GUIDELINE:

PREVENTIVE CHEMOTHERAPY TO **CONTROL SOIL-TRANSMITTED HELMINTH INFECTIONS** IN AT-RISK POPULATION GROUPS

2017

World Health Organization

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CONTENTS

PUBLICATION HISTORY

This guideline on *Preventive chemotherapy to control soil-transmitted helminth infections in at-risk population groups* updates and supersedes previous recommendations contained in the World Health Organization (WHO) publication *Preventive chemotherapy in human helminthiasis: coordinated use of anthelminthic drugs in control interventions: a manual for health professionals and programme managers*, which was reviewed at the Informal Consultation on Preventive Chemotherapy in Human Helminthiasis (Geneva, March 2006), and complements some of the operational guidance of *Helminth control in school-age children: a guide for managers of control programmes*, published by WHO in 2011.

In order to produce this guideline, the rigorous procedures described in the *WHO handbook for guideline development* were followed. This document presents the evidence that served to inform the recommendations contained herein, and provides expanded sections on dissemination as well as on ethical and equity considerations, summarized in the most recent reviews on these topics.

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WHO acknowledges the technical guidance provided by the members of the WHO steering committee for this normative work, namely: Dr Shannon Barkley (Department of Service Delivery and Safety), Dr Sophie Boisson (Department of Public Health, Environment and Social Determinants), Dr Lorenzo Moja (Department of Essential Medicines and Health Products), Dr Antonio Montresor (Department of Control of Neglected Tropical Diseases), Dr Eyerusalem Kebede Negussie (Department of HIV/AIDS), Dr Piero Luigi Olliaro (Special Programme for Research and Training in Tropical Diseases), Dr Juan Pablo Peña-Rosas (Department of Nutrition for Health and Development), Dr Pura Rayco-Solon (Department of Nutrition for Health and Development) and Dr Özge Tuncalp (Department of Reproductive Health and Research).

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GLOSSARY

The definitions described below apply to the terms as used in this guideline and may have different meanings in other contexts and WHO documents.

Adolescence

A period in human growth and development that occurs after childhood and before adulthood, from ages 10 to 19.

Anthelminthic

A medicine used to kill helminths (worms) and facilitate their expulsion from the human body. The anthelminthics most commonly used to treat intestinal worm infections in children are the benzimidazoles (albendazole and mebendazole).

Disability-adjusted life years (DALYs)

The number of years of healthy life lost attributable to a disease (or group of diseases). DALYs are used as a measure of disease burden and provide a comparative indication of the importance of the disease to public health.

Ineligible population

A group of individuals not qualified or entitled to receive anthelminthic treatment in preventive chemotherapy interventions, primarily due to lack of evidence of their safety. In the case of soil-transmitted helminth infections, this includes children in the first year of life and pregnant women during the first trimester.

Intensity of infection

The number of helminths infecting an individual (also known as worm burden). In the case of soil-transmitted helminths, it can be measured directly, by counting expelled worms after anthelminthic treatment, or indirectly, by counting helminth eggs excreted in faeces (expressed as eggs per gram, epg). Indirect methods are less intrusive, more convenient and more commonly used. WHO classifies soil-transmitted helminth infections as light, moderate and heavy, according to the number of helminth eggs excreted in human faeces.

Morbidity

The clinical consequences of infections and diseases that adversely affect human health. Morbidity from soil-transmitted helminth infections is usually subtle (for example, malabsorption, stunted growth) and proportional to the number of worms infecting an individual. The soil-transmitted helminth infections that cause morbidity are those of moderate or heavy intensity (see intensity of infection).

Preschool children

All children between the ages of 24 to 59 months who are usually not yet attending primary school. Young children refer to children between the ages of 12 to 23 months of age.

Prevalence of any soil-transmitted helminth infection

The percentage of individuals in a population infected with at least one species of soil-transmitted helminth.

The periodic use of anthelminthic medicines (i.e. deworming) as a public health tool against soil-transmitted helminth infections. Preventive chemotherapy can be applied with different modalities:

- *Mass drug administration*. The entire population of an area (e.g. state, region, province, district, sub-district, village) is given anthelminthic medicines at regular intervals, irrespective of the individual infection status.
- *Targeted chemotherapy*. Specific risk groups in the population, defined by age, sex or other social characteristic such as occupation (e.g. school-age children), are given anthelminthic medicines at regular intervals, irrespective of the individual infection status.
- *Selective chemotherapy*. After a regular screening exercise in a population group living in an area where soil-transmitted helminths are endemic, all individuals found (or suspected) to be infected are given anthelminthic medicines.

School-age children

We defined school-age children as those between 5 and 12 years of age. Although many children unfortunately do not attend schools, these ages are compulsory school years in most settings, providing with it an entry point to address the nutritional needs of this age group. In some settings the upper range may be 14 years of age.

Soil-transmitted helminthiases

Parasitic diseases attributable to soil-transmitted helminths.

Soil-transmitted helminths

Four main species of nematodes are collectively referred to as soil-transmitted helminths: the roundworm, *Ascaris lumbricoides*; the whipworm, *Trichuris trichiura*; and the hookworms, *Necator americanus* and *Ancylostoma duodenale*.

Women of reproductive age

Post-menarcheal adolescent girls and adult women, including pregnant and lactating women, between the ages of 15 and 49. This age range can vary depending on the context. Also see Adolescence.

Guideline[1]: Preventive chemotherapy to control soil-transmitted helminth infections in at-risk population groups

EXECUTIVE SUMMARY

The World Health Organization (WHO) estimates that infections with the main soil-transmitted helminths – the roundworm (*Ascaris lumbricoides*), the whipworm (*Trichuris trichiura*) and the hookworms (*Ancylostoma duodenale* and *Necator americanus*) – contribute 5.18 million disability-adjusted life-years worldwide in 2010. Globally, an estimated 820 million people are infected with roundworms, 460 million with whipworms and 440 million with hookworms.

Although each species has specific characteristics, these soil-transmitted helminthiases are grouped together for control purposes, owing to: (i) similar geographical endemicity and at-risk groups that are affected; (ii) treatment by the same medicines; (iii) the same tools used for diagnosis; and (iv) similar mechanism of negative impact on human health (linked to the intensity of infection).

Purpose of the guideline

This guideline provides global, evidence-informed recommendations on preventive chemotherapy, as a public health intervention in areas endemic for soil-transmitted helminths, to decrease the worm burden of soil-transmitted helminth infection in children, adolescent girls, women of reproductive age and pregnant women, including those coinfected with HIV.

The recommendations contained in this guideline are intended for a wide audience, including policy-makers and their expert advisers as well as technical and programme staff at government institutions and organizations involved in the design, implementation and expansion of programmes to control soil-transmitted helminth infections and nutrition-sensitive actions for a safe and hygienic environment to improve public health.

This guideline aims to help WHO Member States and their partners to make evidence-informed decisions on the appropriate actions in their efforts to achieve the United Nations Sustainable Development Goals[2] and the global targets presented in the World Health Assembly resolution WHA66.12 on *Neglected tropical diseases*,[3] the *Comprehensive implementation plan on maternal, infant and young child nutrition*,[4] the *Global strategy for women's, children's, and adolescents' health (2016–2030)*,[5] *Water, sanitation and hygiene for accelerating and sustaining progress on neglected tropical diseases: a global*

[1] This publication is a World Health Organization (WHO) guideline. 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 Guidelines Review Committee.

[2] United Nations Sustainable Development Knowledge Platform. Sustainable Development Goals (https://sustainabledevelopment.un.org/sdg)

[3] Resolution WHA66.12. Neglected tropical diseases. In: Sixty-sixth World Health Assembly, Geneva, 20–27 May 2013. Resolutions and decisions, annexes. Geneva: World Health Organization; 2013:23–26 (WHA66/2013/REC/1; http://apps.who.int/gb/ebwha/pdf_files/WHA66-REC1/WHA66_2013_REC1_complete.pdf).

[4] Resolution WHA65.6. Comprehensive implementation plan on maternal, infant and young child nutrition. In: Sixty-fifth World Health Assembly, Geneva, 21–26 May 2012. Resolutions and decisions, annexes. Geneva: World Health Organization; 2012:12–13 (WHA65/2012/REC/1; http://www.who.int/nutrition/topics/WHA65.6_resolution_en.pdf).

[5] The global strategy for women's, children's and adolescents' health (2016–2023). Survive, thrive transform. Geneva: World Health Organization; 2015 (http://www.who.int/life-course/partners/global-strategy/global-strategy-2016–2030/en/).

strategy 2015–2020,[1] *Accelerating work to overcome the global impact of neglected tropical diseases: a roadmap for implementation*,[2] *Accelerating progress on HIV, tuberculosis, malaria, hepatitis and neglected tropical diseases: a new agenda for 2016–2030*[3] and *Eliminating soil-transmitted helminthiases as a public health problem in children: progress report 2001–2010 and strategic plan 2011–2020*.[4]

Guideline development methodology

WHO developed the present evidence-informed recommendations using the procedures outlined in the *WHO handbook for guideline development*.[5] The steps in this process included: (i) identification of priority questions and outcomes; (ii) retrieval of the evidence; (iii) assessment and synthesis of the evidence; (iv) formulation of recommendations, including research priorities; and planning for (v) dissemination; (vi) implementation, equity and ethical considerations; and (vii) impact evaluation and updating of the guideline. The Grading of Recommendations Assessment, Development and Evaluation (GRADE)[6] methodology was followed, to prepare evidence profiles related to preselected topics, based on up-to-date systematic reviews. The Developing and Evaluating Communication Strategies to support Informed Decisions and Practice based on Evidence (DECIDE)[7] framework, an evidence-to-decision tool that includes intervention effects, values, resources, equity, acceptability and feasibility criteria, was used to guide the formulation of the recommendations by the guideline development group.

The scoping of the guideline and the prioritization of the outcomes were done by the guideline development group – nutrition actions 2013–2014 (Geneva, 18–21 February 2013). The evidence-informed recommendations were developed and finalized at a meeting of the guideline development group – deworming (Geneva, 13–15 April 2016). Three options for types of recommendations were agreed, namely: (i) strong recommendation; (ii) conditional recommendation (recommended only in specific contexts); and (iii) not recommended. Five external experts served as technical peer reviewers of a preliminary version of this guideline.

Available evidence

The available evidence included five systematic reviews of randomized controlled trials (RCTs) that followed the procedures of the *Cochrane handbook for systematic reviews of interventions*[8] and assessed the effects of preventive chemotherapy on controlling soil-transmitted helminth infections in preschool and school-age children, adolescent girls, women of reproductive age, pregnant women and individuals coinfected with HIV. All studies compared a group of participants who had received anthelminthic medicines for soil-transmitted helminth infections with a group that had received a placebo or no treatment. For the studies to be included in the reviews, co-interventions other than anthelminthic medicines had to have been used for both the control and intervention arms. The overall quality of the available evidence was very low to moderate for the critical outcomes of worm burden, weight gain and haemoglobin concentrations.[9]

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1 Water, sanitation and hygiene for accelerating and sustaining progress on neglected tropical diseases: a global strategy 2015–2020. Geneva: World Health Organization; 2015 (http://apps.who.int/iris/bitstream/10665/182735/1/WHO_FWC_WSH_15.12_eng.pdf).

2 Accelerating work to overcome the global impact of neglected tropical diseases: a roadmap for implementation. Geneva: World Health Organization; 2012 (http://www.who.int/neglected_diseases/NTD_RoadMap_2012_Fullversion.pdf).

3 Accelerating progress on HIV, tuberculosis, malaria, hepatitis and neglected tropical diseases: a new agenda for 2016–2030. Geneva: World Health Organization; 2015 (http://apps.who.int/medicinedocs/documents/s22340en/s22340en.pdf).

4 Eliminating soil-transmitted helminthiases as a public health problem in children: progress report 2001–2010 and strategic plan 2011–2020. Geneva: World Health Organization; 2012 (http://apps.who.int/iris/bitstream/10665/44804/1/9789241503129_eng.pdf).

5 WHO handbook for guideline development, 2nd edition. Geneva: World Health Organization; 2014 (http://www.who.int/kms/handbook_2nd_ed.pdf?ua=1).

6 GRADE (http://www.gradeworkinggroup.org/).

7 DECIDE (http://www.decide-collaboration.eu/evidence-decision-etd-framework).

8 Higgins JPT, Green S, editors. Cochrane handbook for systematic reviews of interventions. York: The Cochrane Collaboration; 2011 (http://handbook.cochrane.org/).

9 According to GRADE, moderate-quality evidence indicates we are moderately confident in the estimate of the effect and the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. Low-quality evidence indicates that our confidence in the effect estimate is limited and the true effect may be substantially different from the estimate of the effect. Very low-quality evidence indicates that we have very little confidence in the effect estimate and the true effect is likely to be substantially different from the estimate of effect.

Additional reviews of evidence were presented in response to the complexities of evaluating preventive chemotherapy programmes using only RCT designs. Evidence contributing to the decision-making process came from reviews of the morbidity caused by soil-transmitted helminth infections, the direct effects and safety of anthelminthic treatment, the values and preferences of the target beneficiaries and end-users, and cost analyses of the delivery of preventive chemotherapy interventions.

A decision-making framework was used to lead deliberations and consensus decision-making. This included the following considerations: (i) the quality of the evidence across outcomes critical to decision-making; (ii) the balance of benefits and harms; (iii) values and preferences related to the recommended preventive chemotherapy intervention in different settings and for different stakeholders, including the populations at risk; (iv) the acceptability of the intervention among key stakeholders; (v) resource implications for programme managers in different settings; (vi) equity; and (vii) the feasibility of implementation of the intervention.

Recommendations

- Preventive chemotherapy (deworming), using annual or biannual[a] single-dose albendazole (400 mg) or mebendazole (500 mg),[b] is recommended as a public health intervention for all young children (12-23 months of age), preschool (24-59 months of age) and school-age children[1] living in areas where the baseline prevalence of any soil-transmitted infection is 20% or higher among children, in order to reduce the worm burden of soil-transmitted helminth infections (*strong recommendation, low-quality evidence*).

  [a] Biannual administration is recommended where the baseline prevalence is over 50%.

  [b] A half-dose of albendazole (i.e. 200 mg) is recommended for children younger than 24 months of age.

- Preventive chemotherapy (deworming), using annual or biannual[a] single-dose albendazole (400 mg) or mebendazole (500 mg), is recommended as a public health intervention for all non-pregnant adolescent girls (10–19 years of age) and non-pregnant women of reproductive age (15–49 years of age) living in areas where the baseline prevalence of any soil-transmitted helminth infection is 20% or higher among non-pregnant adolescent girls and non-pregnant women of reproductive age, in order to reduce the worm burden of soil-transmitted helminth infection (*strong recommendation, moderate-quality evidence*).

  [a] Biannual administration is recommended where the baseline prevalence is over 50%.

- Preventive chemotherapy (deworming), using single-dose albendazole (400 mg) or mebendazole (500 mg), is recommended as a public health intervention for pregnant women, after the first trimester, living in areas where both: (i) the baseline prevalence of hookworm and/or *T. trichiura* infection is 20% or higher among pregnant women, and (ii) anaemia is a severe public health problem, with a prevalence of 40% or higher among pregnant women,[a] in order to reduce the worm burden of hookworm and *T. trichiura* infection (*conditional recommendation, moderate-quality evidence*).

  [a] For the most recent estimates of prevalence of anaemia, visit the WHO-hosted Vitamin and Mineral Nutrition Information System (VMNIS).

The current guideline updates and supersedes previous recommendations contained in the WHO publication *Preventive chemotherapy in human helminthiasis: coordinated use of anthelminthic drugs in control interventions: a manual for health professionals and programme managers*,[2] reviewed at the Informal Consultation on Preventive Chemotherapy in Human Helminthiasis (Geneva, March 2006), and complements some of the operational guidance of *Helminth control in school-age children: a guide for managers of control programmes*,[3] published by WHO in 2011.

[1] We defined school-age children as those between 5 and 12 years of age. Although many children unfortunately do not attend schools, these ages are compulsory school years in most settings, providing with it an entry point to address the nutritional needs of this age group. In some settings the upper range may be 14 years of age.

[2] Preventive chemotherapy in human helminthiasis. Coordinated use of antihelminthic drugs in control interventions: a manual for health professionals and programme managers. Geneva: World Health Organization; 2006 (http://apps.who.int/iris/bitstream/10665/43545/1/9241547103_eng.pdf).

[3] Helminth control in school-age children: a guide for managers of control programmes, 2nd edition. Geneva: World Health Organization; 2011 (http://apps.who.int/iris/bitstream/10665/44671/1/9789241548267_eng.pdf).

Rationale

During the deliberations, the guideline development group took into particular consideration the following evidence:

- the morbidity caused by the different soil-transmitted helminth species in infected individuals is well documented and severe;
- those infected with soil-transmitted helminths benefit significantly from anthelminthic treatment in terms of a reduction in worm burden;
- albendazole and mebendazole are well tolerated, with only minor and transient side-effects reported;
- preventive chemotherapy to control soil-transmitted helminth infections is well accepted among programme beneficiaries and implementers; and
- logistical difficulties and additional costs of alternative methods to identify and treat infected individuals are prohibitive.

Remarks

Preventive chemotherapy, or the periodic large-scale administration of anthelminthic medicines to populations at risk, can dramatically reduce the burden of worms caused by soil-transmitted helminth infections. In areas of varying soil-transmitted helminth endemicity, no average benefit of preventive chemotherapy was detected for outcomes related to morbidity, nutritional outcomes or development in the entire population (composed of infected and uninfected individuals).

However, a decreasing worm burden of soil-transmitted helminths decreases morbidity among individuals heavily infected by soil-transmitted helminths. Because preventive chemotherapy does not break the cycle of infection and reinfection, populations living in contaminated environments continue to be at risk of infection and need frequent administrations of anthelminthic medicines.

Long-term solutions to soil-transmitted helminthiases require improvements in water, sanitation and hygiene.[1] Moreover, multisectoral, integrated programmes will be needed to maximize and sustain the benefits of a decreased worm burden of soil-transmitted helminth infections. Preventive chemotherapy is an important but insufficient part of a comprehensive package to eliminate morbidity due to soil-transmitted helminths in at-risk populations.

The remarks in this section are intended to guide implementation of the recommendations.

- As the prevalence and intensity of soil-transmitted helminth infections are related, only light-intensity infection and low morbidity are expected where the prevalence of any soil-transmitted helminth infection at baseline is lower than 20%. Large-scale preventive chemotherapy programmes are, therefore, not required in these situations.
- Delivering preventive chemotherapy to adolescent girls and women of reproductive age entails extra care and precaution in ensuring that women and girls receiving anthelminthic medicines are not pregnant. Policy-makers may decide to withhold preventive chemotherapy among adolescent girls and women of reproductive age when the pregnancy status or gestational age of women and girls is uncertain, or in areas where rates of unplanned pregnancies are high and coverage of antenatal care is low.
- Extra resources may be required for delivery of preventive chemotherapy to adolescent girls, who may not be easily reached within the existing infrastructure.
- Anthelminthic medicines can be given to individuals coinfected with HIV, who are otherwise eligible for inclusion in large-scale preventive chemotherapy interventions.

[1] Water, sanitation and hygiene to combat neglected tropical diseases: initial lessons from project implementation. Geneva: World Health Organization; 2017 (http://apps.who.int/iris/bitstream/10665/255563/1/WHO-FWC-WSH-17.02-eng.pdf?ua=1).

- Provision of adequate water, sanitation and hygiene services is fundamental to break the cycle of infection and reinfection and sustainably control soil-transmitted helminth infections. Collaboration between programmes for control of soil-transmitted helminth infections and water, sanitation and hygiene programmes is essential to ensure prioritization of water and sanitation services to areas that are endemic for soil-transmitted helminths.
- Deworming should be delivered together with promotion of health and hygiene, to reduce transmission by encouraging healthy behaviours, such as hand washing, use of footwear and proper disposal of faeces.
- Routine monitoring for effective coverage and evaluation of the impact of the intervention should be an integral part of preventive chemotherapy programmes to help inform the decision on continuation or cessation of the programme.

Research gaps

Discussions between the members of the WHO guideline development group and the external resource group highlighted the limited evidence available in some areas of knowledge, meriting further research on preventive chemotherapy to control soil-transmitted helminth infections, particularly in the following areas:

- diagnostic or proxy indicators, to identify households at risk and individuals infected with soil-transmitted helminths;
- alternative anthelminthic medicines (or combinations of existing ones) in the event that drug resistance against albendazole or mebendazole becomes a significant concern;
- estimation of the species-specific intensity of infection that is relevant to cause a specific morbidity related to nutrient absorption and utilization and growth;
- implementation research on innovative distribution systems to reach vulnerable groups such as adolescent girls, including equity considerations;
- the effects of co-interventions of anthelminthic medicines with other nutritional, environmental, water, sanitation or hygiene interventions on nutritional outcomes and reinfection rates;
- active identification and documentation of adverse effects in specific populations, such as individuals living with HIV (especially in children and those on antiretroviral therapy), breastfeeding mothers and their infants, pregnant mothers and their unborn babies, and infants (less than 12 months of age); and
- factors that influence compliance with large-scale preventive chemotherapy programmes, including the values and preferences of children, adolescent girls and adult women, as well as the prevailing social attitudes about treatment of soil-transmitted helminth infections and how health education can improve compliance rates.

Plans for updating the guideline

The WHO steering group will continue to follow research developments in the area of preventive chemotherapy in at-risk population groups, particularly for questions in which the quality of evidence was found to be low or very low. If the guideline merits updating, or if concerns arise about their validity, the Department of Control of Neglected Tropical Diseases and the Department of Nutrition for Health and Development will coordinate the guideline update, following the formal procedures of the *WHO handbook for guideline development*.[1]

As the guideline nears its 10-year review period, the Department of Control of Neglected Tropical Diseases and the Department of Nutrition for Health and Development at WHO's headquarters (Geneva, Switzerland) along with its internal partners, will be responsible for conducting a search for appropriate new evidence.

[1] WHO handbook for guideline development, 2nd edition. Geneva: World Health Organization; 2014 (http://www.who.int/kms/handbook_2nd_ed.pdf?ua=1).

Guideline[1]: Preventive chemotherapy to control soil-transmitted helminth infections in at-risk population groups

INTRODUCTION

Objectives

This guideline provides global, evidence-informed recommendations on preventive chemotherapy, as a public health intervention in areas endemic for soil-transmitted helminths, to decrease the worm burden of soil-transmitted helminth infections in children, adolescent girls, women of reproductive age and pregnant women, including those coinfected with HIV.

The purpose of the guideline is to contribute to discussions among stakeholders when selecting or prioritizing interventions to be undertaken in their specific context. This document presents the key recommendations and a summary of the supporting evidence.

Scope

The current guideline updates and supersedes previous recommendations contained in the WHO publication *Preventive chemotherapy in human helminthiasis: coordinated use of anthelminthic drugs in control interventions: a manual for health professionals and programme managers (1)*, reviewed at the Informal Consultation on Preventive Chemotherapy in Human Helminthiasis, and complements some of the operational guidance of *Helminth control in school-age children: a guide for managers of control programmes (2)*, published by WHO in 2011.

This guideline aims to help WHO Member States and their partners to make evidence-informed decisions on appropriate actions in their efforts to achieve the United Nations Sustainable Development Goals *(1)*, and the global targets as presented in the World Health Assembly resolution WHA66.12 on *Neglected tropical diseases (3)*, the *Comprehensive implementation plan on maternal, infant and young child nutrition (4)*, the *Global strategy for women's, children's, and adolescents' health (2016–2030 (5)*, *Water, sanitation and hygiene for accelerating and sustaining progress on neglected tropical diseases: a global strategy 2015–2020 (6)*, *Accelerating work to overcome the global impact of neglected tropical diseases: a roadmap for implementation (7)*, *Accelerating progress on HIV, tuberculosis, malaria, hepatitis and neglected tropical diseases: a new agenda for 2016–2030 (8)* and *Eliminating soil-transmitted helminthiases as a public health problem in children: progress report 2001–2010 and strategic plan 2011–2020 (9)*.

Population of interest

The guideline will affect young children (12-23 months of age), preschool (24-59 months of age) and school-age children,[2] adolescent girls (10–19 years of age), women of reproductive age (15–49 years of age) and pregnant women in any health-care and community setting. Special considerations for children, adolescents and women living with HIV will be examined, as will deworming for pregnant women as it relates to outcomes related to worm burden and safety.

[1] This publication is a World Health Organization (WHO) guideline. 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, and 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 health and that have ramifications for the use of resources. All publications containing WHO recommendations are approved by the WHO Guidelines Review Committee.

[2] We defined school-age children as those between 5 and 12 years of age. Although many children unfortunately do not attend schools, these ages are compulsory school years in most settings, providing with it an entry point to address the nutritional needs of this age group. In some settings the upper range may be 14 years of age.

Key questions

The following key questions were posed, based on the needs for guidance on policy and programmes of Member States and their partners.

- Should preventive chemotherapy (deworming medicines) be given for the control of soil-transmitted helminth infections, compared to not giving preventive chemotherapy, to all young children (12–23 months of age), preschool (24–59 months of age) and school-age children living in areas that are endemic for soil-transmitted helminth infections, to improve nutrition and health? If so, at what dose and frequency?
- Should preventive chemotherapy (deworming medicines) be given for the control of soil-transmitted helminth infections, compared to not giving preventive chemotherapy, to all non-pregnant adolescent girls and adult women (15–49 years of age) living in areas that are endemic for soil-transmitted helminth infections, to improve nutrition and health? If so, at what dose and frequency?
- Should preventive chemotherapy (deworming medicines) be given for the control of soil-transmitted helminth infections, compared to not giving preventive chemotherapy, to all pregnant women living in areas that are endemic for soil-transmitted helminth infections, for improving nutrition and health outcomes? If so, at what dose and frequency?

Outcomes of interest

The outcomes of interest considered critical for decision-making included the following:

Infection burden

- Worm burden (egg count/g of faeces)

Nutrition

- Anthropometry and growth (specific to preschool and school-age children), including measures of height, weight, wasting, stunting and body-mass-index-for-age
- Anaemia (defined as haemoglobin concentration of less than 110 g/L for children aged 24–59 months, less than 115 g/L for school-age children aged 5–12 years, less than 120 g/L for non-pregnant women, and less than 110 g/L at 34 weeks' gestation or more for pregnant women, adjusted by altitude where appropriate); moderate maternal anaemia during the postpartum period (defined as haemoglobin concentration between 80–109 g/L, adjusted by altitude where appropriate); severe anaemia (defined as haemoglobin concentration lower than 70 g/L at any time for non-pregnant women, or during the second or third trimesters for pregnant women, adjusted by altitude where appropriate)
- Iron deficiency (as defined by using WHO ferritin concentrations thresholds)

Morbidity

- Diarrhoea (three liquid stools or more per day)
- All-cause morbidity (number of patients with at least one episode of any disease during the study period)
- All-cause mortality

Development (specific to preschool and school-age children)

- Cognitive development and school performance (as defined by trialists)

Maternal and infant (specific to pregnant women)

- Maternal mortality (death while pregnant or within 42 days of termination of pregnancy)
- Birthweight
- Perinatal mortality (pregnancy losses of at least seven months' gestation and deaths of live births within the first seven days of life)

The key questions and outcomes guiding the evidence review and synthesis for the recommendations in this guideline are listed in Annex 1.

Target audience

The recommendations contained in this guideline are intended for a wide audience, including policy-makers and their expert advisers as well as technical and programme staff at governmental institutions and organizations involved in the design, implementation and expansion of programmes for the control of soil-transmitted helminth infections and nutrition-sensitive actions for a safe and hygienic environment to improve public health. The end-users of this guideline are:

- national and local policy-makers;
- implementers and managers of national and local programmes for the prevention and control of neglected tropical diseases;
- nongovernmental and other organizations and professional societies involved in the planning and management of nutrition actions and prevention and control of soil-transmitted helminthiases; and
- health professionals, including managers of nutrition and health programmes and public health policy-makers in all settings.

BACKGROUND

Soil-transmitted helminth infections

Soil-transmitted helminthiases are caused by infection with the nematodes *Ascaris lumbricoides* (roundworm), *Trichuris trichiura* (whipworm) and *Ancylostoma duodenale* or *Necator americanus* (hookworms) and are among the commonest infections in humans. Those living in poverty are most vulnerable to infection.

In warm, tropical environments, where soil-transmitted helminthiases are endemic and where sanitation is inadequate, parasite eggs are excreted in the faeces of infected individuals and contaminate the soil. Humans become infected through ingestion of eggs or larvae that are passed in the faeces of infected people. In addition, hookworm eggs hatch in the soil, releasing larvae that mature into a form that can actively penetrate the skin.

There is no direct person-to-person transmission, or infection from fresh faeces, because eggs passed in faeces need about 3 weeks to mature in the soil before they become infective. Since these worms do not multiply in the human host, reinfection occurs only as a result of contact with infective stages in the environment.

Burden of the disease

Almost 2 billion people (about a quarter of the world's population) are infected with soil-transmitted helminths worldwide. Approximately 270 million preschool children and more than 550 million school-age children live in areas where these parasites are extensively transmitted *(10)*. Approximately 250 million girls and adult women are living in areas that are endemic for soil-transmitted helminths. Infections are widely distributed in all WHO regions, with the greatest numbers occurring in sub-Saharan Africa, the Americas and Asia *(2)*. More than 100 countries are endemic for soil-transmitted helminth infections *(10)*.

Although each species has specific characteristics, these soil-transmitted helminthiases are grouped together for control purposes, owing to: (i) similar geographical endemicity and at-risk groups that are affected; (ii) treatment by the same medicines; (iii) the same tools used for diagnosis; and (iv) similar mechanism of negative impact on human health (linked to the intensity of infection).

Morbidity caused by soil-transmitted helminth infections

A review of the literature on the predominant morbidity related to soil-transmitted helminth infections was done *(11)*. The review summarized the evidence on the following themes related to soil-transmitted helminth species: (i) mechanism of morbidity; (ii) evidence of the mechanism of morbidity; (iii) quantification of morbidity; and (iv) evidence of non-quantifiable morbidity. Evidence included directly reported measures of morbidity from infected populations and individuals.

In critically evaluating studies on the effect of helminth infection on nutrition, attention must be paid to definitions of worm burden, the medicines used for deworming, the status of coinfection that could blur comparisons and the downstream effects of infection on metabolism of nutrients. For instance, classifications of the intensity of infection prior to 1987 were study-specific, as the WHO classifications for infection intensity were first published in 1987 (arbitrary for trichuriasis and ascariasis and justified for hookworms based on quantified blood in stools) *(12, 13)*. Citing the mean or median eggs per gram of faeces in the study and situating that with the current standard classification of intensity helped to contextualize the study findings.

Studies showing the effect of deworming on nutrition outcomes will be influenced by the efficacy of the medicine in curing infection and reducing worm burden. A meta-analysis of the efficacy of different medicines shows that their efficacy are not the same for all worms, with *T. trichiura* having the lowest cure rates *(14)*. Furthermore,

studies that compare nutritional outcomes between cases and controls focus on defining cases as having the worm in question and may not determine the presence of other parasites. Of particular concern would be protozoan parasites (e.g. *Giardia*) that can go undetected in glycerine-based stool exams (Kato method, Kato-Katz method), or potential pathogens such as blastocysts that may go unreported. Giardiasis, which causes malabsorption, is also treatable with albendazole and in areas where giardiasis and helminthiases are co-endemic, understanding the variability of the impact of albendazole on nutritional outcomes may depend on the intensity and prevalence of these coinfections. Studies that document the impact of worm infection on the absorption of nutrients through functional or structural abnormalities of the gut may not take into account the changes in transport, metabolism and storage of nutrients that may ultimately affect nutritional indicators measured via biochemistry or health outcomes.

Ancylostoma duodenale **and** ***Necator americanus*** **(hookworms)**

An estimated 460 million people are infected with hookworms *(15, 16)*. Disability-adjusted life-years (DALYs), a measure of overall disease burden expressed as the number of years lost due to ill health or early death, from *A. duodenale* or *N. americanus* infection have been most recently estimated at 3.2 million, which corresponds to more than half of the DALYs attributable to soil-transmitted helminth infections *(16, 17)*. Adult hookworms reside in the small intestine, attached to the intestinal mucosa by their mouthparts.

Hookworm infections cause morbidity through blood loss from feeding of the parasite and through mechanical damage due to attachment of the adult parasite to the intestinal mucosa.

Blood loss

Hookworms bite into intestinal mucosa to feed on blood, secreting anticoagulants so that lesions continue to bleed even between feeds. It has been estimated that a single hookworm can cause blood loss of 0.03–0.26 mL per day *(18–27)*. Infection with *N. americanus* causes greater blood loss at an individual and population level than infection with *A. duodenale (28)*. The blood loss results in anaemia when the nutritional input is insufficient to compensate for the loss. In the case of heavy-intensity infections, the daily loss of iron has been calculated to be more than double the daily requirements of an average, healthy, school-age child *(24)*. Globally, hookworm infection ranks in the leading five causes of anaemia *(29)*.

Mechanical damage

Additional sequelae from hookworm infection include ulcers and inflammation due to the mechanical damage caused by the parasite *(30, 31)*.

Ascaris lumbricoides **(roundworms)**

An estimated 820 million people are infected with *A. lumbricoides (15, 16)*. DALYs attributable to *A. lumbricoides* infection have been estimated at more than 1.33 million, corresponding to just over 20% of the DALYs from soil-transmitted helminth infections *(16, 17)*. Adult *A. lumbricoides* most frequently reside in the jejunum of the small intestine.

Roundworm infections cause morbidity through impairment of nutrient intake, digestion and absorption, through intestinal obstruction and owing to larval migration.

Malabsorption and nutrient losses

Micronutrient and macronutrient losses resulting from infection with *A. lumbricoides* have been reported for nitrogen, albumin and protein *(32–35)*, fat *(33, 34, 36)*, lactose *(32, 37)* and vitamin A *(36–38)*. Other studies,

after controlling for coinfection with *Giardia* and other protozoa that cause malabsorption, do not show correlation between ascariasis and malabsorption *(39–44)* except possibly at levels exceeding 3200 eggs per gram of faeces *(44)*, corresponding to moderate-intensity infection.

Intestinal obstruction

A. lumbricoides may cause intestinal obstruction when a large number of worms are present in the small intestine. Hospitalization and surgery can be required in more severe cases *(45–48)*. The likelihood of obstruction is associated with the intensity of infection *(37, 49, 50)*. Most cases have been seen in children under 5 years of age *(50, 51)*, probably due to the smaller volume in which worms reside inside the intestines. In rare cases, intestinal obstruction or biliary complications can be fatal *(16, 52–54)*, with a recent (2014) estimate of 2824 cases of *A. lumbricoides*-related deaths in 2010 *(16)*.

Larval migration

During the parasite life-cycle, larvae migrate through the lungs and liver. Several reports suggest an important influence of ascariasis on the pathogenesis and prevalence of allergy and respiratory difficulties, including asthma and Loeffler's syndrome during the acute stage of the infection *(55–57)*.

Trichuris trichiura **(whipworms)**

About 440 million people are estimated to be affected by trichuriasis *(15, 16)*. The estimated DALYs attributable to *T. trichiura* infection are approximately 0.65 million *(16, 17)*. Evidence from animal models shows the adult worm embeds via the whip-like anterior portion of the parasite in the epithelial layer of the caecum *(58)*.

Whipworm infections cause morbidity through dysentery (*Trichuris* dysentery syndrome) with direct and indirect blood and iron losses and anaemia.

Trichuris dysentery syndrome

Symptoms of the *Trichuris* dysentery syndrome include abdominal distention *(59)*, anaemia *(59, 60)*, diarrhoea and dysentery *(59–62)*, growth impairment *(59–63)*, pallor *(59, 60, 62)* and rectal prolapse *(61)*. Cases of *Trichuris* dysentery syndrome usually report "massive" *T. trichiura* worm burden, necessitating more than one course of deworming treatment *(64–69)*.

Blood loss

The estimated mean blood loss per day per *T. trichiura* is 0.005 mL *(70)*. Faecal blood loss has been estimated at 0.8–8.6 mL per day, and has been found to be highly correlated with worm burden; iron-deficiency anaemia is estimated to occur with infections of 800 worms or more *(70)*. There is evidence to suggest that hookworm and *T. trichiura* coinfection can exacerbate anaemia *(71)*. Since these worms reside in different areas of the intestine, it has been hypothesized that coinfection constrains the potential reabsorption of iron that can normally occur with hookworm infection alone *(71)*.

Overall evidence on morbidity due to soil-transmitted helminth infections

The combined evidence on morbidity demonstrates an important association between soil-transmitted helminth infection and an alteration to normal nutritional processes. Light-intensity infections are often asymptomatic, but greater morbidity is apparent with moderate-intensity and heavy-intensity infections. The exact sequelae depend on the helminth species and the intensity of infection and coinfections, among others.

At a population level, there is a greater proportion of moderate-intensity to heavy-intensity infection with increasing prevalence of any soil-transmitted helminth infection *(71)*. Only light-intensity infection and, therefore, low morbidity is expected in areas with less than 20% prevalence of any soil-transmitted helminth infection, based on a Markov transition probability model to predict the change in prevalence of soil-transmitted helminth infections during public-health control activities *(72, 73)*.

Efficacy of deworming medicines

A previous systematic review of anthelminthic efficacy was updated *(74)*. The authors of the review conducted a literature search for recent trials reporting information on the efficacy of anthelminthic medicines against soil-transmitted helminth infections. The search included studies that: (i) evaluated drug efficacy using the egg-reduction rate (ERR); (ii) used treatment with single-dose albendazole or mebendazole, the two main medicines used in large-scale preventive chemotherapy programmes; and (iii) used a randomized, placebo-controlled trial design.

Results from 46 drug trials involving more than 4800 individuals indicate a mean ERR for albendazole and mebendazole against *A. lumbricoides* of 98.7% and 98.3%, respectively; against hookworm of 89.8% and 68.2%, respectively; and against *T. trichiura* of 60.7% and 69.0%, respectively.

When the analysis was restricted to data from 31 trials which used the WHO-recommended methodology to assess the efficacy of anthelminthic medicines, the average ERRs were higher than the reference thresholds for both medicines against all soil-transmitted helminth species. With albendazole, the ERR increased to 99.9%, 64.4% and 92.4% for *A. lumbricoides, T. trichiura*, and hookworms, respectively. With mebendazole, the ERR increased to 69.3% and 76.5% for *T. trichiura* and hookworms, respectively. The ERR for mebendazole against *A. lumbricoides* was only slightly lower in this subgroup of trials (97.6%) compared to the full group of studies.

Overall, the ERRs of both albendazole and mebendazole were all above the reference threshold, and were considered to be sufficient to control morbidity caused by soil-transmitted helminth infections when regularly administered *(75–78)*.

Safety of deworming medicines

A review was conducted to assess the safety of benzimidazoles (i.e. albendazole and mebendazole) *(79)*. The review used the following sources of data: (i) published safety trials; (ii) individual case-safety reports (ICSRs) of suspected adverse effects following administration of benzimidazoles between 1971 and 2015, from VigiBase™[1] *(80)*; (iii) soil-transmitted helminth control campaigns in Sierra Leone implemented between 2010 and 2014 and considered to have valid safety data, owing to an integrated pharmacovigilance component; and (iv) studies investigating congenital anomalies after maternal exposure to benzimidazoles during pregnancy. The evidence base for use of benzimidazoles during pregnancy is limited due to the ethical constraints in conducting appropriate studies. From the limited data available from inadvertent treatment during the first trimester, there appears to be no increased risk of congenital anomalies. However, because of this uncertainty during the first trimester, deworming medicines are not prescribed during this period.

A review of drug-safety trials involving more than 6500 administrations of albendazole and mebendazole showed no occurrence of severe adverse events. All adverse effects (9.7% for albendazole and 6.3% for mebendazole) were minor and transient, with durations of less than 48 h. The most frequent adverse events reported were epigastric pain or discomfort (37%), headache (24%), nausea (17%), dizziness (10%), oedema (10%), myalgia (6%) and vomiting (4%).

[1] VigiBase™ is the name of the WHO global database of Individual Case Safety Reports (ICSRs). It is the largest and most comprehensive database in the world, and is developed and maintained by the Uppsala Monitoring Centre on behalf WHO and its Member States.

A review of VigiBase™ *(3)* identified 306 ICSRs of suspected adverse drug reactions observed in children and women who had received albendazole or mebendazole. The total number of treatments provided by preventive chemotherapy from 2010 to 2014 was approximately 4 billion tablets. The rate of reporting of events is thus less than one suspected adverse event per 10 million treatments *(3, 79)*. However, a known limitation of spontaneous reporting systems is underreporting, particularly in countries with limited surveillance systems. In Sierra Leone, with over 22 million tablets distributed and a good reporting system, there were no serious adverse events and 185 side-effects, which were all minor and transient *(79)*.

Cost of delivering deworming medicines

A review was conducted to compare the costs of different delivery models of anthelminthic medicines *(81)*. The costs of the following treatment approaches (adjusted to 2015 US$) were compared: (i) targeted chemotherapy, i.e. targeted to specific groups at risk; (ii) mass drug administration, i.e. targeted to an entire population in an area of soil-transmitted helminth transmission; and (iii) selective chemotherapy, i.e. screening entire groups and treating positive cases. The review compared costs in areas with a prevalence of soil-transmitted helminth infection ranging from 20% to 90%, and assessed the resources required of the approaches in terms of the personnel needed to treat one million school-age children.

Forty-five cost estimations were identified for school-age children, preschool children or entire populations, and eight reports provided the cost of individual diagnosis. The mean treatment cost was estimated at US$ 0.63 for a preschool child, US$ 0.30 for a school-age child through a school-based programme, US$ 0.63 for an individual through community treatment, and US$ 4.89 for screening and treating a single individual annually.

The cost of treating an infected individual (including the cost of treating individuals not infected with soil-transmitted helminths) progressively decreased from US$ 1.50–3.15 when the prevalence of soil-transmitted helminths was 20% to US$ 0.33–0.70 when the prevalence was 90%. The cost of screening and treating an infected individual (including the cost of screening individuals not infected with soil-transmitted helminths) decreased from US$ 22.78 with a 20% prevalence of soil-transmitted helminths to US$ 5.28 with a 90% prevalence. The number of personnel needed was not considered to interfere with normal school activities for the targeted approach, whereas the screening approach would absorb the entire laboratory workforce in the area for the entire year.

The results demonstrated that targeted treatment had consistently lower cost than alternative approaches, regardless of the epidemiological setting.

Current strategies to reduce soil-transmitted helminth infections

Although soil-transmitted helminth infections affect already vulnerable populations, such as children and women living in low-resource settings, and the global prevalence is high, helminths remain a neglected infection *(2)*. Public health interventions to control soil-transmitted helminth infections include improvements in sanitation; improvements in health and hygiene behaviours, such as hand washing and the use of footwear, through health education; and periodic administration of treatment to populations or targeted groups in the community. Preventive chemotherapy, the large-scale distribution of anthelminthic medicines to at-risk population groups, is the public health measure currently used by WHO for preventing morbidity due to soil-transmitted helminth infections.

WHO has endorsed a strategy to control morbidity from soil-transmitted helminth infections through preventive chemotherapy without previous individual diagnosis to specific at-risk groups living in endemic areas (i.e. a targeted treatment approach) *(1, 2, 82)*. Individuals with no infection or light-intensity infection of soil-transmitted helminths are often asymptomatic and may bear little or no harm from soil-transmitted

helminth infections. Significant morbidity is found among individuals with moderate-intensity or heavy-intensity infections; however, even these infections are associated with non-specific symptomatology, which leads to difficulty in identifying those in need of treatment through a clinical approach alone (i.e. dependent on presentation of infected individuals to the health system). Public health interventions to control soil-transmitted helminth infections aim to reduce the worm burden in populations and decrease the intensity of infection among heavily-infected individuals.

In 2001, delegates at the Fifty-fourth World Health Assembly unanimously endorsed a resolution (WHA54.19) urging endemic countries to mobilize resources for the control of soil-transmitted helminth infections *(83)*. Previous WHO recommendations included providing anthelminthic treatment to the following at-risk groups: children (1–14 years of age) and women (15–45 years of age). Treatment was to be given once per year for low-risk communities with 20% to 50% prevalence of soil-transmitted helminth infection, or twice per year in at-risk communities with more than 50% prevalence of soil-transmitted helminth infections *(1, 2)*. Large-scale programmes are implemented in more than 60 endemic countries with support from local governments, particularly for school-based programmes. In 2015, coverage of preventive chemotherapy in populations at-risk of soil-transmitted helminth infections was almost 60% *(10)*. The target is to reach 75% coverage by 2020 *(9)*.

The current guideline updates and supersedes previous WHO guidelines on preventive chemotherapy to control soil-transmitted helminth infections, where they pertain specifically to deworming in children, adolescent girls, women of reproductive age and pregnant women *(1, 2, 82)*.

EVIDENCE AND RECOMMENDATIONS

Effects and safety of preventive chemotherapy in preschool and school-age children

Summary of evidence

The evidence that formed the recommendation on periodic preventive chemotherapy in children is based on two systematic reviews from the Cochrane Infectious Diseases Group and the Campbell Collaboration *(84, 85)*. The key question and outcomes guiding the evidence review and synthesis for the recommendations in this guideline are listed in Annex 1.

The systematic review of the use of anthelminthic (deworming) medicines for soil-transmitted helminth infections in children summarized the effects on growth, haemoglobin and cognition *(84)*. The review included randomized controlled trials and quasi-randomized controlled trials comparing anthelminthic medicines (i.e. albendazole, levamisole, mebendazole, pyrantel pamoate, piperazine, piperazine citrate and tetrachloroethylene) for treatment of soil-transmitted helminth infections with a placebo or no treatment in children aged 16 years or younger. It also included trials that combined deworming programmes with other interventions, such as health education or micronutrient supplementation, provided it was given to both, intervention and control groups.

The review authors searched the Cochrane Central Register of Controlled Trials (CENTRAL), Embase, Literatura Latino Americana e do Caribe em Ciências da Saúde (LILACS) and MEDLINE. They also searched the reference lists and registers of ongoing and completed trials, including the *meta*Register of Controlled Trials (*m*RCT). The last search for evidence was done in April 2015.

The review identified 45 trials, including nine cluster-randomized controlled trials that met the inclusion criteria. One trial evaluating mortality included over 1 000 000 children, and the remaining 44 trials included a total of 67 672 participants. Eight trials were in children known to be infected (selected by screening, or living in areas where all children are infected), and 37 trials were carried out in areas endemic for soil-transmitted helminths, including areas of high (defined as prevalence > 70%; 15 trials), moderate (defined as prevalence > 50% but < 70%; 12 trials) and low prevalence (defined as prevalence < 50%; 10 trials) of infection.

In children known to be infected with soil-transmitted helminths, those who were given a single dose of deworming medicines had statistically significant increased weight gain over the next 1–6 months (mean difference [MD]: 0.75 kg; 95% confidence interval [CI]: 0.24 kg to 1.26 kg; 5 trials; 627 participants), and increased height gain (MD: 0.25 cm; 95% CI: 0.01 cm to 0.49 cm; 5 trials; 647 participants) but no difference in body mass index (MD: –0.20 kg/m^2; 95% CI: –0.46 kg/m^2 to 0.06 kg/m^2; 1 trial; 407 participants) compared to those who did not receive deworming medicines. There was no difference in haemoglobin levels between those who received deworming medicines and those who did not receive them (MD: 1.0 g/L; 95% CI: –6.5 g/L to 8.6 g/L; 2 trials; 247 participants). Two trials measured cognitive functioning but they showed insufficient evidence of effect (results not pooled; 2 trials; 103 participants). The overall quality of evidence for these critical outcomes was very low to low for interventions given to children known to be infected with soil-transmitted helminths (see Annex 2).

When all children in areas that were endemic for soil-transmitted helminths were treated (as in large-scale distribution of anthelminthic medicines to infected and uninfected children without prior screening of infection status), there was no difference in the critical outcome measures between children given a dose of deworming medicines and those given a placebo or receiving no treatment: weight gain MD: –0.04 kg; 95% CI: –0.11 kg to 0.04 kg; 7 trials; 2719 participants; height gain MD: –0.12 cm; 95% CI –0.33 cm to 0.10 cm; 5 trials; 1974 participants; haemoglobin level

MD: 0.6 g/L; 95% CI: –0.5 g/L to 1.7 g/L; 3 trials; 1005 participants; or cognitive functioning (across different formal tests of cognition, therefore results not pooled; 2 trials; 1361 participants).

The results for treating all children in areas that were endemic for soil-transmitted helminths were consistent, even when the deworming medicines were given every 3–6 months: weight gain MD: 0.08 kg; 95% CI: –0.11 kg to 0.27 kg; 10 trials; *n* = 38 392; height gain MD: 0.02 cm; 95% CI: –0.14 cm to 0.17 cm; 7 trials; 7057 participants; haemoglobin concentration MD: –0.2 g/L; 95% CI: –0.8 g/L to 0.4 g/L; 7 trials; 3595 participants; for cognitive functioning (across different formal tests of cognition, therefore, results not pooled; 5 trials; 32 486 participants). Three trials were able to measure mortality risk and showed no difference between those receiving multiple doses of deworming medicines and those receiving placebo or no treatment (risk ratio [RR]: 0.95; 95% CI: 0.89 to 1.92; 3 trials; 1 005 135 participants). The overall quality of evidence for these critical outcomes was low to moderate for large-scale distribution of anthelminthic medicines.

A Campbell Collaboration systematic review of preventive chemotherapy in preschool and school-age children used network meta-analysis to assess the evidence further *(85)*. The review included trials that could explain possible effect modifiers, such as concomitant food or micronutrient interventions, worm species, reinfection, intensity of infection and baseline nutritional status, as well as qualitative measures such as measures of school attendance. The review included randomized controlled trials and quasi-randomized controlled trials, as well as quasi-experimental non-randomized trials (controlled before-and-after studies and interrupted time-series studies) comparing deworming medicines for soil-transmitted helminths with a placebo or no treatment, in children aged 6 months to 16 years.

The review authors searched the Cumulative Index to Nursing and Allied Health Literature (CINAHL), the Cochrane Library, EconLit, Embase, Global Health CABI and CAB Abstracts, Internet Documents in Economics Access Service (IDEAS), LILACS, MEDLINE, the Public Affairs Information Service (PAIS) and Social Services Abstracts. Grey literature databases were also searched, including thesis dissertations and the System for Information on Grey Literature in Europe (SIGLE). The search for evidence was done in September 2015.

The review identified 65 trials, including 34 randomized controlled trials, 16 cluster randomized controlled trials, 10 controlled before-and-after studies, 5 long-run interrupted time-series studies and 2 ongoing randomized controlled trials that met the inclusion criteria. A total of 14 trials that screened for infection were included. These studies were conducted in 23 low-income and middle-income countries, in areas where the prevalence of soil-transmitted helminth infections ranged from 0.5% to 90% infected. Most of the studies used deworming twice per year or more frequently; only two studies used deworming once per year.

The review found that among children treated with anthelminthic medicines twice a year in areas that were endemic for soil-transmitted helminths (preventive chemotherapy without previous individual diagnosis in infected and uninfected individuals living in areas of various levels of prevalence) compared to children given a placebo or no treatment, there was no difference in weight gain (MD: 0.09 kg; 95% CI: –0.04 kg to 0.20 kg; 11 trials; 35 430 participants); height gain (MD: 0.07 cm; 95% CI: –0.1 cm to 0.24 cm; 9 trials; 6839 participants); proportion stunted (RR: 0.98; 95% CI: 0.88 to 1.08; 4 trials; 4286 participants); cognitive function as measured using short-term working memory in a 100-point scale (MD: –0.23 points; 95% CI –0.60 points to 0.14 points; 3 trials; 4078 participants); or mortality (1 per 1000 fewer; 95% CI: –3 to 1 per 1000; 6 trials; *n* > 1 000 000). The overall quality of evidence for these critical outcomes was moderate to high for large-scale distribution of anthelminthic medicines (see Annex 2).

Preventive chemotherapy was effective overall at reducing the worm burden of all soil-transmitted helminths in comparison to a placebo, although the effect sizes were highly variable (high heterogeneity within each species). Worm burden decreased with preventive chemotherapy compared to placebo for *A. lumbricoides* (RR: 0.52; 95% CI: 0.44 to 0.61; 22 trials; 13 914 participants), hookworms (RR: 0.37; 95% CI: 0.16 to 0.85; 10 trials;

6214 participants) and *T. trichiura* (RR: 0.72; 95% CI: 0.57 to 0.92; 9 trials; 5053 participants). The overall quality of evidence for reduction in worm burden through large-scale distribution of anthelminthic medicines was low (see Annex 2).

Because periodic preventive chemotherapy as a public health intervention is not intended to benefit uninfected individuals, several concerns in evaluating the impact of periodic preventive chemotherapy through clinical trials or summaries of trials were addressed by the review. These concerns include (i) effect dilution of inclusion of uninfected individuals in both the control and treatment groups; (ii) exclusion of severe cases (for example, those who have severe anaemia, undernutrition or a stool sample that tests positive for soil-transmitted helminths); (iii) involvement of different soil-transmitted helminth species (e.g. *A. lumbricoides* is not expected to cause blood loss); (iv) non-compliance among those allocated to placebo groups, that is, those in the placebo group may seek to procure and take their own deworming medicines; and (v) short follow-up time in that the benefits of living worm-free throughout childhood can only be determined in the long-term.

In addressing the concerns on the dilution effect of including uninfected individuals, areas with lower parasite intensities or older and well-nourished children, the review found little or no effect on weight or height when restricted to studies with heavy intensity of infection (that is, where the dilution effect of uninfected individuals is minimal); no relationship between the baseline prevalence of soil-transmitted helminth infections and effects on outcomes; no difference in effects between studies with a greater or lesser proportion of underweight children; and no relationship between the age of children and the treatment effect.

In order to address concerns that different helminths need to be considered separately, the review conducted sensitivity analyses to take into account different prevalences of infection for the different species of soil-transmitted helminths, and found no differences in the effects of deworming medicines on outcomes.

In order to take into account the possible effect of differential non-compliance, the review performed a sensitivity analysis with studies that had more than 75% compliance, less than 2% differential attrition and low risk of bias for allocation concealment, and found that these studies were congruent with the findings of the main analyses.

The review included four long-term studies 8–10 years after mass large-scale deworming programmes that followed up 160 000 children. However, owing to the risk of bias (unclear or non-random sampling, potential confounding factors not controlld for or not presented, blinding not described or not done, high attrition rates and potential selective reporting bias), indirectness and imprecision, the review authors were very uncertain about the effect of the preventive chemotherapy on child health. That is, there is severe uncertainty as to whether the effects on child health were due to the deworming or to other potential confounding factors such as, for instance, access to safe water, sanitation and hygiene.

The review also addressed additional concerns that combination treatment (with food, iron or other micronutrients) was necessary for deworming to have a measurable effect. However, the review found no greater effect on any outcome with combined treatment (deworming medicines with food, iron supplementation or micronutrients) versus deworming alone.

Reinfection immediately after deworming has also been hypothesized to have a possible dilution effect, in that higher reinfection rates would nullify the overall difference in outcomes between the control and intervention groups. The review, however, found no relationship between the impact on worm prevalence (as an indication of reinfection) and the treatment effects.

The review was also able to address the hypotheses that overall effects are diluted by positive indirect (spillover) effects; that is, that individuals in the control groups would likewise benefit from the overall

decrease in worm burden from the treated group. However, the review found that weight gain among children in the control groups of individually randomized trials (where the spillover effect should be greater because the control groups were exposed to the treated groups in the same classroom or school) was less than that among children in the control groups of cluster randomized trials (where presumably there would be fewer spillover effects, owing to geographical separation between the control and treatment groups). Restricting the analysis to cluster randomized trials showed no effect on weight or height.

In summary, none of the hypothesized effect modifiers significantly altered the main findings. Given that the analyses were limited by data availability, it is possible that interaction between factors may still be hidden by the analyses on aggregate-level data that may mask individual-level differences.

Overall result of evidence on preventive chemotherapy in preschool and school-age children

1. Soil-transmitted helminthiases cause morbidity at moderate-intensity or heavy-intensity of infection (see "Morbidity caused by soil-transmitted helminth infections" above)
2. Albendazole and mebendazole are effective against soil-transmitted helminthses that significantly reduce the number of infecting worms (see "Efficacy of deworming medicines" above) and are considered safe for children over 12 months of age at appropriate doses (see "Safety of deworming medicines" above).
3. Weight and height increased with preventive chemotherapy in infected children.
4. With meta-analyses of randomized controlled trials, controlled before-and-after studies and interrupted time-series studies, no average benefit of preventive chemotherapy was detected for outcomes related to morbidity, nutritional outcomes or development.
5. Preventive chemotherapy is intended to provide benefits only to infected individuals (uninfected individuals are treated only for logistical reasons). Measuring the benefit of preventive chemotherapy in the entire group treated (comprising infected and uninfected preschool and school-age children) reduces the capacity to properly evaluate the benefits obtained by the infected individuals.
6. The most cost–effective approach to reach infected individuals is to treat the entire group at risk without individual diagnosis (see "Cost of delivering deworming medicines" above).

Summary of considerations of members of the guideline development group for determining the direction and strength of the recommendations

The guideline development group, with the support of the steering group, formulated recommendations that were informed by the evidence presented and with explicit consideration of the factors listed next.

Quality of evidence

The overall quality of evidence for the effect of preventive chemotherapy on the critical outcomes for preschool and school-age children is low.[1]

[1] According to GRADE, low-quality evidence indicates that our confidence in the effect estimate is limited and the true effect may be substantially different from the estimate of the effect.

Balance of benefits and harms

Short-term, average nutritional benefits in the treated community (comprising infected and uninfected children) were not significant in the two reviews. The reviews found statistically significant nutritional benefits when all individuals treated are infected.

No adverse events were reported in the systematic reviews and included trials. A review of safety trials with deworming medicines showed no severe adverse events and only rare, reversible and mild adverse events *(74, 86)*.

Moderate-intensity or heavy-intensity infection causes significant species-specific morbidity among individuals infected with soil-transmitted helminths. Those who have light-intensity infection are likely to derive little benefit from deworming. Those who are not infected will gain no benefit from deworming, although safety reports also show little or no harm.

Values and preferences

The members of the guideline development group agreed that there was little variability in the importance that populations assign to interventions to control soil-transmitted helminth infections.

A review of the literature on values and preferences towards soil-transmitted helminths and their control identified six studies from seven countries: China, Côte d'Ivoire, Egypt, Ghana, Turkey, United Republic of Tanzania, and Viet Nam *(87–92)*. Most populations recognized worms as a cause of infection and as harmful to health. However, soil-transmitted helminths have also been considered a common or ubiquitous infection affecting mostly children, without being associated with stigmatization *(87)*. In the study in China, positive attitudes towards helminth infection were noted as being critical for health *(90)*.

Parents surveyed after a school-based deworming programme showed favourable attitudes towards the intervention, describing benefits such as reduced stomach aches, better appetite and worm expulsion in children *(87–93)*. Parents from Egypt, Ghana, Lao People's Democratic Republic, Turkey and the United Republic of Tanzania were willing to pay for deworming medicines for their children *(88, 89, 92, 93)*. In the study in Turkey, 17% of teachers reported beliefs of parents that anthelminthic medicines caused sexual sterility *(92)*.

Although there were some reservations towards interventions to control soil-transmitted helminths expressed in some studies, they were not extrapolated more generally to the rest of the population. In general, concerns and misconceptions around deworming were an indication of the (lack of) public health promotion and awareness campaigns in the area.

Acceptability

Preventive chemotherapy is generally widely accepted by policy-makers, health workers and teachers involved in school-based deworming programmes. More than 60 countries currently implement school-based programmes.

Ministries of health have included education campaigns as part of their programmes to control soil-transmitted helminth infections. Teachers favoured treatment of soil-transmitted helminth infections and commended the health benefits of deworming for children and the importance of hygiene *(87–92)*.

Resource implications

The guideline development group agreed that, overall, the implementation of deworming in children would entail relatively minor resources.

Using a strategy that includes either mass drug administration or targeted treatment for the treatment of soil-transmitted helminth infections is of an order of magnitude cheaper than that of performing selective treatment (where individuals are screened and positive cases are treated) *(94, 95)*. Consequently, the cost per infected individual treated would be significantly higher if selective treatment was used, regardless of the pre-control prevalence. This analysis included the cost of procuring and distributing medicines in the analysis. In addition, selective treatment requires clinic visits, diagnostic screening and treatment and puts an unnecessary burden on the health systems in low-resource areas compared to the targeted treatment approach, which requires no screening and minimal time for teachers to distribute medicines.

In 2010, a review of cost in seven countries from four WHO geographical regions estimated the average cost of treating 1 000 000 children in schools at US$ 72 000 (US$ 0.07 per child). This estimate included procurement and distribution of medicines, training and supervision of teachers, and monitoring *(9)*.

The costs of preventive chemotherapy are largely determined by the costs related to distribution and monitoring, rather than to the costs of the actual medicines. From the perspective of distribution to children, integration with other health-care and school-based interventions (such as during immunization days or child health days) allows this intervention to use up only minor incremental resources.

Safe water, sanitation and hygiene access and practices are generally associated with a reduced risk of soil-transmitted helminth infections, of at least 33%, based on pooled estimates from meta-analyses *(96–98)*. Collaboration with sectors that implement hygiene, water and sanitation interventions are important to minimize the costs and maximize and sustain the benefits of reducing soil-transmitted helminth infections.

Equity

The guideline development group agreed that preventive chemotherapy in children can improve equity though strategies to identify and reach children who may be poor, vulnerable or unable to attend school. These strategies need to be in place in order to reduce inequities.

The social and environmental determinants related to soil-transmitted helminth infections show that poor and vulnerable families and communities have both the highest risk of infection as well as the least access to health services *(99–101)*. Programmes to control soil-transmitted helminth infections and to break the cycle of chronic poverty need to be implemented alongside an improvement in delivery of health services. Large-scale deworming may reduce health inequities if it is an intervention that reduces disparities in levels of infections among population groups according to place of residence, income and other social stratifiers (e.g. caste, social group) *(100)*.

Feasibility

Programmes of large-scale treatment have been run through school systems, covering 200 million children in more than 60 countries *(9)*.

The guideline development group agreed that preventive chemotherapy in children is technically feasible. Among school-age children, this is facilitated by school-based delivery systems, which are supported by ministries of health and education. Among preschool-age children and children not attending schools, a robust health system that reaches these populations though immunizations, micronutrient supplementation programmes, child health days and routine health care can increase the feasibility of access to deworming.

Recommendation: young children, preschool and school-age children

Preventive chemotherapy (deworming), using annual or biannual[a] single-dose albendazole (400 mg)[b] or mebendazole (500 mg), is recommended as a public health intervention for all young children (12-23 months of age), preschool (24-59 months of age) and school-age children living in areas where the baseline prevalence of any soil-transmitted infection is 20% or more among children, in order to reduce the worm burden of soil-transmitted helminths (*strong recommendation*[c]*, low quality of evidence*).

[a] Biannual administration is recommended where the baseline prevalence is over 50%.

[b] A half-dose of albendazole (i.e. 200 mg) is recommended for children 12–23 months of age.

[c] A strong recommendation is one for which the guideline development group is confident that the desirable effects of adherence outweigh the undesirable effects. Implications of a strong recommendation for patients are that most people in their situation would desire the recommended course of action and only a small proportion would not. Implications for clinicians are that most patients should receive the recommended course of action, and adherence to this recommendation is a reasonable measure of good-quality care. With regard to policy-makers, a strong recommendation means that it can be adapted as a policy in mostsituations, and for funding agencies it means the intervention probably represents an appropriate allocation of resources (i.e. large net benefits relative to alternative allocation of resources).

Rationale

During the deliberations, the guideline development group took into particular consideration the following evidence that resulted in a strong recommendation:

- children infected with soil-transmitted helminths benefit significantly from anthelminthic treatment in terms of reduction of worm burden and weight and height gain.
- the morbidity caused by the different soil-transmitted helminth species in heavily infected individuals is well documented and severe;
- albendazole and mebendazole are well tolerated among children over 12 months of age at appropriate doses, with only minor and transient side-effects reported;
- preventive chemotherapy to control soil-transmitted helminth infections in children is generally well accepted among children, parents, teachers and health workers;
- logistical difficulties and additional costs of alternative methods to identify and treat infected individuals can be prohibitive; and
- soil-transmitted helminth-endemic areas with at least 20% soil-transmitted helminth prevalence were considered the priority for large-scale programmes due to the presence of infections of moderate and heavy intensity and, therefore, soil-transmitted helminth-related morbidity.

Overall, in areas endemic for soil-transmitted helminths, it was considered essential to treat all preschool and school-age children for the purpose of reducing the worm burden in those who are moderately to heavily infected. A "strong recommendation" is given despite the low quality of evidence in favour of a potentially equivalent option in terms of benefit (targeted chemotherapy or mass drug administration) but more costly comparator (selective chemotherapy).

Remarks

The remarks in this section are intended to guide implementation of the recommendation, based on the discussion of the guideline development group.

- The guideline development group stressed that the recommendation for preventive chemotherapy among children is being made for the outcome of decreasing the worm burden in areas that are endemic for soil-transmitted helminths. The prevalence of soil-transmitted helminths among children is changing and this needs to be taken into account by regularly assessing the worm burden, to ensure that the intervention remains relevant.
- Provision of adequate water, sanitation and hygiene services is fundamental, to break the cycle of infection and reinfection and sustainably control soil-transmitted helminth infections. Collaboration between programmes for control of soil-transmitted helminth infection and water, sanitation and hygiene programmes is essential to ensure prioritization of water and sanitation services to areas that are endemic for soil-transmitted helminths.
- Deworming should be delivered together with promotion of health and hygiene, to reduce transmission by encouraging healthy behaviours, such as hand washing, use of footwear and proper disposal of faeces.
- Routine monitoring for effective coverage and evaluation of the impact of the intervention should be an integral part of preventive chemotherapy programmes, to help inform the decision on continuation or cessation of the programme.

Effects and safety of preventive chemotherapy in non-pregnant adolescent girls and women of reproductive age

Summary of evidence

The evidence that informed the recommendation on preventive chemotherapy in non-pregnant adolescent girls and women of reproductive age includes a systematic review from the Campbell Collaboration *(102)*. The key question on this intervention, along with the outcomes that were identified as critical for decision-making, is listed in PICO (Population, Intervention, Comparator and Outcomes) format in Annex 1.

The systematic review of the use of deworming medicines for soil-transmitted helminths in adolescent girls and adult women *(102)* summarized the effects on worm burden, anaemia and morbidity. Randomized controlled trials and before-and-after studies comparing deworming medicines for soil-transmitted helminths with a placebo or no treatment, in non-pregnant women aged 12–49 years, were eligible for inclusion in the review.

The review authors searched the Cumulative Index to Nursing and Allied Health Literature (CINAHL), the Cochrane Library, EconLit, Embase, Global Health CABI and CAB Abstracts, Internet Documents in Economics Access Service (IDEAS), LILACS, MEDLINE, PAIS and Social Services Abstracts. Grey literature databases were also searched, including thesis dissertations and the System for Information on Grey Literature in Europe (SIGLE). The last search for evidence was done in March 2016.

The search identified six randomized controlled trials that met the inclusion criteria. However, data were not disaggregated by sex in four of the trials. Thus, only two randomized controlled trials were included, on the effect of anthelminthic medicines for soil-transmitted helminths given to non-pregnant adolescent girls and adult women.

The review showed that adolescent girls and women of reproductive age from areas that were endemic for soil-transmitted helminths who were given deworming medicines had lower worm burden at a mean follow-up time of 6 months compared to those who were given a placebo or no treatment: prevalence of roundworm (*A. lumbricoides*) infection RR: 0.29; 95% CI: 0.14 to 0.62; 2 trials; 1498 participants; prevalence of hookworm (*A. duodenale* or *N. americanus*) infection RR: 0.32; 95% CI: 0.18 to 0.59; 2 trials; 1498 participants; prevalence of whipworm (*T. trichiura*) infection RR: 0.77; 95% CI: 0.65 to 0.91; 2 trials; 1498 participants. The prevalence rate of anaemia and iron deficiency among adolescent girls and women of reproductive age given deworming medicines was not significantly different from that for those given a placebo or no treatment (anaemia: RR: 0.82; 95% CI: 0.60 to 1.11; 3 trials; 683 participants; iron deficiency anaemia: RR: 0.89; 95% CI: 0.64 to 1.23; 1 trial; 186 participants). All-cause morbidity (conjunctival xerosis) was measured in one study but did not show a significant difference between groups (RR: 1.00: 95% CI: 0.24 to 4.23; 1 trial; 32 participants). The quality of the evidence was moderate for worm burden and low for anaemia, iron deficiency and morbidity (see Annex 2).

Overall result of evidence on preventive chemotherapy in non-pregnant adolescent girls and women of reproductive age

1. Soil-transmitted heliminthiases cause morbidity at moderate or heavy intensity of infection (see "Morbidity caused by soil-transmitted helminth infections" above).
2. Albendazole and mebendazole are effective against soil-transmitted helminthiases to significantly reduce the number of infecting worms (see "Efficacy of deworming medicines" above) and are considered safe for use by non-pregnant adolescent girls and non-pregnant women of reproductive age (see "Safety of deworming medicines" above).
3. With meta-analyses of randomized controlled trials, no average benefit of preventive chemotherapy was detected for outcomes related to morbidity, anaemia or iron deficiency anaemia.
4. Preventive chemotherapy is intended to provide benefits only to infected individuals (uninfected individuals are treated only for logistical reasons). Measuring the benefit of preventive chemotherapy in the entire group treated (comprising infected and uninfected non-pregnant adolescent girls and women of reproductive age) reduces the capacity to properly evaluate the benefits obtained by the infected individuals.
5. The most cost–effective approach to reach infected individuals is to treat the entire group at risk without individual diagnosis (see "Cost of delivering deworming medicines" above).

Summary of considerations of members of the guideline development group for determining the direction and strength of the recommendations

The guideline development group, with the support of the steering group, formulated recommendations that were informed by the evidence presented and with explicit consideration of the factors listed next.

Quality of evidence

The overall quality of evidence for the effect of preventive chemotherapy on the critical outcomes for non-pregnant adolescent girls and women of reproductive age is moderate.[1]

Balance of benefits and harms

Reduced morbidity, in terms of a decrease in worm burden, was found with preventive chemotherapy. However, no average benefit of preventive chemotherapy was detected on haemoglobin levels.

Six episodes of conjunctival xerosis were reported in one of the trials, three each for the group treated with mebendazole and the group given placebo, signifying that the xerosis was unlikely to be due to the intervention *(103)*.

Moderate-intensity or heavy-intensity infection may cause significant species-specific morbidity among individuals infected with soil-transmitted helminths. Those who have light-intensity infection are likely to derive little benefit from deworming. Those who are not infected will gain no benefit from deworming, although safety reports also show little or no harm. No evidence was available from studies conducted in only infected populations.

Values and preferences

A review of the literature on values and preferences towards soil-transmitted helminths and their control among adolescent girls and adult women identified a study from the Philippines *(104)* that surveyed 226 women of reproductive age. The study showed that 75% believed that treatment of soil-transmitted helminths would cause side-effects. A survey of 192 household leaders in Lao People's Democratic Republic showed that they appreciated the effectiveness of deworming. Many were willing to purchase albendazole or mebendazole when it was not provided free of charge by the health system *(105)*.

Values and preferences related to soil-transmitted helminths and their control can vary, depending on the context of the health system; in environments with lack of trust of the public systems, efforts for health promotion should accompany the deworming interventions.

Acceptability

Ministries of health have generally included awareness campaigns as part of programmes for control of soil-transmitted helminths, to boost compliance.

Preventive chemotherapy is generally widely accepted by policy-makers and health workers, although acceptability among stakeholders who may unknowingly be giving deworming tablets to women with undetected early pregnancy is not known.

[1] According to GRADE, moderate-quality evidence indicates we are moderately confident in the estimate of the effect and the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Resource implications

Expanding the intervention to non-pregnant adolescent girls and adult women has the potential to dramatically increase the number of people eligible to receive preventive chemotherapy to control soil-transmitted helminth infections, and thus to increase the total cost of delivering services, especially in settings in which there are limited structures and programmes to reach this population. In some settings, existing infrastructures may be different for adolescent girls than for women of reproductive age. Stakeholders should explicitly take into account the heterogeneity within this broad population group, in order to effectively implement this intervention.

Furthermore, delivering preventive chemotherapy to adolescent girls and women of reproductive age entails extra care and precaution in ensuring that women and girls receiving anthelminthic medicines are not pregnant. This is of particular concern in areas where rates of unplanned pregnancies are high and coverage of antenatal care is low.

Member States that will adapt preventive chemotherapy among adolescent girls and women of reproductive age should be able to regularly assess the worm burden in this population, in order to ensure the relevance of the intervention, as well as be able to determine the stage of gestation among those who are (knowingly or unknowingly) pregnant. If the pregnancy status or gestational age of women and girls is uncertain, preventive chemotherapy should be withheld.

As with children, using a preventive chemotherapy strategy (large-scale deworming) to treat soil-transmitted helminth infections among adolescents and adult women is much less resource intensive than performing large-scale selective treatment (where individuals are screened and positive cases are treated) *(94, 95)*, although most of the studies included in these cost analyses were on school-age children and only two studies investigated the cost of distributing deworming medicines to women of reproductive age. The studies on women of reproductive age assessed costs within existing immunization and vitamin A campaigns through child health days *(105)* or iron-supplementation campaigns using village health workers *(106)*.

Water, sanitation and hygiene access and practices are generally associated with a reduced risk of soil-transmitted helminth infections, of at least 33%, based on pooled estimates from meta-analyses *(96–98)*. Collaboration with sectors that implement hygiene, water and sanitation interventions are important to minimize the costs and maximize and sustain the benefits of reducing soil-transmitted helminth infections.

Equity

Preventive chemotherapy among non-pregnant adolescent girls and adult women could improve access to health services, although strategies to reach this population group need to be planned so as not to further increase disparities.

The promotion of women's health literacy and empowerment is essential and can increase the success of public health interventions, such as large-scale deworming *(100)*. This approach may contribute to a reduction of persistent health inequities with respect to helminth infections in women.

Feasibility

There have been programmes of mass distribution of albendazole (in combination with ivermectin or diethylcarbamazine against lymphatic filariasis) covering over 140 million non-pregnant women in 60 countries *(9)*.

Some uncertainty exists around the provision of such an intervention in this population, as the existing infrastructure may vary by country and by group (for example, adolescents versus adult women of reproductive age).

Recommendation: non-pregnant adolescent girls and non-pregnant women of reproductive age

Preventive chemotherapy (deworming), using annual or biannual[a] single-dose albendazole (400 mg) or mebendazole (500 mg), is recommended as a public health intervention for all non-pregnant adolescent girls and women of reproductive age living in areas where the baseline prevalence of any soil-transmitted helminth infection is 20% or more among adolescent girls and women of reproductive age, in order to reduce the worm burden of soil-transmitted helminths (*strong recommendation[b], moderate quality of evidence*).

[a] Biannual administration is recommended where the baseline prevalence exceeds 50%.

[b] A strong recommendation is one for which the guideline development group is confident that the desirable effects of adherence outweigh the undesirable effects. Implications of a strong recommendation for patients are that most people in their situation would desire the recommended course of action and only a small proportion would not. Implications for clinicians are that most patients should receive the recommended course of action, and adherence to this recommendation is a reasonable measure of good-quality care. With regard to policy-makers, a strong recommendation means that it can be adapted as a policy in mostsituations, and for funding agencies it means the intervention probably represents an appropriate allocation of resources (i.e. large net benefits relative to alternative allocation of resources).

Rationale

During the deliberations, the guideline development group took into particular consideration the following evidence that resulted in a strong recommendation:

- non-pregnant adolescent girls and women of reproductive age benefit significantly from anthelminthic treatment in terms of a reduction in worm burden;
- the morbidity caused by the different soil-transmitted helminth species in heavily infected individuals is well documented and severe;
- albendazole and mebendazole are well tolerated among non-pregnant adolescent girls and non-pregnant women, with only minor and transient side-effects reported;
- preventive chemotherapy is generally well accepted among women, health workers and policy-makers, though uncertainty exists around the feasibility of providing this intervention among adolescent girls, as existing infrastructure may vary by country and context;
- logistical difficulties and additional costs of alternative methods to identify and treat infected individuals can be prohibitive; and
- soil-transmitted helminth-endemic areas with at least 20% soil-transmitted helminth prevalence were considered the priority for large-scale programmes due to the presence of infections of moderate and heavy intensity and, therefore, soil-transmitted helminth-related morbidity.

Overall, in areas endemic for soil-transmitted helminths, it was considered essential to periodically treat all non-pregnant adolescent girls and women of reproductive age for the purpose of reducing the worm burden in those who are moderately to heavily infected. A "strong recommendation" is given despite low quality of evidence in favour of a potentially equivalent option in terms of benefit (targeted chemotherapy or mass drug administration) but more costly comparator (selective chemotherapy).

Remarks

The remarks in this section are intended guide implementation of the recommendation, based on the discussion of the guideline development group.

- As the prevalence and intensity of soil-transmitted helminth infections are related, only light-intensity infection and low morbidity are expected where the prevalence of any soil-transmitted helminth infection is lower than 20%. Large-scale preventive chemotherapy programmes are not recommended in these situations.
- Delivering preventive chemotherapy to adolescent girls and women of reproductive age entails extra care and precaution in ensuring that women and girls receiving anthelminthic medicines are not pregnant. Policy-makers may decide to withhold preventive chemotherapy among adolescent girls and women of reproductive age if the pregnancy status or gestational age of women and girls is uncertain, or in areas where rates of unplanned pregnancies are high and coverage of antenatal care is low.
- As the cost of preventive chemotherapy is largely determined by operational challenges, settings that do not have health services offering preventive health care to non-pregnant adult women and adolescent girls may find this intervention more resource intensive. Therefore, extra resources may be required for delivery of preventive chemotherapy to adolescent girls, who may not be easily reached within existing infrastructures.
- Provision of safe water, sanitation and hygiene services is fundamental, to break the cycle of infection and reinfection and sustainably control soil-transmitted helminth infections. Collaboration between programmes for control of soil-transmitted helminth infection and water, sanitation and hygiene programmes is essential to ensure prioritization of water and sanitation services to areas that are endemic for soil-transmitted helminths and will further minimize costs and sustain the benefits of reducing soil-transmitted helminth infections.
- Deworming should be delivered together with promotion of health and hygiene, to reduce transmission by encouraging healthy behaviours, such as hand washing, use of footwear and proper disposal of faeces.
- Routine monitoring for effective coverage and evaluation of the impact of the intervention should be an integral part of preventive chemotherapy programmes to help inform the decision on continuation or cessation of the programme.

Effects and safety of preventive chemotherapy in pregnant women

Summary of evidence

The evidence that formed the recommendation on deworming in pregnant women includes a systematic review from the Cochrane Pregnancy and Childbirth Group *(107)*. The key question on this intervention, along with the outcomes that were identified as critical for decision-making, is listed in PICO format in Annex 1.

The systematic review *(107)* aimed to determine the effects of administration of anthelminthic medicines on worm burden, maternal anaemia and pregnancy outcomes, from prospective randomized controlled trials comparing deworming medicines for soil-transmitted helminths with a placebo or no treatment, given during the second or third trimester of pregnancy.

The review authors searched the Cochrane Pregnancy and Childbirth Group Trials Register, which is maintained with monthly searches of CENTRAL; weekly searches of MEDLINE (Ovid); weekly searches of Embase (Ovid); monthly searches of CINAHL (EBSCO); hand searches of 30 journals and the proceedings of major conferences; weekly current-awareness alerts for a further 44 journals; and monthly BioMed Central email alerts.

Four trials were included in this review. In two studies, the women were also given a daily iron or iron–folate supplement, along with anthelminthic treatment.

The review showed that pregnant women in the second trimester of pregnancy who were given a single dose of deworming medicines had lower worm burdens overall than pregnant women who were given a placebo or no treatment (RR: 0.29; 95% CI: 0.10 to 0.81; 3 trials; 4788 participants), although there was a significant degree of heterogeneity by type of worm: prevalence ratio of roundworm (*A. lumbricoides*) infection RR: 0.16; 95% CI: 0.05 to 0.50; 2 trials; 1393 participants; prevalence ratio of hookworm (*A. duodenale* or *N. americanus*) infection RR: 0.18; 95% CI: 0.03 to 1.13; 3 trials; 2002 participants; prevalence ratio of whipworm (*T. trichiura*) infection RR: 0.86; 95% CI: 0.59 to 1.24; 2 trials; 1393 participants.

Pregnant women who were given deworming medicines were as likely to have anaemia in the third trimester as those who were given a placebo or no treatment (RR: 0.94; 95% CI: 0.81 to 1.10; 4 trials; 3266 participants). This outcome was consistent when iron supplementation was given to both groups (RR: 0.76; 95% CI: 0.47 to 1.23; 3 trials; 1290 participants). There were no significant differences between pregnant women given deworming medicines and those who were given a placebo or no treatment, in terms of risk of low birth weight (RR: 1.00; 95% CI: 0.79 to 1.27; 3 trials; 3255 participants) and perinatal mortality (RR: 1.09; 95% CI: 0.71 to 1.67; 2 trials; 3385 participants). The overall quality of the evidence was low for the outcome of anaemia, and moderate for the outcomes of worm burden, low birth weight and perinatal mortality (see Annex 2).

Overall result of evidence on preventive chemotherapy in pregnant women

1. Soil-transmitted helminthiasies cause morbidity at heavy intensity of infection (see "Morbidity caused by soil-transmitted helminth infections" above).
2. Albendazole and mebendazole are effective against soil-transmitted helminthiases to significantly reduce the number of infecting worms (see "Efficacy of deworming medicines" above) and are considered safe for use among pregnant women after the first trimester of pregnancy (see "Safety of deworming medicines"). Pregnant woman in the first trimester should be excluded from preventive chemotherapy interventions.
3. With meta-analyses of randomized controlled trials, no average benefit of preventive chemotherapy was detected for outcomes related to anaemia, low birth weight or perinatal mortality probably due to dilution effect.
4. Preventive chemotherapy is intended to provide benefits only to infected individuals (uninfected individuals are treated only for logistical reasons). Measuring the benefit of preventive chemotherapy in the entire group treated (comprising infected and uninfected pregnant women) reduces the capacity to properly evaluate the benefits obtained by the infected individuals.
5. The most cost–effective approach to reach infected individuals is to treat the entire group at risk without individual diagnosis (see "Cost of delivering deworming medicines" above).

Summary of the considerations of the members of guideline development group for determining the direction and strength of the recommendations

The guideline development group, with the support of the steering group, formulated recommendations informed by the evidence presented and with explicit consideration of the following factors:

Quality of evidence

The overall quality of evidence for the effect of preventive chemotherapy on the critical outcomes for pregnant women is moderate.[1]

Balance of benefits and harms

Decrease in worm burden was found with preventive chemotherapy. However, no average benefit of preventive chemotherapy was detected on haemoglobin levels, infant birthweight or perinatal mortality. No evidence was available from randomized controlled trials conducted in only infected populations of pregnant women.

No adverse events were reported in the systematic review and included trials. A review of evidence from safety trials and observational studies with deworming medicines showed no adverse events in mothers or neonates in more than 15 000 treatments with albendazole or mebendazole during pregnancy *(74, 86)*. Both medicines are approved after the first trimester in the WHO Model Formulary, which states that, ideally, all cases of hookworm infection should be treated but that this should be done in the second and third trimester of pregnancy *(108)*.

Moderate-intensity or heavy-intensity infection may cause significant species-specific morbidity among individuals infected with soil-transmitted helminths. Those who have light-intensity infection are likely to derive little benefit from deworming. Those who are not infected will gain no benefit from deworming, although safety reports also show little or no harm among pregnant mothers and their neonates.

Values and preferences

The members of the guideline development group considered that there may be uncertainty or variability in how much pregnant women value preventive chemotherapy against soil-transmitted helminths.

A review of the literature on values and preferences towards soil-transmitted helminths and their control among pregnant women identified studies in Peru *(109, 110)* and the Philippines *(104)*.

In Peru, of the 99 pregnant women interviewed, 52% reported knowledge about parasites and 74% reported knowing how they were transmitted *(109, 110)*. The majority (61%) of the pregnant women believed that taking medicine during pregnancy could harm the fetus. When asked if they would be willing to be treated for parasites during pregnancy if found to be infected, 70% responded positively *(109, 110)*.

In the Philippines, a survey of 226 women of reproductive age showed that 75% believed that treatment of soil-transmitted helminths would cause side-effects, 67% believed treatment would cause maternal harm, and 78% believed treatment would cause fetal harm *(104)*.

While ministries of health have made efforts to include education campaigns as part of large-scale deworming programmes, anxiety about deworming during pregnancy may, in part, be caused by lack of strong evidence for benefit.

[1] According to GRADE, moderate-quality evidence indicates we are moderately confident in the estimate of the effect and the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Acceptability

In the Philippines, key informant interviews of health workers, nurses and midwives showed that they were concerned and anxious about the safety of deworming treatment during pregnancy. Many would refer to a physician if a pregnant mother was found, on faecal analysis, to be infected with soil-transmitted helminths. This anxiety is due to fear of teratogenic effects to the fetus *(104)*.

Although health workers are generally supportive of preventive chemotherapy campaigns, their acceptability for treating pregnant women may be uncertain.

Resource implications

In settings with routine antenatal care, provision of deworming medicines to pregnant women may entail only minor incremental costs. This may not be the case in settings where rates of antenatal care coverage are low. The cost will largely be determined by the operational challenges rather than the cost of the intervention itself. The difficulty will lie in attempting to set up vertical programmes, which can prove costly. Costing studies on large-scale preventive chemotherapy for soil-transmitted helminth infections have not been able to identify studies that detail costs for reaching pregnant women.

Access to safe water, sanitation and hygiene interventions and practices are generally associated with a reduced risk of soil-transmitted helminth infections, of at least 33%, based on pooled estimates from meta-analyses *(96–98)*.

Equity

In general, providing treatment to an at-risk group will enhance equity. Acceptability will also be linked to equity. If acceptability is low in this population group, this may affect equity.

Feasibility

Several countries have already incorporated preventive chemotherapy into routine antenatal care services. Feasibility can be enhanced by improving access to existing infrastructure and maternal health programmes.

Recommendation: pregnant women in the second or third trimester

Preventive chemotherapy (deworming), using single-dose albendazole (400 mg) or mebendazole (500 mg), is recommended as a public health intervention for pregnant women, after the first trimester, living in areas where both: (i) the baseline prevalence of hookworm and/or *T. trichiura* infection is 20% or more among pregnant women, and (ii) where anaemia is a severe public health problem, with a prevalence of 40% or higher among pregnant women,[a] in order to reduce the worm burden of hookworm and *T. trichiura* infection (*conditional recommendation*[b]*, moderate quality of evidence*).

[a] For the most recent estimates of prevalence of anaemia, visit the WHO-hosted Vitamin and Mineral Nutrition Information System (VMNIS).

[b] This is a conditional recommendation. A conditional recommendation is one for which the guideline development group concludes that the desirable effects of adherence probably outweigh the undesirable effects, although the trade-offs are uncertain. Implications of a conditional recommendation for populations are that, while many people would desire preventive chemotherapy, a considerable proportion would not. With regard to policy-makers, a conditional recommendation means that there is a need for substantial debate and involvement from stakeholders before considering the adoption of preventive chemotherapy (deworming), as a public health intervention for pregnant women.

Rationale

During the deliberations, the guideline development group took into particular consideration the following evidence that resulted in a conditional recommendation:

- the morbidity caused by the different soil-transmitted helminths is species-specific: hookworm and *T. trichiura* infections cause anaemia, which is particularly detrimental for pregnant women, while morbidity due to *A. lumbricoides* is less relevant for this group;
- in areas where anaemia is not a public health problem, the parasite control intervention is probably not necessary;
- albendazole and mebendazole are well tolerated, with no adverse events in pregnant women and their fetuses when given after the first trimester of pregnancy. Anthelminthic medicines must not be given during the first trimester;
- preventive chemotherapy could be implemented as part of routine antenatal care in settings in which there are existing infrastructure and maternal health programmes; and
- logistical difficulties and additional costs of alternative methods to identify and treat infected individuals can be prohibitive.

Overall, in areas endemic for hookworm and/or *T. trichiura*, it was considered essential to periodically treat all pregnant women after the first trimester for the purpose of reducing the worm burden in those who are moderately to heavily infected, and provide optimal conditions for a healthy pregnancy for both mother and child. This recommendation is consistent with the WHO recommendations on antenatal care for a positive pregnancy experience *(111)*.

Remarks

The remarks in this section are intended to guide implementation of the recommendation, based on the discussion of the guideline development group.

- Provision of safe water, sanitation and hygiene services is fundamental, to break the cycle of infection and reinfection and sustainably control soil-transmitted helminth infections. Collaboration between programmes for control of soil-transmitted helminth infection and water, sanitation and hygiene programmes is essential to ensure prioritization of water and sanitation services to areas that are endemic for soil-transmitted helminths.
- Deworming should be delivered together with promotion of health and hygiene, to reduce transmission by encouraging healthy behaviours, such as hand washing, use of footwear and proper disposal of faeces.
- Routine monitoring for effective coverage and evaluation of the impact of the intervention should be an integral part of preventive chemotherapy programmes, to help inform the decision on continuation or cessation of the programme.
- Member States may consider this intervention for pregnant women after debate and involvement from stakeholders. They should base their decision on their context, health-system infrastructure and ability to monitor and evaluate results.

Effects and safety of preventive chemotherapy in the context of HIV infection

Given that there is significant geographical overlap between the prevalence of soil-transmitted helminths and HIV infection, a review of the safety of anthelminthic treatment in persons living with HIV, including those receiving antiretroviral therapy, was done. A systematic review from the Cochrane HIV/AIDS Group evaluated the effects of deworming medicines on adverse events among individuals coinfected with HIV and soil-transmitted helminths *(112)*.

The review authors searched for published and unpublished studies in CENTRAL, ClinicalTrials.gov, the Cochrane Library, Embase, MEDLINE, the WHO International Clinical Trials Registry Platform (ICRTP) and the WHO Global Health Library, in September 2015. They also searched databases listing conference abstracts, scanned reference lists of articles, and contacted the authors of included studies. The search included randomized controlled trials that compared deworming medicines with a placebo or no intervention in people living with HIV.

Eight trials were included in the review: three trials evaluated the effect of providing deworming medicines to all adults with HIV without knowledge of their helminth-infection status, and five trials evaluated the effects of providing deworming medicines to individuals living with HIV and confirmed helminth infections.

The review showed that treatment of confirmed helminth infections in individuals living with HIV may have short-term beneficial effects on the progression of HIV infection, although evidence of long-term benefit is lacking. There is no indication that deworming medicines confer additional risks in populations infected with HIV. Based on the lack of reports of other than mild adverse events during and after anthelminthic treatment, from programmatic surveillance in populations with a high prevalence of HIV infection and from a number of clinical trials conducted in people infected with HIV, anthelmintic therapy appears to be well tolerated in individuals living with HIV. There is no evidence of an adverse safety signal, although studies specifically designed to evaluate safety have not been conducted.

Based on the results and the discussion around this review, it was concluded by the guideline development group that anthelminthic medicines can be given to those coinfected with HIV, who are otherwise eligible for inclusion in large-scale preventive chemotherapy interventions.

IMPLEMENTATION OF THE GUIDELINE

Preventive chemotherapy, or the periodic large-scale administration of anthelminthic medicines to at-risk populations, can dramatically reduce the burden of worms caused by soil-transmitted helminth infections. This intervention can potentially decrease morbidity among individuals who are heavily infected by soil-transmitted helminths. Owing to the mechanism of transmission of soil-transmitted helminths, however, there is also a high reinfection rate. A systematic review and meta-analysis of literature showed a reinfection rate at 3, 6 and 12 months after treatment for *A. lumbricoides* of 26% (95% CI: 16% to 43%), 68% (95% CI: 60% to 76%), and 94% (95% CI: 88% to 100%), respectively. For *T. trichiura*, respective reinfection rates were 36% (95% CI: 28% to 47%), 67% (95% CI: 42% to 100%), and 82% (95% CI: 62% to 100%), and for hookworm, 30% (95% CI: 26% to 34%), 55% (95% CI: 34% to 87%) and 57% (95% CI: 49% to 67%) *(113)*. Because preventive chemotherapy does not break the cycle of infection and reinfection, populations living in environments conducive to hatching or embryonation of soil-transmitted helminth eggs or the development of larvae continue to be at risk of infection and need periodic administrations of anthelminthic medicines.

Long-term solutions to soil-transmitted helminthiases require improvements in water, sanitation and hygiene. A systematic review and meta-analysis on the effect of sanitation (access and use of facilities for the safe disposal of human urine and faeces) on infection with soil-transmitted helminths *(84)* showed that the availability and use of sanitation was associated with a significant protection against infection with soil-transmitted helminths (odds ratio [OR]: 0.51; 95% CI: 0.44 to 0.61) *(98)*. A further comprehensive systematic review that examined the effect of improved water, sanitation and hygiene on soil-transmitted infections showed that the likelihood of any soil-transmitted infection was less with use of treated water (OR: 0.46; 95% CI: 0.36 to 0.60), wearing of shoes (OR: 0.30: 95% CI: 0.11 to 0.83), hand washing before eating (OR: 0.38; 95% CI: 0.26 to 0.55), and hand washing after defecating (OR: 0.45; 95% CI: 0.35 to 0.58) *(97)*. The reviewers concluded that pooled estimates from meta-analyses indicated at least a 33% reduction in the odds of soil-transmitted helminth infection with individual water, sanitation and hygiene access or practices.

These reviews highlight that control of soil-transmitted helminth infections will need multisectoral and integrated programmes to maximize and sustain the benefits of a decreased worm burden of soil-transmitted helminth infections. Preventive chemotherapy is an important but insufficient part of a comprehensive package to eliminate morbidity due to soil-transmitted helminths in at-risk populations. A range of water, sanitation and hygiene services and practices reduce the incidence of soil-transmitted helminths, and have further been linked to improved nutritional outcomes *(114)*.

A logic model depicting the plausible relationship between inputs and expected sustainable development goals relevant to deworming is presented in Annex 3.

Implementation considerations

As this is a global guideline, Member States are expected to adapt the recommendation according to their setting and its feasibility. Neglected tropical diseases, public health nutrition and child health programmes that include preventive chemotherapy for the control of soil-transmitted helminths require supportive policies, supply-chain management and health-care services that enable the proper availability, access and distribution of anthelminthic medicines. WHO regional and country offices assist with these processes.

School-based control of soil-transmitted helminth infections has been used by many countries, and lessons learnt on planning, implementation and monitoring have subsequently improved the coverage of preventive chemotherapy among children *(2, 9, 115)*. Inclusion of younger age groups has promoted and expanded community-based services such as child health days, so that vulnerable infants and young children have access to large-scale programmes of preventive chemotherapy *(2)*.

Expanding the intervention to adolescent girls and women of reproductive age has the potential to dramatically increase the number of people eligible to receive preventive chemotherapy to control soil-transmitted helminth infections, and thus to increase the total cost of delivering services, especially in settings in which there are limited structures and programmes to reach this population. Member States that will adapt these guidelines to include this population should explicitly take into account the heterogeneity of adolescent girls and adult women in general (for instance, in their state of physical growth and social development), as well as the diversity within their country (for instance, in terms of the expected responsibilities in the family and community, the numbers out of school or out of work and the existing social norms).

Delivering preventive chemotherapy to adolescent girls and women of reproductive age entails extra care and precaution in ensuring that women and girls receiving anthelminthic medicines are not pregnant. This is of particular concern in areas where rates of unplanned pregnancies are high and coverage of antenatal care is low. Member States that will adapt preventive chemotherapy among adolescent girls and women of reproductive age should be able to regularly assess the worm burden in women and girls aged 15–49 years, in order to ensure the relevance of the intervention, as well as be able to determine the stage of gestation among those who are (knowingly or unknowingly) pregnant. If the pregnancy status or gestational age of women and girls is uncertain, preventive chemotherapy should be withheld.

Meaningful involvement of adolescent girls and women of reproductive age in formulating strategies to integrate preventive chemotherapy with other interventions can increase compliance. In addition, when there is significant geographical overlap between the prevalence of helminth and HIV infection, care should be taken in formulation of policies on preventive chemotherapy among adolescent girls and adult women that do not exclude individuals living with HIV. National and subnational strategic planning can help address challenges and direct actions, so that deworming treatment can be practicable, feasible and acceptable to adolescent girls and adult women.

Access to accurate knowledge and information about soil-transmitted helmiths and the control of these infections improves treatment coverage. It is thus important to ensure that relevant persons involved in the implementation of interventions, such as programme managers, teachers and health-care staff, are informed of the positive and possible adverse effects of preventive chemotherapy, as well as the values and preferences of the end-beneficiaries of the intervention. Developing awareness campaigns and educational materials that are especially suited to adolescent girls and key populations, such as parents of young children, may be useful in improving and sustaining compliance.

Engaging with multiple stakeholders and partners will be critical in strengthening implementation and sustaining gains in controlling soil-transmitted helminth infections. Working in collaboration with sectors involved in child and adolescent well-being; reproductive health; water, sanitation and hygiene; early childhood development and education; social marketing; and others can help ensure a comprehensive, cross-sectoral and more sustainable approach to controlling soil-transmitted helminths.

Regulatory considerations

The *WHO Model List of Essential Medicines* (EML) compiles medicines that satisfy the priority health-care needs of populations and are selected with due regard to disease prevalence, evidence on efficacy and safety, and comparative costs *(116)*. The WHO EML is, thus, used by countries to develop their own national essential medicines lists. In this context, albendazole chewable tablet (400 mg), mebendazole chewable tablet (100 mg) and mebendazole chewable tablet (500 mg) are listed in the sixth version of the *Model List of Essential Medicines For Children* *(116, 117)*. Albendazole is listed under intestinal anthelminthic and antifilarial therapeutic indication, and mebendazole as an intestinal anthelminthic medicine *(116)*.

Besides albendazole and mebendazole, the WHO EML includes ivermectin, levamisole and pyrantel as intestinal anthelminthics. This guideline specifically assessed the evidence and additional factors on albendazole and mebendazole to inform its recommendations.

Pharmacopoeial standards help ensure the quality and safety of essential medicines. The monographs for albendazole and mebendazole included in The International Pharmacopoeia provide publicly available quality standards, including a new test for the dissolution of the albendazole chewable tablets *(118)*.

Ethical and equity considerations

Ethical principles lead to consideration of whether an intervention produces benefits to individuals and communities, prevents harm, also at the individual and societal levels, and distributes health benefits across social groups; that is, how much an intervention contributes to health equity, and respects and promotes the exercise of human rights.

Helminthiases occur mostly in poor communities, where conditions for transmission are rife and where they may play an important role in contributing to poverty *(100)*. Poor individuals, families and communities characteristically live in degraded and high-risk environments lacking adequate housing, water supply and sanitation, resulting in close contact with pathogens, and where access to health services is limited. Anthelminthic treatment must be considered a necessary but insufficient intervention that contributes to breaking the cycle between helminth infection, illness and chronic poverty, and should be complemented by an important and necessary improvement in delivery of services.

Anthelminthic treatment is less likely to increase health equity if it is not accompanied by concurrent interventions that tackle the root cause of what led these populations to get infected: their living conditions. Large-scale preventive chemotherapy programmes may reduce health inequities if they involve an intervention that reduces disparities in levels of infection among population groups according to place of residence, income and other social stratifiers (e.g. caste, social group) *(99–101)*.

The promotion of women's health literacy and empowerment is essential and can increase the success of public health interventions, such as large-scale deworming *(100)*. This approach may contribute to a reduction of persistent health inequities with respect to helminth infections in women and children.

Monitoring and evaluation of guideline implementation

Monitoring and evaluation should be built into the implementation process, in order to provide important lessons for uptake and further implementation. A number of indicators are suggested for monitoring of soil-transmitted helminth infection control programmes *(2)*. The indicators are classified into: (i) process indicators (to determine whether organizational elements of the control programme are in place and are functioning properly); (ii) performance indicators (to assess whether the control programme reached its coverage goal); and (iii) impact indicators (to assess whether the health impact of the control programme has been reached). The two recommended impact indicators are the prevalence of soil-transmitted helminths (overall and by species), and the prevalence of the different classes of intensity of infection. These indicators are recommended to be collected at baseline and every 3 or 4 years.

For evaluation at the global level, the WHO Department of Nutrition for Health and Development has developed a centralized platform for sharing information on nutrition actions in public health practice implemented around the world. By sharing programmatic details, specific country adaptations and lessons learnt, this platform provides examples of how guidelines are being translated into actions. The Global database on the Implementation of Nutrition Action (GINA) *(4)* provides valuable information on the implementation of numerous nutrition policies and interventions.

RESEARCH GAPS

Discussions between the members of the WHO guideline development group and the external resource group highlighted the limited evidence available in some knowledge areas, meriting further research on preventive chemotherapy for the control of soil-transmitted helminth infections, particularly in the following areas:

- diagnostic or proxy indicators, to identify households at risk and individuals infected with soil-transmitted helminths;
- alternative althelminthic medicines (or combinations of existing ones) in the event that drug resistance against albendazole or mebendazole becomes a significant concern;
- estimation of the species-specific intensity of infection that is relevant to cause a specific morbidity related to nutrient absorption and utilization and growth;
- implementation research on innovative distribution systems to reach vulnerable groups such as adolescent girls, including equity considerations;
- the effects of cointerventions of deworming medicines with other nutritional, environmental, water, sanitation or hygiene interventions on nutritional outcomes and reinfection rates;
- active identification and documentation of adverse effects in specific populations, such as individuals living with HIV (especially in children and those on antiretroviral therapy), breastfeeding mothers and their infants, pregnant mothers and their unborn babies, and very young infants (less than 6 months of age); and
- factors that influence compliance with large-scale preventive chemotherapy programmes, including the values and preferences of children, adolescent girls and adult women, as well as the prevailing social attitudes around treatment of soil-transmitted helminth infections and how health education can improve compliance rates.

GUIDELINE DEVELOPMENT GROUPS

This guideline was developed in accordance with the WHO evidence-informed guideline-development procedures, as outlined in the *WHO handbook for guideline development (119)*.

WHO steering group

A WHO steering group (see Annex 4), led by the Department of Nutrition for Health and Development, was established with representatives of the departments of Control of Neglected Tropical Diseases; Essential Medicines and Health Products; HIV/AIDS; Service Delivery and Safety; Reproductive Health Research; and Public Health, Environment and Social Determinants, as well as the Special Programme for Research and Training in Tropical Diseases. The steering group guided the overall guideline development process, as well as the retrieval, assessment and summary of the evidence.

The steering group drafted the scope of the guideline and the key questions in PICO format; identified the systematic review teams and guideline methodologist; developed and finalized the planning proposal; helped with the selection of the guideline development group and the external resource group; oversaw the evidence retrieval, assessment and synthesis; collected and assessed disclosures of interest; and managed conflicts in consultation with the WHO Office of Compliance, Risk Management and Ethics. The steering group drafted the recommendation, based on the decisions of the guideline development group; drafted the final guideline, including management of the peer-review process; and oversaw the dissemination of the guideline. Regional advisers from the WHO regions also participated in the meetings of the guideline development group.

Guideline development groups

The scoping of the guideline, the drafting of the key questions in PICO format and the prioritization of the outcomes were done by the guideline development group – nutrition actions 2013–2014 (Geneva, 18–21 February 2013).

The steering group identified candidates for the guideline development group – deworming from the roster of WHO advisers and experts, and issued a call for expressions of interest (October 2015), recommendations from other WHO departments and results from literature reviews were also considered. Twenty persons were informally asked whether they were interested in becoming part of the guideline development group – deworming. Of those 20 persons, 16 gave a positive response. Those interested were then asked to submit their latest curriculum vitae and filled in declaration-of-interest forms.

A final guideline development group was established with 16 members, to advise WHO in the areas of epidemiology and control of neglected tropical diseases, infectious diseases, health systems, social-impact evaluation, nutrition, infant and maternal health care, paediatrics, bioethics and systematic reviews. There were 10 women and six men, representing the six WHO regions.

The guideline development group examined the evidence used to inform the recommendation and appraised it using the *Grading of Recommendation Assessment, Development and Evaluation* (GRADE) evidence profiles *(120, 121)*. They interpreted the evidence, taking in consideration the Developing and Evaluating Communication Strategies to support Informed Decisions and Practice based on Evidence (DECIDE) framework *(7)*, an evidence-to-decision tool that includes intervention effects, values, resources, equity, acceptability and feasibility criteria, to guide the formulation of the recommendations *(122, 123)*. The members of the guideline development group and their areas of expertise are listed in Annex 5.

External resource groups

The external resource group for this guideline was composed of nine persons identified by the steering group whose role was to provide valuable insights to the guideline development group on issues relevant to the topic. Their expertise included bioethics, hygiene and sanitation, costing and cost analyses, economics, infectious disease epidemiology, reproductive health and HIV/AIDS.

The external resource group provided valuable insights during the open sessions of the group discussions. They were not present during the closed-session deliberations of the guideline development group. That is, they participated in general discussions on the evidence and factors to consider for the crafting of the recommendations but did not contribute to the decision on their wording, direction or strength. The members of the external resource group are listed in Annex 6.

Systematic review teams

The following groups were commissioned to conduct systematic reviews relevant to the key questions identified during the guideline development group scoping meeting:

- Cochrane Infectious Diseases Group (deworming in children)
- Cochrane Pregnancy and Childbirth Group (deworming during pregnancy)
- Cochrane HIV/AIDS Group (deworming in populations living with HIV)
- Campbell Collaboration (externalities and synergistic effects with cointerventions including quasi-experimental studies for deworming in children; and deworming in non-pregnant adolescent girls and adult women).

The systematic review teams provided comprehensive, objective syntheses of the evidence for each of the key questions to inform the recommendations. They also assessed the quality of the body of evidence and developed the GRADE evidence profiles. These systematic reviews were presented at the guideline development group meeting (Geneva, April 2016). The members of the systematic review teams are listed in Annex 6.

Management of conflicts of interests

The steering group, in compliance with the WHO *Guidelines for declaration of interests for WHO experts (124)* and in collaboration with the Office of Compliance and Risk Management and Ethics, managed the potential conflicts of interests. All potential guideline development group members were asked to fill in and sign the standard WHO declaration-of-interests and confidentiality undertaking forms. Updated curriculum vitae were also required from the prospective members of the guideline development group, as they engage in their individual capacity and not as institutional representatives.

The steering group reviewed the declarations-of-interest statements in conjunction with the curriculum vitae for all guideline development group members. Information from the internet or media were gathered, in order to identify any public statements made or positions held by the prospective guideline development group members and experts on the issue of deworming. These were assessed for intellectual bias that may be perceived to, or actually, affect impartiality. All concerns or potential issues were discussed with the Office of Compliance, Risk Management and Ethics. All potential conflicts of interest were managed on a case-by-case basis.

The following members of the guideline development group were assessed to have no perceived or real conflicts of interests on the topic. They were asked to verbally declare their research and programme

experiences and sources of funding: **Dr Huda Mustafa Al Hourani; Dr Beverley-Ann Biggs; Professor Anbrasi Edward; Professor Heba El Laithy; Ms Monica Muti; Professor Malden Nesheim; Ms Ifeoma Uzoamaka Onoja; Dr Tech Chuan Voo.**

The following members of the guideline development group were assessed to have no perceived or real conflicts of interests on the topic, but did not attend the meeting of the guideline development group and therefore made no verbal declaration of research and programme experiences or sources of funding: **Ms Claudia Lema Dodobara; Professor Serge Paul Eholié.**

The members listed next had declared interests that were further discussed with the Office of Compliance, Risk Management and Ethics. They were assessed to merit conditional participation that allowed their involvement in the meeting after publicly disclosing their interests at the start of the meeting to all meeting participants, and in the guideline document. Aside from their research and programme experiences and sources of funding, they were asked to specifically declare the following:

Professor Nilanthi de Silva declared that she has been Chair of the WHO Working Group on Access to Quality-Assured Essential Medicines for Neglected Tropical Diseases and has been a member of the WHO Strategic and Technical Advisory Group for Neglected Tropical Diseases since May 2009. She is also a member of the WHO Regional Office for South-East Asia Regional Programme Review Group for lymphatic filariasis and soil-transmitted helminths.

Dr Fiona Fleming declared that she works for an organization receiving research support from the Department for International Development of the Government of the United Kingdom of Great Britain and Northern Ireland to a value of £35 million. She disclosed that this funding was for the implementation, monitoring and evaluation of integrated control of schistosomiasis and intestinal helminth infections in Sub-Saharan Africa.

Professor Theresa Gyorkos declared that she received approximately US$ 1000 from Children Without Worms as a current member of the Soil-Transmitted Helminthiasis Advisory Committee. The advisory committee meets annually to provide independent expert scientific and technical advice on prevention and control of soil-transmitted helminth infections to members of the Soil-Transmitted Helminth Coalition, a group composed of about 50 partners from multiple sectors who "share a vision for reducing intestinal worm infections to create a world in which children are healthy and develop to their full potential". The coalition membership includes Johnson & Johnson (manufacturer of mebendazole) and GlaxoSmithKline (manufacturer of albendazole), who financially support Children Without Worms, as secretariat to the Soil-Transmitted Helminthiasis Advisory Committee. She also declared being the principal investigator of a US$ 1.5 million ongoing grant awarded by the Bill & Melinda Gates Foundation. This grant was awarded to her after an open competition. The research topic is on postpartum deworming.

Professor Celia Holland declared that she has conducted extensive research on the topic of discussion and that she also serves as a member of the WHO advisory panel on parasitic diseases.

Dr Narcis Kabaterine declared that he has served as a consultant to Merck KGaA (manufacturer of praziquantel) for work related to schistosomiasis. This work is not related to soil-transmitted helminths but to another condition, schistosomiasis, which is caused by a different parasite and treated with different medicines.

Professor Harshpal Singh Sachdev declared that he had published a systematic review in the *British Medical Journal* in 2007 on the effect of deworming on haemoglobin, and two commentaries on the subject in 2015 (in the *Lancet* and the *Internal Journal of Epidemiology*), in which he stressed the importance of evidence.

Names and brief biographies of the guideline development group, along with a description of the objectives of the meeting, were published on the WHO website, for public notice and comment. No additional information on any interests or biases relating to the individuals being considered for membership of the guideline development group were brought to light from the public notice.

Identification of priority questions and outcomes

An initial set of questions to be addressed in the guideline was the starting point for formulating the recommendation. The questions were drafted by technical staff at the Evidence and Programme Guidance unit of the Department of Nutrition for Health and Development, based on the policy and programme guidance needs of Member States and their partners. The questions were discussed and reviewed by the steering group.

A meeting of the guideline development group – nutrition actions 2013–2014 (Geneva, 18–21 February 2013) was held to finalize the scope of the questions and to rank the outcomes and populations of interest for the recommendation on preventive chemotherapy to control soil-transmitted helminth infections in at-risk groups. The guideline development group discussed the relevance of the questions and modified them as needed. The group scored the relative importance of each outcome from 1 to 9 (where 7–9 indicated that the outcome was critical for a decision, 4–6 indicated that it was important and 1–3 indicated that it was not important). The final key questions on this intervention, along with the outcomes that were identified as critical for decision-making, are listed in PICO format in Annex 1.

Evidence identification and retrieval

Previous Cochrane reviews assessing the effect of using deworming medicines on nutritional outcomes in children were done in 2000 *(125)*, 2007 *(126)* and 2012 *(127)*. New trials since the publication of the last systematic review included a large trial among children published in 2013 *(128)* with over one million study participants. A previous trial from Kenya was also replicated and published recently [2015] *(129)*. In light of these important new trials, an update of the systematic reviews was contracted with the Cochrane Infectious Diseases Group, to systematically review the evidence for the critical health outcomes of deworming for soil-transmitted intestinal helminth infections in children.

A previous systematic review of the impact of deworming on the prevalence of anaemia among adult women included both pregnant and non-pregnant women *(130)*. Thus, two new systematic reviews, one focusing on pregnant women and another on non-pregnant adolescent girls and adult women, were commissioned from the Cochrane Pregnancy and Childbirth Group and the Campbell Collaboration, respectively.

A previous Cochrane systematic review of deworming treatment in persons coinfected with HIV and helminth infections was published in 2009 *(131)*. This earlier systematic review assessed the impact of treating helminth infections on the progression of HIV among people living with HIV/AIDS. An update of this systematic review was contracted from the Cochrane HIV/AIDS Group, the same group that published the earlier review, on evidence of the effect of preventive chemotherapy in children and adult non-pregnant women living with HIV on health outcomes and adverse events.

In order to assess the synergistic effects of co-interventions (such as micronutrient supplementation or hygiene interventions) and potential confounding factors or externalities (such as the prevalence of soil-transmitted infections or the baseline nutritional status of children), an additional systematic review was commissioned from the Campbell Collaboration, which included quasi-experimental and non-randomized studies.

Quality assessment and grading of evidence

Systematic reviews *(84, 85, 102, 107, 112)* based on the PICO questions were used to summarize and appraise the evidence. These reviews followed the procedures of the *Cochrane handbook for systematic reviews of interventions (132)*. Each study included in the systematic reviews was assessed for risk of bias. This was recorded and contributed towards the assessment of the overall quality of the evidence. During the discussion and deliberations, the steering group and the guideline development group carefully reviewed the quality, scope and study inclusion criteria for the systematic reviews. The relative weight given to the trials and non-randomized studies was taken into account when evaluating the quality assessment for each study. When possible, the findings were synthesized with a pooled estimate of effect. The results of the systematic reviews were presented to the guideline development group, along with an assessment of the confidence in the estimates of effect for the critical outcomes.

Evidence profiles were prepared according to the GRADE approach, to assess the overall quality of the evidence *(120, 121)*. The quality of evidence for each outcome was rated as "high", "moderate", "low", or "very low", based on a set of criteria including risk of bias, inconsistency, imprecision, indirectness and publication bias.

Formulation of recommendations

The draft recommendations were discussed at a meeting of the steering group and in consultation with the guideline development group (Geneva, 13–15 April 2016).

Three options for types of recommendations were agreed, namely:

- strong recommendation
- conditional recommendation (recommended only in specific contexts)
- not recommended.

The systematic review and the GRADE evidence profiles for each of the critical outcomes were used to draft the recommendations. An evidence-to-decision framework (based on the DECIDE framework was used to lead the discussion and decision-making *(122, 123)*.

The domains listed next were prepared by the steering group and discussed during the guideline development group meeting for each of the key PICO questions.

Quality of evidence

The overall degree of confidence in the estimates of effect as presented in the GRADE profile was considered in the drafting of the recommendations. The higher the quality of evidence across critical outcomes that is relevant to decision-making, the higher the likelihood is of a clear, positive recommendation. A conditional recommendation is likely to be warranted when the overall quality is rated "low" or "very low".

Balance of benefits and harms

The guideline development group evaluated the balance of desirable and undesirable consequences, including the magnitude of the effects and relative importance of these consequences. Where benefits clearly outweigh harms or vice versa, the greater the likelihood is of a recommendation in favour of or against the intervention, respectively. Uncertainty about the net benefits or harms often leads to a conditional recommendation.

Values and preferences

The relative importance of the outcome to the individuals or populations directly affected by the recommendation describes the values and preferences. The steering group performed a review of qualitative information on how end-users (children, adolescent girls, women of reproductive age and pregnant women) perceived soil-transmitted helminths, deworming and their effects. These were presented during the guideline development group meeting. When there is uncertainty or wide variability in the values and preferences of the target beneficiaries, a conditional recommendation may be warranted.

Acceptability

A review of qualitative information on how health-care workers and service providers perceive soil-transmitted helminths, preventive chemotherapy and their effects for each of the at-risk groups was done and presented during the guideline development group meeting. The higher the acceptability of the intervention among stakeholders, the more likely it is that an intervention will be clearly recommended. When it was deemed necessary to recommend an intervention that is associated with low acceptability, strategies to address concerns about acceptability during implementation were discussed.

Resource use

This relates to evaluation of how resource intensive and costly the intervention is to service users and health systems in different settings. A recommendation in favour of or against the intervention is likely where the resource implications are clearly advantageous or disadvantageous, whereas a conditional recommendation may be justified if the resource implications are uncertain.

Equity

An intervention is likely to be recommended if it will reduce health inequities among different groups of women and their families.

Feasibility

The steering group presented instances in which deworming was implemented in the at-risk groups in different settings, to highlight the feasibility of implementation and whether barriers exist. Where there is greater feasibility, the more likely it is that the intervention will be recommended.

Based on the discussions during the meeting, each recommendation was supported by a rationale, implementation considerations and research priorities.

Decision-making during the guideline development group meeting

The chairpersons, Dr Biggs and Professor Nesheim, were nominated at the opening of the consultation and the nominations were approved by the guideline development group.

The procedures for decision-making were established at the beginning of the meetings, including a minimal set of rules for agreement and documentation of decision-making. At least two-thirds of the guideline development group were present for an initial discussion of the evidence, and proposed recommendation and remarks. By secret ballot, each member of the guideline development group noted the direction and strength of each of the recommendations, using an online form specifically designed for this purpose. Abstentions were not allowed.

Once voting was complete, subsequent deliberations among the members of the guideline development group could take place. If there was no unanimous consensus (primary decision rule), more time was given for deliberations and a second round of online voting took place. If no unanimous agreement was reached, a two-thirds vote of the guideline development group was required for approval of the proposed recommendation (secondary decision rule). The results from voting forms will be kept on file by WHO for up to 5 years.

Document preparation and peer review

The responsible technical officer wrote the first draft of the guideline, with comments from the steering group. Technical editing and proofreading were done by a contracted party.

The final draft guideline was peer-reviewed by content experts, to provided technical feedback; identify errors of fact; ensure that there were no important omissions, contradictions or inconsistencies with scientific evidence or programmatic feasibility; and assist with clarifying the language, especially in relation to implementation, adaptation and contextual issues. The independent peer-reviewers were selected by the steering group. Eight potential peer-reviewers were approached after assessment of the declarations of interests, and five agreed. The list of peer-reviewers appears in Annex 8.

The steering group reviewed all comments and revised the document, in order to ensure clarity of the recommendation while maintaining consistency with the original meaning.

DISSEMINATION AND PLANS FOR UPDATING

Dissemination

The current guideline will be posted on the WHO website, including the WHO Nutrition website *(8)*, the WHO Neglected Tropical Diseases website *(9)* and the WHO e-Library of Evidence for Nutrition Actions (eLENA) *(10)*. In addition, it will be disseminated through a broad network of international partners, including WHO country and regional offices, ministries of health, WHO collaborating centres, universities, other United Nations agencies and nongovernmental organizations.

Plans for updating the guideline

The WHO steering group will continue to follow research developments in the area of preventive chemotherapy in at-risk groups, particularly for questions in which the quality of evidence was found to be low or very low. If the guideline merits updating, or if there are concerns about its validity, the Department of Control of Neglected Tropical Diseases will coordinate the guideline update, following the formal procedures of the *WHO handbook for guideline development (119)*.

As the guideline nears its 10-year review period, the Department of Control of Neglected Tropical Diseases and the Department of Nutrition for Health and Development at WHO headquarters (Geneva, Switzerland) along with its internal partners, will be responsible for conducting a search for new evidence.

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ANNEX 1. QUESTION IN POPULATION, INTERVENTION, CONTROL, OUTCOMES (PICO) FORMAT

A. Effects and safety of preventive chemotherapy in young children, preschool and school-age children

Should preventive chemotherapy (deworming medicines) be given for the control of soil-transmitted helminth infections, compared to not giving preventive chemotherapy, to all yound children 12–23 months of age, preschool 24–59 months of age and school-age children[1] living in areas that are endemic for soil-transmitted helminth infections, to improve nutrition and health? If so, at what dose and frequency?

Population:	**Young children 12–23 months of age, preschool children (4–59 months of age) and school-age children[1]** Subgroups • By baseline prevalence of any soil-transmitted helminth in the trial: < 20%, 20–49%, ≥ 50%, unknown/not reported • By anaemia prevalence in the study: anaemia, no anaemia, mixed/not reported • With screening: yes versus no • With concomitant HIV infection
Intervention:	**Deworming treatment (albendazole, mebendazole)** Subgroups: • By frequency: annual, biannual • By medicine: albendazole, mebendazole • By duration: 0–35 months, 36–72 months, ≥ 73 months • By concomitant iron supplementation: yes, no, unknown/not reported
Control:	**No intervention or placebo**
Outcomes:	• Worm burden (egg count per gram of faeces) • Anaemia (defined as haemoglobin concentration < 110 g/L for children aged 24–59 months and < 115 g/L for children aged 5–12 years, adjusted by altitude where appropriate); severe anaemia (defined as haemoglobin concentration < 70 g/L, adjusted by altitude where appropriate) • Iron deficiency (as defined by using ferritin concentrations < 15 µg/L) • Diarrhoea (three liquid stools or more per day) • Growth: Weight (weight-for-age z-scores) Wasting (weight-for-height z-scores) Stunting (length/height-for-age z-scores) Body-mass-index-for-age • Cognitive development and school performance (as defined by trialists)

[1] We defined school-age children as those between 5 and 12 years of age. Although many children unfortunately do not attend schools, these ages are compulsory school years in most settings, providing with it an entry point to address the nutritional needs of this age group. In some settings the upper range may be 14 years of age.

B. Effects and safety of preventive chemotherapy in non-pregnant adolescent girls and women of reproductive age

Should preventive chemotherapy (deworming medicines) be given for the control of soil-transmitted helminth infections, compared to not giving preventive chemotherapy, to all non-pregnant adolescent girls and adult women (approximately 15–49 years of age) living in areas that are endemic for soil-transmitted helminth infections, to improve nutrition and health? If so, at what dose and frequency?

Population:	**Non-pregnant menstruating adolescents (10–19 years of age) and women of reproductive age (15–49 years)** Subgroups • By baseline prevalence of any soil-transmitted helminth in the trial: <20%, 20–49%, ≥50%, unknown/not reported • By anaemia prevalence in the study: anaemia, no anaemia, mixed/not reported • With screening: yes versus no • With concomitant HIV infection
Intervention:	**Deworming treatment (albendazole, mebendazole)** Subgroups: • By frequency: annual, biannual • By medicine: albendazole alone versus mebendazole alone versus combined treatment • By duration: 0–35 months, 36–72 months, ≥ 73 months • By concomitant iron supplementation: yes, no, unknown/not reported
Control:	**No intervention or placebo**
Outcomes:	• Worm burden (egg count per gram of faeces) • Anaemia (defined as haemoglobin concentration < 120 g/L for non-pregnant women, adjusted by altitude where appropriate); severe anaemia (defined as haemoglobin concentration < 70 g/L, adjusted by altitude where appropriate) • Iron deficiency (as defined by using ferritin concentrations < 15 µg/L) • Diarrhoea (three liquid stools or more per day) • Reinfection • All-cause morbidity (number of patients with at least one episode of any disease during the study period)

C. Effects and safety of preventive chemotherapy in pregnant women

Should preventive chemotherapy (deworming medicines) be given for the control of soil-transmitted helminth infections, compared to not giving preventive chemotherapy, to all pregnant women living in areas that are endemic for soil-transmitted helminth infections, for improving nutrition and health outcomes? If so, at what dose and frequency?

Population:	**Pregnant women** Subgroups • By baseline prevalence of any soil-transmitted helminth in the trial: < 20%, 20–49%, ≥ 50%, unknown/not reported • By anaemia prevalence in the study: anaemia, no anaemia, mixed/not reported • With screening: yes versus no • With concomitant HIV infection
Intervention:	**Deworming treatment (albendazole, mebendazole)** Subgroups: • By frequency: annual, biannual • By medicine: albendazole alone versus mebendazole alone versus combined treatment • By delivery system: clinic versus health days/weeks • By concomitant iron supplementation: yes, no, unknown/not reported
Control:	**No intervention or placebo**
Outcomes:	• Worm burden (egg count per gram of faeces) • Maternal anaemia at or near term (defined as haemoglobin concentration < 110 g/L at 34 weeks' gestation or more); moderate anaemia during the postpartum period (defined as haemoglobin concentration of 80–109 g/L); severe anaemia at any time during the second or third trimesters (defined as haemoglobin concentration < 70 g/L) • Maternal iron deficiency at or near term (as defined by trialists, based on any indicator of iron status at 34 weeks' gestation or more) • Reinfection • Maternal mortality (death while pregnant or within 42 days of termination of pregnancy) • Birthweight • Perinatal mortality (pregnancy losses of at least seven months' gestation and deaths to live births within the first seven days of life)

ANNEX 2. GRADE SUMMARY OF FINDINGS TABLES

A. Preventive chemotherapy in preschool and school-age children

Preventive chemotherapy in preschool and school-age children known to be infected with soil-transmitted helminths

Patient or population: preschool and school-age children known to be infected with soil-transmitted helminths
Setting: areas endemic for soil-transmitted helminths
Intervention: preventive chemotherapy (deworming medicines)
Comparison: placebo or no treatment

Outcomes	**Anticipated absolute effects*** (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)	Comments
	Without preventive chemotherapy	**With preventive chemotherapy**				
Haemoglobin (g/L) Follow-up: 9 weeks to 6 months	—	—	MD 1.0 g/dL (–6.5 to 8.6 g/L)	247 (2 studies)	⨁⊖⊖⊖ VERY LOW[1]	
Formal test on cognition	—	—	Not pooled	103 (2 studies)	⨁⊖⊖⊖ VERY LOW[2]	
Weight gain (kg) Follow-up: 1 to 6 months	—	—	MD 0.75 kg (0.24 to 1.26 kg)	627 (5 studies)	⨁⨁⊖⊖ LOW[3]	
Height gain (cm) Follow-up: 1 to 6 months	—	—	MD 0.25 cm (0.01 to 0.49 cm)	647 (5 studies)	⨁⨁⊖⊖ LOW[4]	
Body mass index (kg/m^2) Follow-up: 1 to 6 months	—	—	MD -0.20 kg/m^2 (–0.46 to 0.06 kg/m^2)	407 (1 study)	⨁⨁⊖⊖ LOW[5]	

Preventive chemotherapy (single dose) in all preschool and school-age children

Patient or population: all preschool and school-age children
Setting: areas endemic for soil-transmitted helminths
Intervention: preventive chemotherapy (deworming medicines)
Comparison: placebo or no treatment

Outcomes	**Anticipated absolute effects*** (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)	Comments
	Without preventive chemotherapy	**With preventive chemotherapy**				
Haemoglobin (g/L) Follow-up: 9 weeks to 6 months	—	—	MD 0.6 g/L (–0.5 to 1.7 g/L)	1005 (3 studies)	⨁⨁⨁⊖ MODERATE[6]	
Formal test on cognition	—	One trial reported that deworming had no effect, and the other that deworming reduces cognitive scores	Not pooled	1361 (2 studies)	⨁⨁⊖⊖ LOW[7]	
Weight gain (kg) Follow-up: 7 weeks to 1 year	—	—	MD -0.04 kg (–0.11 to 0.04 kg)	2719 (7 studies)	⨁⨁⨁⊖ MODERATE[8]	
Height gain (cm) Follow-up: 7 weeks to 1 year	—	—	MD –0.12 cm (–0.33 to 0.10 cm)	1974 (5 studies)	⨁⨁⨁⊖ MODERATE[9]	
Mortality (between the ages of 1–6 years)	27 per 1000	25 per 1000	RR 0.95 (0.89 to 1.92)	1005,135 (3 trials)	⨁⨁⊖⊖ LOW[10]	

Preventive chemotherapy (multiple doses) in all preschool and school-age children

Patient or population: all preschool and school-age children
Setting: areas endemic for soil-transmitted helminths
Intervention: preventive chemotherapy (deworming medicines)
Comparison: placebo or no treatment

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)	Comments
	Without preventive chemotherapy	**With preventive chemotherapy**				
Worm burden – *Ascaris* Assessed with: prevalence Follow-up: mean 12 months	403 per 1000	209 per 1000 (177 to 246)	RR 0.52 (0.44 to 0.61)	13 914 (22 studies)	⊕⊕⊖⊖ LOW[11]	
Worm burden – hookworm Assessed with: prevalence Follow-up: mean 12 months	481 per 1000	178 per 1000 (77 to 409)	RR 0.37 (0.16 to 0.85)	6214 (10 studies)	⊕⊕⊖⊖ LOW[12]	
Worm burden – *Trichuris* Assessed with: prevalence Follow-up: mean 12 months	591 per 1000	425 per 1000 (337 to 543)	RR 0.72 (0.57 to 0.92)	5053 (9 studies)	⊕⊕⊖⊖ LOW[13]	
Cognitive processing: short-term attention (converted to WISC IV working memory index, 100-point scale) Follow-up: one year	—	—	MD –0.23 points (–0.6 to 0.14 points)	4078 (3 studies)	⊕⊕⊕⊕ HIGH	
Weight gain (kg) Follow-up: one year	—	—	MD 0.09 kg (–0.04 to 0.20 kg)	35 430 (11 studies)	⊕⊕⊕⊖ MODERATE[14]	
Height gain (cm) Follow-up: one year	—	—	MD 0.07 cm (–0.10 to 0.24 cm)	6839 (9 studies)	⊕⊕⊕⊖ MODERATE[15]	
Proportion stunted Follow-up: measured at 1–2 years	411 per 1000	403 per 1000 (361 to 444)	RR 0.98 (0.88 to 1.08)	4286 (4 studies)	⊕⊕⊕⊕ HIGH	
Mortality Follow-up: 1–5 years	25 per 1000	24 per 1000 (22 to 26)	RR 0.95 (0.89 to 1.02)	Over 1 million (6 trials)	⊕⊕⊕⊕ HIGH	

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; RR: risk ratio; MD: mean difference.

GRADE Working Group grades of evidence

High quality: We are very confident that the true effect lies close to that of the estimate of the effect.

Moderate quality: 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.

Low quality: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

Very low quality: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[1] Downgraded for risk of bias (none of the trials adequately described allocation concealment), for inconsistency (high level of heterogeneity) and for indirectness (one of the trials showing large effects was from a highly endemic area with intense worm burden).

[2] Downgraded for serious risk of bias and for indirectness (two trials measured cognitive functioning but did not clearly report the changes in cognitive scores). Neither is easily generalized to other settings.

[3] Downgraded for risk of bias (none of the trials adequately described allocation concealment) and for inconsistency (high level of heterogeneity).

[4] Downgraded for risk of bias (none of the trials adequately described allocation concealment) and for inconsistency (high level of heterogeneity).

[5] Downgraded for risk of bias (none of the trials adequately described allocation concealment) and for inconsistency (high level of heterogeneity).

[6] Downgraded for risk of bias (none of the trials were classified as having low risk of bias).

[7] Downgraded for risk of bias (none of the trials were classified as having low risk of bias) and for indirectness (only two trials assessed this outcome and the results are not easily generalized to other settings).

[8] Downgraded for risk of bias (none of the trials were classified as having low risk of bias).

[9] Downgraded for risk of bias (none of the trials were classified as having low risk of bias).

[10] Downgraded for risk of bias (none of the trials described allocation concealment) and indirectness (the largest study was conducted in a low-prevalence area which may not be generalizable to other settings).

[11] Downgraded for risk of bias (major baseline imbalance and selective reporting of worm burden in some studies) and inconsistency (high level of heterogeneity).

[12] Downgraded for risk of bias (major baseline imbalance and selective reporting of worm burden in some studies) and inconsistency (high level of heterogeneity).

[13] Downgraded for risk of bias (major baseline imbalance and selective reporting of worm burden in some studies) and inconsistency (high level of heterogeneity).

[14] Downgraded for inconsistency (baseline imbalance and heterogeneity).

[15] Downgraded for inconsistency (high level of heterogeneity).

For details of studies included in the review, see references *(84, 85)*.

B. Preventive chemotherapy in non-pregnant adolescent girls and women of reproductive age

Patient or population: non-pregnant adolescent girls and women of reproductive age
Setting: areas endemic for soil-transmitted helminths
Intervention: preventive chemotherapy (deworming medicines)
Comparison: placebo or no treatment

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)	Comments
	Without preventive chemotherapy	**With preventive chemotherapy**				
Worm burden – *Ascaris* Follow-up: mean 6 months	327 per 1000	95 per 1000 (46 to 202)	RR 0.29 (0.14 to 0.62)	1498 (2 studies)	⊕⊕⊕⊖ MODERATE[1]	
Worm burden – hookworm Follow-up: mean 6 months	331 per 1000	106 per 1000 (60 to 195)	RR 0.32 (0.18 to 0.59)	1498 (2 studies)	⊕⊕⊕⊖ MODERATE[2]	
Worm burden – *Trichuris* Follow-up: mean 6 months	277 per 1000	213 per 1000 (180 to 252)	RR 0.77 (0.65 to 0.91)	1498 (2 studies)	⊕⊕⊕⊖ MODERATE[3]	
Anaemia (end haemoglobin level < 120 g/L) Follow-up: mean 6 months	398 per 1000	327 per 1000 (239 to 442)	RR 0.82 (0.60 to 1.11)	683 (3 studies)	⊕⊕⊖⊖ LOW[4]	
Severe anaemia (end haemoglobin level < 70 g/L) Follow-up: mean 6 months	–	–	RR 6.25 (0.34 to 115.15)	51 (1 study)	⊕⊖⊖⊖ VERY LOW[5]	
Iron-deficiency anaemia (ferritin levels < 12 µg/L) Follow-up: mean 6 months	464 per 1000	413 per 1000 (297 to 571)	RR 0.89 (0.64 to 1.23)	186 (1 study)	⊕⊕⊖⊖ LOW[6]	
All-cause morbidity – conjunctival xerosis Follow-up: mean 8 months	188 per 1000	188 per 1000 (45 to 793)	RR 1.00 (0.24 to 4.23)	32 (1 study)	⊕⊕⊖⊖ LOW[7]	

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; RR: risk ratio.

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate quality: 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.
Low quality: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low quality: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

1 Downgraded for risk of bias (blinding of participants and outcome assessors were not reported).
2 Downgraded for risk of bias (blinding of participants and outcome assessors were not reported).
3 Downgraded for risk of bias (blinding of participants and outcome assessors were not reported).
4 Downgraded for risk of bias (blinding of participants and outcome assessors were not reported) and for imprecision (confidence interval includes the null effect as well as appreciable benefit).
5 Downgraded for risk of bias (blinding of participants and outcome assessors were not reported) and for serious imprecision (small sample size and only one event).
6 Downgraded for risk of bias (blinding of participants and outcome assessors were not reported) and for imprecision (confidence interval includes the null effect as well as appreciable benefit).
7 Downgraded for risk of bias (randomization, allocation concealment and blinding of participants, personnel, outcome assessors were not reported) and imprecision (wide confidence intervals).

For details of studies included in the review, see reference *(102)*.

C. Preventive chemotherapy in pregnant women

Patient or population: pregnant women
Setting: areas endemic for soil-transmitted helminths
Intervention: preventive chemotherapy (deworming medicines)
Comparison: placebo or no treatment

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)	Comments
	Without preventive chemotherapy	**With preventive chemotherapy**				
Worm burden (all parasites)	60 per 1000	17 per 1000 (6 to 49)	RR 0.29 (0.10 to 0.81)	4788 (3 studies)	⊕⊕⊕⊖ MODERATE[1]	
Maternal anaemia in the third trimester (< 110 g/L)	341 per 1000	320 per 1000 (276 to 375)	RR 0.94 (0.81 to 1.10)	3266 (4 studies)	⊕⊕⊖⊖ LOW[2]	
Low birth weight	88 per 1000	88 per 1000 (69 to 112)	RR 1.00 (0.79 to 1.27)	3255 (3 studies)	⊕⊕⊕⊖ MODERATE[3]	
Perinatal mortality	27 per 1000	30 per 1000 (19 to 46)	RR 1.09 (0.71 to 1.67)	3385 (2 studies)	⊕⊕⊕⊖ MODERATE[4]	

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).
CI: confidence interval; RR: risk ratio.

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate quality: 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.
Low quality: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low quality: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[1] Downgraded for inconsistency (high level of heterogeneity).

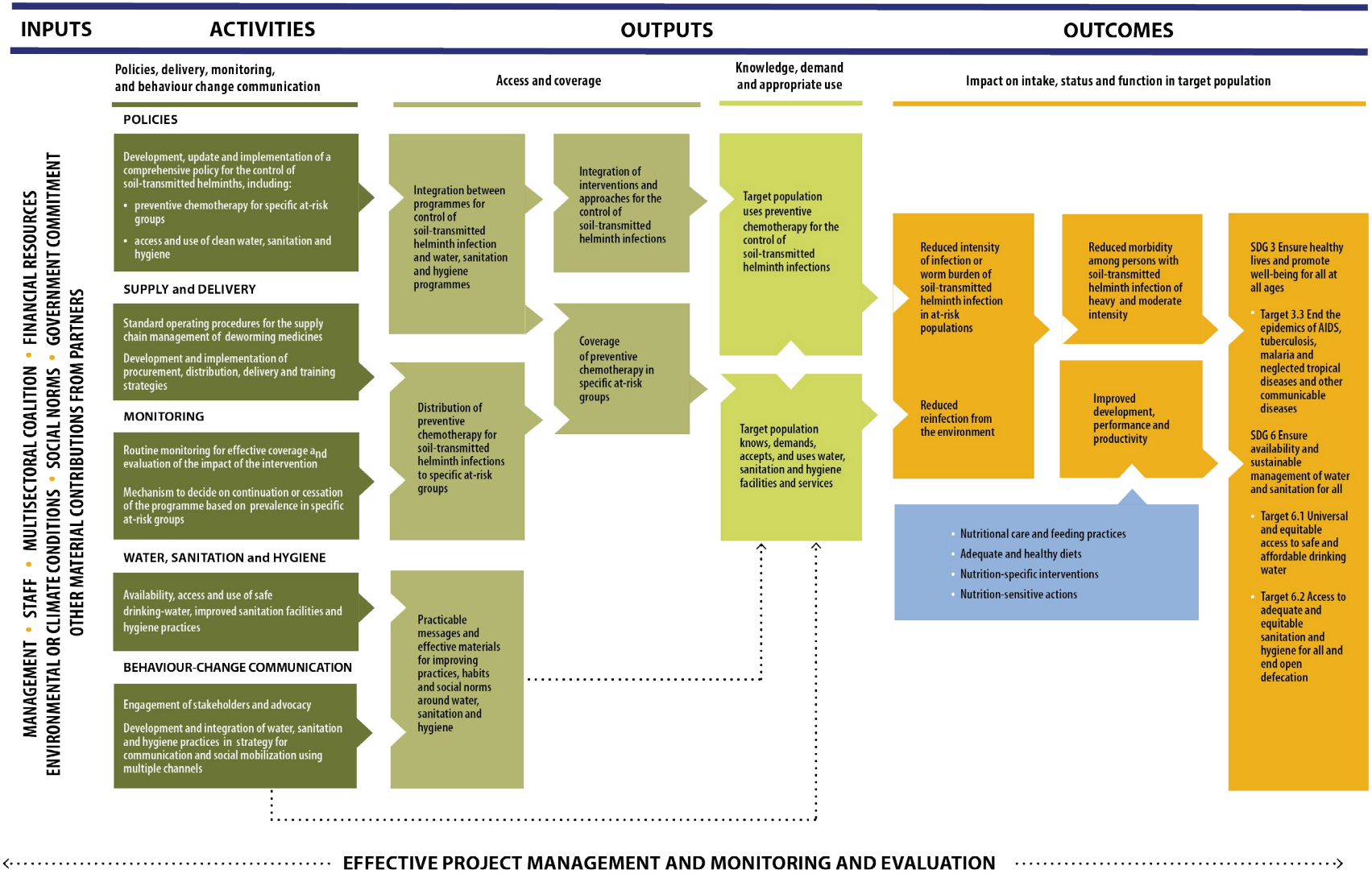
[2] Downgraded for risk of bias (high rate of attrition) and for inconsistency (high level or heterogeneity).

[3] Downgraded for risk of bias (unclear selection bias).

[4] Downgraded for indirectness (neither study was powered to capture perinatal mortality).

For details of studies included in the review, see reference *(107)*.

ANNEX 3. LOGIC MODEL FOR THE CONTROL OF SOIL-TRANSMITTED HELMINTH INFECTIONS



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ANNEX 5. WHO GUIDELINE DEVELOPMENT GROUPS

(Note: the areas of expertise of each guideline group member are given in italics)

Guideline development group – nutrition actions 2013–2014

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Micronutrients supplementation, clinical infectious diseases

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University of Kelaniya
Sri Lanka

Medical parasitology, neglected tropical diseases

Ms Claudia Lema Dodobara**

Executive Director
Salud Sin Límites Perú
Peru

Medical anthropology, qualitative research on health

Professor Anbrasi Edward

Associate Scientist
Center for Refugee and Disaster Studies, Department of International Health
Johns Hopkins Bloomberg School of Public Health
United States of America

Health systems and community-based research

Professor Serge Paul Eholié**

Professor of Tropical and Infectious Diseases
Treichville University Teaching Hospital
Côte d'Ivoire

HIV, infectious diseases, noncommunicable diseases

Professor Heba El Laithy

Professor of Statistics
Faculty of Economics and Political Science
Cairo University
Egypt

Social impact evaluation, micro-data analysis

Dr Fiona Fleming

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School of Public Health
Imperial College London
United Kingdom of Great Britain and Northern Ireland

Control of infectious diseases, neglected tropical diseases

Professor Theresa Gyorkos

Professor
Department of Epidemiology, Biostatistics and Occupational Health
McGill University
Canada

Global health, parasite disease epidemiology, neglected tropical diseases

Professor Celia Holland

Professor of Parasitology
School of Natural Sciences
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United Kingdom of Great Britain and Northern Ireland

Epidemiology and control of soil-transmitted helminths

Dr Narcis Kabatereine

Head of Vector Control Division
Ministry of Health
Uganda

Control of neglected tropical diseases

Ms Monica Muti

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Nutrition, national implementation programmes

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Nutrition, nutritional consequences of neglected tropical diseases

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Meeting of the WHO guideline development group – deworming

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ANNEX 7. SYSTEMATIC REVIEW TEAMS

Systematic review 1

Deworming drugs for soil-transmitted intestinal worms in children: effects on nutritional indicators, haemoglobin, and school performance *(84)*

David C Taylor-Robinson[1], Nicola Maayan, Karla Soares-Weiser, Sarah Donegan, Paul A Garner

[1] Department of Public Health and Policy, University of Liverpool, Liverpool, Merseyside, United Kingdom of Great Britain and Northern Ireland

Systematic review 2

Deworming and adjuvant interventions for improving the developmental health and well-being of children in low- and middle-income countries: a systematic review and meta-analysis *(85)*

Vivian Andrea Welch[1], Shally Awasthi, Chisa Cumberbatch, Robert Fletcher, Jessie McGowan, Katelynn Merritt, Shari Krishnaratne, Salim Sohani, Shalini Suresh, Peter Tugwell, George A Wells

[1] Director, Methods Centre, Bruyere Research Institute; Assistant Professor, School of Epidemiology, Public Health and Preventive Medicine, University of Ottawa, Canada

Systematic review 3

Deworming for non-pregnant adolescent and adult women: a systematic review *(102)*

Vivian A Welch[1], Shalini Suresh, Elizabeth Ghogomu, Jessie McGowan

[1] Director, Methods Centre, Bruyere Research Institute; Assistant Professor, School of Epidemiology, Public Health and Preventive Medicine, University of Ottawa, Canada

Note: We report in this document a summary of the results from a recent systematic review (March 2016). The systematic review has been submitted for publication and is undergoing peer-review. A pre-publication summary is available from the Department of Nutrition for Health and Development, World Health Organization, Geneva, Switzerland (nutrition@who.int).

Systematic review 4

Effect of administration of antihelminthics for soil-transmitted helminths during pregnancy *(107)*

Rehana A Salam, Batool A Haider, Quratulain Humayun, Zulfiqar A Bhutta[1]

[1] Center for Global Child Health, Hospital for Sick Children, Toronto, Canada

Systematic review 5

Antihelminthics in helminth-endemic areas: effects on HIV disease progression *(112)*

Arianna Rubin Means[1], Paul Burns, David Sinclair, Judd L Walson

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Note: The names and affiliations of peer-reviewers are provided here as an acknowledgement and by no means indicate their endorsement of the recommendations in this guideline. The acknowledgement of the peer-reviewers does not necessarily represent the views, decisions or policies of the institutions with which they are affiliated.

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