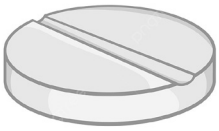
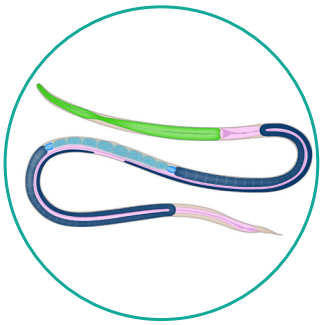
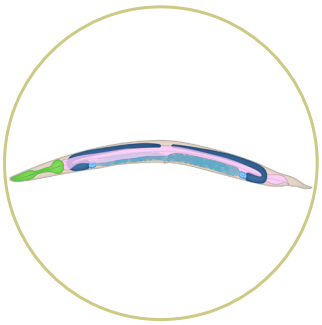
World Health Organization

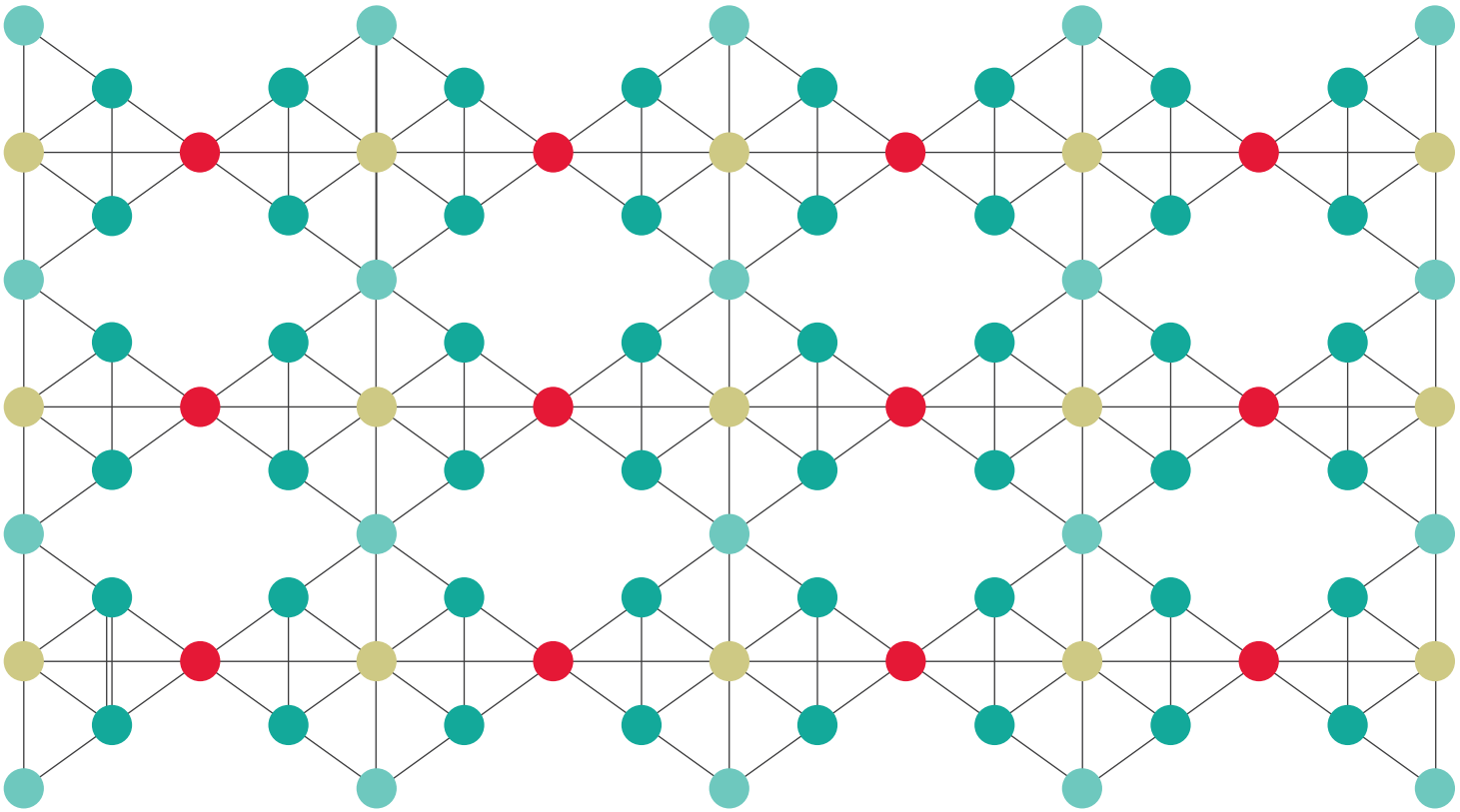
WHO guideline on preventive chemotherapy

for public health control of strongyloidiasis









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Contents

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Guideline development group

The guideline development group (GDG) was co-chaired by David Addiss (The Task Force for Global Health, Decatur, United States of America) and Dora Buonfrate (IRCCS Sacro Cuore don Calabria Hospital, Negrar, Italy). The guideline methodologists were Lorenzo Moja (WHO Health Product Policy and Standards (WHO/HPS)) and Jessica Bartoszko (McMaster University, Hamilton, Canada).

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This panel of experts was selected to represent a diversity of perspectives, including by gender, race, ethnicity, geography and technical expertise, among other categories.

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Abbreviations and acronyms

COVID-19	coronavirus disease 2019
DALY	disability-adjusted life year
GDG	guideline development group
GRADE	Grading of Recommendations, Assessment, Development and Evaluation
MDA	mass drug administration
NTD	neglected tropical disease
PICO	population, intervention, comparator and outcome
YLD	years lived with a disability
YLL	years of life lost due to premature mortality
WHO	World Health Organization

Glossary

The definitions below apply to the terms used in this document; they may have different meanings in other contexts.

control

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

disseminated strongyloidiasis

Life-threating infection due to the migration of *Strongyloides* larvae outside the gastrointestinal tract and lungs into areas such as the central nervous system, liver, heart, urinary tract and elsewhere.

endemic setting

Geographical area or population in which *Strongyloides stercoralis* infection is present and maintained over time.

prevalence of infection

Percentage of individuals of all ages in a population who are infected with *Strongyloides stercoralis*. Prevalence is often defined based on the diagnostic tool used.

preventive chemotherapy

Periodic use of anthelminthic medicines as a public health tool against helminth infections. Preventive chemotherapy can be applied with different modalities:

- mass drug administration, whereby the entire population of an area (e.g. state, region, province, district, subdistrict, village) is given anthelminthic medicines at regular intervals, irrespective of the individual infection status;
- targeted chemotherapy, whereby specific risk groups in the population, defined by age, sex or other social characteristic such as occupation (e.g. school-aged children) are given anthelminthic medicines at regular intervals, irrespective of the individual infection status; and
- selective chemotherapy, whereby after a regular screening in a population group living in an area where helminths are endemic, all individuals found (or suspected) to be infected are given anthelminthic medicines.

In this document, we define preventive chemotherapy as the overarching strategy of mass distribution of medications for control of strongyloidiasis. We define targeted preventive chemotherapy when treating school-aged children alone, and mass drug administration when treating the entire community.

quality-assured serological tests

Tests that have gone through the total process of quality assurance to guarantee the accuracy of final results reported by a laboratory. The process involves inspecting specimens, reviewing quality measures, using the most reliable assays and verifying final reports.

school-aged children

All children between the ages of 5 and 14 years (usually), regardless of whether they are attending school. The exact ages of school enrolment can vary slightly between different countries. In some countries, a primary school's enrolment may include individuals older than 14 years of age.

soil-transmitted helminths

Different species of parasitic worms that infect people. The roundworm (*Ascaris lumbricoides*), the whipworm (*Trichuris trichiura*) and hookworms (*Necator americanus* and *Ancylostoma duodenale*) are normally addressed as a group because they need similar diagnostic procedures and respond to the same medicines.

Strongyloides stercoralis is a soil-transmitted intestinal helminth with unique characteristics: the parasite requires different diagnostic methods than those for other soil-transmitted helminthiases; for this reason it is frequently not identified. In addition, the parasite is treated with ivermectin, and not with albendazole or mebendazole, and therefore is not impacted by large-scale preventive treatment campaigns targeting other soil-transmitted helminthiases.

Strongyloides stercoralis infection

Infection due to *Strongyloides stercoralis*, a soil-transmitted helminth that infects an estimated 3–100 million people worldwide.

target population

Population in a district or implementation unit that is targeted for treatment.

Executive summary

Background

Human strongyloidiasis is a chronic parasitic disease caused by infection with *Strongyloides stercoralis*, a soil-transmitted helminth that is estimated to infect 300–600 million people worldwide *(1,2)*. This neglected tropical disease (NTD) is endemic globally, predominately in the South-East Asia, African and Western Pacific regions, and in South and Central America *(1,3)*. Strongyloidiasis has a wide range of clinical presentations, including subclinical disease, symptomatic disease (often with diarrhoea, abdominal pain and urticaria) and a rare but deadly complication of hyperinfection with disseminated disease *(4)*. The feared complication of disseminated strongyloidiasis can occur in the setting of immunocompromising conditions (e.g. human T-cell lymphotropic virus type 1 infection and malignancies) or immunosuppressive medications (e.g. steroids) and has an estimated case-fatality rate exceeding 60% *(5)*. The standard treatment for chronic *S. stercoralis* infection is oral medication with ivermectin *(6)*.

In recent years, the World Health Organization (WHO) has been contacted by the health ministries of several countries in which strongyloidiasis is endemic for advice on how to address the disease as a public health problem, as no current WHO guidance exists. While there are no public health programmes specifically for control of strongyloidiasis, in some settings, large-scale mass drug administration (MDA) programmes with ivermectin are being conducted to control lymphatic filariasis and onchocerciasis *(7,8)*. These programmes have demonstrated a reduction in prevalence of *S. stercoralis* infection, suggesting that preventive chemotherapy may be a potential public health strategy in areas endemic for strongyloidiasis *(9)*. Furthermore, secondary patents for ivermectin have now expired, leading to two generic formulations of ivermectin being prequalified by WHO in 2020 and 2021 with preferential pricing for public health use *(10)*.

In 2021, WHO published a road map to guide the global strategy and targets for NTDs from 2021 to 2030 *(11)*. This global strategy outlined a need for formal guidance on whether to recommend preventive chemotherapy against strongyloidiasis and provided an opportunity to integrate strongyloidiasis control programmes into existing public health programmes for NTDs. These programmes could be targeted at school-aged children alone (i.e. targeted preventive chemotherapy) or to the entire community (i.e. MDA) in endemic settings. Consequently, a guideline development group (GDG) was convened to address the need to control strongyloidiasis and develop guidance.

Goal and objective

The objective of this WHO guideline is aligned with that of Sustainable Development Goal 3: to "ensure healthy lives and promote well-being for all at all ages" and the World Health Assembly resolution to expand access to prevention, diagnosis, treatment and care interventions for NTDs as a contribution towards the achievement of universal health coverage by 2030 *(12)*.

Its goal is to provide an evidence-informed recommendation on whether preventive chemotherapy with ivermectin as a public health intervention to reduce the disease burden caused by strongyloidiasis should:

- be implemented as a programme targeting both adults and school-aged children (i.e. MDA) in endemic settings that are above a defined prevalence threshold of strongyloidiasis;
- be implemented as a school-based programme alone (i.e. targeted preventive chemotherapy) in endemic settings that are above a defined prevalence threshold of strongyloidiasis; or
- not be implemented through preventive chemotherapy and instead be given following standard clinical care of individual cases.

This public health guideline recommendation is not intended to replace any standard of care for treatment of clinical strongyloidiasis. No public health approach replaces the need for timely diagnosis and treatment for strongyloidiasis through accessible health care.

Guideline development methodology

In June 2023, the WHO Global Neglected Tropical Diseases Programme convened a meeting of technical experts on strongyloidiasis to review available evidence on the global disease burden of strongyloidiasis as well as the efficacy, safety and population-level effectiveness of preventive chemotherapy with ivermectin to inform a WHO guideline recommendation.

The guideline development group (GDG) followed the procedures outlined in the *WHO handbook for guideline development, 2nd edition (13)*. The panel applied the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach to synthesize and appraise the key evidence and systematic reviews, which were presented to the committee *(14)*. A mathematical modelling study and cost–effectiveness analysis was commissioned to address the population-level impact of preventive chemotherapy with ivermectin against strongyloidiasis, comparing targeted preventive chemotherapy (school-aged children alone; often utilizing existing school-based treatment infrastructure) and MDA (community-wide) at different prevalence levels. The committee followed the GRADE evidence-to-decision framework to inform a recommendation, including consideration of the following criteria: certainty of evidence, balance of benefits and harms, values and preferences, resource use, equity, acceptability and feasibility *(15)*.

The general scope of the guideline and the prioritization of outcomes were carried out by the GDG. Evidence-informed recommendations were developed and finalized at a meeting of the GDG in Geneva (6–8 June 2023). Subsequent remote meetings were held during the preparation of this guideline document and revision. External experts served as technical peer reviewers for the preliminary version of the guideline.

Available evidence

TThe GDG considered three key systematic reviews (mostly observational data) and one recent randomized trial to inform the guideline recommendation *(9,16–18)*. It also considered evidence from a commissioned modelling and cost–effectiveness study on preventive chemotherapy against strongyloidiasis *(19)* and other literature. After review of the data, the GDG summarized the evidence as follows:

- Since the late 1980s, the efficacy of ivermectin to treat individual cases of *S. stercoralis* infection has been well-accepted in clinical care and guidelines *(6)*. Multiple experimental studies in patients with chronic strongyloidiasis have shown that a single dose of ivermectin is associated with a high parasitological cure rate – over 90% of treated patients *(20,21)*. Later, randomized trials compared ivermectin with albendazole and thiabendazole, two potential

treatment alternatives. A systematic review and meta-analysis provided convincing evidence of ivermectin's superiority to albendazole. For the comparison of ivermectin and thiabendazole, another benzimidazole, cumulative evidence was limited and therefore inconclusive *(17)*. Other considerations, such as safety, favour ivermectin for treatment of *S. stercoralis* infection over benzimidazoles.

- A systematic review and meta-analysis of low-quality observational data on MDA (community-wide) with ivermectin (conducted for the control of other diseases) found significant reductions in the prevalence of *S. stercoralis* infection (measured with faecal testing or serology) after the intervention in endemic settings.
- Extensive evidence from other diseases (e.g. lymphatic filariasis, onchocerciasis, scabies) supports the safety of ivermectin *(22)*. Furthermore, a systematic review and meta-analysis of six randomized trials that included patients with *S. stercoralis* infection demonstrated the safety of ivermectin even when administered at high dose (> 400 µg/kg), which is at least double the standard dose of 200 µg/kg proposed for preventive chemotherapy for strongyloidiasis *(18)*.
- In a mathematical modelling study, MDA (community-wide) with ivermectin was a cost–effective approach for controlling strongyloidiasis (reducing morbidity from infection and mortality from disseminated disease) in settings above 4–10% true prevalence of *S. stercoralis* infection in school-aged children (2–5% observed prevalence using an imperfect diagnostic with 50% sensitivity but perfect specificity). This prevalence in school-aged children was considered low but still relevant given the severe disease morbidity and potential for death. In older age groups, the prevalence of strongyloidiasis and risk of immunosuppression would be expected to be higher based on epidemiological studies; inclusion of adult populations in MDA in the model therefore improved cost–effectiveness compared with treatment of school-aged children alone.

Recommendation

The GDG made a single recommendation on preventive chemotherapy with ivermectin for reducing the public health burden of strongyloidiasis. This recommendation considered multiple factors including the certainty of evidence along with the benefits and potential harms of the intervention, the values and preferences of the target population, and the ethical, acceptability and feasibility issues of using preventive chemotherapy.

In endemic settings with prevalence of *Strongyloides stercoralis* infection ≥ 5%, WHO recommends annual mass drug administration with single-dose ivermectin in all age groups from 5 years and above to reduce strongyloidiasis.

Conditional recommendation

Low quality of evidence

Remarks relevant to interpretation of the recommendation

Target population

- The target population for MDA includes the entire community (currently for age groups 5 years and above). Based on modelling evidence, epidemiological data and expert judgement, a larger public health impact is expected for treatment of the entire community through MDA compared with treatment of school-aged children alone. This is specifically due to older populations being at higher cumulative risk for infection and potential for disseminated disease (due to immunosuppression), therefore benefiting from MDA.

- Ivermectin is currently indicated for children weighing more than 15 kg. The safety of ivermectin administration in children weighing less than 15 kg (corresponding to the age cut-off of 5 years) is not established and is therefore not recommended *(23)*. However, further study of the safety of ivermectin in children weighing less than 15 kg alongside the development of paediatric formulations of ivermectin is ongoing *(23)*. The GDG anticipates this age and/or weight limitation may be removed in the future if sufficient data on safety of ivermectin in this younger population can be established *(24)*.
- Women who are pregnant or lactating within the first week after giving birth should be excluded from MDA with ivermectin due to a current lack of safety data and regulatory approval for ivermectin in these groups *(23)*. These exclusion criteria will be reassessed pending new data on evaluation of ivermectin safety and alternative formulations of ivermectin.
- In settings with any evidence of *Loa loa* infection, MDA with ivermectin may not be advised due to risk of adverse events in patients with high-density *L. loa* infections. In such settings, safety precautions are needed as outlined in WHO guidelines on human onchocerciasis and/or lymphatic filariasis *(7,8)*. In most circumstances, MDA with ivermectin is not recommended in these settings.
- In settings with ongoing MDA with ivermectin for another indication (e.g. lymphatic filariasis, onchocerciasis), the ongoing programme of MDA with ivermectin is sufficient, assuming that coverage of the entire community is adequate.

Prevalence threshold

- The prevalence threshold of ≥ 5% is based on estimation by a coprological method, using either the Baermann technique or agar plate culture on a single stool specimen, in a survey of school-aged children (5–14 years). Coprological methods are preferred as they ensure measurement of active infection.
- The panel noted that multiple diagnostic techniques are available and can be potentially used to estimate the prevalence of *S. stercoralis* infection in the population. The laboratory infrastructure and expertise requirements differ by technique. For this reason, the panel decided to include information on different diagnostic techniques and sampling considerations. Given that diagnostic sensitivity and/or specificity will vary among techniques, the prevalence threshold applied must be specific to the corresponding diagnostic tool. A summary of alternative prevalence thresholds is provided in the table below.
- Quality-assured serological (antibody) tests can be used to estimate prevalence of *S. stercoralis* infection to determine the need for MDA; a ≥ 15% prevalence by quality-assured serological test (or assay responding to a future WHO target product profile for *S. stercoralis* diagnostics) in school-aged children is considered equivalent to ≥ 5% based on use of the Baermann technique or agar plate culture. This adjustment was based on estimation using assumed diagnostic performance characteristics for these tests (see table). However, a limitation of serological testing is that it may measure prior exposure and not active infection (although significant seroreversion after treatment is documented for many serological assays for *S. stercoralis*); furthermore, performance may vary by assay. For these reasons, serology is not the preferred mode of testing but does remain an option.
- The panel noted that the prevalence threshold of ≥ 5% is defined based on sampling from a population of school-aged children (5–14 years). The panel considered that the prevalence of *S. stercoralis* infection is expected to rise with age, meaning that the corresponding prevalence in adolescents and adults is likely higher than the prevalence measured in school-aged children. If a national programme decides to perform a community-wide prevalence survey (i.e. sampling people aged 5 years and older, including adults), then a community prevalence

threshold of ≥ 10% (in a community survey, including adults) by Baermann technique or agar plate culture is a reasonable alternative to the ≥ 5% threshold measured in school-aged children alone. If a serological (antibody) test is applied through a community-wide prevalence survey, then a prevalence threshold of ≥ 25% (in a community survey, including adults) is a reasonable alternative to the ≥ 15% prevalence by serological test in school-aged children. This adjustment was based on estimation using assumed test performance characteristics and age trends in infection. A summary of prevalence thresholds is provided in the table below.

- In recommending the prevalence thresholds, the GDG considered multiple sources of information, including epidemiological data, a modelling study, expert judgement, surveillance considerations and the need to balance resource requirements with expected public health impacts. The modelling study estimated the expected public health impact, resource requirements and cost–effectiveness of different prevalence thresholds for MDA; the selected prevalence threshold of 5% would be expected to be cost effective in low- and middle-income countries across a wide variety of assumptions on natural history and disease assumptions, and projected to have a large public health impact, while being feasible to measure with current surveillance methods. Furthermore, in settings with *S. stercoralis* infection above this prevalence threshold, strongyloidiasis is a large public health burden.

Prevalence thresholds for *S. stercoralis* above which MDA is recommended, by population and diagnostic test

Diagnostic test	Population	
	School-aged children	Community
Coprological test[a]	≥ 5 %	≥ 10 %
Antibody assay	≥ 15 %	≥ 25 %

[a] Defined as Baermann technique or agar plate culture of stool.
Note: Calculation and assumptions underlying these prevalence thresholds are described in the Recommendation section.

Implementation

- The suggested dose of ivermectin is a single dose of 200 µg/kg oral therapy.
- The implementation unit for MDA against strongyloidiasis is a district (defined as a geographical area with a population of approximately 100 000–250 000 people) but can vary based on the local context, including implementation on a national or subdistrict level informed by surveillance data.
- MDA should be prioritized in the highest-prevalence regions and settings, where it is expected to have the largest public health impact. The intervention can be evaluated within the health priorities of a country.
- Although there is limited evidence comparing different frequencies of MDA, the panel considered annual frequency of MDA ivermectin to be effective and technically feasible.
- Further guidance on design of prevalence surveys for surveillance to measure strongyloidiasis prevalence will be forthcoming in technical manuals, which will be necessary to inform decisions on indication and operational guidance for MDA.
- The MDA programme should be conducted for a minimum of 5 years. Surveillance of *S. stercoralis* infection prevalence is needed after 5 years of MDA to inform ongoing need for treatment, although earlier surveillance is also reasonable. Further guidance on surveillance and stopping MDA criteria will be forthcoming in a WHO technical manual.

- Local consultation with leaders and the community is important to confirm the acceptability of any public health strategy. Guiding principles include that informed consent, and assent, should be obtained whenever an MDA programme is being implemented. This should be conducted based on the country requirements and local context and may vary between programmes. For example, community and/or parent meetings with verbal consent and assent may be sufficient in some contexts; however, written consent approaches may be required in some contexts. The decision to participate in MDA should be voluntary for all persons.
- National programmes should leverage opportunities to integrate an MDA programme against strongyloidiasis into existing public health programmes, especially for NTDs (e.g. other soil-transmitted helminthiases, onchocerciasis and lymphatic filariasis).
- The panel noted that routine monitoring for effective coverage, impact evaluation of the intervention, emergence of drug resistance and safety should be a key part of any programme.
- The guideline recommendation supports the need for access to timely diagnosis and treatment for strongyloidiasis in the clinical setting, with special attention to testing for *S. stercoralis* infection and treatment prior to immunosuppression or other risk factors for disseminated strongyloidiasis.
- Water, sanitation and hygiene measures are needed as a complementary intervention to reduce transmission.

Construction of the recommendation

- The public health goal of this guideline recommendation is to reduce the burden of strongyloidiasis, both infection and disseminated disease. The GDG determined that control of parasitologically-confirmed *S. stercoralis* infection (symptomatic, chronic infection) is a meaningful public health outcome based on its morbidity and complication of disseminated disease. The evidence that supported the recommendation for MDA was primarily available for the outcome of infection, and focused on chronic infection. The GDG was not aware of direct evidence of MDA leading to reduced disseminated disease, but considered it reasonable to expect a reduction in disseminated disease through decreased infection prevalence. Therefore, the certainty of evidence that MDA would reduce chronic *S. stercoralis* infection is higher than the certainty of evidence that MDA would reduce disseminated strongyloidiasis.
- The panel issued a conditional recommendation based on a low quality of evidence. This decision was largely based on considering the entire body of evidence across dimensions.

Remarks relevant to interpretation of the recommendation

The GDG made its recommendation based on the following considerations. A more complete description of the rationale can be found in the Recommendation section.

Benefits

- Strongyloidiasis has a large global burden of disease, including morbidity from infection and mortality from the rare complication of disseminated strongyloidiasis, which has an estimated 60% case fatality rate *(5)*.
- Treatment with ivermectin results in a high cure rate for *S. stercoralis* infection, and curing infection will eliminate future risk of disseminated strongyloidiasis for an individual if there is no reinfection. The panel considered that the effects of ivermectin in observational studies were sufficiently large and that they occurred over relatively short periods of time, reinforcing confidence in the effect of ivermectin to cure infection.

- MDA with ivermectin in endemic areas reduced community prevalence of *S. stercoralis* infection, although empirical evidence here is limited to low-quality observational studies.
- The GDG extrapolated that MDA with ivermectin would therefore be likely to reduce the global burden of disseminated strongyloidiasis, although this is associated with some uncertainty.
- In settings co-endemic for *Trichuris trichiura* and/or scabies, a strategy using MDA with ivermectin (alongside existing preventive chemotherapy programmes co-administering albendazole for *T. trichiura*) may further reduce the prevalence of these additional infections.

Harms

- In treated children, mild and moderate adverse events can occur, but evidence suggests these are transient *(18,25)*. The adverse events described include ocular symptoms such as blurry vision or pain, although these are in the context of onchocerciasis elimination programmes. Others are described as neurological or cutaneous and are self-resolving.
- In treated children, rare case reports of severe adverse events including anaphylaxis and QTc prolongation have been reported (although they may be incidental or due to concomitant medications). Choking of young children on whole tablets of anthelminthic medicines has been observed during MDA, but this is less likely for ivermectin tablets, which are small.
- If a person is infected with *Loa loa* and has high-intensity microfilaraemia, ivermectin may present a risk of *L. loa* encephalopathy.
- Repeated mass treatment with ivermectin could theoretically lead to drug resistance against endemic pathogens, although this has not been observed in previous MDA campaigns.
- Widespread use of ivermectin may have ecological impacts *(26)*.

Values and preferences

- The GDG members rated chronic infection, disseminated disease and mortality outcomes as critical outcomes to persons and in their decision-making process.
- GDG members determined that despite chronic *S. stercoralis* infection being much less severe than disseminated strongyloidiasis, the high prevalence of chronic infection warrants its consideration as a critical public health outcome.

Acceptability

- Based on the experience of the GDG members and large-scale programmes for onchocerciasis and lymphatic filariasis, MDA with ivermectin would likely be accepted in the target population and delivered within national health systems following similar programmes for other endemic NTDs, although this was not formally studied.

Feasibility and resource use considerations

- The cost of MDA with ivermectin is reasonable for most endemic settings in low- and middle-income countries. The intervention could be implemented within national health programmes and ongoing MDA programmes for other diseases. Studies have estimated the cost of ivermectin medication to be US$ 0.10 for school-aged children and US$ 0.30 for adults, and the cost of delivery to be US$ 0.65 for school-based and 0.68 for community-wide MDA *(27)*. These costs may be lower with integration into existing MDA programmes.
- A reliable, sustainable multinational supply chain of ivermectin and operational programmes resourced to support community drug distributors for delivery of medication would be needed.

Equity

- The aim of this recommendation is to reduce the global burden of strongyloidiasis, which disproportionately affects marginalized populations in low- and middle-income countries. Therefore, a strategy to reduce this burden would probably improve health equity.

Ethical considerations

- MDA provides empirical treatment with ivermectin without individual diagnosis, meaning some people receive medication who are not infected and would not directly benefit from treatment and may have minor side-effects.

Regulatory considerations

- The US Food and Drug Administration, the United Kingdom of Great Britain and Northern Ireland Medicines & Healthcare products Regulatory Agency, the WHO Model List of Essential Medicines and others approve the use of ivermectin as treatment for strongyloidiasis.

Limitations

The guideline is based on the best available evidence on treatment and public health control of strongyloidiasis as of June 2023; however, the evidence base used to inform the guideline recommendation was limited, including lack of randomized controlled trials on MDA strategies. Specifically, while observational evidence suggests MDA with ivermectin reduces *S. stercoralis* infection, no randomized controlled trial is available to confirm this finding.

The GDG does not consider that this guideline will reduce the need for, or interest in, future research, including randomized or quasi-randomized studies. The findings of the cost–effectiveness modelling study were driven by the morbidity associated with chronic *S. stercoralis* infection, although these symptoms are subtle and difficult to measure. However, the GDG used the best available evidence on symptomology of chronic infection and measuring the disability from comparable chronic helminth infections. Additional key uncertainties exist on the global incidence of disseminated strongyloidiasis in endemic settings, age distribution of risk for *S. stercoralis* infection and heterogeneity in strongyloidiasis epidemiology across endemic settings. The selection of prevalence thresholds is ultimately informed by modelling evidence balancing expected public health impact and resource requirements and other diverse data sources, assuming broad equivalence between different diagnostic tests and age-specific prevalence trends. This guideline did not perform a systematic review on the values and preferences, equity, acceptability and feasibility for MDA.

The guideline will be updated accordingly as new evidence is available.

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Kenya: A school-teatcher communicating with her students about the danger of human strongyloidiasis: a chronic parasitic disease caused by infection with *Strongyloides stercoralis*.

1. Introduction

1.1 Background

Strongyloidiasis, a soil-transmitted helminthiasis and a neglected tropical disease (NTD), causes a large global burden of disease and infects an estimated 300–600 million people worldwide *(1,2)*. The disease is endemic predominately across the South-East Asia, African and Western Pacific regions, and in South and Central America *(1,3)*. It is caused by infection with *Strongyloides stercoralis* and has a complex life cycle, involving both free-living and parasitic phases as well as the unique ability for auto-infection within the human host *(4,5)*. Humans become infected upon exposure to the free-living infective filariform larvae in the environment (e.g. contaminated soil), which directly penetrates intact skin and enters the human host *(4,5)*. The larvae migrate through the body tissue and eventually mature into adult worms residing in the small intestines, where the female worms produce eggs via parthenogenesis (asexual reproduction) that hatch into rhabditiform larvae *(4,5)*. The larvae then can either: (i) enter a unique "auto-infective" cycle, where they mature to larvae and penetrate the intestinal mucosa or perianal skin to continue their life cycle within the human host (leading to a lifelong infection); or (ii) be excreted in stool and enter the environment, where they molt into infective filariform larvae directly (homogenic cycle) or into free-living male and female adult worms and undergo sexual reproduction *(4,5)*. The infective larvae produced by free-living adult worms in the environment must find a new host or perish.

Strongyloidiasis has a wide range of clinical presentations, including the rare potential for the complication of hyperinfection with dissemination. The majority of chronic infections are subclinical, with a fraction of patients experiencing symptomatic disease that is often characterized by diarrhoea, abdominal pain and bloating, urticaria and, rarely, other end-organ sequelae *(6)*. Most notably, strongyloidiasis has a feared complication of hyperinfection with disseminated disease that can occur in the setting of immunosuppression *(7–9)*. Frequently, affected persons may have chronic and subclinical strongyloidiasis, but develop an immunocompromising medical condition which puts them at risk for hyperinfection. Immunosuppression can be caused by infection (e.g. HTLV-1 or HIV infection), cancer and medications (e.g. steroids, immunosuppressive medications and biologicals) *(7–9)*. Strongyloidiasis hyperinfection is characterized by a rapid increase in the number of worms due to dysregulated and suppressed immune response *(7–9)*. During hyperinfection, the worms remain limited to the gastrointestinal, pulmonary and cutaneous system, but the number of worms rapidly expands *(7–9)*. Hyperinfection often will progress to disseminated disease in which the worms migrate throughout the body organs and tissues leading to widespread disease *(7–9)*. Hyperinfection and disseminated disease are often fatal syndromes accompanied by septic shock, respiratory failure, bacteraemia and meningitis, disseminated intravascular coagulopathy and renal or multi-organ failure *(7–9)*. During dissemination, a high larval load can be found throughout organ systems, including the central nervous system. The estimated case-fatality rate exceeds 60% *(7)*. Diagnosis of hyperinfection with disseminated disease is made clinically and is based on identification of larvae in multiple body fluids and tissues.

This guideline recommendation focuses on chronic strongyloidiasis. The diagnosis of chronic strongyloidiasis is based on identification of larvae in stool on direct microscopic evaluation, often with specific diagnostic techniques (e.g. Baermann or agar plate culture), polymerase chain reaction (PCR) or, alternatively, serology *(10,11)*. The current standard of care for treatment of chronic strongyloidiasis is administration of oral ivermectin (200 µg/kg) once daily for 1–2 days (although evidence indicates that a single dose is sufficient). Ivermectin is donated by the pharmaceutical company MSD to endemic countries for the elimination of onchocerciasis and lymphatic filariasis, but not for use against *S. stercoralis*.

1.2 Justification

Historically, there has been no formal public health guidance on control of strongyloidiasis in endemic settings. In recent years, the World Health Organization (WHO) has been contacted by the health ministries of several countries in which strongyloidiasis is endemic for advice on how to address the disease. This has prompted interest in consideration of preventive chemotherapy with ivermectin for control of strongyloidiasis. This strategy has been successfully applied for control and elimination of lymphatic filariasis and onchocerciasis; these programmes have been associated with reductions in strongyloidiasis prevalence. For example, in areas of Ecuador where ivermectin was administered via mass drug administration (MDA), the prevalence of strongyloidiasis fell from 7% in 1990 to 0% in 1999 and remained at 0% in 2013 *(12)*; in Pemba Island of the United Republic of Tanzania during widespread ivermectin distribution, prevalence fell from 41% in 1998 to 7% in 2013 *(13)*.

In 2021 and 2022, WHO prequalified two generic formulations of ivermectin for public health use that are available at reduced price when compared with branded ivermectin. This presents a unique opportunity to consider new public health control programmes for strongyloidiasis, which leverage existing infrastructure for preventive chemotherapy. This goal is supported by WHO, which published a road map to guide the global strategy for NTDs from 2021 to 2030 *(14)*. This global strategy outlined a need for formal guidance on implementation of a control programme against strongyloidiasis using a preventive chemotherapy strategy.

These events have supported the creation of a guideline development group (GDG) to provide a recommendation on the need for preventive chemotherapy against strongyloidiasis. WHO is now positioned to evaluate the latest evidence on drug efficacy, population level impact, safety and model-based cost–effectiveness estimates of preventive chemotherapy with ivermectin.

1.3 Purpose and scope

The goal of this WHO guideline[1] is to provide an evidence-informed recommendation on whether preventive chemotherapy with ivermectin, as a public health intervention to reduce the disease burden caused by strongyloidiasis, should:

- be implemented as a programme targeting both adults and school-aged children (i.e. MDA) in endemic settings that are above a defined prevalence threshold of strongyloidiasis;
- be implemented as a school-based programme alone (i.e. targeted preventive chemotherapy) in endemic settings that are above a defined prevalence threshold of strongyloidiasis; or
- not be implemented through preventive chemotherapy and instead be given following standard clinical care of individual cases.

[1] A WHO guideline is any document, whatever its title, containing WHO recommendations about health interventions, whether they be clinical, public health or policy interventions. A standard guideline is produced in response to a request for guidance in relation to a change in practice, or controversy in a single clinical or policy area; it is not expected to cover the full scope of the condition or public health problem. A recommendation provides information about what policy-makers, health-care providers or patients should do; it implies a choice between different interventions that have an impact on public health and that have ramifications for the use of resources. All publications containing WHO recommendations are approved by the WHO Guideline Review Committee.

1.4 Target audience

The guideline's target audience are policy-makers, national NTD control programmes, health workers, national health ministries, regional programme groups and implementation partners. This guideline is meant to serve as a reference document for all stakeholders, including WHO, governments, nongovernmental organizations, pharmaceutical manufacturers, donor organizations and academic institutions.

1.5 Key questions

A WHO guideline steering group[1] was established to formulate the key questions to inform a guideline recommendation on preventive chemotherapy with ivermectin to reduce strongyloidiasis. The group identified three key questions, and additional questions of interest.

Each key question was formulated in PICO (population, intervention, comparator and outcome) format.

1. Among individuals infected with *S. stercoralis* (P), does periodic single-dose ivermectin (200 µg/kg oral) (I), rather than placebo, co-intervention or no treatment (C), reduce infection with *S. stercoralis* (O)?

2. Among children aged 5–17 years and/or adults 18 years or older living in a region endemic for *S. stercoralis* (P), does periodic preventive chemotherapy with ivermectin at intervals of up to 12 months (I), rather than placebo, co-intervention or no treatment (C), reduce the recipients' relative or absolute overall mortality and/or morbidity risk from strongyloidiasis (O)?

3. Among infected or non-infected individuals (P), does treatment with ivermectin (I), rather than placebo, co-intervention or no treatment (C), increase the recipients' relative or absolute risk of adverse effects (O) to ivermectin?

The committee formulated additional questions of interest (defined later as "supporting questions"), which include the following:

1. What is the prevalence of strongyloidiasis among children and adults living in an endemic setting globally and in different WHO regions?

2. What is the mortality and morbidity caused by strongyloidiasis?

3. Which is the preferred diagnostic approach to measure the prevalence of strongyloidiasis at a community level?

4. What are the estimated costs of a public health intervention for control of strongyloidiasis and the cost of disease?

5. What is the benefit of distribution of ivermectin on scabies and *Trichuris trichiura*?

6. What is the expected public health impact and cost-effectiveness of different preventive chemotherapy strategies for strongyloidiasis at different levels of endemicity?

[1] The WHO steering group includes members from all WHO departments and regional offices whose work deals directly with the topic of the guideline.

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14. Ending the neglect to attain the Sustainable Development Goals: a road map for neglected tropical diseases 2021–2030. Geneva: World Health Organization; 2021 (https://iris.who.int/handle/10665/338565).

2. Guideline development process

In June 2023, the WHO Global Neglected Tropical Diseases Programme convened a meeting of technical experts on strongyloidiasis to review available evidence on the global disease burden of strongyloidiasis as well as the efficacy, safety and population-level effectiveness of ivermectin against strongyloidiasis to inform a recommendation.

2.1 Guideline development group

The guideline development group (GDG)[1] on strongyloidiasis was composed of internationally recognized experts in different fields related to the guideline. The full list of members is available in Annex 1. At its meeting on 6–8 June 2023, the group reviewed the evidence on possible benefits and harms of different public health control strategies for strongyloidiasis and relevant considerations for decision-making.

2.2 Managing conflicts of interest

All members of the GDG and external experts completed and submitted WHO declaration of interests and confidentiality agreement forms before the meeting. The declarations submitted by each member were reviewed and assessed for any conflict of interest that warranted action in accordance with standard WHO procedures, and were cleared by the Office of Compliance, Risk Management and Ethics. In accordance with WHO policy on conflicts of interest and in order to strengthen public trust and transparency, the WHO guideline steering group posted the names and brief biographies of all GDG members on the WHO website 10 weeks before the GDG meeting, to allow the public to comment on any competing interests that may have gone unnoticed or that may not have been reported during earlier assessments. No conflicts of interest that could have compromised the experts' objectivity and independence in providing advice to WHO in formulating these recommendations were detected. The declarations of interest and their management are summarized in Annex 2. Additionally, at the beginning of the GDG meeting, the members verbally disclosed any new interests since the original declaration of interests; no member had financial, commercial or intellectual conflicts of interest related to the guideline topic.

2.3 Certainty of evidence assessment

The guideline process followed an evidence-informed process using the procedures outlined in the *WHO handbook for guideline development, 2nd edition (1)*. The GDG applied the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach to synthesize and appraise the key evidence and systematic reviews, which were presented to the committee *(2)*.

[1] The GDG is made up of external experts independent from WHO whose central task is to develop evidence-based recommendations. It also performs the important task of finalizing the scope and key questions of the guideline in PICO (population, intervention, comparator and outcome) format. This group is established early in the guideline development process, once the WHO steering group has defined the guideline's general scope and target audience and begun drafting the key questions..

In GRADE, the certainty of evidence is rated as high, moderate, low or very low. These four levels of certainty describe the trustworthiness of estimates of effect of the intervention on an outcome. Randomized trials start with a rating of high, whereas non-randomized studies (observational studies) start with a rating of low. The low starting rating for non-randomized studies is the result of the potential bias induced by the lack of randomization (i.e. confounding and selection bias). This initial level of certainty of evidence can be increased or decreased based on several factors as follows. The GRADE rating can be decreased due to risk of bias, imprecision, inconsistency, indirectness, and/or publication bias. Conversely, a GRADE rating can be increased for consistent and large effects, the presence of a dose–response gradient and/or plausible confounding that works to underestimate an apparent intervention effect. High certainty implies that future research is less likely to change the current estimates of effect of the intervention. Application of the GRADE methodology to population-level interventions and outcomes in public health may be more challenging. For example, public health interventions (including MDA with ivermectin) more often rely on non-randomized data to evaluate population-level impact, include individuals both at high and low risk for an outcome, may need to account for indirect effects (e.g. transmission implications for infectious diseases), and have numerous operational features, costs and logistical complexity that often limit the feasibility of randomized trials *(3,4)*.

Additional information regarding the GRADE approach is presented in Annex 3, including the detailed guidance developed to facilitate the certainty of evidence assessment in this guideline.

2.4 Decision-making process

After determining the certainty of the evidence relevant to the guideline recommendation, the panel applied the evidence-to-decision framework developed by the GRADE Working Group *(5)*. This framework incorporates factors other than the certainty of evidence, such as consideration of balance of benefits and harms, values and preferences, resource use, equity, acceptability and feasibility. Although the GDG focused on an individual person's perspective for values and preferences, they also considered a population perspective in which feasibility, acceptability, equity and cost are important considerations in the creation of this public health recommendation. The final recommendation is directed at the entire population within a community.

Based on the evidence-to-decision framework, the recommendations are graded as either strong or conditional (also called "weak") or no recommendation. A strong recommendation implies that the guideline developers believe that all or almost all informed people would accept the recommended intervention. A conditional (weak) recommendation is made when the committee believes that most informed people would choose the recommended course of action, but a substantial number may not. No recommendation is chosen when no consensus is reached.

Relative to clinical interventions, randomized trial data for public health interventions are scarce and less often available. Thus, evidence informing guidelines addressing public health interventions is often based on non-randomized, often before-after studies, which provide lower certainty evidence due to the potential bias induced by the lack of randomization (i.e. confounding and selection bias). Nevertheless, non-randomized before-after studies can provide evidence regarding the effectiveness of public health interventions and their population-level impact. Furthermore, if the population-level effects are large and precise, the confidence in the public health intervention increases and is reflected in the overall rating of the certainty of evidence informing the recommendation.

The GDG co-chairs, lead writer, and guideline methodologists facilitated the discussion and consensus process during the guideline meeting. First, the GDG discussed whether the public health goal of a guideline recommendation was to reduce *S. stercoralis* infection, disseminated strongyloidiasis or the overall disease burden of strongyloidiasis. Second, the GDG discussed whether preventive chemotherapy should be recommended for control of strongyloidiasis.

Third, the GDG discussed whether distribution of ivermectin should target school-aged children alone (targeted preventive chemotherapy) or the entire community (mass drug administration). Fourth, the GDG discussed the prevalence threshold (and associated diagnostic tool) above which preventive chemotherapy would be recommended. Finally, the GDG discussed implementation considerations for the recommendation.

At the guideline meeting, the GDG formulated an initial guideline recommendation and strength of recommendation. Following the meeting, the GDG held virtual meetings and maintained interaction via email throughout this process. External peer review and WHO Guideline Review Committee review were conducted. Upon completion of these activities, decisions on the recommendations and their strength along with the associated implementation considerations were reached by discussion and consensus.

2.5 Peer review process

The draft guideline document was reviewed by an external peer review group to ensure rigorous review of available evidence and clarity of the recommendations. Experts were requested to review the draft document, some of whom completed their review and forwarded comments and suggestions. The list of peer reviewers from various WHO regions and different disciplines and affiliations is provided in Annex 1.

2.6 Key literature

The GDG identified several published systematic reviews and one randomized trial to provide the evidence base for the guideline recommendation, along with additional key contextual literature and a commissioned modelling study.

2.6.1 Key evidence base (evaluated with GRADE)

- Ivermectin versus albendazole or thiabendazole for *S. stercoralis* infection *(6)*.
- Multiple-dose versus single-dose ivermectin for *Strongyloides stercoralis* infection (Strong Treat 1 to 4): a multicentre, open-label, phase 3, randomised controlled superiority trial *(7)*.
- Impact of preventive chemotherapy on *Strongyloides stercoralis*: a systematic review and meta-analysis *(8)*.
- Safety of high-dose ivermectin: a systematic review and meta-analysis *(9)*.

2.6.2 Modelling and cost–effectiveness study (commissioned)

- Cost–effectiveness of MDA with ivermectin against strongyloidiasis: a modeling study *(10)*.

2.6.3 Additional literature

- Global prevalence of strongyloidiasis and estimated number of people in endemic settings *(11–13)*.
- Morbidity and mortality from strongyloidiasis *(14–16)*.
- Control programs for strongyloidiasis in areas of high endemicity: an economic analysis of different approaches *(17)*.
- MDA for the control of scabies: a systematic review and meta-analysis *(18)*.
- Efficacy and safety of co-administered ivermectin plus albendazole for treating soil-transmitted helminths: a systematic review, meta-analysis and individual patient data analysis *(19)*.
- Effectiveness of ivermectin mass drug administration in controlling soil-transmitted helminth infections in endemic populations: a systematic review and meta-analysis *(20)*.

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3. Summary of the evidence

3.1 Question 1: Efficacy of ivermectin against *S. stercoralis* infection

This question (PICO question 1) was considered as two sub-questions. The first question evaluated the efficacy of ivermectin against *S. stercoralis* infection when compared with placebo or no treatment. The second question evaluated the efficacy of ivermectin against potential alternatives and different administration strategies (dose and number of administrations).

There is strong clinical experience and evidence to support ivermectin as an active drug against *S. stercoralis (1,2)*. Ivermectin was first introduced for animal use around 1981 and approved for human use in 1988 *(3)*. This potent anthelminthic has been increasingly used worldwide to treat NTDs, including strongyloidiasis, onchocerciasis, lymphatic filariasis and scabies. The efficacy of ivermectin to treat individual cases of *S. stercoralis* infection was investigated as soon as ivermectin entered the market and was approved for use in humans. Ivermectin was tested in patients with *S. stercoralis* infections based on stool examination. Experimental studies were conducted in Peru, Guatemala and central Africa, including in patients with chronic strongyloidiasis. In all studies, ivermectin was associated with high infection cure rates (about 90% of treated patients) when the dose used was 200 µg/kg *(4–6)*. Key findings were the large magnitude of effect, the rapid effect of the drug and the absence of plausible confounders. Ivermectin has now been used to treat individual cases of *S. stercoralis* infection for decades. It is recommended in most guidelines and national essential medicines lists *(7)*.

The primary evidence addressing the efficacy of ivermectin against *S. stercoralis* infection compared with other anthelminthics and on the optimal dosing schedule was drawn from one systematic review and meta-analysis *(8)* and one randomized trial *(9)*. The review compared the efficacy of ivermectin with benzimidazoles (albendazole and thiabendazole), and two doses of ivermectin compared with one. The randomized trial compared the efficacy of four doses of ivermectin with one dose of ivermectin. These studies evaluated the efficacy of ivermectin on the outcome infection cure in people with *S. stercoralis* infection.

In the systematic review, the authors searched the following databases from inception to August 2015: the Cochrane Infectious Diseases Group (CIDG) Specialized Register; the Cochrane Central Register of Controlled Trials (CENTRAL), published in the Cochrane Library; MEDLINE; EMBASE; and LILACS. They also searched a randomized trial registry and conference proceedings. One review author extracted the data, while two other review authors crossed-checked the extracted data against the original publications. The review's authors included randomized trials of ivermectin versus albendazole or thiabendazole for treating chronic *S. stercoralis* infection. The primary outcome was elimination of infection or parasitological cure, defined as any negative parasitological examination during the follow-up period (more than two negative stool samples).

After screening 51 unique titles and abstracts, the review's authors identified seven randomized trials eligible for meta-analysis, which enrolled 1147 participants and were conducted between 1994 and 2011 across Africa, South-East Asia, America and Europe. They found that ivermectin probably increases the incidence of infection cure when compared with albendazole (RR 1.79,

95% CI 1.55 to 2.08; 478 participants; four trials; moderate certainty evidence); however, whether or not the same is true for ivermectin when compared to thiabendazole is uncertain (risk ratio (RR) 1.07, 95% confidence interval (CI) 0.96 to 1.20; 467 participants; three trials; very low certainty evidence). Thiabendazole is less frequently used and is included as an essential medicine in only a few countries *(7)*. Both albendazole and thiabendazole were considered active comparators at the time of the study.

The review addressed the efficacy of ivermectin in people with *S. stercoralis* infection; of whom the majority were immunocompetent. Thus, the review results cannot be generalized to other clinical stages (e.g. disseminated disease), immunocompromised people or for the prevention of *S. stercoralis* infections; however, this guideline focuses on treatment that targets immunocompetent people with chronic strongyloidiasis, the commonest clinical form.

Evidence informing the optimal dose of ivermectin came from three studies, two of which were meta-analysed in the aforementioned review *(8)*. Low-certainty evidence suggests that the efficacy of two doses of ivermectin may be comparable to a single dose (RR 1.02, 95% CI 0.94 to 1.11; 94 participants, two trials). The third study is a randomized trial of 309 patients randomized to one dose (*n*=155) or four doses (*n*=154) of ivermectin *(9)*. In the group randomized to four doses, ivermectin was given on days 1, 2, 15 and 16. The trial included patients who were infected with *S. stercoralis*, aged older than 5 years, weighed more than 15 kg and resided in an area not endemic for *S. stercoralis*. In the trial, the principal finding was that at 12 months, 86% (102 of 118 participants) had responded to treatment in the single-dose group compared with 85% (96 of 113 participants) in the four-dose group (absolute risk difference 1.48%, 95% CI -7.55 to 10.52); therefore, higher cure from additional doses is unlikely. Like the review findings, the generalizability of the trial findings is limited to *S. stercoralis* chronic infection.

3.2 Question 2: Impact of mass drug administration with ivermectin on strongyloidiasis

This question (PICO question 2) addressed the population-level impact of mass distribution of ivermectin on the prevalence of strongyloidiasis in endemic settings *(10)*. The GDG considered one systematic review and meta-analysis to provide evidence on the effectiveness of MDA with ivermectin to achieve an objective of reduced strongyloidiasis. An additional systematic review and meta-analysis was discussed.

The systematic review evaluated literature to assess the relationship between preventive chemotherapy with ivermectin, school-based or community-based programmes and an outcome of prevalence of *S. stercoralis* infection in any age group. The review's search criteria included all study types including observational studies. The exposure of interest (intervention) was MDA with ivermectin. The outcome of interest was *S. stercoralis* infection (measured with faecal testing or serology).

The review's authors searched PubMed, EMBASE, the Cochrane Central Register of Controlled Trials and LILACS. The authors searched for literature published between 1990 and 2022. The last search was conducted in August 2022. There were no language restrictions. The systematic review was registered in PROSPERO (record CRD42022355118).

The review identified 933 studies, of which eight were included in the meta-analysis. This included zero randomized control trials and eight observational studies (retrospective and prospective cohorts). All studies followed a pre-post design and only assessed MDA (community-wide).

In the meta-analysis, MDA with ivermectin was associated with a significant reduction of *S. stercoralis* prevalence comparing before and after MDA. The study estimated a prevalence RR of 0.18 (95% CI 0.14–0.23), corresponding to an 82% relative reduction in prevalence after MDA, a

magnitude of effect that it is considered large by GRADE. The authors found a similar finding when considering serology as the diagnostic tool, with a RR of 0.35 (95% CI 0.26–0.48) for *S. stercoralis* prevalence, corresponding to a 65% relative reduction. This pre-post design did not include a control group. Data were limited to make comparisons of the relative effectiveness of annual and biannual treatment.

The key limitation of the meta-analysis was that the included data were observational and followed a pre-post design without a control group, although one included study included a non-intervention group; therefore, there is a risk for confounding. The GDG noted that the effect size of the association between MDA with ivermectin and the reduction of *S. stercoralis* prevalence is consistently large across primary studies, reinforcing the assumption of a strong association and that weak unmeasured confounders or other sources of modest bias would not change the result. The GDG articulated a public health goal of reducing the overall disease burden caused by strongyloidiasis, but these studies did not examine cases of disseminated strongyloidiasis. This is understandable given that disseminated strongyloidiasis is a rare disease with limited literature. The included studies only examined MDA (community-wide) and not school-based preventive chemotherapy. Finally, diagnostic differences in the included studies limits comparability.

The GDG reviewed preliminary data from a second systematic review and meta-analysis that is unpublished on the population-level impact of mass distribution of ivermectin on the prevalence of strongyloidiasis *(11)*. This systematic review applied modified inclusion and exclusion criteria, resulting in some differences in the included studies. This review found that the pooled prevalence reduction of *S. stercoralis* following MDA with ivermectin alone was 84.49% (95% CI 54.96–94.66) across five studies, and was 81.37% (95% CI 61.62–90.96) across seven studies with or without albendazole. Again, the reduction of *S. stercoralis* prevalence was considerably large and consistent across primary studies. Overall, both reviews concluded that MDA with ivermectin reduces *S. stercoralis* prevalence.

3.3 Question 3: Safety of ivermectin in the population

This question (PICO question 3) was considered as two sub-questions. The first question evaluated the safety of ivermectin in humans, regardless of infection status, when compared with placebo or no treatment. The second question evaluated the safety of different ivermectin dosing.

Three systematic reviews assessing the safety of ivermectin compared to placebo or no treatment were examined: one addressed the safety of ivermectin treatment in patients with coronavirus disease 2019 (COVID-19) *(12)*: one addressed the safety of ivermectin combined with iota-carrageenan prophylaxis in people at risk for COVID-19 *(13)*; the other addressed the safety of ivermectin in children aged under 5 years *(14)*. Among 718 people with COVID-19 from seven randomized trials, there was no convincing evidence that ivermectin was different than standard care or placebo for this outcome (3 more per 1000, 4 fewer to 9 more, moderate certainty evidence) *(12)*. Among people at risk for COVID-19 and when compared with standard care or placebo, ivermectin combined with iota-carrageenan probably has trivial to no effect on adverse effects leading to drug discontinuation (0 difference per 1000, 17 fewer to 17 more, moderate certainty evidence, 1 randomized trial, 117 participants) *(13)*. For children aged under 5 years and 15 kg in weight, the review's authors identified nine eligible studies: one randomized controlled trial, two non-randomized cohort studies, three case series and three case reports. Of these, two reported on the safety of oral ivermectin in *S. stercoralis* infection specifically. Of the 60 children aged under 5 years for whom safety data were available, four children (4/60; 7%) reported an adverse event. In this review, the duration of follow-up periods ranged from 3 weeks to 2 years – periods which allowed sufficient time to ascertain safety data *(14)*.

Evidence addressing the safety of different ivermectin administration strategies was drawn from one systematic review and meta-analysis, which assessed the safety of ivermectin when used at doses of > 200 and > 400 mg/kg/day *(15)*.

The review's authors searched the following databases from inception to January 2018: MEDLINE (PubMed); Web of Science Core Collection; Cumulative Index to Nursing and Allied Health Literature (CINAHL data- base); Tropical Diseases Bulletin; CAB Direct; Scopus (Elsevier API); Science Direct; International Pharmaceutical Abs (Ovid); and Conference Papers Index (CSA) (ProQuest XML). They completed screening and data extraction independently and in duplicate; included all studies evaluating the safety of ivermectin in humans, including case–control studies; and considered studies that compared participants receiving higher doses of ivermectin with participants receiving standard doses of ivermectin eligible for meta-analysis. The primary outcome was adverse events, which the review authors considered drug-related unless specifically attributed and documented to other causes in the publication.

After screening 458 unique titles and abstracts, the review's authors identified six studies eligible for meta-analysis. All six were randomized trials and published between 1993 and 2018. Five trials included infected participants (e.g. onchocerciasis, trichuriasis and malaria) and were conducted in Africa (*n*=4) and Australia (*n*=1). One trial included non-infected participants and was conducted in Europe. The age of participants in the randomized trials ranged from 2 to 60 years – one trial addressed the safety of high-dose ivermectin in children specifically. Overall, the incidence of adverse events, regardless of ivermectin dose, was low. Furthermore, the odds of adverse events did not significantly differ between participants randomized to ivermectin > 400 ug/kg and 400 ug/kg (odds ratio (OR) 1.06, 95% CI 0.67 to 1.69, 1426 participants) or participants randomized to ivermectin > 400 ug/kg and 200 ug/kg (OR 1.16, 95% CI 0.89 to 1.52, 1427 participants). Regarding the severity of adverse events, all studies reported that 100% of the adverse events were mild or moderate in both arms (standard and high-dose), with serious adverse events, described as life-threatening, reported in just one study with one case in the standard dose (anaphylactic reaction) and another in the high-dose group (QTc prolongation in the electrocardiogram, most likely due to a concomitant drug). Choking is a possibility, although it has not been reported and is unlikely due the small size of ivermectin tablets.

The certainty of evidence addressing both the safety of ivermectin > 400 ug/kg compared with 400 ug/kg and to 200 ug/kg was moderate due to some imprecision. Thus, as high-dose ivermectin probably has trivial to no effect on safety, smaller doses often used in MDA should at least carry even lower risk.

3.4 Additional relevant literature

The following are supporting questions that provided evidence broadly relevant to the topic and evidence-to-decision factors, but were not key evidence.

3.4.1 Burden of disease (supporting question 1)

The GDG considered the global burden of disease of strongyloidiasis and the implication of an MDA recommendation on the number of people who would require treatment. In a modelling study, the global prevalence of strongyloidiasis in 2017 was estimated at 8%, meaning approximately 614 million people would have chronic strongyloidiasis. The WHO regions with the largest number of infected persons included the South-East Asia, Western Pacific and African regions *(16)*. Subsequently, based on these global prevalence estimates, a second study estimated that, as an example, with a 10% observed prevalence threshold for MDA against strongyloidiasis, 900 million people would need to receive treatment *(17)*. Additional modeling work estimated the global distribution of regions at risk for strongyloidiasis *(18)*.

3.4.2 Morbidity and mortality from strongyloidiasis (supporting question 2)

The GDG considered disease morbidity and mortality from strongyloidiasis *(19–21)*. In a systematic review and meta-analysis of the symptoms associated with chronic strongyloidiasis *(19)*, the authors found that urticaria was the most common and robust, followed by abdominal pain and diarrhoea. The GDG noted that symptomology of chronic strongyloidiasis is subtle and may be hard to elicit, but agreed with these findings.

In a retrospective study of strongyloidiasis-related deaths in the United States of America from 1991 to 2006, the authors identified a total of 347 deaths, for a total incidence of 0.79 per 10 million deaths. Limitations noted by the GDG included that the United States of America is a low-prevalence setting, that the study's methodology of reviewing death certificate data is limited and that the diagnosis is commonly missed meaning case ascertainment is likely quite low. However, this study established the presence of strongyloidiasis-related deaths even in a low-prevalence setting. These conclusions were further supported by a systematic review of case reports of severe strongyloidiasis *(20)*. There is overall uncertainty about the incidence of disseminated disease and death from strongyloidiasis.

3.4.3 Diagnostic methods (supporting question 3)

The GDG referred to a recently published WHO document summarizing diagnostic methods for *S. stercoralis* infection *(22)*.

3.4.4 Economic literature (supporting question 4)

The GDG considered literature on the projected economic considerations of MDA against strongyloidiasis *(23)*. In a modelling study *(23)*, the authors estimated the costs and public health impact of different preventive chemotherapy strategies using ivermectin to empirically treat strongyloidiasis in endemic populations. This study estimated that to effectively cure one person from strongyloidiasis would additionally cost US$ 2.83 for an MDA (community-based) programme and US$ 1.13 for a targeted preventive chemotherapy (school-based) programme. These costs were assumed to be small compared with the costs of other essential medicines recommended by WHO. More deaths were averted with the MDA programme than with the targeted preventive chemotherapy programme. The model assumed a hypothetical population of one million people living in a region endemic for strongyloidiasis with 15% prevalence. Limitations of the study included simplifying assumptions and uncertainty related to S. stercoralis biology, epidemiology and transmission as well as heterogeneity in costs and implementation by setting.

3.4.5 Implications for other infectious diseases (supporting question 5)

The GDG considered that MDA with ivermectin would have effects against other infectious diseases such as *Trichuris trichiura* and scabies *(24,25)*. MDA with ivermectin is currently recommended by WHO for public health control and elimination of lymphatic filariasis (alongside other anthelminthics) and onchocerciasis *(26,27)*. However, this present guideline considers whether to implement MDA with ivermectin with a goal of reducing strongyloidiasis in areas nonendemic for either lymphatic filariasis or onchocerciasis. Additional benefit will be derived from reductions in whipworm and scabies prevalence where they are co-endemic.

In a systematic review and meta-analysis on scabies (24), the authors reviewed studies of MDA with ivermectin or permethrin (8 out of 11 included studies used ivermectin) on scabies and impetigo prevalence. This study found a 79% (95% CI 55–90%) reduction in prevalence of scabies associated with MDA with ivermectin or permethrin. The included studies were mostly observational, with small sample sizes with a high degree of heterogeneity and short follow-up period.

In a systematic review and meta-analysis on *T. trichiura (25)*, the authors reviewed studies of MDA with co-administration of albendazole with ivermectin. In the meta-analysis of the four included studies, the authors found the combination of ivermectin and albendazole was associated with a lower risk for *T. trichiura* infection compared with albendazole alone (RR 0.44; 95% CI 0.31–0.62). MDA programmes for *T. trichiura* infection currently use albendazole alone. The meta-analysis was limited by a small sample size which precluded additional analysis, including further assessment of heterogeneity and subgroup analyses. An unpublished meta-analysis found a prevalence reduction of *T. trichiura* was 49.93% (95% CI 18.23–69.34) across five studies with ivermectin alone, and 89.40% (95% CI 73.66–95.73) across three studies with the addition of albendazole with ivermectin *(28)*.

3.4.6 Modelling and cost–effectiveness study (supporting question 6)

The WHO guideline steering group commissioned a modelling analysis to estimate the public health impact and cost–effectiveness of preventive chemotherapy with ivermectin against strongyloidiasis and disseminated disease *(29)*. The GDG considered the modelling evidence that included the potential public health impact (averted mortality and morbidity), costs and cost–effectiveness of preventive chemotherapy for strongyloidiasis, as well as extensive sensitivity and uncertainty analyses.

The modelling team developed a stochastic individual-based susceptible-exposed-infection (S-E-I) model describing transmission and control of *S. stercoralis*, with the intervention of targeted preventive chemotherapy (school-based) or MDA (community-based) with ivermectin. In the model, the authors simulated key features of the biology and epidemiology of *S. stercoralis*, and then predicted the impact of school- and community-based preventive chemotherapy in terms of infection prevalence and disability-adjusted life years (DALYs) lost across a range of epidemiological settings (model calibrated to baseline true prevalence of 1–80%) and levels of target population coverage of treatment. DALYs are the sum of years of life lost due to premature disability (YLL) and years lived with disability (YLD); the latter is weighted by a disability weight reflecting the severity of morbidity. The simulation was performed over a 10-year time period with a 3% discount rate for both costs and health effects. The goal of the study was to identify a prevalence threshold for the implementation of preventive chemotherapy against strongyloidiasis based on cost–effectiveness, measured by the incremental cost–effectiveness ratio (ICER).

The main finding of the modelling study was that MDA (community-wide) implemented at 65% coverage in those aged 5 years and older was the most cost–effective strategy for settings with a minimum 2–5% baseline prevalence in school-aged children (measured with a 50% sensitivity diagnostic test, therefore a 4–10% true prevalence), given a minimal willingness to pay (WTP) of US$ 600 per DALY averted. The required minimal WTP was even lower for more highly endemic settings (down to US$ 160 per DALY averted). School-based treatment programmes were "dominated" by community-based programmes, meaning that school-based treatment alone would not be optimal from a cost–effectiveness perspective. The majority of strongyloidiasis infections and disseminated cases occur in adults (aged ≥ 15 years) based on an assumed profile of immunocompromised status; the majority of overall DALYs were averted in adults from morbidity. Even when considering only YLDs averted (i.e. assuming zero strongyloidiasis-related mortality), MDA was still the most cost–effective strategy for a WTP of at least US$ 800 per DALY

averted. In a wide range of sensitivity analyses for assumptions about cost of MDA, drug efficacy, systematic non-participation to MDA, duration of treatment and the time horizon considered, MDA remained the most cost–effective strategy with the minimal WTP ranging from US$ 350 to US$ 800. The full uncertainty analysis also yielded robust study conclusions.

The model's assumptions were as follows. First, there are limited data on age-specific incidence and prevalence of strongyloidiasis across diverse endemic settings. The model assumed exposure heterogeneity and age patterns from existing transmission models for hookworm. Second, there are limited data on the age-specific incidence of disseminated strongyloidiasis across diverse endemic settings. Therefore, the outcome of interest (disseminated strongyloidiasis) was extrapolated from model-based estimates of *S. stercoralis* infection and a range of assumptions about the risk of dissemination. Third, the majority of DALYs was driven by disability from chronic infection and an assumed disability weight of 0.02 based on literature, although these symptoms are subtle and hard to measure. Fourth, the model assumed that infections were lifelong, and their infectiousness was constant over the infection period. Fifth, the model did not explicitly include biological complexities such as density-dependent worm fecundity or host immune response; instead, the authors assumed that all infections are equally fecund due to a strong regulating host response. Sixth, the model predictions for "true" prevalence were translated to prevalence as we might observe it, assuming a simplified representation of diagnostic testing with diagnostic test sensitivity of 50% or 80%, reflecting stool-based and serological tests, respectively. Seventh, the model assumed a closed population (no migration in or out of the population). Eighth, the model was not formally validated, although the general results agreed with the observed data. Finally, and importantly, the model did not account for variation in clinical practice between settings for testing, diagnosis and treatment of strongyloidiasis, assuming that these are so limited that they have little impact on transmission in the general population.

The conclusion of the study is that MDA (community-wide) was the most cost–effective approach to control of strongyloidiasis, compared with targeted preventive chemotherapy (school-based) and no preventive chemotherapy. Even in settings where improved access to health care will reduce or already has reduced strongyloidiasis-related mortality, implementation of MDA would still be cost–effective where baseline infection prevalence exceeds 2% (based on a diagnostic tool with 50% sensitivity) in school-aged children.

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4. Recommendation

In endemic settings with prevalence of *Strongyloides stercoralis* infection ≥ 5%, WHO recommends annual mass drug administration with single dose ivermectin in all age groups from 5 years and above to reduce strongyloidiasis.

Conditional recommendation

Low quality of evidence

The following includes multiple remarks relevant to interpretation of the guideline recommendation.

4.1 Remarks

4.1.1 Target population

The target population for MDA includes the entire community (currently for age groups 5 years and above). Based on modelling evidence, epidemiological data and expert judgement, a larger public health impact is expected for treatment of the entire community through MDA compared with treatment of school-aged children alone. This is specifically due to older populations being at higher cumulative risk for infection and potential for disseminated disease (due to immunosuppression), therefore benefiting from MDA.

Ivermectin is currently indicated for children weighing more than 15 kg. The safety of ivermectin administration in children weighing less than 15 kg (corresponding to the age cut-off of 5 years) is not established and therefore not recommended *(1)*; however, further study of the safety of ivermectin in them, alongside development of paediatric formulations of ivermectin is ongoing *(1)*. The GDG anticipates this age and/or weight limitation may be removed in the future if sufficient data on safety of ivermectin in this younger population can be established *(2)*.

Women who are pregnant or lactating within the first week after giving birth should be excluded from MDA with ivermectin due to a current lack of safety data and regulatory approval for ivermectin in these groups *(1)*. These exclusion criteria will be reassessed pending new data on evaluation of ivermectin safety and alternative formulations of ivermectin.

In settings with any evidence of *Loa loa* infection, MDA with ivermectin may not be advised due to risk of adverse events in patients with high-density *L. loa* infections. In such settings, safety precautions are needed as outlined in WHO guidelines on onchocerciasis and/or lymphatic filariasis *(3,4)*. In most circumstances, MDA with ivermectin is not recommended in these settings.

In settings with ongoing MDA with ivermectin for another indication (e.g. lymphatic filariasis, onchocerciasis), the ongoing programme of MDA with ivermectin is sufficient, assuming adequate coverage of the entire community.

4.1.2 Prevalence threshold

The prevalence threshold of ≥ 5% is based on estimation by a coprological method, using either the Baermann technique or agar plate culture on a single stool specimen, in a survey of school-aged children (5–14 years). Coprological methods are the preferred method as they ensure measurement of active infection.

The panel noted that multiple diagnostic techniques are available and can be potentially used to estimate the prevalence of *S. stercoralis* infection in the population. The laboratory infrastructure and expertise requirements differ by technique. For this reason, the panel decided to include information on different diagnostic techniques and sampling considerations. Given that diagnostic sensitivity and/or specificity will vary among techniques, the prevalence threshold applied must be specific to the corresponding diagnostic tool. A summary of alternative prevalence thresholds is provided in Table 1.

Quality-assured serological (antibody) tests can be used to estimate prevalence of *S. stercoralis* infection to determine the need for MDA; a ≥ 15% prevalence by quality-assured serological test (or assay responding to a future WHO target product profile for *S. stercoralis* diagnostics) in school-aged children is considered equivalent to ≥ 5% based on use of the Baermann technique or agar plate culture. This adjustment was based on estimation using assumed diagnostic performance characteristics for these tests (see Table 1). However, a limitation of serological testing is that it may measure prior exposure and not active infection (although significant seroreversion after treatment is documented for many serological assays for *S. stercoralis*); furthermore, performance may vary by assay. For these reasons, serology is not the preferred mode of testing but does remain an option.

The panel noted that the prevalence threshold of ≥ 5% is defined based on sampling from a population of school-aged children (5–14 years). The panel considered that the prevalence of *S. stercoralis* infection is expected to rise with age, meaning that the corresponding prevalence in adolescents and adults is likely higher than the prevalence measured in school-aged children. If a national programme decides to perform a community-wide prevalence survey (i.e. sampling people aged 5 years and older, including adults), then a community prevalence threshold of ≥ 10% (in a community survey, including adults) by Baermann technique or agar plate culture is a reasonable alternative to the ≥ 5% threshold measured in school-aged children alone. If a serological (antibody) test is applied through a community-wide prevalence survey, then a prevalence threshold of ≥ 25% (in a community survey, including adults) is a reasonable alternative to the ≥ 15% prevalence by serological test in school-aged children. This adjustment was based estimation using assumed test performance characteristics and age trends in infection. A summary of prevalence thresholds is provided in Table 1.

In recommending the prevalence thresholds, the GDG considered multiple sources of information, including epidemiological data, a modelling study, expert judgement, surveillance considerations and the need to balance resource requirements with expected public health impacts. The modelling study estimated the expected public health impact, resource requirements and cost–effectiveness of different prevalence thresholds for MDA; the selected prevalence threshold of 5% would be expected to be cost–effective in low- and middle-income countries across a wide variety of assumptions on natural history and disease assumptions, and projected to have a large public health impact, while being feasible to measure with current surveillance methods. Furthermore, in settings with *S. stercoralis* infection above this prevalence threshold, strongyloidiasis is a large public health burden.

Table 1. Prevalence thresholds for *S. stercoralis* above which MDA is recommended, by population and diagnostic test

Diagnostic test	Population	
	School-aged children	Community
Coprological test[a]	≥ 5 %	≥ 10 %
Antibody assay	≥ 15 %	≥ 25 %

[a] A coprological (faecal) test is defined as either the Baermann test or agar plate culture, with assumed sensitivity of 50% and specificity of 100%. The serological threshold assumed that antibody assays have an approximate sensitivity of 90% and a specificity of 93% *(5)*; the WHO target product profile for diagnostic tests for *S. stercoralis* is under development. Informed by review of epidemiological data, a modelling study, and expert opinion, the guideline recommendation uses a prevalence threshold of 5% to recommend MDA, defined by use of a faecal test and sampling a population of school-aged children. This prevalence threshold corresponded to a true prevalence of 10% in school-aged children given imperfect sensitivity of a faecal test. Given age-specific trends in *S. stercoralis* prevalence (higher in adults), we assumed a corresponding 20% true prevalence in a community-wide population survey. The four prevalence thresholds are approximately based upon the test characteristics of faecal tests and antibody assays, as well as the age group being sampled, with rounding for ease of measurement.

4.1.3 Implementation

The suggested dose of ivermectin is a single dose of 200 µg/kg oral therapy.

The implementation unit for MDA against strongyloidiasis is a district (defined as a geographical area with a population of approximately 100 000–250 000 people), but can vary based on the local context, including implementation on a national or subdistrict level informed by surveillance data.

MDA should be prioritized in the highest-prevalence regions and settings, where it is expected to have the largest public health impact. The intervention can be evaluated within the health priorities of a country.

Although there is limited evidence comparing different frequencies of MDA, the panel considered annual frequency of MDA ivermectin to be effective and technically feasible.

Further guidance on design of prevalence surveys for surveillance to measure strongyloidiasis prevalence will be forthcoming in technical manuals, which will be necessary to inform decisions on indication and operational guidance for MDA.

The MDA programme should be conducted for a minimum of 5 years. Surveillance of *S. stercoralis* infection prevalence is needed after 5 years of MDA to inform ongoing need for treatment, although earlier surveillance is also reasonable. Further guidance on surveillance and stopping MDA criteria will be forthcoming in a WHO technical manual.

Local consultation with leaders and the community is important to confirm acceptability of any public health strategy. Guiding principles include that informed consent, and assent, should be obtained whenever an MDA programme is being implemented. This should be conducted based on the country requirements and local context and may vary between programmes. For example, community and/or parent meetings with verbal consent and assent may be sufficient in some contexts. However, written consent approaches may be required in some contexts. The decision to participate in MDA should be voluntary for all persons.

National programmes should leverage opportunities to integrate an MDA programme against strongyloidiasis into existing public health programmes, especially for NTDs (e.g. other soil-transmitted helminthiases, onchocerciasis and lymphatic filariasis).

The panel noted that routine monitoring for effective coverage, impact evaluation of the intervention, emergence of drug resistance and safety should be a key part of any programme.

The guideline recommendation supports the need for access to timely diagnosis and treatment for strongyloidiasis in the clinical setting, with special attention to testing for S. stercoralis infection and treatment prior to immunosuppression or other risk factors for disseminated strongyloidiasis.

Water, sanitation and hygiene measures are needed as a complementary intervention to reduce transmission.

4.1.4 Construction of the recommendation

The public health goal of this guideline recommendation is to reduce the burden of strongyloidiasis, both infection and disseminated disease. The GDG determined that control of parasitologically-confirmed *S. stercoralis* infection (symptomatic, chronic infection) is a meaningful public health outcome based on its morbidity and complication of disseminated disease. The evidence that supported the recommendation for MDA was primarily available for the outcome of infection, and focused on chronic infection. The GDG was not aware of any direct evidence of MDA leading to reduced disseminated disease, but considered it reasonable to expect a reduction in disseminated disease through decreased infection prevalence. Therefore, the certainty of evidence that MDA would reduce chronic *S. stercoralis* infection is higher than the certainty of evidence that MDA would reduce disseminated strongyloidiasis.

The panel issued a conditional recommendation based on a low quality of evidence. This decision was largely based on considering the entire body of evidence across dimensions.

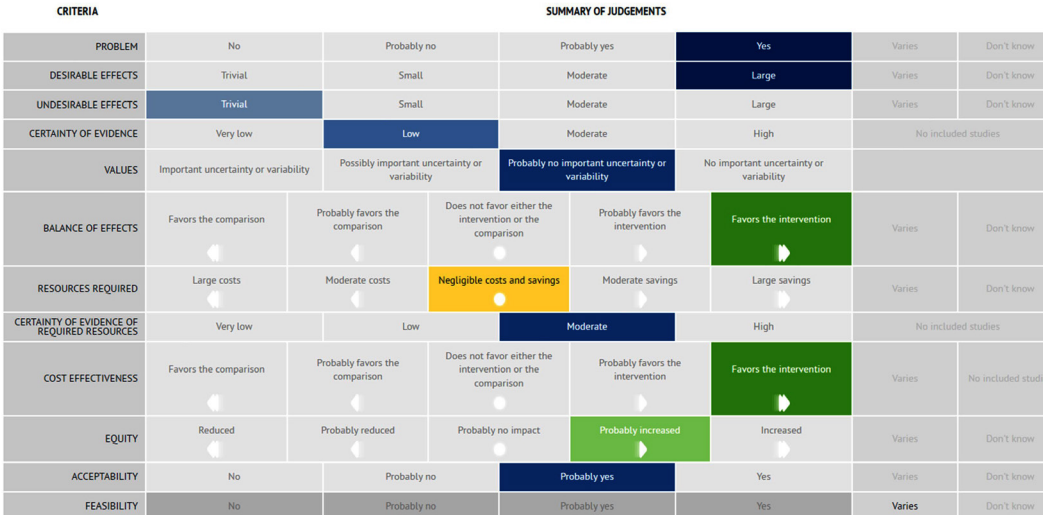
4.2 Opportunity for integration with health programmes

Prior to initiation of MDA for strongyloidiasis, the GDG recommended that national programmes should complete a review of existing public health programmes to identify opportunities for integration, especially with other NTD programmes. MDA programmes against onchocerciasis and lymphatic filariasis provide community-wide ivermectin, and in settings with these programmes, this treatment is sufficient. In settings with community-wide programmes such as MDA for other infectious diseases (e.g. schistosomiasis), ideally ivermectin can be added to current medications for cost efficiency. In some cases, participation of school-aged children may be lower in a community-based delivery platform; in these settings, school-based delivery can be leveraged to maximize coverage in this population, ideally alongside other school-based public health programmes.

4.3 Rationale for the recommendation

The GDG made its recommendation based on the considerations and judgements summarized in Fig. 1 and detailed below.

Fig 1. Evidence-to-decision frameworka for guideline recommendation on MDA with ivermectin for control of strongyloidiasis



[a] Column one lists the considerations important for this public health recommendation. Possible judgement values for each consideration are reported across the columns. Judgement values on the left side of the matrix correspond to a weaker rationale, while judgement values on the right side of the matrix correspond to a stronger rationale. All judgements in the evidence-to-decision framework originated from the data reported in the framework. Blue and green favor the intervention, while yellow is neutral.

4.3.1 Benefits and harms

Research evidence

Extensive historical evidence supports the use of ivermectin to treat *S. stercoralis* infection *(6,7)*.

Furthermore, ivermectin probably increases the incidence of infection cure when compared with albendazole (moderate certainty evidence); however, we are uncertain whether or not the same is true for ivermectin when compared with thiabendazole because of the paucity of data (very low certainty evidence). Randomized trial data addressing the use of multiple doses of ivermectin when compared with a single dose did not support a large benefit of multiple doses over a single dose *(8)*.

In terms of effectiveness, non-randomized before-after studies measuring the prevalence of *S. stercoralis* infection before and after MDA with ivermectin provide an overall low certainty evidence of a benefit *(9)*. Although the risk of bias in non-randomized studies is increased, the observed associations on prevalence post-MDA with ivermectin were large and precise, and drop in prevalence was rapid. These factors increase our confidence in the effectiveness of ivermectin for *S. stercoralis* infection. Further, efficacy data repeatedly demonstrate a high cure rate of *S. stercoralis* infection with ivermectin and increases our confidence in the population-level impact of MDA with ivermectin *(6,7)*.

Data regarding the public health impact and cost–effectiveness of MDA with ivermectin were drawn from one commissioned modelling analysis. Because results were robust across a range of epidemiological settings and sensitivity analyses, the GDG is confident in the modelled evidence supporting MDA with ivermectin for the control of strongyloidiasis, with the limitations and assumptions of a modeling study.

The safety of ivermectin has been repeatedly demonstrated *(6)*. Evidence regarding its excellent safety profile is drawn from other diseases (e.g. lymphatic filariasis) and data from six randomized trials of patients with *S. stercoralis* infection, which showed the safety of high-dose ivermectin (> 400 µg/kg, at least double of the standard dose of 200 µg/kg) *(10,6)*. Because higher-dose compared with lower-dose ivermectin probably has trivial to no effect on adverse effects (moderate certainty evidence), smaller doses often used in MDA should at least carry even lower risk.

Additional information is available in the GRADE ---> summary of findings tables regarding the efficacy, effectiveness and safety of ivermectin, and in the modelled evidence regarding the public health impact and cost–effectiveness of MDA with ivermectin (Annex 4).

Additional considerations:

Benefits

For an individual, ivermectin has a high cure rate for *S. stercoralis* infection, which can be symptomatic and associated with high morbidity. Symptomatic infection is a significant contributor to the global burden of strongyloidiasis-associated morbidity.

Curing infection may eliminate future risk of disseminated strongyloidiasis if there is no reinfection. Disseminated disease has an estimated 60% case-fatality rate. The committee extrapolated that MDA with ivermectin would likely reduce the global burden of disseminated strongyloidiasis, which is a high-mortality complication of infection. As health care systems improve in many endemic low- and middle-income settings, the number of immunosuppressed patients may rise due to availability of immunosuppressive medications for treatment of disease, and so the risk of disseminated disease may increase.

MDA involves treatment of infected and uninfected persons. This should reduce community prevalence of *S. stercoralis* infection and can potentially interrupt transmission. MDA therefore can potentially, over a long period, achieve interruption of transmission and elimination of the infection, although empirical evidence here is lacking.

In settings co-endemic for *T. trichiura*, MDA with ivermectin (co-administered with albendazole for other preventive chemotherapy programmes) may lead to larger reductions in prevalence of *T. trichiura* than with MDA with albendazole alone. This is because cure rates for individuals infected with *T. trichiura* are higher with a combination of albendazole and ivermectin than with albendazole alone. Scabies (caused by *Sarcoptes scabiei*) control would also benefit from an ivermectin MDA programne. There are also resource efficiencies of integrated programmes.

Harms

In treated children, mild and moderate adverse events can occur, but evidence suggests these are transient *(10,11)*. The adverse events described include ocular symptoms such as blurry vision or pain, although these are in the context of onchocerciasis programmes *(10,11)*. Others are described as neurological or cutaneous.

In treated children, rare case reports of severe adverse events including anaphylaxis and QTc prolongation have been reported (although they may be incidental or due to concomitant medications). Choking of young children on whole tablets of anthelminthic drugs has been observed during MDA, but this has not been reported for ivermectin tablets, which are small.

If a person is infected with *L. loa* or lives in an area considered endemic for *L. loa*, ivermectin may present a risk of *L. loa* encephalopathy.

Repeated use of ivermectin could theoretically lead to drug resistance against endemic pathogens. In an experimental animal model, researchers induced resistance to ivermectin in *Strongyloides ratti* by frequent treatment with subtherapeutic doses of ivermectin. Researchers evaluated resistance by the expression levels of ABC transporter genes. Despite this proof-of-concept, the evidence is from animal models and a different *Strongyloides* species, and thus indirect *(12)*. To note, upregulation of genes in the worm was obtained through prolonged use across multiple generations of subtherapeutic doses (100 µg/kg). Both events are unlikely to occur during MDA. Other studies have shown that ABC transporter genes may play a role in modulating the effects of ivermectin, but are unlikely, individually, to be the critical gene responsible for resistance to ivermectin *(13)*. The GDG acknowledged this risk but decided to not modify its overall judgement on harms.

Widespread use of ivermectin may have ecological impacts *(14)*.

Summary

Ultimately, the recommendation was made on the following basis: MDA demonstrated large reductions in the prevalence of *S. stercoralis* infection in endemic settings; safety of ivermectin, even in high-doses; and public health impact that is robust to changes in epidemiological settings and model assumptions. It is acknowledged that adverse events that can occur in treated children, albeit evidence suggesting these are infrequent, mild and transient, and the limited information related to emergence of resistance to ivermectin.

Judgement

Large benefits, trivial/no harms

4.3.2 Certainty of the evidence

The GDG rated the overall certainty of the evidence supporting MDA of ivermectin for strongyloidiasis as low.

The GDG is highly confident in the efficacy and safety of ivermectin against *S. stercoralis* infection. However, evidence addressing the effectiveness of MDA (population level) with ivermectin was based on non-randomized data from pre-post studies, mostly without a control group. This is the main reason why the certainty of evidence was rated as low. However, the association of post-MDA prevalence with ivermectin was large and precise, elements that might lead to rating up the quality of evidence in GRADE. The GDG discussed whether to increase the rating of our confidence in the effectiveness of MDA with ivermectin against *S. stercoralis* infection from low to moderate, finally preferring to maintain the rating as low. Modelled evidence addressing the cost–effectiveness of MDA with ivermectin was also an important contributor to the evidence base for the recommendation. Again, the model was populated with evidence based on non-randomized data from pre-post studies. Since the model consistently demonstrated the cost–effectiveness of MDA with ivermectin across a range of epidemiological settings and sensitivity analyses, the GDG decided to not rate down our confidence from low to very low, being reassured of the modelled reductions in infection prevalence and DALYs post-MDA with ivermectin.

The guideline recommendation applies to strongyloidiasis, which refers to a range of disease stages, including infection, disseminated disease and mortality. Our certainty in the evidence for severe manifestations of strongyloidiasis is lower than for chronic infection because data reporting on disseminated disease and mortality outcomes are scarce *(15–17)*. We identified only one study that evaluated mortality for disseminated strongyloidiasis. Unfortunately, the study does not reflect the settings in which the burden of severe disease is common. In fact, this was a population-based case-control study conducted in the United States of America – a non-endemic country. This study identified 347 strongyloidiasis deaths (0.79 per 10 million deaths) between 1991 and 2006

(17). This is likely an underestimation of the true burden of mortality in endemic countries. Based on extensive experience and limited direct data available, the GDG relied on modelled evidence, which is believed to reflect the burden of severe disease and mortality in endemic settings.

Accounting for differences in the certainty of evidence across all outcomes considered critical to patients and the construction of this guideline recommendation, the GDG ultimately rated the overall certainty of the evidence base informing the recommendation of MDA with ivermectin for strongyloidiasis as low. Annex 4 provides additional information, including narrative summaries of the evidence base, GRADE summary of finding tables reporting on the efficacy, effectiveness and safety of ivermectin, and Annex 5 the results from the GDG rating the importance of outcomes.

Judgement

Low certainty of evidence

4.3.3 Values and preferences

Research evidence

The GDG took an individual person's perspective with regard values and preferences. The GDG members rated infection, disseminated disease and mortality outcomes as relevant public health outcomes for construction of the guideline recommendation (Annex 4). However, because the morbidity associated with strongyloidiasis is vastly more common than mortality in endemic settings, the GDG placed greater importance on addressing *S. stercoralis* infection (i.e. the threat of contagion by infection) in this guideline *(18,19)*. This is consistent with other WHO guidelines, such as the WHO guideline for the care and treatment of persons diagnosed with chronic hepatitis C virus (HCV) infection, in which health-care workers highly valued cure for persons with HCV infection and programme managers understood that cure of more individuals would lead to progress towards elimination *(20)*. In the context of strongyloidiasis, MDA with ivermectin will lead to progress towards control via increasing cure in persons with *S. stercoralis* infection and, ultimately, will reduce morbidity and mortality.

Summary

The GDG inferred that the majority of people in endemic settings would choose to receive ivermectin due to its safety, effectiveness against *S. stercoralis* infection (i.e. curing infection), and possible reduction in strongyloidiasis morbidity (e.g. disseminated disease) and mortality. It is believed there will be little variation in values and preferences assigned to ivermectin, but participation is voluntary, and thus people will choose either to receive or not receive ivermectin.

Judgement

No substantial variability expected

4.3.4 Resource use

Research evidence

The primary evidence addressing the cost–effectiveness of MDA with ivermectin was drawn from one commissioned modelling analysis which consistently favoured community-based distribution of ivermectin for strongyloidiasis over school-based distribution across a range of epidemiological settings and sensitivity analyses. Further, results showed that MDA with ivermectin was cost–effective in settings with 2–5% prevalence based on imperfect diagnostics (4–10% true prevalence) or higher prevalence of strongyloidiasis. Its cost–effectiveness was well below or comparable to willingness to pay thresholds for low- and middle-income countries *(21)*.

In the modelling analysis, the cost per ivermectin medication was assumed to be US$ 0.10 for school-aged children and US$ 0.30 for adults, with 95% probability that costs were in a range of ± 10%. These values were based on the expected cost of generic ivermectin prequalified by WHO, as also recently used in an independent cost–effectiveness analysis *(22)*. Cost of distribution of ivermectin was assumed to be as reported in literature by different authors for various contexts where the delivery cost per treatment of community-based distribution of ivermectin was US$ 0.68 and the cost per treatment of school-based distribution of ivermectin was US$ 0.65 *(22)*.

The model development process included multiple quality check points. During each, the GDG reviewed model inputs and provided feedback. The above-mentioned figures for cost–effectiveness are based on the final model. This iterative approach ensured the best evidence was used for model inputs and increases the credibility of the model itself.

Given the interpretations of model results were consistent across sensitivity analyses addressing drug cost, drug efficacy, systematic non-participation to preventive chemotherapy, duration of preventive chemotherapy and the time horizon considered, the GDG is confident in the modelled evidence and cost–effectiveness of preventive chemotherapy with ivermectin for the control of strongyloidiasis. Further, the costs per person may be lower with larger programmes and integration with other programmes due to economies of scale. For the purpose of identifying priority areas, modelled evidence showed that the cost of MDA with ivermectin per averted DALY strongly dropped with increases in baseline prevalence.

A global supply of ivermectin and operational programmes with resources to support community drug distributors for delivery of medication would be needed. Thus, additional cost considerations include: staff, training, transport, supplies, equipment, infrastructure, communication and governance/programme management. The GDG considered that the sum of these costs could be significant, but that the total cost should be interpreted in the light of the number of people who are treated, and would benefit, including benefit against other infectious diseases.

Summary

Ivermectin is among the least expensive public health interventions and the cost–effectiveness of MDA with ivermectin was demonstrated across a range of epidemiological settings. Relative to other public health interventions, the GDG assessed that MDA with ivermectin will have a low cost to public health.

Judgement

Low cost

4.3.5 Equity

Research evidence

No studies directly addressed the issue of whether or not MDA with ivermectin increases or decreases equity. However, *S. stercoralis* is an NTD, mostly prevalent in resource-poor countries, and affecting the poorest, those living in rural areas *(23)*. The disease is likely to keep people in poverty through a cycle that includes gastro-intestinal symptoms, malnutrition, and may have a long-term impact on fitness and productivity. Ivermectin is a low-cost drug and included in the WHO list of essential medicines *(24)*. Based on modelled evidence which quantified strongyloidiasis burden in terms of DALYs, which are the sum of YLL and YLD, MDA of ivermectin was cost–effective at reducing DALYs across a range of epidemiological settings. Further, MDA provides empiric treatment with ivermectin without individual diagnosis of *S. stercoralis* infection, meaning that treatment with ivermectin may have indirect benefits on the population not infected with *S. stercoralis*. For example, a systematic review of pre-post studies demonstrated that MDA with

ivermectin was highly effective in reducing the prevalence of scabies at 12 months after MDA with ivermectin and that the impact was greater in settings with a higher prevalence of scabies prior to MDA with ivermectin *(25)*.

Summary

The aim of this recommendation is to reduce the global burden of strongyloidiasis, which disproportionality affects marginalized populations in low- and middle-income countries. Therefore, a strategy to reduce this burden will probably increase equity. Water, sanitation and hygiene (WASH) interventions are fundamental to such a strategy. MDA with ivermectin also falls within such a strategy, with individuals at low risk being potentially exposed to a treatment that may not directly benefit them, but would be beneficial to those that are poor and vulnerable.

Judgement

Probably increases equity.

4.3.6 Acceptability

Research evidence

MDA programmes for other endemic NTDs are widely accepted by policy-makers, health-care workers and communities globally. Acceptability among the at-risk population is critical to the success of an MDA programme. A systematic review addressing the acceptability of MDA for filariasis (which uses ivermectin) found that knowledge, awareness, attitude and perceptions, communications, delivery and accessibility of MDA, gender and age were each associated with MDA acceptability *(26)*. For onchocerciasis programmes that use ivermectin, a cross-sectional questionnaire-based study of community members found that acceptability of ivermectin MDA was positively associated with gender (female), higher level of general education, employment, self-rated knowledge of the disease itself and higher level of education received on MDA, and negatively associated with perceived side-effects of ivermectin *(27)*. The GDG anticipates these factors will also drive the acceptability of MDA with ivermectin for strongyloidiasis.

Summary

MDA with ivermectin will likely be accepted by the at-risk population similar to other MDA programmes for other endemic NTDs. Addressing factors associated with acceptability during planning and implementation of MDA with ivermectin will be key to improved community coverage.

Judgement

Probably acceptable

4.3.7 Feasibility

Research evidence

Feasibility of MDA with ivermectin for treatment of onchocerciasis and lymphatic filariasis has been demonstrated, but not strongyloidiasis. Because the present guideline is more relevant to settings not endemic for either lymphatic filariasis or onchocerciasis where the intervention considered in this guideline is already implemented, other MDA programmes may be targeted to increase feasibility. For example, MDA with azithromycin is the primary strategy for global trachoma control efforts *(28)*. Implementation of MDA with ivermectin may be more feasible in settings with existing infrastructure for MDA. Additional factors that may increase the feasibility of implementing MDA

with ivermectin are drug-specific: low cost (US$ 0.10 per dose for school-aged children and US$ 0.30 per dose for adults) and ease of administration (single-dose, oral).

Factors that may decrease the feasibility of implementing MDA with ivermectin are a lack of existing MDA infrastructure, large population to be treated spread across vast geographical areas and potential reliance on donated medicine. In settings lacking infrastructure for MDA, targeted programmes such as those for school-aged children should be leveraged to expand into the community. Low population density and sparsely populated regions are likely to face more barriers in implementing ivermectin mass administration without increased resources. Further, ivermectin has been donated by the pharmaceutical company MSD to endemic countries for the elimination of onchocerciasis and lymphatic filariasis, but not for use against strongyloidiasis. A lack of donation of ivermectin for strongyloidiasis may further reduce feasibility.

Summary

Because feasibility exists on a spectrum, implementation of MDA with ivermectin for strongyloidiasis control will vary across endemic settings.

Judgement

Feasibility of implementation varies.

Ethical considerations

MDA against a particular pathogen is ethically justified when (i) the medicines are safe and effective against that pathogen; (ii) adverse reactions are minimal to non-existent; (iii) diagnostics to support a test-and-treat strategy lack sensitivity or are too costly; and (iv) the disease caused by the pathogen represents a significant public health problem. All the above conditions are met with regard to MDA with ivermectin for strongyloidiasis.

Ivermectin is effective against *S. stercoralis* infection and is safe overall: more than 1.5 billion doses have been given in MDA against lymphatic filariasis alone, and hundreds of millions more for onchocerciasis and scabies. The only exception to safety of ivermectin is in areas with intense *Loa loa* transmission – which is why these populations are mostly excluded from this recommendation. The strongyloidiasis programme will adopt the same precautions to those used by lymphatic filariasis and onchocerciasis control programmes. A key consideration is that MDA provides empirical treatment with ivermectin without individual diagnosis, meaning some persons who receive medication are not infected with *S. stercoralis* and would not directly benefit, but would still be subject to potential harms (albeit rare and mild). For persons who receive treatment that are not infected with *S. stercoralis*, the risk of harm is low and there are additional benefits for other infectious diseases that the individual may have. Furthermore, each person's residence in an endemic area puts them at risk for infection. In all cases, MDA is not compulsory and preserves individual autonomy on whether or not to take part in MDA. Participation in MDA is voluntary. Additional disadvantages of MDA include cost to national programmes, inconvenience for children and adults participating in the programme if ivermectin is distributed at fixed posts rather than door-to-door, and possible drug resistance (though not demonstrated). Overall, balancing individual and public interests and all the above points, MDA seems to represent an effective option that does not raise major ethical issues.

Regulatory considerations

The United States Food and Drug Administration, the United Kingdom Medicines Regulatory Agency, the WHO Model List of Essential Medicines and others approve the use of ivermectin as treatment for strongyloidiasis.

4.3.8 Justification for strength of recommendation

The GDG issued the strength of recommendation to be conditional, aligning with the low certainty of evidence. The GDG carefully considered the strength of recommendation that would best match the entire set of evidence available on the decision to recommend MDA for strongyloidiasis, either a strong recommendation, i.e. confidence that the desirable effects outweigh the undesired consequences, or conditional (weak) recommendation, i.e. uncertainty regarding potential scale or benefits and/or harms or disadvantages. The GDG concurred that, overall, the quality (certainty) of the evidence was low, a level that is not uncommon, especially in the field of NTDs where there is a paucity of large-scale randomized trials *(29,30)*. The fundamental reason is most data used in this recommendation to inform key categories of "desirable and undesirable effects" and for "resources required" were observational data. Other dimensions in the evidence-to-decision framework (Fig. 1) reinforced a positive recommendation in favour of the intervention. These include the large scale of the public health problem of strongyloidiasis and the large, expected magnitude of the benefits of MDA, alongside the favourable data on cost–effectiveness, and the overall balance of benefits and risks. However, based on the low quality of evidence, a conditional recommendation was made.

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5. Dissemination

This WHO guideline will be published on the Organization's website and will be freely downloadable (in PDF and other electronic formats). It is also expected that the evidence reviews (e.g. modelling study) and recommendations will be published in peer-reviewed journals to improve dissemination of the main messages. Printed and electronic copies of this guideline will be distributed across a broad network of international partners, including WHO country and regional offices, health ministries, WHO collaborating centres, universities, other United Nations agencies and nongovernmental organizations. In countries where strongyloidiasis is endemic, the guideline recommendations will be translated into local languages to facilitate their implementation. A technical manual will be developed to facilitate understanding and implementation of technical aspects of the guideline, particularly for surveillance, impact assessment and implementation of MDA. WHO will support adaptation at regional and national levels to reflect local circumstances and resource constraints.

The panel emphasized that additional research on the potential reductions in prevalence of *S. stercoralis* infection (measured with faecal testing or serology) after the intervention in endemic settings is highly desirable and should be considered a research priority and supported by WHO. Future research directions are highlighted in the next section.

Acknowledging the limitations of the evidence that informed the recommendations of this guideline, WHO will strive to identify and assess new clinical evidence that can inform this guideline. In the least favourable scenario, where there will be no or very minor new clinical data, the GDG determined that evidence and recommendations will be formally reviewed 5 years after the date of publication, evaluating adoption of MDA at country level. This may be done earlier pending availability of evidence that would significantly change the recommendation.

6. Future research needs

The discussion among the GDG during the meeting and consultation with the external review group highlighted the limitations in available evidence for control of strongyloidiasis. The areas of most pressing need for future research include those outlined in this section. The GDG noted the first two bullet points correspond to data needed to improve the quality of evidence of future recommendations.

- Estimation of causal impact of guideline-directed MDA against strongyloidiasis, ideally in a quasi-experimental study design (e.g. step-wedge implementation);
- Studies to estimate the impact of MDA against strongyloidiasis on clinical morbidity and disseminated disease;
- Studies to define the age-specific incidence and prevalence of strongyloidiasis across diverse endemic settings;
- Studies to define the age-specific incidence of disseminated strongyloidiasis and risk factors for dissemination across diverse endemic settings;
- Studies to measure the spatial variation in strongyloidiasis in endemic settings and optimal geographic scale for implementation of MDA;
- Research on the optimal strategies to reduce disseminated strongyloidiasis, including comparing MDA against test-and-treat strategies, including randomized controlled trials;
- Research on the optimal frequency of MDA to reduce strongyloidiasis, including randomized trials;
- Research on the duration of MDA required for control and elimination, and associated surveillance strategies to evaluate for rebound, including randomized controlled trials;
- Research on optimal surveillance strategies to detect endemic settings with strongyloidiasis and potential for hot spots of transmission;
- Research on the significance of canine, feline, non-human primate infection and other non-human reservoirs of transmission and maintenance of human disease in endemic areas;
- Monitoring of drug efficacy to detect emergence of drug resistance;
- Research on strategies to reduce the burden of strongyloidiasis in low-prevalence settings;
- Operational research on optimal implementation of MDA with ivermectin, including to ensure equitable coverage, acceptance and sustained high coverage;
- Operational research on the integration of mass ivermectin into existing MDA programmes, to minimize the resource implications;
- Development of new diagnostics that are rapid and more sensitive than current tools and additional comparisons across existing methods;

- Development of mathematical modeling tools to guide surveillance and MDA programmes;
- Identification of which WASH strategies are most effective against *S. stercoralis* and can be most effectively implemented;
- Evaluation of the impact of MDA for strongyloidiasis on equity and/or human rights, including equitable coverage of treatment in high burden settings.

Annexes

Annex 1. List of contributors

Name	Cluster, Department, Unit, Office, Location	Perspective
Members of the WHO guideline steering group		
Sophie Boisson	Healthier Populations Environment, Climate Change and Health Water, Sanitation and Hygiene WHO headquarters Geneva, Switzerland	Water, sanitation and hygiene
Albis Francesco Gabrielli	Communicable and Noncommunicable Diseases Neglected Tropical Diseases Strategic Information and Analytics WHO headquarters Geneva, Switzerland	Programme management
Benedikt Huttner	Access to Medicines and Health Products Surveillance, Prevention and Control Control and Response Strategies WHO headquarters Geneva, Switzerland	Drug safety
Sung Hye Kim	WP/RGO/DDC/MTD WHO Regional Office for the Western Pacific	Regional programme management
Annette Kuesel	Research for Implementation Special Programme for Research and Training in Tropical Diseases Intervention Research WHO headquarters Geneva, Switzerland	Impact on other diseases (onchocerciasis)
Ana Luciañez	Communicable Diseases Prevention, Control and Elimination Neglected, Tropical and Vector-Borne Diseases Neglected Infectious Diseases WHO Regional Office for the Americas Washington DC, United States of America	Regional programme management

Name	Cluster, Department, Unit, Office, Location	Perspective
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Name	Cluster, Department, Unit, Office, Location	Perspective
Members of the guideline development group		
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Arancha Amor	Mundo Sano Bahir Dar, Ethiopia	Drug efficacy
Zeno Bisoffi	WHO Collaborating Centre on strongyloidiasis IRCCS Sacro Cuore Don Calabria Hospital Negrar, Italy	Clinical expertise, diagnosis
Richard Bradbury	Health Innovation and Transformation Centre Federation University, Berwick, Victoria, Australia	Randomized controlled trials
Dora Buonfrate[b]	WHO Collaborating Centre on strongyloidiasis IRCCS Sacro Cuore Don Calabria Hospital Negrar, Italy	Randomized controlled trials, diagnosis
Jennifer Keiser	WHO Collaborating Centre on Neglected Tropical Diseases Swiss Tropical and Public Health Institute Basel, Switzerland	Randomized controlled trials
Stella Kepha	Eastern and Southern Africa Centre of International Parasite Control, Medical Research Institute, Nairobi, Kenya	Programme implementation
Virak Khieu	Ministry of Health, Cambodia	Programme implementation
Alejandro Krolewiecki	Instituto de Investigaciones de Enfermedades Tropicales Universidad Nacional de Salta/CONICET Orán, Argentina	Randomized controlled trials
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Melaku Mekonen	Mundo Sano Bahir Dar, Ethiopia	Nongovernmental organizations
Jose Muñoz	Barcelona Institute for Global Health (ISGlobal) Hospital Clinic University of Barcelona Barcelona, Spain	Drug efficacy in preventive chemotherapy
Francisca Mutapi	Tackling Infections to Benefit Africa (TIBA) University of Edinburgh, Edinburgh, United Kingdom of Great Britain and Northern Ireland	Research
Susana Vaz Nery	Kirby Institute University of New South Wales, Sydney, Australia	Research
Valdemiro Novela	Centro de Investigação em Saúde de Manhiça, Maputo, Mozambique	Programme implementation

[a] Chair; [b] Vice-Chair.

Annex 2. Summary of declarations of interests and their management

Management of conflicts of interest was a key priority throughout the process of development of recommendations. Prior to the guideline development meeting, all experts submitted written disclosures of competing interests that were relevant for consideration before their confirmation as members of the meeting. These included employment by a commercial entity, consultancy, board or advisory board membership, lecture fees, expert witness income, industry sponsored grants including contracted research, patents received or pending, royalties, stock ownership or options, other personal financial interests; and whether the institution or employer has a financial relationship with a commercial entity that has an interest in medicines or diagnostics evaluated by the guideline panel.

Experts were also asked to disclose academic or scientific activities: this included leadership of research or grant applications, in either primary clinical studies or reviews, directly bearing on a decision about preventive chemotherapy. Written disclosures were in some cases further investigated through interviews with a technical officer of the World Health Organization (WHO). In addition, at the start of the guideline development meeting, all members were asked to update their declaration if any new conflicts may have originated in the meantime. Institutional grants and funding were considered not to create potential for inappropriate influence over the experts.

The following experts declared having no nonfinancial or financial conflicts of interests: David Addiss, Arancha Amor, Zeno Bisoffi, Jennifer Keiser, Stella Kepha, Virak Khieu, Alejandro Krolewiecki, Jean Bosco Mbonigaba, Melaku Mekonen, Jose Muñoz, Francisca Mutapi, Susana Vaz Nery and Vladimiro Novela.

Dr Richard Bradbury declared having received a research grant to his research unit from the University of Mississippi to support a consultancy on surveillance for parasitic diseases. Part of this grant covers his salary. This amount was below the threshold for significant financial interest (i.e. US$ 5000). Dr Bradbury served as a panellist in a meeting sponsored by Seegene Inc. (Seoul, Republic of Korea) on future directions in parasite diagnostics. Remuneration was below the threshold for significant financial interest. Dr Bradbury is the Co-Vice President of *Strongyloides* Australia, an Australian nongovernmental, non-profit society that advocates for increasing awareness of strongyloidiasis. Conflicts of interests declared by Dr Bradbury were considered minor and did not require further management, with full participation in the deliberations and decision-making process.

Dr Dora Buonfrate declared having led a trial on assessing whether multiple doses of ivermectin were superior to a single dose of ivermectin for the treatment of non-disseminated strongyloidiasis, and having participated in a second trial to compare efficacy and safety of ivermectin versus thiabendazole to cure strongyloidiasis. She also declared having led a review to estimate the global burden of patients in need of treatment for strongyloidiasis, a modelling study estimating the cost of different approaches for strongyloidiasis control, and multiple studies that reviewed and evaluated different diagnostic tests for strongyloidiasis. Study diagnostic kits were provided from the producer pro bono and no compensation was provided to conduct the

study. Dr Buonfrate declared having personally received no direct financial/salary benefit for any of this work. These intellectual interests originated by participation in the above-mentioned studies and were considered to not create risks that characterize conflicts of interest; namely, the risk that Dr Buonfrate would not exercise independent judgement and would not serve in the interest of future patients. After revising the declaration of Dr Buonfrate, and given Dr Buonfrate's role as co-chair of the guideline meeting, she was advised to consider, of her own volition, recusing herself from deliberations to avoid a perceived nonfinancial conflict of interest. Dr Buonfrate decided not to participate in any vote process.

Dr Susana Vaz Nery declared having been involved in multiple studies presented and discussed during the meeting, acting as senior investigator on studies evaluating the diagnostic test accuracy of different infection diagnostic techniques. Given the primary focus of this guideline on effectiveness of population-based treatment with preventive chemotherapy, these studies were judged to be only marginally related to the subject of the current Guideline Development Group and were determined not to represent an impediment to her full participation.

Dr Nathan Lo declared having no nonfinancial or financial conflicts of interests.

Dr Luc E. Coffeng and Dr Sake J. de Vlas were commissioned by WHO to develop the mathematical modelling study and cost effectiveness analysis to evaluate the transmission and control of strongyloidiasis in populations exposed to mass drug administration of ivermectin. Dr Coffeng and Dr de Vlas declared having no nonfinancial or financial conflicts of interests. They did not participate in any panel deliberation.

Annex 3. GRADE guidance

The use of the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) framework to assess the certainty of evidence and make recommendations is widespread. More than 100 organizations worldwide have adopted the principles of the GRADE framework *(1)*.

We used GRADE to independently assess the certainty of evidence for each meta-analysed outcome *(2,3)*. Criteria for rating the certainty of evidence included considerations for risk of bias, inconsistency, indirectness, imprecision and publication bias *(3)*. Judgements of imprecision were made using a non-contextualized approach. This approach considers whether confidence intervals include the null effect and if the intervention is effective.

Based on GRADE guidance for randomized trials, we started with high certainty evidence for each meta-analysis. Based on GRADE guidance for non-randomized studies of interventions, we started with low certainty evidence for each meta-analysis. The lower starting rating is the result of the potential bias induced by the lack of randomization (i.e. confounding and selection bias) *(4)*.

Each GRADE domain was rated as "Not serious" (no downgrade), "Serious" (downgrade once) or "Very Serious" (downgrade twice). The final GRADE rating consolidates all of the domains: High (no downgrade in any of the domains), Moderate (downgraded once in total), Low (downgraded twice in total) or Very low (downgraded three or more times in total) *(3)*. Possible decision outputs and terminology used to report GRADE ratings are summarized in Table A3.1 *(5)*. Circumstances that may lead to an increase in the certainty level (i.e. "upgrade") include the presence of consistent and large effects, the presence of a dose–response gradient or plausible confounding that works to underestimate an apparent intervention effect *(6)*.

To facilitate interpretation of the results in which the summary measure was an odds ratio or risk ratio, we used the median event rate in the reference group of studies reporting proportions to calculate baseline risks and subsequently calculated absolute effects. GRADE evidence summaries (Summary of Findings tables) were generated in the MAGIC Authoring and Publication Platform *(7)*.

We developed the below criteria to reduce the subjectivity associated with GRADE; however, the GRADE ratings are based on guideline member and methodologist judgements, and may not be reproducible.

⊕⊕⊕⊕ High quality (certainty) evidence	We are very confident that the true effect lies close to that of the estimate of effect. Intervention X increases/reduces outcome.
⊕⊕⊕⊙ Moderate quality (certainty) evidence	We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. Intervention X probably increases/reduces outcome.
⊕⊕⊙⊙ Low quality (certainty) evidence	Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect. Intervention X may increase/reduce outcome.
⊕⊙⊙⊙ Very low quality (certainty) evidence	We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect. The evidence of intervention X on outcome is very uncertain.

A3.1 Risk of bias

For each meta-analysis, independent of the risk of bias tool used by systematic review authors, we downgraded the certainty of the evidence once for risk of bias when studies at high risk of bias overall contributed > 50% weight to the pooled effect estimates (i.e. serious risk of bias). We downgraded the certainty of the evidence twice for risk of bias when studies at high risk of bias overall contributed > 80% weight to the pooled effect estimates (i.e. very serious risk of bias).

A3.2 Inconsistency

We used visual inspection of the forest plots and the I^2 statistic to assess inconsistency. For visual inspection of the forest plots, we considered the variability in point estimates and confidence interval overlap in relation to the null effect. Further, we downgraded the certainty of the evidence once when there was substantial (I^2 50–75%) heterogeneity and twice when there was considerable (I^2 75–100%) heterogeneity.

A3.3 Imprecision

We downgraded the certainty of the evidence once for imprecision if:

(i) The effect on the patient or clinical action would differ depending on whether the upper or the lower boundary of the confidence interval represented the truth, **OR**

(ii) In cases where we had large effects that did not cross the null, we assessed the optimal information size. For dichotomous outcomes, if the ratio of the upper to the lower limit of the confidence interval was more than 2.5 for odds ratio or 3 for risk ratio, the optimal information size would never be met; thus, we rated down once for imprecision, **OR**

(iii) The event rate was very low (e.g. fewer than 10 outcome events in the intervention arm) and the sample size very large (e.g. at least 2000 people).

A3.4 Indirectness

We rated down once if the study population, the intervention(s) addressed and/or the outcome in the primary studies did not accurately reflect the review question.

A3.5 Publication bias

Given the randomized trial evidence base, publication bias is unlikely to be a concern; thus, we did not rate down for imprecision.

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Annex 4. PICO questions and GRADE summary tables

A4.1 Efficacy of ivermectin against *Strongyloides stercoralis* infection

PICO question

Population	Individuals infected with *S. stercoralis*
Intervention	Periodic single dose ivermectin
Comparator	Placebo, co-interventions or no treatment
Outcome	Infection with *S. stercoralis*

GRADE summary table of the findings

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates**		**Certainty of the evidence** (Quality of evidence)
		Reference	**Ivermectin**	
Cure (ivermectin with albendazole comparator) Mean 5 weeks	Relative risk: 1.79 (CI 95% 1.55–2.08) Based on data from 478 participants in four studies	**475** per 1000	**850** per 1000	**Moderate** Downgraded due to very serious risk of bias; upgraded due to large effect
		Difference: **375 more per 1000** (CI 95% 261 more–513 more)		
Cure (ivermectin with thiabendazole comparator) Mean 11 weeks	Relative risk: 1.07 (CI 95% 0.96–1.2) Based on data from 467 participants in three studies	**786** per 1000	**841** per 1000	**Very low**[a] Downgraded due to very serious risk of bias and serious imprecision
		Difference: **55 more per 1000** (CI 95% 31 fewer–157 more)		
Cure (two-dose ivermectin vs one-dose)	Relative risk: 1.02 (CI 95% 0.94–1.11) Based on data from 94 participants in two studies	**967** per 1000	**986** per 1000	**Low** Downgraded due to very serious risk of bias
		Difference: **19 more per 1000** (CI 95% 58 fewer–106 more)		
Cure (four-dose ivermectin vs one-dose)	Risk difference: 15.0 (CI 95% -76.0–105.0) Based on data from 231 participants in one study	NA	NA	**Moderate** Downgraded due to serious imprecision
		NA		

CI: confidence interval; GRADE: Grading of Recommendations, Assessment, Development and Evaluation NA: not applicable.

A relative risk greater than one is a higher cure rate against the comparator, while a relative risk less than one is a lower cure rate. The absolute effect estimates refer to the number of persons with infection that are cured.

[a] The GRADE ratings are based on guideline member and methodologist judgements using pre-defined criteria specific to the guideline. Thus, ratings may differ from those in published literature.

A4.2 Impact of mass drug administration with ivermectin on strongyloidiasis

PICO question

Population	Children aged 5-17 years and/or adults 18 years or older living in a region endemic for *S. stercoralis*
Intervention	Periodic preventive chemotherapy with ivermectin at intervals of up to 12 months
Comparator	Placebo, co-interventions or no treatment
Outcome	Mortality and/or morbidity risk from strongyloidiasis

GRADE summary table of the findings

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates**		**Certainty of the evidence** (Quality of evidence)
		Pre PC ivermectin	**Post PC ivermectin**	
Prevalence (faecal test)	Relative risk: 0.18 (CI 95% 0.14–0.23) Based on data from 5262 participants in six studies	**139** per 1000	**25** per 1000	**Moderate** Downgraded due to non-randomized data and very serious risk of bias; upgraded due to very large effect
		Difference: **114 fewer per 1000** (CI 95% 120 fewer–107 fewer)		
Prevalence (serology)	Relative risk: 0.35 (CI 95% 0.26–0.48) Based on data from 1763 participants in three studies	**214** per 1000	**75** per 1000	**Moderate** Downgraded due to non-randomized data; upgraded due to large effect
		Difference: **139 fewer per 1000** (CI 95% 158 fewer–111 fewer)		
Prevalence (post 1 round)	Relative risk: 0.22 (CI 95% 0.02 - 2.25) Based on data from 2083 participants in two studies	**61** per 1000	**13** per 1000	**Very low** Downgraded due to non-randomized data, very serious inconsistency and serious imprecision
		Difference: **48 fewer per 1000** (CI 95% 60 fewer–76 more)		
Prevalence (post 2+ rounds)	Relative risk: 0.18 (CI 95% 0.14 – 0.23) Based on data from 3179 participants in four studies	**258** per 1000	**46** per 1000	**Low** Downgraded due to non-randomized data and very serious risk of bias; upgraded due to large effect
		Difference: **212 fewer per 1000** (CI 95% 222 fewer–199 fewer)		

CI: confidence interval; PC: preventive chemotherapy.

A4.3 Safety of ivermectin used in large scale and in particular the risk for non-infected to be treated

PICO question

Population	Infected or non-infected individuals
Intervention	Ivermectin treatment
Comparator	Placebo, co-interventions or no treatment
Outcome	Adverse effects

GRADE summary table of the findings

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates**		**Certainty of the evidence** (Quality of evidence)
		Lower-dose ivermectin	**Higher-dose ivermectin**	
Adverse effects (comparator = 400 ug/kg)	Odds ratio: 1.06 (CI 95% 0.67–1.69) Based on data from 1426 participants in five studies	**234** per 1000	**245** per 1000	**Moderate** Downgraded due to serious imprecision
		Difference: **11 more per 1000** (CI 95% 64 fewer–106 more)		
Adverse effects (comparator = 200 ug/kg)	Odds ratio: 1.16 (CI 95% 0.89–1.52) Based on data from 1427 participants in four studies	**172** per 1000	**194** per 1000	**Moderate** Downgraded due to serious imprecision
		Difference: **22 more per 1000** (CI 95% 16 fewer–68 more)		

A4.4 Modelling and cost-effectiveness analysis

We followed recent GRADE guidance to evaluate certainty of evidence for modelling studies with a qualitative appraisal of the modelling evidence in this study *(1,2)*.

A4.4.1 Risk of bias

We assessed the risk of bias of model outputs by considering the credibility of the model itself (e.g. structure, performance on calibration and validation) and the certainty of evidence for each model input (e.g. infection incidence, disseminated disease incidence; for economic model outputs, resource use, utility values and baseline risks of outcomes). In our evaluation, there is some risk of bias for the key model inputs of incidence of disseminated strongyloidiasis and disability weight for chronic infection. Given the lack of longitudinal data, model validation was not formally undertaken, but the findings broadly align with observational studies.

A4.4.2 Inconsistency

We assessed consistency in the model inputs ascertained from the literature. Overall model inputs were consistent. Further, the model consistently demonstrated the cost–effectiveness of mass drug administration (MDA) with ivermectin across a range of epidemiological settings and sensitivity analyses. This increased confidence in the modelled reductions in infection prevalence and disability-adjusted life years (DALYs) post-MDA with ivermectin.

A4.4.3 Imprecision

We considered the point estimates and the variability from the results of the modelling study. The modelling study did include information about the output variability and the key findings on cost–effectiveness were precise overall.

A4.4.4 Indirectness

We evaluated the indirectness of the modelling evidence, based on whether the modelling input data were discrepant with the ideal target model's input or the modelling outputs were discrepant with the intended population, intervention(s), time horizon, analytic perspective and/or outcome(s), and/or did not accurately reflect the decision question at hand. Overall, the Guideline Development Group did not identify issues with indirectness.

A4.4.5 Publication bias

Risk of publication bias was not relevant when assessing this modelling evidence because this is a single model that was constructed de novo. Publication bias may be possible for model inputs.

References

1. **Coffeng LE, Lo NC, de Vlas SJ. Cost-effectiveness of mass drug administration with vermectin against strongyloidiasis: a modelling study. medRxiv. 2024. doi:10.1101/2024.04.04.24305312.**

2. **Brozek JL, Canelo-Aybar C, Akl EA, Bowen JM, Bucher J, Chiu WA, et al. GRADE Guidelines 30: the GRADE approach to assessing the certainty of modeled evidence–An overview in the context of health decision-making. J Clin Epidemiol. 2021;129:138–50.**

Annex 5. Rating the importance of outcomes

Members of the guideline development group (GDG) prioritized clinical outcomes in strongyloidiasis from the perspective of patients. A voluntary poll was conducted within the GDG to define the importance of three clinical outcomes related to strongyloidiasis from a patient's perspective. Although the GDG focused on an individual's perspective for values and preferences, it also considered a population perspective in which feasibility, acceptability, equity and cost are important considerations in the creation of this public health recommendation. The final recommendation is directed at the entire population within a community

Table A5.1. Panel outcome rating from a patient perspective

Outcome	Mean	SD	Range
Strongyloides stercoralis infection	8.0	1.1	6–9
Disseminated strongyloidiasis disease	7.9	1.1	6–9
Death	7.6	1.1	6–9

SD: standard deviation.

Note: 7–9: critical; 4–6: important; 1–3: of limited importance.

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