proof-of-concept spurred further studies with commercially available antibiotics as well as discovery programmes for antibiotics with potentially shorter treatment regimens, no contraindication in children and ideally safe in pregnant women [90, 91, 92, 93].

Flubentylosin emerged from discovery programs at the Anti-*Wolbachia* Consortium funded by the Bill and Melinda Gates Foundation since 2007 [90, 91, 94] and the pharmaceutical company AbbVie Inc. (North Chicago, Illinois, USA). Studies in *Litomosoides sigmodontis* mice and Mongolian gerbil models showing that flubentylosin reduced *Wolbachia* levels by ≥99.9% [90] encouraged progression into development. The results of Phase 1 studies conducted by AbbVie justified preparation of a Phase 2 study. The Phase 2 study investigating the safety, efficacy, and pharmacokinetics of 7 or 14 days of dosing with TylAMac alone or in combination with albendazole, ivermectin or albendazole plus ivermectin started recruitment in 2021 (PACTRI: PACTR202104600961505, CTI: NCT04913610). The study is sponsored by AbbVie and conducted in collaboration between DNDi and researchers in DRC.

Fosravuconazole

Fosravuconazole L-lysine ethanolate (Fosravuconazole, E1224) is a prodrug of ravuconazole. It is an orally available broad-spectrum antifungal triazole, developed by Esai Co., Japan, since 2007. Since 2018, fosravuconazole containing medication is available in Japan for treatment of onychomycosis [95, 96].

The *in vitro* minimum inhibitory concentrations of ravuconazole against *Madurella mycetomatis*, the most common causative species of eumycetoma, were substantially lower than those of ketoconazole [97]. Esai and DNDi concluded a collaboration and license agreement for development of fosravuconazole for Chagas disease in 2009 and for eumycetoma in 2015 [95].

The primary target of ravuconazole in *Trypanosoma cruzi* is the cytochrome P450 dependent sterol C14α demethylase resulting in inhibition of ergosterol biosynthesis, a mechanism of action common to the azoles [98, 99, 100].

Fosravuconazole treatment of adults with chronic indeterminate Chagas disease induced sustained parasitological clearance to month 12 in 13/45 (29%) of participants treated with the highest dose (4000 mg over 8 weeks) compared to 37/45 (82%) of participants treated with benznidazole (5 mg/kg/day for 60 days) [101]. These findings resulted in discontinuation of development of fosravuconazole as monotherapy for Chagas disease and initiation of a trial in Bolivia in adults with chronic indeterminate Chagas disease comparing benznidazole regimens with and without fosravuconazole. The rates of sustained parasitological clearance 6 and 12 months after the end of treatment suggested that shorter or lower dose benznidazole treatment has efficacy comparable to that of the standard benznidazole regimen with a better safety profile. Fosravuconazole addition did not increase clearance rates [102]. With only 27 to 30 participants per treatment arm, additional data are needed to confirm the efficacy and safety of shorter or lower dose and thus safer/better tolerable benznidazole regimens [7, 102].

In vitro, minimum inhibitory concentrations against *M. mycetomatis* isolates were lower than those of ketoconazole, itraconazole [97] and other azoles [95] and ravuconazole also showed activity in an invertebrate *in vivo* model [103]. The *in vitro* results in combination with fosravuconazole's half-life of 7-11 days and safety profile motivated initiation of a trial in eumycetoma at the Mycetoma Research Centre in Sudan in 2017 [95, 97, 104]. The trial (CTI: NCT03086226) compares the efficacy of weekly treatment with 200 or 300 mg fosravuconazole in *M. mycetomatis* infected patients to that of daily treatment with 400 mg itraconazole. Follow up of all participants has been completed and database lock planned for March 2022 [105].

JNJ-64281802

Janssen Research & Development, LLC is conducting three Phase 2 trials to assess the ability of its compound JNJ-64281802 to reduce dengue viral load and to assess its safety (CTI: NCT04480736, NCT05048875, NCT04906980). A study to assess safety and efficacy for the prevention of dengue infection is in preparation (CTI: NCT05201794).

Neither HINARI nor Pubmed search for publications including JNJ-64281802 in any field identified any publications. A March 2022 search of the Janssen website and the website on the Johnson&Johnson pharmaceutical pipeline for investors also did not identify any information.

LXE408

LXE408 emerged from optimization of GNF6702, a selective inhibitor of the kinetoplastid proteasome. While GNF6702 showed excellent efficacy in murine models of leishmaniasis, as well as of Chagas disease and human African trypanosomiasis, formulation of GNF6702 for oral availability would have resulted in an expensive drug. In *Leishmania donovani* infected mice, oral doses of 1 mg/kg LXE408 twice per day for 8 days resulted in a 95% liver parasite reduction, the reduction achieved with oral doses of 12 mg/kg miltefosine four times a day. Data from murine models suggest that LXE408 may also be a potential drug candidate for cutaneous leishmaniasis [106, 107].

A Phase 1 multiple ascending dose study of LXE408 was completed in September 2021 and a Phase 2 study in patients with visceral leishmaniasis is planned (Clinical Trials Registry – India identifier: CTRI/2022/03/040775). The Drugs for Neglected Diseases *initiative* (DND*i*) concluded a collaboration and license agreement in early 2022 with Novartis to develop LXE408 as a potential oral

treatment for visceral leishmaniasis. The development is financially supported by Wellcome [108].

Oxantel Pamoate

Oxantel Pamoate is a tetrahydropyrimidine derivative and *m*-oxyphenol analog of pyrantel discovered in the 1970s. Oxantel activates parasite nicotinic acetylcholine receptors (AchR), leading to overstimulation of the muscles, muscle spasms and paralysis [109, 110, 111]. An AchR subtype recently discovered in the pig whipworm *Trichuris suis* was named O-AchR because of its sensitivity to oxantel [109]. The responsible O-AchR subunit was also identified in *T. muris* [112]. This receptor may explain oxantel efficacy against *Trichuris spp.*

Oral formulations of oxantel pamoate in combination with pyrantel pamoate and praziquantel have been marketed for companion animals for many years. Oral formulations in combination with pyrantel pamoate are approved for human use in six South American countries and the Philippines, including for children in the Philippines, Ecuador and Peru [111].

Clinical studies demonstrating the efficacy of oxantel pamoate against *T. trichiura* date back to the 1970ies and were recently reviewed together with the available non-clinical data [111]. The data support development of oxantel pamoate for approval by a stringent regulatory authority. The Helminth Elimination Platform (HELP) consortium, formed in 2019 to develop drugs for STH and onchocerciasis, is pursuing this with European Union funding (European Union's Horizon 2020 research and innovation programme grant agreement No. 815628). Studies should include not only oxantel mono-treatment arms but also two or three drug combination treatment arms [113, 114] to inform both regulatory approval and WHO guidelines and country policies.

Oxfendazole

Oxfendazole is a benzimidazole veterinary anthelmintic approved in the US [115] and in Europe for treatment of roundworms and tapeworms in ruminants and horses, and giardiasis in dogs [116].

The 'Oxfendazole Development Group' (ODG, [117]), which obtained non-profit status in the US in 2016, is pursuing oxfendazole registration for treatment of *Fasciola hepatica*, *Taenia solium* cysticercosis, *Echinococcus granulosus*, and STH, in particular *Trichuris*. The US FDA granted Fast-track designation for trichuriasis recognizing its public health importance and the unmet medical need [118, 119].

An important question for oxfendazole development for tissue dwelling parasites is whether the required systemic exposure has unacceptable, benzimidazole class effect, toxicity. Such toxicity resulted in discontinuation of flubendazole development for onchocerciasis [120, 121, 122, 123]. Non-clinical pharmacology, pharmacokinetic and toxicology data to date were recently reviewed and support development for both gut and tissue dwelling parasites [116, 124].

A single and a multiple ascending dose Phase 1 study with a veterinary oral liquid formulation in healthy volunteers [125, 126] identified no safety concerns. The pharmacokinetic data showed a significant food effect as well as significant nonlinear pharmacokinetics with less than dose-proportional exposure attributed to absorption due to low oxfendazole solubility. A single and multiple dose Phase 1 trial (CTI: NCT04920292) of a tablet formulation is expected to complete primary outcome measure collection in September 2022.

An ODG and Asociacion Benefica Prisma sponsored Phase 2 trial (CTI: NCT03435718; Clinical Trials Peruvian Registry identifier PER-083-20) comparing single 6 mg/kg, 15 mg/kg or 30 mg/kg oxfendazole doses, three daily (15 mg/kg) oxfendazole doses and a single 400 mg albendazole dose in *T. trichiura* infection is planned to start recruitment in July 2022 in Peru. An Asociacion Benefica Prisma sponsored Phase 2 trial (CTI: NCT04713787) in Peru plans to compare single 400 mg or 800 mg oxfendazole doses with a single 400 mg albendazole dose against *T. trichiura*.

Treatment of the rodent filaria *L. sigmodontis* for 3-5 days showed macrofilaricidal without microfilaricidal activity [127], suggesting oxfendazole could be a macrofilaricide for control and elimination of onchocerciasis (and potentially LF) safe in loiasis co-endemic areas due to the lack of microfilaricidal activity. An STPH sponsored phase 1 trial in Tanzania (CTI: NCT04920292,) was initiated in May 2022 to examine pharmacokinetics, safety and tolerability of single and multiple doses of a new tablet formulation of oxfendazole. Should the dose of oxfendazole needed for anti-onchocercal activity prove well-tolerated, the EU-funded HELP consortium will conduct a Phase 2 trial comparing oxfendazole with ivermectin in onchocerciasis. In addition, clinical trials are being designed to investigate the efficacy and safety of oxfendazole for STH.

In an *in vitro* assay exposing *O. volvulus* larvae for 6 days to oxfendazole, the IC_{50} and IC_{90} for inhibition of L3 moulting were higher than those of emodepside but lower than those of moxidectin and ivermectin. In conjunction with available pharmacokinetic data, it was concluded that oxfendazole could have a prophylactic effect against new infections [36].

Close collaboration between the ODG and the HELP consortium could make development of oxfendazole more cost-effective and address potential safety concerns, e.g., whether undiagnosed neurocysticercosis could result in adverse reactions to oxfendazole in participants of trials for onchocerciasis or STH.

From first registration to effective use for NTD control and elimination

Regulatory approval

Not all drugs described above may ultimately obtain regulatory approval. Based on historical data, out of 2-5 drugs entering Phase 2 development on average only 1-2 enter Phase 3 and out of those on average one will achieve regulatory approval [3].

Drugs for NTDs which are not also a health problem in high income countries, i.e., are of economic interest, face the additional hurdle of the willingness of pharmaceutical company partners to continue the development/collaboration and/or the willingness or ability of donors to continue financial support to complete all activities required for a submission for regulatory approval. As described above, a case in point for this hurdle is moxidectin development which was put in jeopardy, and regulatory registration delayed by several years, because Pfizer withdrew from the collaboration agreement with WHO [29, 30].

Prior to use in any LMIC, the regulatory authority of that country needs to approve the use of the drug in their country. The dossier that sponsors have to submit for regulatory approval has to include all information from the required non-clinical studies, clinical studies and pharmaceutical development and qualification of the drug substance and drug product. An overview of the elements of a dossier is

available in guideline M4 of the 'Common Technical Document' of the 'International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use' (ICH). A dossier consequently includes hundreds of thousands of pages and demands extensive regulatory authority staff and time capacity. For example, the New Drug Application submitted by MDGH to the US FDA for registration of moxidectin included more than 400,000 pages and at least 28 US FDA staff were involved in the review as deduced from the publicly available 525 pages of US FDA review summaries [128]. In recognition of the fact that the required review capacity is not available in all LMIC, WHO has established the 'Collaborative Procedure for Accelerated Registration' of Medicines that have been prequalified by WHO or approved by a 'stringent regulatory authority' (SRA) [12]). A SRA is defined as a regulatory authority which is a member of the ICH, being: the European Commission; the US Food and Drug Administration; and the Ministry of Health, Labour and Welfare of Japan, also represented by the Pharmaceuticals and Medical Devices Agency (as before 23 October 2015); or, is an ICH observer, being the European Free Trade Association, as represented by Swissmedic, and Health Canada (as before 23 October 2015); or a regulatory authority associated with an ICH member through a legally-binding, mutual recognition agreement, including Australia, Iceland, Liechtenstein and Norway (as before 23 October 2015) [12]. The list of stringent regulatory authorities and the list of countries participating in the Collaborative Procedure for SRA approved drugs are available on the WHO website.

Inclusion in WHO guidelines and country policies

Notwithstanding the increasing requirement for pricing agreements between pharmaceutical companies and health care payers [129, 130], for drugs that will be marketed by a company for prescription by physicians, regulatory approval (marketing authorization) can be regarded as the 'final milestone'. This is not necessarily the case for drugs that will be used by the public health systems of LMICs. For such drugs, inclusion into WHO guidelines is frequently a prerequisite for inclusion in country policies. Inclusion in WHO guidelines may require evidence beyond that needed for regulatory registration [131].

Additional data are, in particular, needed for drugs for disease control and elimination via 'Preventive Chemotherapy' (PC), i.e., administration of the drug to specified populations irrespective of the presence of symptoms or infection, such as occurs for lymphatic filariasis, onchocerciasis, soil-transmitted helminths, taeniasis and cysticercosis, schistosomiasis, foodborne trematodiases, yaws, trachoma, or scabies (Additional File 1 Table S2) [1, 132, 133]. During PC many of the people taking the drug will not be infected and will consequently not derive a direct benefit from taking the drug. This means that any adverse reactions to the drug have to be minimal to ensure the risk is acceptable relative to the indirect benefit that the uninfected individuals will derive from PC. The indirect benefit is the reduced probability of becoming infected via the impact on parasite transmission due to the treatment of infected community members. The number of uninfected individuals included in studies conducted for regulatory registration, typically not exceeding a few hundred healthy volunteers in Phase 1 studies, is insufficient to support decisions on use of drugs for PC, and consequently additional studies need to be conducted. During PC, the availability of trained health care staff to assess and, as required, treat any adverse reactions is significantly lower than when physicians prescribe a drug for case management of an individual patient. Consequently, the safety database for infected individuals required to recommend use of a new drug for

PC also needs to be larger than required for regulatory approval of a drug for case management. Thus, infected individuals also need to be included in additional studies to ensure data are available on the type and frequency of rare adverse reactions in a study population representative of that which will be included in PC.

For drugs to be used for case management (See Additional File 1 Table S2 for NTDs whose control and/or elimination strategy is case management based), the need for additional data to inform WHO guidelines may not be as extensive since the population included in clinical studies for regulatory approval is more representative of the population that will be treated by the health systems. Furthermore, patients will be treated and followed up by health care professionals similar to how they were treated and followed up during the clinical studies. For example, the inclusion of fexinidazole in the 2019 'WHO interim guidelines for the treatment of gambiense human African trypanosomiasis' was based exclusively on the clinical studies submitted to the EMA for registration [15].

Regulatory agencies such as the US FDA and the EMA have established processes through which sponsors can obtain advice on drug/indication specific data the agencies will expect and plan the relevant studies accordingly. In contrast, WHO guidelines are usually developed 'post-hoc', i.e., based on systematic review and evaluation of publicly available data, initiated when 'Member States, WHO country offices, external experts or other stakeholders ask for guidance on a clinical or public health problem or policy area'. It is at the discretion of the members of the 'Guideline Development Group,' established by WHO for a specific guideline under consideration, to decide whether the data available are those they consider necessary to support a new guideline [131]. This approach may reflect the fact that, in the past, few drugs have been developed specifically to address health problems that do not provide the prospect of return/profit from investment, i.e., for diseases in LMIC, the countries that are typically requesting WHO guidelines to inform their policies [134, 135, 136]. Exceptions were the development of ivermectin for onchocerciasis and triclabendazole for human fascioliasis (see Additional File 1). Both development programs occurred when WHO guideline development was less formalized. For sponsors and funders of drugs developed for NTDs and in particular for PC, the current approach to WHO guideline development constitutes a big problem: resources and time into studies to complement the data acquired for regulatory registration are invested based on consultation with experts and possibly WHO NTD staff. Their views on the type and amount of data required to inform guidelines may be different from the views of the Guideline Development Group. WHO has started to address this problem by piloting a 'WHO Coordinated Scientific Advice procedure' [137].

Implementation research

Effective translation of WHO Guidelines and country policies into practice may require implementation research (IR, also referred to as 'operational research'), defined here as research to identify, understand and address barriers to effective and quality implementation of health interventions, strategies, and policies in a particular setting [131].

Depending on the differences between the drug currently used for PC and the new drug, in particular with respect to treatment regimen, safety profile and eligible population, IR may be needed on how best to implement PC with the new drug and to gather information on the acceptability of the new treatment and how it is provided

at the individual, community, and health system level. Beyond data on the adverse reactions that will impact acceptability by the population (defined here as the percentage of the eligible population willing to take the drug each time it is provided and the willingness of the communities to engage in drug distribution, if applicable), such data cannot be obtained during clinical studies for registration or post-registration studies to gather additional safety and efficacy data since those are typically double-blinded studies. Even if not double-blinded, such studies include many elements that are not part of distribution during PC (or case management) and will impact participants' perceptions of the drug. Such elements include informed consent/assent, pre- and post-treatment examinations and compensation for time lost from gainful activities due to study participation.

'Acceptability' of a new drug to the individuals/communities to be treated and other stakeholders, such as local health care workers, national programmes/Ministries of Health, collaborating non-governmental organisations and funders as well as effective integration of the new intervention into local practice depend on many factors. These include not only the benefit/risk ratio of the drug but also the specific economic, health system, and political and social-cultural context in which the new intervention will be implemented. Locally adapted IR studies may be needed to address implementation challenges. IR may also be needed to provide further evidence to inform guidelines and country policies. Ideally such research would be conducted based on a common 'core-protocol' to ensure data can be analysed across studies/countries and should be implemented in collaboration between different national programmes and researchers to ensure timely sharing of lessons learnt. Such an approach has been initiated to address research needs identified in the 'WHO consolidated guidelines on drug-resistant tuberculosis treatment' [138, 139, 140].

Based on the certainty of evidence that informed a guideline and on the knowledge gaps identified in the systematic reviews and by the Guideline Development Group, WHO guidelines specify research needs [131].

Conclusions

Between 1975 - 1999 and between 2000 - 2011, 13 and five drugs, respectively, were approved by the US FDA and/or the EMA for an NTD [141, 142]. Even assuming our criteria for categorization drugs as in 'development for regulatory registration' were too strict, the number of drugs in at least Phase 2 clinical development, and the 2018 registration of fexinidazole for treatment of first and second stage *T. b. gambiense* HAT and moxidectin for onchocerciasis show that investment into drug development continues to be disproportionate to the number of people affected by NTDs. Another sad 'continuation' is that development of drugs for NTDs depends heavily on public funding (government, intergovernmental organization) or funding from private not-for-profit organizations.

Entry of new actors such as the HELP consortium and the Oxfendazole Development Group is encouraging. Development for regulatory approval requires specific experience and expertise to ensure all elements of a submission meet regulatory requirements for registration and to ensure that the post-registration obligations can be met (e.g., regular updates on safety data acquired in any context and anywhere in the world). Such experience, expertise and systems are concentrated in pharmaceutical companies. Lack of such expertise was identified as a significant obstacle in a 2019 workshop 'Repurposing of off-patent drugs:

Research and Regulatory Challenges', hosted by the US National Institute for Health National Center for Advancing Translational Sciences (NCATS) and co-sponsored by the NCATS Cures Acceleration Network Review Board, NCATS Drug Development Partnership Programs, US FDA, and the Reagan-Udall Foundation for the US FDA [143]. We hope that relevant expertise is available to, or will be sought by, the HELP consortium and the Oxfendazole Development Group. An 'NTD drug developer working group' joining all organisations developing drugs for registration for NTDs might be helpful to share lessons learnt.

The short period between the first 'registration' (EMA 'positive scientific opinion') of fexinidazole and registration in *T. b. gambiense* HAT endemic countries, inclusion in the WHO EML, WHO EML for Children [64] and WHO interim guidelines [15] has been attributed to continuing interactions between all stakeholders, including DNDi, Sanofi, the EMA and WHO [8]. Equivalent interactions had been in place for development of moxidectin. These interactions were 'disrupted' by the withdrawal of Pfizer from the collaboration agreement with WHO as well as by the dissolution of APOC. The 'Expanded Special Project for Elimination of Neglected Tropical Diseases' in WHO/AFRO (ESPEN, [144]), while sometimes perceived as the APOC 'successor', differs substantially from APOC in terms of its mandate, resources, and operating model as does the WHO/NTD department. The moxidectin development plan to registration had been generated based on a series of meetings with the EMA for scientific advice in view of submission for an EMA 'scientific opinion'. MDGH chose submission to the US FDA rather than the EMA because they could leverage the possibility of a priority review voucher for the funds they needed [21]. APOC's 'Technical Consultative Committee' [21] had provided input into the clinical development plan as well as the initial plans for studies to acquire additional data needed to inform guidelines. Through APOC, country NTD/onchocerciasis programmes and the non-governmental organizations supporting onchocerciasis control programmes in the endemic countries were kept up-to-date. While the moxidectin example shows that 'the best laid plans' may be compromised by extraneous events, the collaborations 'disrupted' for moxidectin but successfully concluded for fexinidazole appear to be the approach of choice for development of new drugs for NTDs to registration, WHO guidelines, EML inclusion, country policies and practice. The 'WHO Coordinated Scientific Advice procedure' during its pilot phase and beyond will streamline sponsors receiving feedback from different WHO departments.

List of Abbreviations

ADME	Absorption, distribution, metabolism, elimination
APOC	African Programme for Onchocerciasis Research
CR	Cure Rate
CTI	ClinicalTrials.gov Identifier
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
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
LMIC	Low and middle income countries
IR	Implementation Research
LF	Lymphatic Filariasis
MDGH	Medicines Development for Global Health
NDA	New Drug Application
NECT	Nifurtimox-eflornithine combination treatment
NTD	Neglected Tropical Disease
OCP	Onchocerciasis Control Programme in West Africa
ODG	Oxfendazole Development Group
PACTRI	Pan African Clinical Trials Registry identifier
PC	Preventive Chemotherapy
SRA	Stringent regulatory authority
STH	Soil transmitted helminths
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
WHO	World Health Organization

Declarations

Ethics approval and consent to participate

Not applicable

Consent for publication

Not applicable.

Availability of data and material

Not applicable.

Competing interests

ACK managed the development of moxidectin at WHO TDR.

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Supplementary Information

Filename: Additional File 1

File format: pdf

Content:

Tables

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Table S2: Anti-infective drugs, core strategic interventions and gaps in anti-infective drugs as per Roadmap

Table S3: Cure and egg reduction rates in Phase 2 studies evaluating moxidectin efficacy against Strongyloides stercoralis, Trichuris trichiura and concomitant helminths; and against Schistosoma haematobium and S. mansoni

1   Anti-infective drugs for diseases for which preventive chemotherapy is the main strategic core intervention strategy

      1.1   Ivermectin

      1.2   Albendazole, mebendazole and triclabendazole

      1.3   Diethylcarbamazine

      1.4   Praziquantel

      1.5   Azithromycin

      1.6   Benzathine penicillin

      1.7   Topical scabicides

      1.7.1   Permethrin

      1.7.2   Benzyl benzoate

      1.7.3   Malathion

      1.7.4   Sulphur ointment

2   Anti-infective drugs for diseases for which case management is the main control- and elimination strategy

      2.1   Antibiotics

      2.1.1   Rifampicin

      2.1.2   Dapsone

      2.1.3   Clofazimine

      2.1.4   Clarithromycin

      2.1.5   Moxifloxacin

      2.1.6   Tetracycline

      2.2   Anti-trypanosomal drugs

      2.2.1   Fexinidazole

      2.2.2   Pentamidine

      2.2.3   Suramin

      2.2.4   Melarsoprol

      2.2.5   Eflornithine

      2.2.6   Benznidazole

Fungi
- Chromoblastomycosis
- Eumycetoma

Bacteria
- Actinomycetoma
- Buruli ulcer
- Leprosy
- Trachoma
- Yaws

Viruses
- Chikungunya
- Dengue
- Rabies

Neglected Tropical Diseases according to WHO Roadmap 2030

Helminths
- Cysticercosis/Taeniasis
- Dracunculiasis
- Echinococcosis
- Foodborne trematodiases
- Lymphatic filariasis
- Schistosomiases
- Soil-transmitted helminthiases
- Onchocerciasis

Ectoparasites
- Scabies

Protozoa
- African trypanosomiasis
- Chagas disease
- Leishmaniasis
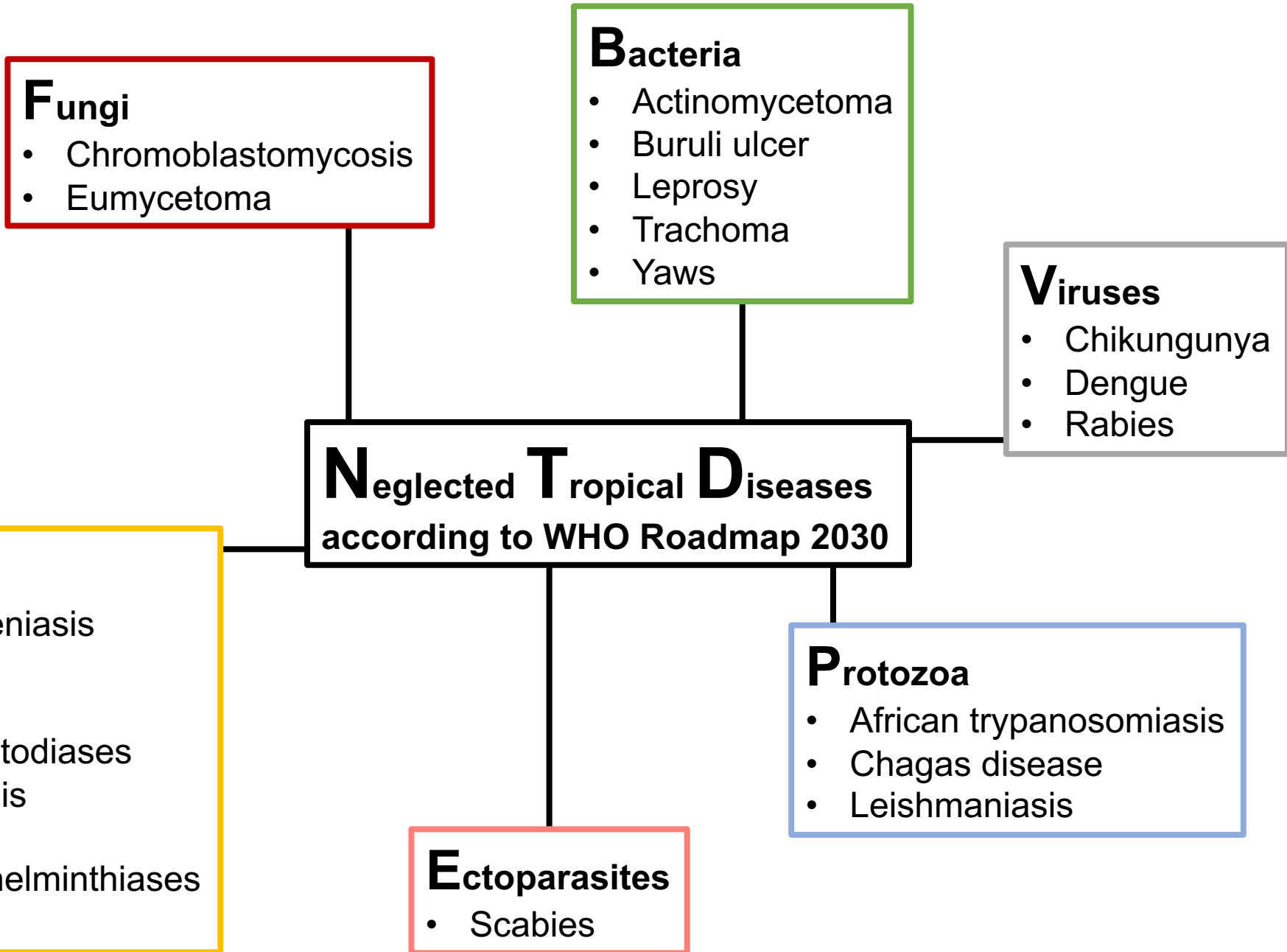
1 **Additional File 1**

2 to

3 **The pipeline for drugs for control and elimination of Neglected Tropical Diseases: 1.**
4 **Anti-infective drugs for regulatory registration**

5

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Tables

Table S1: Source trial registries and last import date into the WHO International Clinical Trials Registry Platform as of 8 October 2021

Australian New Zealand Clinical Trials Registry	5 July 2021
Chinese Clinical Trial Registry	5 July 2021
ClinicalTrials.gov	5 July 2021
EU Clinical Trials Register (EU-CTR)	5 July 2021
ISRCTN	5 July 2021
The Netherlands National Trial Register	5 July 2021
Brazilian Clinical Trials Registry (ReBec)	24 June 2021
Clinical Trials Registry - India	24 May 2021,
Clinical Research Information Service - Republic of Korea	24 June 2021
Cuban Public Registry of Clinical Trials	21 June 2021
German Clinical Trials Register	21 June 2021
Iranian Registry of Clinical Trials	22 June 2021
Japan Primary Registries Network	15 June 2021
Pan African Clinical Trial Registry	21 June 2021
Sri Lanka Clinical Trials Registry	21 June 2021
Thai Clinical Trials Registry (TCTR)	21 June 2021
Peruvian Clinical Trials Registry (REPEC)	28 June 2021
Lebanese Clinical Trials Registry (LBCTR)	21 June 2021

Table S2: Anti-infective drugs, core strategic interventions and gaps in anti-infective drugs as per Roadmap

NTD, species (WHO Fact Sheet link)	Anti-infective drugs as per 2030 Roadmap [1]	Anti-infective drug-based core strategic interventions [1] Selected complementary core interventions [1]	Gaps in anti-infective drugs as per 2030 roadmap [1]
NTDs targeted for eradication			
Dracunculiasis (Guinea worm) · *Dracunculus medinensis* https://www.who.int/health-topics/dracunculiasis	None	· NA **Selected core interventions** **WASH** · Village-based active surveillance for rapid case detection and containment · Communication for behavioral impact · Vector control · Tethering of dogs to prevent contamination of the environment [1, 2]	Drugs to treat cases.
Yaws · *Treponema pallidum pertenue* https://www.who.int/news-room/fact-sheets/detail/yaws	**Azithromycin** EML: oral liquid 200 mg per 5 mL; 250 mg, and 500 mg oral solid capsule (anhydrous). **Benzathine benzylpenicillin** EML: IM 900 mg in vial benzylpenicillin powder for injection (= 1.2 million IU); 1.44 g in vial benzylpenicillin powder for injection (= 2.4 million IU), indications do not include Yaws [1]	**Preventive chemotherapy** · Initial Total community treatment (TCT): single oral azithromycin (30 mg/kg to maximum of 2g) or · Total targeted treatment (TTT, all active clinical cases and contacts during repeat surveys or in response to localized outbreak): single oral azithromycin (30 mg/kg), liquid formulation for <6 year old children may be available to replace crushing tablets and mixing with water. Eligible population: ≥6 months, including pregnant and breastfeeding women. IM Benzathine penicillin (0.6 m units for < 10 years, 1.2 m units for ≥10 years) for people who cannot be treated with azithromycin, fail azithromycin or when azithromycin is not available **Treatment** · Azithromycin (single oral dose) at 30 mg/kg (maximum 2 g) is the preferred treatment. · Benzathine penicillin (single intramuscular dose) at 0.6 million units (children aged under 10 years) and 1.2 million units (people aged over 10 years) can be used for patients with suspected clinical treatment failure after azithromycin, or patients who cannot be treated with azithromycin. [3, 4, 5]	

NTD, species (WHO Fact Sheet link)	Anti-infective drugs as per 2030 Roadmap [1]	Anti-infective drug-based core strategic interventions [1] Selected complementary core interventions [1]	Gaps in anti-infective drugs as per 2030 roadmap [1]
NTDs targeted for elimination (interruption of transmission)			
Human African trypanosomiasis · *Trypanosoma brucei gambiense* https://www.who.int/health-topics/human-african-trypanosomiasis	**Fexinidazole** EML: 600 mg oral solid. **Eflornithine** EML: IV: 100 mg per mL in 100 mL bottle (hydrochloride). **Nifurtimox** EML: 120 mg tablet **Pentamidine** EML: IM, 200 mg (as isethionate) powder for injection.	**Case management** **Patients aged ≥ 6 years and body weight ≥ 20 kg AND in first-(haemo-lymphatic) stage or non-severe second-(neurological) stage (WBC in CSF < 100/µL)** · Oral fexinidazole, 10 days, weight category dependent dosing **Patients in severe second-stage (WBC in CSF ≥ 100/µL)** · NECT: Oral nifurtimox 5mg/kg TID 10 days, eflornithine 400 mg/kg 7 days **Children aged < 6 years or body weight < 20 kg** · 1st stage disease: IM pentamidine, 4 mg/kg · 2nd stage disease: NECT **Pregnant and lactating women** · 2nd, 3rd trimester: fexinidazole or pentamidine · If clinical condition does not allow to delay treatment, fexinidazole, eflornithine monotherapy or NECT, [6] **Selected complementary core interventions [1]** · WASH · Vector control · Treatment of animals (cattle, pigs)	Safe and efficient single oral dose for both stages (e.g. acoziborole) to help integration of treatment into primary health system Oral formulation for age group <6 years
Leprosy · *Mycobacterium leprae* https://www.who.int/health-topics/leprosy	**Rifampicin** EML: 150 mg and 300 mg oral solid. **Dapsone** EML: 25 mg, 50 mg, and 100 mg tablet. **Clofazimine** EML: 50 mg and 100 mg oral solid.	**Case management** **Treatment** · Multibacillary: 12 months treatment, rifampicin, dapsone, clofazimine (doses age dependent) [7] · Paucibacillary: 6 months treatment, rifampicin, dapsone (doses age dependent) [7] **Treatment of drug-resistant leprosy** · Rifampicin resistance: at least two of the following second-line drugs: clarithromycin, minocycline or a quinolone (ofloxacin, levofloxacin or moxifloxacin), plus clofazimine daily for 6 months, followed by clofazimine plus one of the second-line drugs daily for an additional 18 months [7]	New effective medicine or combinations

NTD, species (WHO Fact Sheet link)	Anti-infective drugs as per 2030 Roadmap [1]	Anti-infective drug-based core strategic interventions [1] Selected complementary core interventions [1]	Gaps in anti-infective drugs as per 2030 roadmap [1]
		· Rifampicin and ofloxacin resistance: clarithromycin, minocycline and clofazimine for 6 months followed by clarithromycin or minocycline plus clofazimine for an additional 18 months [7] **Chemoprophylaxis (contacts of leprosy patients, ≥ 2 years upon consent of index case to disclose the disease and adequate management of contacts)** · Single dose rifampicin [7]	
Onchocerciasis · *Onchocerca volvulus* https://www.who.int/health-topics/onchocerciasis	**Ivermectin** EML: 3mg tablet (scored).	**Preventive chemotherapy** Depending on pre-control endemicity in combination with (1) co-endemicity of loiasis due to risk of adverse reactions to ivermectin in individuals very high *Loa loa* microfilaraemia and (2) co-endemicity with lymphatic filariasis (LF, see recommendations for LF below) **Onchocerciasis meso- or hyperendemic areas (prevalence of onchocercal nodules among men >20%)** **Areas without loiasis:** · Once to twice yearly single dose of ivermectin [1, 8, 9]. **Areas with loiasis co-endemicity:** · *Loa loa* microfilaraemia prevalence <20% or RAPLOA prevalence <40% [8, 10] · *Loa loa* microfilaraemia prevalence ≥20% or RAPLOA prevalence ≥40%: Ivermectin MDA after preparation as per [8] and adaptation of treatment strategy depending on number and treatment coverage of prior ivermectin MDA rounds and occurrence of serious adverse reactions. **Onchocerciasis hypoendemic areas (with or without loiasis):** · Individual, clinic-based ivermectin treatment [8, 11] WHO is preparing for new guidance for onchocerciasis elimination strategies for hypoendemic areas where loiasis is co-endemic [1] considering the recommendations of its advisory committees [1, 12, 13]. **Dose:** 150μg/kg **Eligible population excludes:** < 90 cm, too sick to be treated (i.e. present for treatment), women having given birth in the last week, pregnant women (note those	Macrofilaricide. Efficacy and safety of moxidectin in children and community settings. Safe drugs safe in *Loa loa* co-endemic areas

NTD, species (WHO Fact Sheet link)	Anti-infective drugs as per 2030 Roadmap [1]	Anti-infective drug-based core strategic interventions [1] Selected complementary core interventions [1]	Gaps in anti-infective drugs as per 2030 roadmap [1]
		excluded should be treated as soon as the exclusion criterion is not met anymore) [11, 14]	
NTDs targeted for elimination as a public health problem			

Chagas disease
 	
· *Trypanosoma cruzi*
https://www.who.int/health-topics/chagas-disease
	Benznidazole
	EML: 12.5 mg tablet, 50 mg tablet (scored), and 100 mg tablet.
	
	Nifurtimox
	EML: 30 mg tablet, 120 mg tablet, and 250 mg tablet.
		Case management
		
		· Benznidazole or nifurtimox treatment to cure infection during acute or early chronic phase, prevent or curb disease progression, in cases of congenital infection
		· Acute cases: 60 day treatment with
		  · first option - Benznidazole 7.5-10 mg/kg/day for ≤40 kg, 5-7 mg/kg/day for >40 kg in 2-3 fractional daily doses
		  · second option – Nifurtimox 10-15 mg/kg/day for ≤40 kg, 8-10 mf/kg/day for >40 kg in 2-3 fractional doses/day
		· Congenital cases: 60 day treatment with
		  · First option – Benznidazole 10 mg/kg/ day in 2 to 3 fractional daily doses
		  · Second option – Nifurtimox 10-15 mg/kg in 2 to 3 fractional daily doses
		· Recent chronic infection
		  · Benznidazole 7.5 mg/kg/day for ≤40 kg, 5 mg/kg/day for >40 kg in 2-3 fractional daily doses
		Benznidazole ineligible cases: pregnant women, people with kidney or liver failure, chronic cases with specific organ damage
		Nifurtimox ineligible cases: pregnant women, people with kidney or liver failure, background of neurological or psychiatric disorders, chronic cases with specific organ damage [1, 15, 16]
		
		Selected complementary core interventions [1]
		
		· Treatment of disease manifestations
		· Treatment of women of childbearing potential to prevent congenital transmission
		· WASH
		· Vector control
		· Blood screening
			Dosage and duration of benznidazole and nifurtimox treatment, combination treatment, new drugs

NTD, species (WHO Fact Sheet link)	Anti-infective drugs as per 2030 Roadmap [1]	Anti-infective drug-based core strategic interventions [1] Selected complementary core interventions [1]	Gaps in anti-infective drugs as per 2030 roadmap [1]
Human African trypanosomiasis · *T. brucei rhodesiense* https://www.who.int/health-topics/human-african-trypanosomiasis	**Suramin sodium** EML: IV, 1 g in vial. **Melarsoprol** EML: IV, 3.6% in 5 mL in ampoule as solution (180 mg active compound).	**Case management** · First stage: Suramin (test dose 4-5 mg/kg day 1, 20 mg/kg every 7 days for 5 weeks (maximum dose/injection 1g) · Second stage: Melarsoprol 2.2 mg/kg per day for 10 days [17] **Selected complementary core interventions** [1] · WASH · Vector control · Treatment of animals (cattle, pigs)	Safe, efficient treatments (e.g., fexinidazole, acoziborole) to replace toxic arsenic-based melarsoprol.
Visceral leishmaniasis (VL) · *Leishmania donovani* · *L. infantum* https://www.who.int/health-topics/leishmaniasis	**Pentavalent antimonials** EML: Meglumin antimoniate, IM, 30% in 5 mL ampoule (81 mg/ml), equivalent to about 8.1% antimonate, Sodium stibogluconate, IM-IV, 30-ml vial of 100 mg/ml **Liposomal amphotericin B** EML: IV, 50 mg powder for injection in vial as liposomal complex. **Paromomycin** EML: IM, 750 mg paromomycin as sulfate. **Miltefosine** EML: 10 mg and 50 mg tablet	The treatment of leishmaniasis depends on various factors, e.g., disease, concomitant pathologies, parasite species, and location [1]. **Case management for visceral leishmaniasis (VL) based on national guidelines [1]** · *L. infantum*: pentavalent antimonials, liposomal amphotericin B · *L. donovani*: pentavalent antimonials, liposomal amphotericin B, paromomycin, miltefosine For details and ranking of treatment options by causative species and region by the WHO Expert Committee on the Control of Leishmaniases, 2010 see [17] · HIV co-infected patients in patients in East Africa and South-East Asia: liposomal amphotericin B + miltefosine [18, 19, 20] WHO is working on expanding guidance [1] **Selected complementary core interventions** [1] · Vector control · Early diagnosis and treatment	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.
Trachoma · *Chlamydia trachomatis* https://www.who.int/health-topics/trachoma	**Azithromycin** EML: 1.5% Eye drops (solution); oral liquid 200 mg per 5 mL; 250 mg, and	**Preventive chemotherapy** **Evaluation units in which the prevalence of trachomatous inflammation—follicular (TF) among 1–9-year-old children is ≥5%:**	-

NTD, species (WHO Fact Sheet link)	Anti-infective drugs as per 2030 Roadmap [1]	Anti-infective drug-based core strategic interventions [1] Selected complementary core interventions [1]	Gaps in anti-infective drugs as per 2030 roadmap [1]
	500 mg oral solid capsule (anhydrous) **Tetracycline** EML: 1% (hydrochloride) eye ointment.	· Annual MDA of oral azithromycin (20 mg/kg) offered to all aged ≥6 months, until TF prevalence drops to <5%. · If azithromycin is unavailable or contraindicated: tetracycline eye ointment BID to both eyes for 6 weeks. **Selected complementary core interventions** [1] · Surgery for trachomatous trichiasis · Facial cleanliness · Environmental improvement, specifically improvements in access to water and sanitation [21, 22, 23, 24]	
Lymphatic filariasis · *Wuchereria bancrofti* · *Brugia malayi* · *Brugia timori* https://www.who.int/health-topics/lymphatic-filariasis	**Ivermectin** EML: 3mg tablet (scored) **Diethylcarbamazine** EML: 50mg and 100 mg tablet. **Albendazole** EML: 400 mg tablet (chewable)	**Preventive chemotherapy** Depending on (1) co-endemicity of loiasis and onchocerciasis due to risk of adverse reactions to ivermectin and diethylcarbamazine and (2) status of MDA programme. **Countries without onchocerciasis or loiasis:** · Annual diethylcarbamazine (6 mg/kg) with 400 mg albendazole (DA) · Annual Ivermectin, diethylcarbamazine plus albendazole (IDA) in areas with less than four two drug treatment rounds; not having met stopping criteria with DA despite having met coverage targets; with infections suggesting local transmission post MDA or post-validation. [25] **Eligible population** excludes pregnant women, children under 2 years of age, and the severely ill. [11] **Countries with onchocerciasis (due to risks of ocular adverse reactions to diethylcarbamazine in *O. volvulus* infected individuals, for review (Awadzi et al., 2015)) in areas without loiasis co-endemicity** · Annual ivermectin (150-200 ug/kg) with 400 mg albendazole (IA), except in areas where biannual ivermectin treatment is being delivered for onchocerciasis [25] **Eligible population** excludes pregnant women, children <90 cm (≈15 kg), severely ill individuals [11] **Countries with onchocerciasis where loiasis is co-endemic (due to risks of severe adverse reactions to ivermectin in individuals with high *Loa loa* microfilaraemia,** [26, 27])	Macrofilaricide, drug safe in *Loa loa* infected individuals

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NTD, species (WHO Fact Sheet link)	Anti-infective drugs as per 2030 Roadmap [1]	Anti-infective drug-based core strategic interventions [1] / Selected complementary core interventions [1]	Gaps in anti-infective drugs as per 2030 roadmap [1]
		· Biannual albendazole (400 mg) in loiasis co-endemic areas where ivermectin has not already been distributed for onchocerciasis or LF [28] **Eligible population** excludes children in the 1st year of life; pregnant women in the 1st trimester of pregnancy. [11] **Selected complementary core interventions [1]** Vector management in appropriate settings (in particular where *Loa loa* co-endemicity prohibits ivermectin use [28]	
Schistosomiasis **Intestinal** · *S. japonicum* · *S. mansoni* · *S. mekongi* **Urinary** · *S. haematobium* https://www.who.int/health-topics/schistosomiasis	**Praziquantel** EML: 600 mg tablet.	**Preventive chemotherapy** Endemic communities with ≥10% *Schistosoma* spp infection prevalence: · Annual treatment with a single dose of all ≥ 2 years of age targeting ≥75% treatment coverage · Consideration should be given to twice yearly preventive chemotherapy in areas with demonstrated lack of appropriate response to annual preventive chemotherapy or high endemicity areas with baseline prevalence ≥50% in school-age children Endemic communities with <10% *Schistosoma* spp infection prevalence with ongoing preventive chemotherapy: · Continuation with same or reduced frequency towards interruption of transmission **Test and treat approach** In endemic communities with <10% *Schistosoma* spp infection **Dose**: 40 mg/kg, based on height pole for people ≥94 cm or ≥ 4 years **Eligible population:** all ≥2 years, including pregnant women after the first trimester and lactating women [11, 29]	Improved praziquantel and pediatric formulation. New drugs to complement praziquantel in case of resistance.
Soil-transmitted helminthiases including strongyloidiasis · *Ascaris lumbricoides* · Hookworms ○ *Ancylostoma duodenale*	**Albendazole** EML: 400 mg tablet (chewable). **Mebendazole** EML: 100 mg tablet (chewable),	**Preventive chemotherapy** ***A. lumbricoides, T. trichiura, Ancylostoma duodenale, Necator americanus*** · Annual single-dose albendazole or mebendazole where baseline prevalence of any soil-transmitted infection is 20% - 50% · Biannual single-dose albendazole or mebendazole where baseline prevalence of any soil-transmitted infection is >50% **Dose**: albendazole 200 mg for 12-23 months, else 400 mg, mebendazole 500 mg	More effective medicines and drug combinations against *T. trichiura* and hookworm infections Drugs and drug combinations to be used

NTD, species (WHO Fact Sheet link)	Anti-infective drugs as per 2030 Roadmap [1]	Anti-infective drug-based core strategic interventions [1] Selected complementary core interventions [1]	Gaps in anti-infective drugs as per 2030 roadmap [1]
o *Necator americanus* · *Trichuris trichiura* · *Strongyloides stercoralis* https://www.who.int/health-topics/soil-transmitted-helminthiases	and 500 mg tablet (chewable). **Ivermectin** EML: 3mg tablet (scored).	**Eligible population**: all young (12-23 months), preschool (24-59 months), school-age children, non-pregnant adolescent girls and women of reproductive age, pregnant women in 2nd and 3rd trimester, lactating women [11, 30] · WHO is preparing guidelines for addition of ivermectin where prevalence of *S. stercoralis* exceeds 10% and in areas with high prevalence of *T. trichiura* [1] **Case management** · Treatment of individuals living in areas endemic for STH and *S. stercoralis* [1] **Selected complementary core interventions [1]** · WASH	in case of emergence of drug resistance
Rabies · *Rabies lyssavirus* https://www.who.int/health-topics/rabies	None.	**Case management of confirmed or suspected cases of human rabies** · Thorough wound washing · Post-exposure prophylaxis (PEP) with the rabies vaccine immediately after exposure to a potentially rabid animal · Rabies immunoglobulin for category III exposures immediately after exposure to a potentially rabid animal · Palliative care **Selected complementary core interventions [1]** · Vaccination of dogs and dog population management · Vaccination of people at high risk of exposure to the rabies virus, e.g., laboratory staff working with the rabies virus, veterinarians and animal handlers [1, 31, 32]	Monoclonal antibodies. Anti-virals and agents promoting entry of drugs, antibodies and immune effectors cells across the blood-brain barrier (World Health Organization, 2018g)
NTDs targeted for control			
Cutaneous Leishmaniasis (CL) · *Leishmania donovani* · *L. infantum* · *L. tropica* · *L. major* · *L. aethiopica* · *L. mexicana* · *L. amazonensis*	**Pentavalent antimoniate** EML: Meglumin antimoniate, IM, 30% in 5 mL ampoule, equivalent to about 8.1% antimonate; Sodium stibogluconate, IM-IV, 30-ml vial of 100 mg/ml **Liposomal amphotericin B**	The treatment of leishmaniasis depends on various factors, e.g., disease, concomitant pathologies, parasite species, location and national guidelines [1]: **Case management** · Topical/intralesional treatment: pentavalent antimonials, paromomycin/methylbenzethonium chloride, cryotherapy, thermotherapy. · Systemic treatment: fluconazole, ketoconazole, liposomal amphotericin B, amphotericin B deoxycholate, pentamidine, pentavalent antimonials (with or without allopurinol), paromomycine, miltefosine.	CL: oral/topical treatment suitable for health center and community level use.

NTD, species (WHO Fact Sheet link)	Anti-infective drugs as per 2030 Roadmap [1]	Anti-infective drug-based core strategic interventions [1] Selected complementary core interventions [1]	Gaps in anti-infective drugs as per 2030 roadmap [1]
· *L. venezuelensis* · *L. Viannia braziliensis* · *L. (V.) guyanensis* · *L. (V.) panamensis* · *L. (V.) peruviana* https://www.who.int/health-topics/leishmaniasis	EML: IV, 50 mg powder for injection in vial as liposomal complex. **Paromomycin** EML: IM, 750 mg paromomycin as sulfate. **Miltefosine** EML: 10 mg and 50 mg tablet	For dose regimens and ranking of treatment options by causative species and region by the WHO Expert Committee on the Control of Leishmaniases, 2010 see [33] **Selected complementary core interventions [1]** · Vector control · Early diagnosis and treatment	
Scabies and other ectoparasites · *Sarcoptes scabiei var hominis* Scabies https://www.who.int/news-room/fact-sheets/detail/scabies	**Ivermectin** EML: 3mg tablet (scored) **Permethrin** EML: topical, 1% lotion and 5% cream **Benzyl benzoate** EML: topical, 25% lotion **Malathion ointment** **Sulfur ointment**	**Preventive chemotherapy [1]** · MDA with ivermectin. · Topical scabicides WHO will be preparing guidelines taking into consideration the outcome of an informal consultation (World Health Organization, 2020b) **Case management [1]** · Topical scabicides (permethrin, benzylbenzoate, malathion and sulfur ointment) · Ivermectin · Specialist case management of crusted scabies cases **Selected complementary core interventions [1]** · Treatment of household contacts · WASH	Determine efficacy of single dose IVM for programmatic use and safe dose in children <15 kg, <90 com or <5 years; Identify alternative strategies for ivermectin MDA including for loiasis co-endemic areas; Evaluate moxidectin [34]
Buruli ulcer · *Mycobacterium ulcerans* https://www.who.int/news-room/fact-sheets/detail/buruli-ulcer-(mycobacterium-ulcerans-infection)	**Rifampicin** EML: not listed for the indication **Clarithromycin** EML: not listed for the indication **Moxifloxacin** EML: not listed for the indication	**Case management** **Direct Observed Treatment after laboratory confirmed diagnosis** · Any age, including in pregnancy: Oral rifampicin (10 mg/kg) daily for 8 weeks and oral clarithromycin (7.5 mg/kg) twice daily for 8 weeks (including for pregnant women) · Adults only: Oral rifampicin (10 mg/kg) once daily for 8 weeks and oral moxifloxacin (400 mg) by mouth once daily for 8 weeks. **Selected complementary core interventions** [1] · Surgery (debridement, skin grafting, scar revision)	New treatment options with reduced treatment duration and lower toxicity, especially for children.

NTD, species (WHO Fact Sheet link)	Anti-infective drugs as per 2030 Roadmap [1]	Anti-infective drug-based core strategic interventions [1] Selected complementary core interventions [1]	Gaps in anti-infective drugs as per 2030 roadmap [1]
		· In case of joint involvement or movement limitation, appropriate positioning with frequent exercise. [35]	

Actinomycetoma
 · Actinomycetoma
   o *Actinomadure madura*
   o *A. pelletieri*
   o *Nocardia brasiliensis*
 https://www.who.int/health-topics/mycetoma-chromoblastomycosis-and-other-deep-mycoses
	None specified
	 EML: Indication not included
		Case management
		 · long term treatment with antibiotic combinations
		 · Wound cleaning, dressing
		 Selected complementary core interventions [1]
		 · WASH
		 · Protective clothing and shoes
			Better treatment regimens (shorter duration, higher efficacy).

Eumycetoma
   o *Madurella mycetomatis*
   o *Mycetoma mycetomatis*
 https://www.who.int/health-topics/mycetoma-chromoblastomycosis-and-other-deep-mycoses
	Itraconazole
	 EML: Indication not included
		Case management
		 · Antifungals (mainly itraconazole 400 mg/day) – combined with surgery
		 · Wound cleaning, dressing
		 Selected complementary core interventions [1]
		 · WASH
		 · Protective clothing and shoes
			Better treatment regimens (shorter duration, higher efficacy).

Chromoblastomycosis · *Cladophialophora carrionii* · *C. bantiana* · *Fonsecaea pedrosoi* · *Fonsecaea compacta* · *Phialophora verrucosa* **Other Deep Mycoses** · *Paracoccidioides spp.* · *Sporothrix spp.*	**Itraconazole** EML chromoblastomycosis, paracoccidioidomycosis, sporotrichosis: oral liquid, 10 mg per mL, oral solid 100 mg **Amphotericin B** EML sporotrichosis: 50 mg powder for injection (as	**Case management [1]** · No "gold standard" treatment; treatment options include antifungals (itraconazole), physical therapies, immune adjuvants and surgery for minor lesions · Treatment of choice for paracoccidioidomycosis and sporotrichosis: itraconazole **Selected complementary core interventions [1]** · WASH · Protective clothing and shoes	Prospectively obtained effectiveness of itraconazole and other antifungals; Improved treatment regimens (shorter duration and increased efficacy)

NTD, species (WHO Fact Sheet link)	Anti-infective drugs as per 2030 Roadmap [1]	Anti-infective drug-based core strategic interventions [1] Selected complementary core interventions [1]	Gaps in anti-infective drugs as per 2030 roadmap [1]
https://www.who.int/health-topics/mycetoma-chromoblastomycosis-and-other-deep-mycoses	deoxycholate or liposomal complex)		
Dengue and Chikungunya · Flavivirus Dengue virus · Alphavirus Chikungunya virus https://www.who.int/health-topics/dengue-and-severe-dengue https://www.who.int/health-topics/chikungunya	None	NA **Selected complementary core interventions** [1] · WASH · Vector control · Symptomatic treatment [1, 36, 37]	Anti-viral drugs.
Echinococcosis [World Health Organization , 2019a] · *Echinococcus granulosus* · *Echinococcus multilocularis* https://www.who.int/health-topics/echinococcosis	**Albendazole** EML: 400 mg tablet (chewable). **Mebendazole** EML: Solid: 100 mg tablet (chewable); 500 mg tablet (chewable)	**Case management** · Treatment with albendazole or mebendazole Albendazole (drug of choice) 10-15mg/kg/day, in two divided doses, with a fat rich meal to increase its bioavailability. Mebendazole may be used at 40-50mg/kg daily, in three divided doses if albendazole is not available or not tolerated. · Other options for cystic echinococcosis include percutaneous methods + albendazole prophylaxis with the PAIR (Puncture, Aspiration, Injection, Re-aspiration) technique, standard catheterization, or the modified catheterization technique, surgery (cyst removal +albendazole prophylaxis, and "watch and wait" · Other option for alveolar echinococcosis: curative surgery [1, 38, 39, 40] **Selected complementary core interventions (WHO, 2020): 'One Health' approach** **In collaboration with veterinary and food safety authorities** · WASH · Periodic deworming of dogs with praziquantel · Livestock vaccination · where feasible, anthelminthic baiting of foxes. [1, 39, 40, 41]	Identification of optimal albendazole treatment courses (indicates that drugs with improved efficacy would add value).

NTD, species (WHO Fact Sheet link)	Anti-infective drugs as per 2030 Roadmap [1]	Anti-infective drug-based core strategic interventions [1] Selected complementary core interventions [1]	Gaps in anti-infective drugs as per 2030 roadmap [1]
Foodborne trematodiases · *Clonorchis sinensis* · *Dicrocoelium dendriticum* · *D. hospes* · *Fasciola hepatica* · *F. gigantica* · *Fasciolopsis buski* · *Heterophyes heterophyes* · *Metagonimus yokogawai* · *Opisthorchis viverrine* · *O. felineus* · *Paragonimus westermani* · *P. kellicotti* https://www.who.int/health-topics/foodborne-trematode-infections	**Praziquantel** EML: 250 mg and 600 mg tablet. **Triclabendazole** EML: 250 mg tablet.	**Preventive chemotherapy** [1] · Small liver flukes and *Paragonimus spp*.: MDA with praziquantel · *Fasciola spp* and *Paragonimus spp*: MDA with triclabendazole **Case management (World Health Organization, 2007; 2008; 2011; 2020a)** · Praziquantel · Triclabendazole **Selected complementary core interventions [1]:** · WASH · Veterinary public health: treatment of livestock and other domestic animals, · Management practices in fish farming · Snail control · Outbreak investigation and control [36]	None
Taeniasis and cysticercosis [World Health Organization , 2018b] · *Taenia solium* https://www.who.int/health-topics/taeniasis-and-cysticercosis	**Albendazole** EML: 400 mg tablet (chewable) **Praziquantel** EML: 600 mg and 150 mg tablet **Niclosamide** EML: 500 mg tablet (chewable)	**Preventive Chemotherapy** · Endemic populations: Single dose praziquantel (10 mg/kg) or, if active surveillance and medical referral of neurological adverse events is in place, niclosamide (2 g, dose adjusted for children), or albendazole 400 mg/day for 3 consecutive days [1, 42]. · Endemic population in communities with school based preventive chemotherapy for soil-transmitted helminths and reporting system with active surveillance and medical referral of neurological adverse events: co-administration of single dose praziquantel (10 mg/kg) and single dose albendazole (400 mg) to school age children [42]. **Case management** · Taeniasis: Single administration of praziquantel (10 mg/kg) or niclosamide (single dose, adults and children >6 years: 2 g, children 2-6 years 1g, children < 2 years 0.5 g, after light meal followed after 2 hours by laxative) [43]	Efficacy of current treatment strategies

NTD, species (WHO Fact Sheet link)	Anti-infective drugs as per 2030 Roadmap [1]	Anti-infective drug-based core strategic interventions [1] Selected complementary core interventions [1]	Gaps in anti-infective drugs as per 2030 roadmap [1]
		· Neurocysticercosis: long courses of praziquantel and/ or albendazole and supporting therapy with corticosteroids and/or antiepileptic medicines. Doses and duration depending on number, size, location and developmental stage of the cysts, surrounding inflammatory edema, acuteness and severity of signs or symptom. Usual doses 15 mg/ kg/day albendazole and 50 mg/kg/day praziquantel, divided in two to three daily doses; proposed length of treatment from one to two weeks for parenchymal and $\geq$ 1 month for subarachnoid lesions. [40, 43] **Selected complementary core interventions [1]:** in collaboration with Food and Agriculture Organization of the United Nations (FAO) and the World Organization for Animal Health (OIE), including · Water, Sanitation and Hygiene (WASH) [1, 43] · Prevention and control in pigs: improved pig farming, pig vaccination with TSOL18 and treatment with oxfendazole, meat inspection and processing, [43]	

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EML: WHO Model List of Essential Medicines, 2021 [44], IM intramuscular, IV intravenous, PC: preventive chemotherapy, WASH: Clean water, sanitation and hygiene.

Table S3: Cure and egg reduction rates in Phase 2 studies evaluating moxidectin efficacy against *Strongyloides stercoralis, Trichuris trichiura* and concomitant helminths; and against *Schistosoma haematobium* and *S. mansoni*

Helminth	Treatment* (n analysed)	CR (%) (95% CI)	% GM ERR/LRR (95% CI)	Additional information
S. stercoralis	IVM 200 µg/kg (62)	95.1 (86.5- 99.0)		Laos Adolescents and adults
	Moxi 8 mg (63)	93.6 (84.5-98.2)		Randomized, single blind, single dose
Hookworm	IVM 200 µg/kg (34)	55.9 (52.1-84.7)	79.4 (61-88)	Baermann assay, Kato-Katz, 2 samples (blinded)
	Moxi 8 mg (37)	56.7 (55.9-79.7)	74.6 (61-90)	21-25 days post-Tx
Opistorchis. viverrini	IVM 200 µg/kg (46)	6.5 (6.4-25.4)	0 (−40-2)	ISRCTN11983645
	Moxi 8 mg (56)	17.8 (11.2-32.2)	12.5 (−2-30)	[2]
T. trichiura	Moxi 8mg + Alb 400mg (197)	50.8 (43.6–57.9)	98.5 (98.0–98.9)	Tanzania 12-18 years
	Alb 400mg + OxP 25 mg/kg (200)	83.0 (77.1–87.9)	99.8 (99.6–99.9)	Randomized, single blind, single dose
	Moxi 8mg + Tri [200mg <15 yrs, 400 mg ≥15 yrs] (119)	22.7 (15.5–31.3)	91.6 (88.2–93.9)	Kato-Katz, 2 samples, 2 smears each (blinded)
	Moxi 8 mg (118)	14.4 (8.6–22.1)	83.2 (77.9–87.6)	14-21 days post-Tx
Hookworm	Moxi 8mg + Alb 400mg (95)	76.8 (66.2–85.4)	98.9 (98.0- 99.5)	ISRCTN20398469
	Alb 400mg + OxP 25 mg/kg (94)	75.9 (65.3–84.6)	98.6 (97.4- 99.3)	[3]
	Moxi 8mg + Tri [200mg <15 yrs, 400 mg ≥15 yrs] (55)	88.2 (76.1–95.6)	99.4 (98.7- 99.8)	
	Moxi 8 mg (51)	34.0 (20.8–49.3)	86.8 (72.7–93.9)	
A. lumbricoides	Moxi 8mg + Alb 400mg (133)	96.6 (91.5–99.1)	>99.9 (99.98–99.99)	
	Alb 400mg + OxP 25 mg/kg (129)	96.6 (91.4–99.1)	>99.9 (99.97–99.99)	
	Moxi 8mg + Tri [200mg <15 yrs, 400 mg ≥15 yrs] (77)	97.1 (90.2–99.6)	>99.9 (99.9–100.0)	
	Moxi 8 mg (71)	98.4 (91.4–99.9)	>99.9 (99.9–100.0)	
T. trichiura	Placebo (40)	12.5	45.9	Tanzania

Helminth	Treatment* (n analysed)	CR (%) (95% CI)	% GM ERR/LRR (95% CI)	Additional information
		(4.2–26.8)	(11.3–67.0)	16-18 years
	Moxi 8 mg (41)	46.3 (30.7–62.6)	94.3 (87.8–97.5)	Randomized, single blind, single dose
	Moxi 16 mg (38)	50.0 (33.4–66.6	95.0 (90.3–97.6)	Kato-Katz, 2 samples, 2 smears, 13-20 days post-Tx,
	Moxi 24 mg (41)	43.9 (28.5–60.3)	95.7 (91.8–97.8)	Blinded
	Moxi 8 mg + Alb 400 mg (40)	62.5 (45.8–77.3)	97.4 (94.2–99.0)	NCT03501251
	Moxi 16 mg + Alb 400 mg (42)	61.9 (45.6–76.4)	98.4 (96.7–99.3)	[4]
	Moxi 24 mg + Alb 400 mg (39)	69.2 (52.4–83.0)	98.6 (97.2–99.4)	
Hookworm	Placebo (12)	25	68.6	
	Moxi 8 mg (12)	50	88.2	
	Moxi 16 mg (11)	25	73.7	
	Moxi 24 mg (12)	33.3	81.3	
	Moxi 8 mg + Alb 400 mg (10)	81.8	99.7	
	Moxi 16 mg + Alb 400 mg (15)	80	93.8	
	Moxi 24 mg + Alb 400 mg (10)	90	99.6	
A. lumbricoides	Placebo (5)	20	89.3	
	Moxi 8 mg (4)	100	100	
	Moxi 16 mg (4)	75	100	
	Moxi 24 mg (6)	100	100	
	Moxi 8 mg + Alb 400 mg (7)	100	100	
	Moxi 16 mg + Alb 400 mg (4)	75	100	
	Moxi 24 mg + Alb 400 mg (7)	100	100	
S. stercoralis	Placebo (29)	14 (4–32)	27·0 (−2·2 to 48·3)	Laos Adults
	Moxi 2 mg (30)	73 (54–88)	98·4 (93·7–99·9)	Randomized, single blind, single dose
	Moxi 4 mg (29)	90 (73–98)	99·4 (98·1–100·0)	Baermann assay, Kato-Katz, 2 samples, 2 smears
	Moxi 6 mg (32)	84 (67–95)	99·8 (99·3–100·0)	28 days post-Tx
	Moxi 8 mg (29)	83 (64–94)	97·8 (93·2–99·9)	NCT04056325
	Moxi 10 mg (30)	97	98·5	[5]

Helminth	Treatment* (n analysed)	CR (%) (95% CI)	% GM ERR/LRR (95% CI)	Additional information
		(83–100)	(95·0–100·0)	
	Moxi 12 mg (30)	87 (69–96)	98·6 (95·7–99·9)	
Hookworm	Placebo (17)	0		
	Moxi 2 mg (17)	0		
	Moxi 4 mg (18)	11		
	Moxi 6 mg (21)	14		
	Moxi 8 mg (17)	0		
	Moxi 10 mg (20)	10		
	Moxi 12 mg (21)	29		
O. viverrini	Placebo (17)	14		
	Moxi 2 mg (17)	12		
	Moxi 4 mg (18)	0		
	Moxi 6 mg (21)	4		
	Moxi 8 mg (17)	-5		
	Moxi 10 mg (20)	-5		
	Moxi 12 mg (21)	14		
S. mansoni	Moxi 8 mg (31)	12.9 0.03–0.3)	70.9 0.4–0.9)	Côte d'Ivoire 12-18 years
	Syn 3 daily doses + PZQ 40 mg/kg (26)	27.0 0.1–0.5)	77.6 0.5–1.1)	Randomized, single blind
	Syn 3 daily doses (30)	6.7 0.01–0.2)	64.9 0.4–0.8)	Kato-Katz, 2 samples, 2 smears, 21 days post-Tx
	PZQ 40 mg/kg (29)	27.6 0.1–0.5)	87.5 0.8–1)	
S. hematobium	Moxi 8 mg (27)	14.8 (0.04–0.3)	8.7 (-0.4–0.6)	3 urine samples, urine filtration
	Syn 3 daily doses + PZQ 40 mg/kg (30)	60 (0.4–0.8)	96 (0.8–1.0)	ISRCTN 63657086
	Syn 3 daily doses (27)	11.1 (0.02–0.3)	0 (-0.8–0.6)	[6]
	PZQ 40 mg/kg (26)	38.5 (0.2–0.6)	93.5 (0.8–1.0)	

* single dose unless otherwise specified.
Alb albendazole, CR cure rate, GM ERR geometric mean-based egg reduction rate, IVM ivermectin, LRR larval reduction rate, Moxi moxidectin, OxP oxantel pamoate, PZQ praziquantel, Syn synriam (150 mg arterolane + 750 mg piperaquine, Tri tribendimidine, Tx treatment

1 Anti-infective drugs for diseases for which preventive chemotherapy is the main strategic core intervention strategy

The strategic core intervention for many NTDs is or includes preventive chemotherapy (PC), i.e., drug administration to specified (eligible, at risk) populations without individual diagnosis. These include NTDs targeted for eradication (yaws), for elimination (i.e., interruption of transmission, onchocerciasis, leprosy), for elimination as a public health

problem (LF, schistosomiasis, STH, trachoma) and for control (food-borne trematodiases, scabies, taeniasis and cysticercosis) by or beyond 2030 (Table S2) [7].

Many drugs were originally developed for veterinary use. Prior registration for veterinary use accelerates and, to some extent, reduces costs and risk for development for human use because of significant overlap between regulatory requirements for veterinary and human drugs for non-clinical studies to characterize the drug toxicity profile (dose-response relationship, affected organs, reversibility of effects [8]). Continued large scale use of the same drug for animal and human health and development of resistance is one of the aspects that require 'One Health' approaches [7, 9]. Monitoring drug susceptibility, including variability of response, is a challenge for PC programmes given the lack of suitable diagnostics for this and other purposes. The WHO NTD department has formed a Diagnostics Technical Advisory Committee. WHO makes the target product profiles and preferred product characteristics emerging from this committee as well as others available within its 'Global Observatory on Health Research and Development (https://www.who.int/observatories/global-observatory-on-health-research-and-development, https://www.who.int/observatories/global-observatory-on-health-research-and-development/analyses-and-syntheses/target-product-profile/who-target-product-profiles) [7, 10].

1.1 Ivermectin

Ivermectin, a macrocyclic lactone discovered in 1975 [11], is a semisynthetic anthelmintic derived from avermectin, a fermentation product of *Streptomyces avermitilis*. Macrocyclic lactones have activity against a broad spectrum of endo- and ecto-parasites. They are agonists of the glutamate-gated chloride channel, present in the neurons and pharyngeal muscles of nematodes and arthropods, but not of humans. Activation of the channel inhibits movement and pharyngeal pumping, leading to paralysis [12, 13, 14]. The role of the human immune system in the efficacy of ivermectin against filarial nematodes is still under investigation [15, 16, 17, 18]. Consideration for development for onchocerciasis started in 1978 [19, 20] before introduction into the veterinary market in 1981 [21, 22].

In heavily *Loa loa* infected individuals, ivermectin treatment can result in severe and potentially fatal adverse reactions [23, 24, 25]. This prohibits ivermectin use in loiasis endemic areas that are not onchocerciasis meso- and hyperendemic due to the overall risk-benefit for the population [26]. Until the advent of drugs safe in *Loa loa* co-infected individuals, alternative treatment strategies are needed [27].

Concern has been raised about *O. volvulus* 'suboptimal response' or potentially emerging resistance to ivermectin's embryostatic effect (i.e., time to resumption of microfilariae production and release by the macrofilariae) in some regions after long term use of ivermectin [23, 28, 29, 30, 31, 32, 33]. However, genome-wide association analyses suggest that *O. volvulus* response to ivermectin is a polygenically determined quantitative trait with different identical or related molecular pathways determining the extent of ivermectin response in different *O. volvulus* populations [34]. Furthermore, 'suboptimal response' to ivermectin was observed in some *O. volvulus* infected individuals in areas without ivermectin treatment history [35, 36]. This highlights the need to include variability of response in monitoring of drug response and interpretation of the results.

1.2 Albendazole, mebendazole and triclabendazole

Albendazole, mebendazole, and triclabendazole belong to the class of benzimidazoles. The class was originally developed as plant fungicides and later as veterinary anthelminthics [37]. Benzimidazole exposure results in inhibition of beta tubulin polymerase causing disruption of cytoplasmic microtubule formation [12, 38]. This leads to the killing of adult stages of gut-

dwelling helminths, as well as sterilization or killing of the eggs and larvae [37].
Albendazole is a broad-spectrum anthelminthic, first approved for use in humans in 1982. In its current formulation for human use it is poorly absorbed [38]. **Mebendazole** is also a broad-spectrum anthelminthic. Its mode of action involves multiple targets including glucose uptake in nematodes and cestodes in addition to inhibition of tubulin polymerization [39]. **Triclabendazole** is a narrow-spectrum anthelminthic originally developed for animal fasciolosis. Its mode of action is not completely understood. Triclabendazole and its metabolites are thought to cross the tegument of the immature and adult worms, resulting in resting membrane potential alternation, interference with microtubule structure and function, inhibition of protein synthesis and ultimately death [40, 41]. Development for human fascioliasis, one of the most widespread foodborne trematode infections, was initiated in the 1990ies by WHO in collaboration with Chemische Industrie Basel (CIBA) after a fascioliasis epidemic in Iran in 1989. Regulatory approval for this indication was obtained in Egypt in 1997 and in France in 2002 [41] . Triclabendazole was approved for treatment of fascioliasis in patients 6 years or older by the US FDA in 2019 [40]. Triclabendazole is currently the only drug available able to kill early immature and adult *Fasciola hepatica* [41]. Triclabendazole is under consideration for repurposing for drug-resistant bacterial infections [42].

1.3 Diethylcarbamazine

Diethylcarbamazine (DEC), discovered in 1947, is a piperazine derivative anthelmintic evaluated for its efficacy and safety for onchocerciasis beginning in the 1950ies [43]. *In vitro* experiments at therapeutic concentrations demonstrated the loss of the microfilarial sheath with subsequent damage of organelles and apoptosis of the filarial nematode *Wuchereria bancrofti* [44], the cause of 90% of lymphatic filariasis cases globally [45]. The Global Programme to Eliminate Lymphatic Filariasis advocated for two elimination strategies in areas not co-endemic for either loiasis or onchocerciasis: annual mass drug administration (MDA) of a single dose of DEC or DEC with albendazole, estimated to require 4-6 years, or substitution of table/cooking salt by DEC-fortified salt (0.2-0.4% w/w) estimated to require 6-12 months [Ottesen et al. 1997]. By 2020, MDA had been implemented in at least one endemic area in 69/72 endemic countries and 17/72 countries had met the criteria for elimination of LF as a public health problem [46]. The data from studies and pilot/small scale use of DEC-fortified salt were encouraging [47, 48]. However, implementation for large scale LF control may have been limited [49] to four countries: Taiwan [48], China, where elimination of LF as a public health problem has been partly attributed to the use of DEC-fortified salt [50], Haiti [51], and some areas in India [52, 53, 54].

1.4 Praziquantel

Praziquantel is a chiral pyrazine-isoquinoline derivative discovered in 1972 and first developed for veterinary use. It has a broad spectrum of activity against trematodes and cestodes [55]. The anti-helminthic action is not fully understood and may include binding to calcium channels, tegument disruption, binding and polymerization of actin and exposure of surface membrane antigens [56, 57, 58]. As for other NTDs, the extent to which long-term preventive chemotherapy affects parasite drug susceptibility is unknown [59].

The WHO recommended single dose of 40 mg/kg praziquantel (Table S2) achieves 95%, 94.1% and 86.3% ERR in *Schistosoma. japonicum*, *S. haematobium* and *S. mansoni*, respectively [57]. A dose of 60mg/kg did not increase efficacy against *S. mansoni* or *S. japonicum* [60, 61, 62]. Known limitations of praziquantel are its inactivity against immature parasites [57].

Praziquantel is well tolerated, but in individuals with cysticercosis and cysts in the central nervous system or eyes, the inflammatory reaction to dying *Taenia solium* can result in seizures, and/or cerebral infarction and permanent eye lesion [57].

The commercially available tablets include both (R)-praziquantel (L) with anthelmintic activity and the inactive (S)-praziquantel (D) which contributes to the bitter taste and a 600 mg tablet size that is unsuitable for pre-school children [63]. The Paediatric Praziquantel Consortium (https://www.pediatricpraziquantelconsortium.org/) has developed a paediatric formulation [64, 65].

1.5   Azithromycin

Azithromycin is a macrolide antibiotic with a 15-member lactone ring structure with two sugars attached via a glycosidic bond that is semi-synthetically produced from erythromycin A. It is the single compound in its azalide subclass. Azithromycin binds to the 50S ribosomal subunit at the peptidyl transferase centre, preventing protein synthesis [66, 67]. Besides broad-spectrum activity against Gram-positive and Gram-negative bacteria, azithromycin has activity against the apicomplexan parasites *Toxoplasma gondii* and *Malaria* spp. [67, 68, 69, 70]. Azithromycin can be taken orally and has a safety profile [71, 72] which supports inclusion of pregnant women and children in MDA [7]. The absence of drug-drug interactions, allows integrating azithromycin, ivermectin, diethylcarbamazine and albendazole MDA [71].

Since studies in Papua New Guinea and Ghana [73, 74] showed non-inferiority to penicillin G, azithromycin is the preferred antibiotic for treating yaws [74, 75, 76]. A single 20 mg/kg dose is highly effective in treating trachoma infections [77, 78]. Yaws and trachoma can be co-endemic and research has shown that 20 mg/kg is as effective as 30 mg/kg against Yaws [79].

1.6   Benzathine penicillin

Benzathine penicillin (penicillin G) was discovered in 1951 [80]. It is a bactericidal beta-lactam that inhibits bacterial peptidoglycan transpeptidases, preventing cell wall formation during cell division [81]. While oral formulations are available, benzathine penicillin is frequently administered intravenously or intramuscularly due to its poor oral bioavailability. Slow-release formulations provide effective serum levels measurable for at least 14 days. Benzathine penicillin has a broad spectrum of activity against Gram-positive and Gram-negative bacteria, including the causative agents of yaws and trachoma [75, 80]. Despite the need for trained health professionals and discomfort of injections for the patient, benzathine penicillin mass treatment of cases and contacts was implemented in 46 countries from 1952-1964 and reduced global yaws and other treponematoses burden by 95% [75]. Care must be taken to ensure individuals with known penicillin sensitivity or history of allergic reactions, including anaphylaxis, are excluded and immediate access to required interventions is available to avoid fatalities [64, 65].

1.7   Topical scabicides

1.7.1   Permethrin

Permethrin is a synthetic pyrethroid insecticide, based on pyrethrum extracts, designed to increase insecticidal activity, lower mammalian toxicity and provide the photostability required for agricultural use. Permethrin acts on the nerve cell membrane of arthropods to disrupt the sodium channel current that regulates the polarization of the membrane. This results in delayed repolarization and subsequent paralysis and death of the parasites. Permethrin is an active ingredient of mosquito nets [82, 83, 84, 85, 86].

Permethrin is available in topical products for human use. The WHO EML 2021 lists a 1% lotion and a 5% cream [1]. A permethrin cream (5%) was approved for the treatment of scabies in children two months of age or older by the US FDA in 1989 [87]. Safety in younger infants is an open question [88, 89] The absorption of permethrin through the skin is limited to 2% of the amount applied with the fraction absorbed being eliminated via rapid metabolism [87, 88].

Five percent (5%) permethrin cream applied head-to-toe including in intimate areas is highly effective for treatment of scabies cases and reducing the risk of infection of contacts [90]. However, large scale use in endemic community settings faces a number challenges ranging from cost to individual acceptance and compliance with the treatment regimen [91, 92, 93, 94]. This limits its utility and drives considerations for use only in individuals for which ivermectin is contra-indicated [91, 95, 96].

1.7.2 Benzyl benzoate

Benzyl benzoate is an ester of benzoic acid and benzyl alcohol which is neurotoxic to mites [97]. *In vitro*, 100% of mites were killed after 3 hours of exposure to 25% benzyl benzoate [98]. The drug has been used for scabies since the late 1930ies [99] and is available as 10-25% lotions or emulsions [100, 101]. Characterized as safe in children ≥1 month [102], a 5% topical cream was identified as the treatment of choice for infants >2 months for whom safe and effective ivermectin doses have not been identified and as an option for infants younger than 2 months with application for four hours [96]. Severe skin irritation can occur within minutes of application [101]. An informal consultation on a framework for scabies control was held by WHO in 2019 to review current data and gather expert views. The experts recommended that, in view of the inferior efficacy and higher rate of adverse effects of benzyl benzoate compared to permethrin, benzyl benzoate should only be used when topical treatment is indicated (i.e. for individuals for which ivermectin is not approved) and permethrin is unavailable [91, 95, 96].

1.7.3 Malathion

Malathion is an organophosphate insecticide. Its toxic metabolite malaoxon irreversibly inhibits acetylcholinesterase, resulting in acetylcholine accumulation and disruption of the nervous system function [103, 104, 105].

Malathion, as an aqueous lotion 0.5% w/v, was first developed for human use in the treatment of headlice. The justification for the use of malathion in scabies comes from a study conducted in 1978 that demonstrated an 83% cure rate in a population of 30 individuals with scabies [106]. A 2013 review did not identify sufficient evidence to assess the relative efficacy of malathion and other scabies treatment options [107]. Malathion is listed as an alternative rather than a recommended treatment of scabies in the European recommendations [108]. In 2015 malathion was classified as probably carcinogenic to humans by the WHO International Agency for Research on Cancer [105, 109].

1.7.4 Sulphur ointment

Sulphur is the oldest antiscabietic, reported to have been used already around 25 AD. The reduction of sulphur to hydrogen sulphide by bacteria on the skin results in killing the scabies mite [97]. Topical sulphur treatments for scabies contain between 2-33% sulphur. They were used in the youngest children (at strengths of <10% sulphur), including those under 2 months as well as pregnant women due to a perceived safety profile resulting from the lack of absorption following dermal application [97]. It was recently used during MDA for a scabies outbreak in Ethiopia for treatment of children under 10 years of age and pregnant and breast-feeding women [110].

The efficacy of sulphur is inferior to that of permethrin and ivermectin [97]. Sulphur is listed as an alternative rather than a recommended treatment of scabies in the European recommendations [108]. Its use can be limited by its strong and unpleasant odour that results from the formation of hydrogen sulphide as well as the fact that it can stain clothing [111].

2 Anti-infective drugs for diseases for which case management is the main control- and elimination strategy

2.1 Antibiotics

2.1.1 Rifampicin

Rifampicin, derived from *Nocardia mediterranei*, was discovered in 1957 and synthesized in 1965. Activity against *Mycobacterium tuberculosis* was determined *in vitro* and *in vivo* in mice, guinea pigs, and rabbits before trials in humans, initiated in 1966, demonstrated efficacy against *M. tuberculosis* strains resistant against all other anti-tuberculosis drugs at the time [112]. Rifampicin inhibits bacterial DNA-dependent RNA synthesis, thus preventing transcription and inhibiting bacterial protein synthesis, resulting in a bactericidal effect. Differences in antimicrobial activity against Gram-positive and Gram-negative bacteria are not related to different binding sites on the RNA polymerase but to other factors like efflux pumps. Different mechanisms of resistance have been described, including changes of the binding pocket of rifampicin on the RNA polymerases [113]. Rifampicin activates the nuclear pregnane X receptor increasing the expression of genes whose products are involved in drug metabolism and transport, inducing cytochrome P450 2B6 (CYP2B6), CYP 3A4 and P-glycoprotein. The resulting potential for drug-drug interaction needs to be considered in particular in treatment of TB and HIV co-infected patients [114].

A systematic review concluded that a single rifampicin dose reduced leprosy incidence in contacts of patients in the first two years by 57% [115]. Rifampicin-associated adverse effects include flu-like syndrome, gastrointestinal and dermatological events, as well as hepatitis and cholestasis [112].

2.1.2 Dapsone

Dapsone, discovered in 1908, is a sulphone bacteriostatic antibiotic and anti-inflammatory agent. Its bacteriostatic effect is due to its sulphonamide-like ability to compete with para-aminobenzoic acid for the active site of dihydropteroate synthetase, thus inhibiting dihydrofolic acid synthesis. The anti-inflammatory effect may be based on different mechanisms including inhibition of chemokine production, neutrophil response to chemotactic signals and adherence to endothelium, generation of toxic and oxygen-derived radicals. Dapsone is metabolized by cytochrome P450, making it susceptible to drug-drug interactions. The resulting hydroxylamines are considered responsible for the dose-dependent adverse effects agranulocytosis, methemoglobinemia and haemolysis. The most important other dose-dependent adverse effects occurring at low frequency within the dose range considered effective for leprosy is peripheral neuropathy. Life-threatening dapsone hypersensitivity syndrome occurs in 0.5% to 3.6% of patients [116]. This syndrome has been linked to *HLA-B*13-1* polymorphism which could provide a path to pre-treatment screening [117, 118, 119].

Dapsone resistance of *Mycobacterium leprae* has been known since 1977 [120, 121] and has been attributed to a mutation of folP1, a gene coding for dihydropteroate synthase [122].

2.1.3 Clofazimine

Clofazimine, first described in 1957, is a riminophenazine antibiotic. It is active against slowly and rapidly growing mycobacteria, as well as many other Gram-positive bacteria *in vitro* but not against Gram-negative bacteria. The primary site of action has been proposed to

be the outer membrane. Putative targets include ion transporters and the bacterial respiratory chain. Besides anti-infective activity, clofazimine also has anti-inflammatory properties benefitting the treatment of leprosy. Its high lipophilicity enables clofazimine to accumulate in skin and nerves which contributes to its efficacy against erythema nodosum leprosum. Adverse effects of clofazimine include reversible discolouration of the skin and conjunctiva and gastrointestinal events which are usually mild to moderate but may in some cases be severe including bleeding, splenic infarction, and bowel obstruction [123, 124]. The primary mechanism of resistance was described to be a mutation in the rv0678 gene, a gene that encodes a transcriptional repressor for the efflux pump MmpL5 [125].

2.1.4 Clarithromycin

Clarithromycin is a macrolide antibiotic which differs from erythromycin through substitution of the hydroxy group at the lactone ring by an O-methyl group. This confers greater acid stability resulting in better oral availability and may contribute to improved intracellular activity. Clarithromycin is metabolized by hepatic cytochrome P450 enzymes. Its metabolite 14-hydroxy-clarithromycin has activity with additive or synergistic activity with clarithromycin. Macrolides inhibit protein synthesis by reversible binding to the 50S ribosomal subunit of susceptible bacteria [126] and have immunomodulatory effects [127]. The potential for drug-drug interactions is based on binding and inhibition of macrolides to cytochrome CYP3A4 isoforms. Clarithromycin has less affinity to CYP3A4 than erythromycin [128, 129]

2.1.5 Moxifloxacin

Moxifloxacin is a fluoroquinolone antibiotic, approved for human use by the US FDA in 1999 (https://www.accessdata.fda.gov/drugsatfda_docs/nda/99/21-085_Avelox.cfm). Compared to fluoroquinolones available at that time it has enhanced activity against Gram-positive and atypical bacteria with a comparable spectrum of activity against Gram-negative bacteria. Fluoroquinolones inhibit DNA replication by affecting DNA gyrase and topoisomerase IV with topoisomerase IV being the primary target in Gram-positive bacteria and DNA gyrase that in Gram-negative bacteria. Data obtained in *S. pneumoniae* and *E. coli* suggest moxifloxacin may have equal and simultaneous activity on both enzymes. Fluoroquinolone resistance is based on alteration of the genes coding for the target enzymes and the gene coding for the efflux pump [130].

2.1.6 Tetracycline

Tetracycline is an antibiotic that was discovered in 1953. The term has also been used to describe the structurally related family of antibiotics, which inhibit the bacterial protein biosynthesis by preventing the attachment of the aminoacyl-tRNA to the ribosomal acceptor site. They are broad-spectrum antibiotics, exhibiting activity against a wide range of Gram-positive and Gram-negative bacteria, as well as atypical pathogens like *Chlamydia* [131]. Before the mid-1950s, pathogens resistant to tetracyclines were rare, but since then, many different tetracycline-resistant genes have been characterized. [131].

2.2 Anti-trypanosomal drugs

2.2.1 Fexinidazole

Fexinidazole is 2-substituted 5-nitroimidazole synthesized in the 1970s by Hoechst AG (now Sanofi). Its anti-trypanosomal activity was initially identified in the 1980s and later confirmed [132, 133]. Fexinidazole is metabolized rapidly to sulfoxide and sulfone derivatives [132, 134]. The subsequent metabolism and mechanism of action in trypanosomes are unknown [135].

In 2005, DNDi initiated development for human African trypanosomiasis (HAT). After completion of preclinical studies and an agreement between DNDi and Sanofi for joint development, fexinidazole entered clinical trials in 2009 and obtained an EMA positive 'scientific opinion' in 2018 through the Article 58 of Regulation (EC) No 726/2004 procedure in the context of cooperation with WHO (now referred to as EU-M4all) for treatment of first and second stage *Trypanosoma brucei gambiense* HAT in adults and children ≥6 years and weighing ≥20 kg. Through the EU-M4all procedure, the EMA assesses drugs not intended for marketing in the European Union according to the same criteria used for drugs for the European market. The EMA scientific opinion facilitated regulatory approval in *T. b. gambiense* endemic countries [135, 136, 137]. In 2019 fexinidazole was added to the WHO EML and included in the 'WHO interim guidelines for the treatment of gambiense human African trypanosomiasis' [138]. In 2020, fexinidazole received US FDA approval [139]. In contrast to all other available treatments for *T.b. gambiense* HAT, fexinidazole is an oral treatment.

A Phase 2/3 study to evaluate the safety and efficacy of fexinidazole for first and second stage *T. b. rhodesiense* HAT (https://clinicaltrials.gov/ct2/show/record/NCT03974178) is expected to be completed in mid 2022. The trial is co-funded by the European & Developing Countries Clinical Trials Partnership (EDCTP) and the Portuguese Fundação para a Ciência e a Tecnologia (https://dndi.org/research-development/portfolio/fexinidazole-tb-rhodesiense/, accessed March 3 2022).

2.2.2 Pentamidine

Pentamidine, a synthetic aromatic diamidine, was introduced in 1940 [140]. The exact target and mode of action is unknown, but may include DNA binding/damage, loss of kinetoplast DNA, and disruption of mitochondrial membrane potential [141, 142]. Loss of kinetoplast DNA has been suggested to precede the loss of mitochondrial membrane potential, but it is unclear if this effect is strictly sequential or if pentamidine also has direct effects on the mitochondrial membrane [141]. Despite 80 years of use, it is still highly effective (cure rate = 93-98%) in treating first-stage *T. b. gambiense* HAT [140, 143], but today is the 1st line treatment only for children <6 years or <20 kg for whom fexinidazole is not yet registered. Pentamidine is administered once daily intramuscularly for 7-10 days [140]. If given intravenously, care must be taken that it is not given as a bolus, but rather slowly over 60 minutes to avoid a possible induction of hypoglycemia. An oral analogue of pentamidine had comparable efficacy to the injected form, but was too toxic [144]. As there is little economic incentive in pentamidine, its production was almost discontinued, but in 2001, Sanofi-Aventis agreed to continue producing it for the WHO [143]. It cannot pass the blood-brain barrier and therefore is not effective for second-stage infections [140].

2.2.3 Suramin

Suramin is a polysulfonated napththyl urea introduced to treat *T. b. gambiense* and *T. brucei rhodesiense* HAT in 1922 and is one of the first anti-infective agents developed from trypan blue and trypane red in one of the first medicinal chemistry programs at Bayer [140, 145]. Due to its six negative charges at physiological pH, it does not pass the blood brain barrier and, therefore, was only effective against first-stage trypanosomiasis disease [145]. Suramin is a multifunctional compound with activity against other parasitic diseases, viruses, cancers, and snakebites, and even autism [145]. Due to the many targets, the mode of action of suramin is not well understood in general and even less-so in trypanosomes [145]. In trypanosomes it has been shown to inhibit cytokinesis as demonstrated by cells with two nuclei [141]. Suramin has been shown to inhibit glycolytic enzymes and inhibit oxidative phosphorylation, although it is not understood how the large and highly negatively charged

molecule can pass the membranes of the glycosomes and mitochondria where the enzymes are located [145]. Life threatening reactions to the 7-day course for *T. b. rhodesiense* HAT and lethal outcomes are rare. Pyrexia and usually mild and reversible nephrotoxicity are driven by concentrations in the kidneys [140]. As *T. b. rhodesiense* HAT progresses quickly to the second stage, treatment of pregnant women with first-stage HAT cannot be delayed until after birth of the child [140].

Suramin administered for 6 weeks is macrofilaricidal in *O. volvulus*, but the adverse reactions make it unsuitable for large scale use [146, 147]. Recent research shows activity against *Leishmania major* and *L. donovani*, and that suramin can block host cell invasion by *Plasmodium falciparum* [145]. Suramin is instable in air and must be administered for HAT by slow intravenous injection every 3-7 days for 4 weeks [140, 144].

2.2.4 Melarsoprol

Melarsoprol is a trivalent organic arsenical compound that, since 1949, was the first-line drug of choice over other arsenic derivatives to treat second-stage *T.b. gambiense* and *T. b. rhodesiense* HAT [140, 143, 144]. The mode of action of melarsoprol is still being elucidated. It forms adducts with trypanothione and is an indiscriminate inhibitor of kinases (mainly dithiol containing trypanosomal enzymes); the latter indicating involvement of signaling cascades [140, 141]. Treatment of trypanosomes results in a defect in mitosis shown by an increased number of cells with replicated but unsegregated nuclear genomes [141]. The compound is liposoluble and administered intravenously in propylene glycol, an irritant. This makes melarsoprol not only difficult to administer, requiring hospitalization, but painful to the patients [143]. For several decades, melarsoprol treatment followed the regimens of other arsenicals and varied from country to country, including serial drug application with 1-week intervals without drug [140, 148]. Pharmacokinetic studies supported the hypothesis that a shorter, uninterrupted treatment regimen could be equally effective [149, 150]. This informed studies which showed the safety and efficacy of a 10-day treatment for second stage *T. b. gambiense* HAT [149, 150, 151] and *T. b. rhodesiense* HAT [148]. The most feared adverse reaction is reactive encephalopathy that can occur in up to 10% of patients with a median fatality rate of 50% [140, 143]. Melarsoprol is still the only drug available to treat second-stage *T. b. rhodesiense* HAT [140] but is today only a rescue treatment for *T. b. gambiense* HAT patients who have failed treatment with Nifurtimox-Eflornithine Combination Treatment (NECT) and fexinidazole [138]. There are few data on the safety of melarsoprol during pregnancy, but theoretically it is contraindicated. However, due to the severity of *T. b. rhodesiense* HAT, its use as treatment cannot be delayed until after the birth of the child [140].

2.2.5 Eflornithine

Eflornithine (D,L-α-difluoromethly ornithine) was at one time evaluated as a cancer drug. It's antitrypanosomal effect was discovered in 1980 through WHO/TDR funded studies on the polyamine metabolism of trypanosomes [152]. Eflornithine irreversibly inhibits ornithine decarboxylase of trypanosomes [143], blocking production of the polyamine putrescine and subsequent DNA synthesis. This results in the parasites entering a dormant state susceptible to the host immune system [140]. Trypanosomes are more sensitive to the drug than mammalian cells, probably due to a slower ornithine decarboxylase turnover rate [144].

Eflornithine's effect on patients with second stage *T. b. gambiense* HAT [153] earned it the name 'resurrection drug'. Despite that, and the fact that public funding provided by WHO/TDR contributed to eflornithine development [153, 154], eflornithine was no longer available after the manufacturer Marion Merrell Dow merged with Hoechst and Roussel. WHO was not able to identify an alternative manufacturer for an affordable price [152, 155].

It took the discovery that eflornithine was being manufactured for a cream to remove unwanted facial hair in women, which had received regulatory approval in 2000 [156], and subsequent intense advocacy by Médecins Sans Frontières and WHO for eflornithine to become available again to save the lives of patients with HAT [152, 157, 158]. Currently, supply until 2025 has been secured through renewal of the WHO and Sanofi agreement [159]. Eflornithine is not used to treat second-stage *T. b. rhodesiense* HAT as these parasites are less susceptible to the compound [143]. Although an oral formulation was available, it did not ensure high enough levels in the cerebral spinal fluid, and eflornithine is therefore given intravenously [140]. As monotherapy, it requires administration 4 times a day every six hours for 14 days [144], which is difficult in the health centers in the remote rural areas where HAT is endemic. Through combination with 10 days of oral nifurtimox treatment every 8 hours (NECT), eflornithine eflornithine infusion can be reduced to twice daily for 7-days [160, 161]. Little information is available on the safety of eflornithine during pregnancy and, when possible, watchful waiting (regular monthly clinical assessment) is used. If the health of the mother is at risk, eflornithine or NECT is given, otherwise pentamidine is used after the first trimester to prevent infection of the fetus [138, 140].

2.2.6 Benznidazole

Benznidazole is a nitroimidazole antiparasitic drug for treatment of acute and early chronic Chagas disease [7]. It is reduced to reactive metabolites by nitroreductases, but the mechanism of its action is not well understood [162, 163, 164]. Despite availability since 1971, its role in the treatment of chronic disease remains under discussion [165, 166]. Its better tolerance in infants and children than adults has been attributed to a faster hepatic elimination compared to adults [167]. A paediatric formulation was developed and registered in Brazil in 2011, in the US in 2017 (for ages 2-12 years https://www.accessdata.fda.gov/drugsatfda_docs/nda/2017/209570Orig1s000TOC.cfm, accessed 20 June 2022) , and in Argentina in 2018 [168]. A recent study concluded that shorter treatment durations and/or lower doses of benznidazole could have similar antiparasitic effects with better tolerability than the current standard treatment, a promising finding to be confirmed via further studies [169, 170].

2.2.7 Nifurtimox

Nifurtimox is a 5-nitrofuran derivative, introduced for treatment of Chagas disease in the late 1960ies [171]. Following demonstration of the efficacy and safety of NECT, the combination of oral nifurtimox with intravenous eflornithine, for treatment of second stage *T. b. gambiense* HAT [160, 161], this combination was added to the WHO EML in 2009 [172] and became the treatment of choice for this indication [158, 173]. Nifurtimox was added to the WHO EML for children for African trypanosomiasis in 2013 [174] after data became available demonstrating that in children NECT efficacy is comparable and safety comparable or better in children than adults [173, 175, 176, 177]. The mechanism of action for both *T. brucei* and *T. cruzi* involves reduction by an NADH-dependent bacterial-like nitroreductase and generation of a cytotoxic, unsaturated open-chain nitrile derivative [133].

2.3 Antileishmanial drugs

2.3.1 Pentavalent antimoniate

The first use of a pentavalent antimonial (urea stibamine) for leishmaniasis dates back to 1922 [178]. Pentavalent antimony (Sb(V)) complexes currently in use include N-methyl-D-glucamine (meglumine antimoniate, Glucantime®, 100 mg Sb/mL) and sodium gluconate (sodium stibogluconate, Pentostam®, 85 mg Sb^+/mL) [179, 180]. Pentavalent antimonials may be prodrugs converted to the active trivalent antimony, act directly, and/or via

stimulation of the immune system [Frezard et al. 2009] [Haldar et al. 2011]. As for other antileishmanial drugs, efficacy and role of pentavalent antimoniates in case management depends on clinical form, pathology, causative species, geographic region, use history, and co-infections [178, 181, 182, 183].

2.3.2 Amphotericin B and liposomal amphotericin B

Amphotericin B is a polyene antibiotic with efficacy against fungal infections as well as *T. cruzi*, *Schistosoma mansoni*, *Echinococcus multilocularis* and *Leishmania spp* [184]. The long-established notion that Amphotericin B mechanism of action is via cell membrane pore formation after binding to ergosterol has been questioned in favour of pleiotropic effects including induction of oxidative damage and an immunomodulatory effect [184]. It is available in several formulations: deoxycholate solution, colloidal dispersion with cholesterol sulphate, a lipid complex with two phospholipids, and in unilamellar liposomes formed from cholesterol and other phospholipids [178, 184, 185].

Liposomal amphotericin B was originally developed for severe systemic and deep mycoses. It was first used to treat a European with mediterranean visceral leishmaniasis who had failed treatment with antimonials, pentamidine and paromomycin [186, 187]. This and subsequent experience motivated a clinical development programme to obtain the data needed for registration of liposomal amphotericin B for treatment of visceral leishmaniasis in collaboration between the company and WHO/TDR [186]. Liposomal amphotericin B (Ambisome) was approved by the US FDA in 1997 for three indications including visceral leishmaniasis (https://www.accessdata.fda.gov/drugsatfda_docs/nda/97/050740_ambisome_toc.cfm). A single dose of liposomal amphotericin B has been shown to be efficacious as well as safe and effective for visceral leishmaniasis in India and Bangladesh [188, 189, 190] and has become the preferred first-line treatment, replacing miltefosine [191]. Further studies are needed to define the optimum treatment liposomal amphotericin B regimen for other clinical presentations, pathology, causative species, geographic region, use history and co-infections. [192].

2.3.3 Miltefosine

Miltefosine (hexadecylphosphocholine) is an alkyl phosphocholine compound and a structural analogue of lecithin [193]. It was evaluated from the 1980ies as a cancer drug resulting in registration of a topical formulation for treatment of skin lesion from breast cancer [194, 195]. Research into miltefosine's antileishmanial effect also dates back to the 1980ies [196].

Mechanisms involved in its antileishmanial action include incorporation into membrane lipid bilayers, disturbance of membrane metabolism and induction of apoptosis-like cell death as well as host-mediated immunomodulation [193].

Dose limiting gastrointestinal adverse reactions during long treatment resulted in discontinuation of development of oral formulations for cancer. The pre-clinical as well as clinical data obtained during that development [194] provided a valuable basis for development of miltefosine as the first oral treatment for visceral leishmaniasis [197]. Miltefosine is teratogenic in rats, but not rabbits. Contraindication during pregnancy is one of its main limitations [194, 198]. The availability of an oral treatment was one of the factors that lead to a regional strategic framework for elimination of visceral leishmaniasis from the Indian Subcontinent [199, 200].

Miltefosine development for treatment of visceral leishmaniasis was accomplished in collaboration between Asta Medica (Zentaris, Germany) and WHO/TDR with WHO/TDR providing both relevant expertise as well as funding. The collaboration was based on a

Memorandum of Understanding concluded in 1995 between WHO and the company which included provisions for availability and affordability of miltefosine for the public health systems in endemic countries, should development be successful and result in registration [195, 201]. Registration was achieved initially in Germany and in India in 2002 and later in other endemic countries. However, affordable access was only temporary. In contrast, the incentives provided by the US congress for investment into the development of drugs for neglected diseases via the 'Priority Review Voucher' (https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/tropical-disease-priority-review-voucher-program) resulted in a company (Knight Therapeutics) who had never invested in miltefosine development, nor committed to making miltefosine available at affordable prices, benefitting from these incentives to the tune of US$125 Million [195, 202]. This has resulted in calls to change the conditions under which a 'Priority Review Voucher' is awarded [202, 203].

2.3.4 Paromomycin

Paromomycin, a highly hydrophilic and lipid insoluble aminoglycoside also known as aminosidine, is a broad-spectrum antibiotic . Its antileishmanial effect was discovered in 1960 [180]. The mechanism of action of paromomycin is inhibition of protozoan protein synthesis by binding to the 30S ribosomal subunit resulting in the accumulation of abnormal 30S–50S ribosomal complexes and finally causing cell death [180]. Paromomycin can be used in pregnant leishmaniasis patients [180].

Starting in 1993, WHO/TDR supported studies of topical paromomycin treatment for cutaneous leishmaniasis **[204, 205, 206]** as well as studies for qualifying injectable formulations for treatment of visceral leishmaniasis (including mutagenicity and genotoxicity studies, a study on the bioequivalence of two injectable formulations and a multi-centre study comparing the efficacy and safety of injectable paromomycin with that of amphotericin B **[154, 207, 208]**. Lack of funding resulted in development being put on hold after completion of a Phase II study in 2000 and was resumed in 2001-2002 in partnership with the Institute of One World Health had received a grant from the Bill and Melinda Gates Foundation (https://www.gatesfoundation.org/ideas/media-center/press-releases/2002/08/institute-for-oneworld-health-receives-grant, accessed 28 June 2022) **[209, 210]**. Paromomycin was registered for visceral leishmaniasis in 2006 **[178]** Paromomycin can be used in pregnant leishmaniasis patients **[180]**.

2.4 Antifungal drugs

2.4.1 Itraconazole

Itraconazole is a broad-spectrum antifungal azole drug, patented in 1978 and approved by the US FDA in 1992 (https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=020083, accessed 28 June 2022). Azoles inhibit the synthesis of ergosterol via the inhibition of lanosterol 14α-demethylase resulting in fungal membrane destruction. Itraconazole also impacts several metabolic pathways important for human cell proliferation resulting in interest in repurposing itraconazole for cancer therapy [211] Itraconazole, like other azoles, is metabolized by cytochome P450 3A4. Therefore, drug-drug interactions with other drugs metabolized by CYP450 3A4 need to be considered [212].

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