WHO GUIDELINE
on control and elimination of human schistosomiasis

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Abbreviations and acronyms

GDG	guideline development group
GRADE	Grading of Recommendations, Assessment, Development and Evaluation
LAMP	loop-mediated isothermal amplification
MDA	mass drug administration
NTD	neglected tropical disease
PCR	polymerase chain reaction
PICO	population, intervention, comparator and outcome
pre-SAC	preschool-aged children
SAC	school-aged children
SCORE	Schistosomiasis Consortium for Operational Research and Evaluation
WASH	water, sanitation and hygiene
WHO	World Health Organization

Glossary

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

control

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

elimination as a public health problem

A term related to both infection and disease, defined by achievement of measurable public health targets set by WHO in relation to a specific disease. When reached, continued actions are required to maintain the targets and/or to advance to the interruption of transmission. The process of documenting achievement of this goal is called **validation**.

haematuria

Presence of red blood cells in the urine. In **macrohaematuria**, blood is present in sufficient quantity to be seen by visual inspection of the urine sample (the urine is red or brown in colour). In **microhaematuria**, blood is present in insufficient quantity to be visible to the naked eye but is detectable using a reagent strip.

high-prevalence settings

Settings with prevalence of schistosomiasis among school-aged children ≥ 50% by parasitological methods (intestinal and urogenital schistosomiasis) or ≥ 75% by point-of-care urine assay for detection of circulating cathodic antigen in areas endemic for *Schistosoma mansoni*.

intensity of infection

The number of schistosomes infecting an individual (also known as worm burden). Intensity of infection is measured indirectly by counting the number of schistosome eggs excreted in faeces (expressed as eggs per gram) and in urine (expressed as the number of schistosome eggs per 10 mL). WHO classifies schistosome infections as of light, moderate or heavy intensity, according to the number of helminth eggs excreted in human faeces or urine.

interruption of transmission (elimination of schistosome transmission)

Achievement of no new human cases of infection, or zero incident cases of infection caused by a specific parasite species in a defined geographical area, with minimal risk of reintroduction, as a result of deliberate efforts; continued action to prevent re-establishment of transmission may be required. Documentation of elimination of schistosome transmission is called verification.

low prevalence settings

Settings with prevalence of schistosomiasis among school-aged children < 10% by parasitological methods (intestinal and urogenital schistosomiasis) or < 30% by point-of-care circulating cathodic antigen in areas endemic for *Schistosoma mansoni*. Many people living in these areas will be asymptomatic (infected but with no symptoms) or have subclinical infection (infection with few or minor symptoms).

mass drug administration

Distribution of medicines to the entire population of a given administrative setting (for instance, state, region, province, district, subdistrict or village), irrespective of the presence of symptoms or infection; however, exclusion criteria may apply.

moderate prevalence settings

Settings with prevalence of schistosomiasis among school-aged children ≥ 10% and < 50% by parasitological methods (intestinal and urogenital schistosomiasis) or ≥ 30% and < 75% by point-of-care circulating cathodic antigen test in areas endemic for *Schistosoma mansoni*.

morbidity

Impact of schistosomiasis on the health and well-being of infected individuals. Evidence of morbidity due to schistosome infection may be overt (such as the presence of blood in the urine, anaemia and lesions caused by schistosome eggs in the genital tract, especially in women (female genital schistosomiasis); micronutrient deficiencies, chronic pain or fatigue) or subtle (such as intestinal damage and pathological changes in the liver, eventually leading to portal hypertension; pathological changes in the kidney and bladder, potentially leading to cancer formation, stunted physical growth and/or impaired cognitive development, impeded school or work performance or increased susceptibility to other diseases).

persistent hot spot

Communities with prevalence of *Schistosoma* spp. infection ≥ 10% that demonstrate lack of an appropriate response to two annual rounds of preventive chemotherapy, despite adequate treatment coverage (≥ 75%). The lack of an appropriate response should be (provisionally) defined as a reduction in prevalence of less than one third relative to the baseline prevalence survey and a repeat prevalence survey completed after two annual rounds of preventive chemotherapy. The intervening period should include a minimum of two rounds of mass drug administration to all at-risk groups at adequate treatment coverage (≥ 75%). The relative reduction in prevalence can be estimated as follows: [(prevalence at baseline - prevalence at year 3)/(prevalence at baseline)]. The science around this threshold is still evolving; this definition is marked provisional for that reason but is nevertheless provided to encourage standardization of reporting.

preschool-aged children

All children between the ages of 24 to 59 months who usually are not yet attending primary school.

prevalence of infection

The percentage of individuals of all ages in a population targeted for treatment who are infected with any species of *Schistosoma*.

preventive chemotherapy

Large-scale use of medicines, either alone or in combination, in public health interventions. Mass drug administration is one form of preventive chemotherapy; other forms could be limited to specific population groups such as school-aged children and women of childbearing age. In this document, preventive chemotherapy is used to indicate large-scale use of anthelmintic medicines in specific population groups, as opposed to mass drug administration to the entire population.

school-aged children

All children between the ages of 5 and 15 years (usually), regardless of whether they are attending school. The exact ages of school enrolment can vary slightly between different countries. In some countries, a primary school's enrolment may include individuals older than 15 years of age.

treatment coverage

The proportion of individuals in a defined population who took the treatment. The defined population can be: (i) a target group for treatment, for instance, school-aged children; (ii) the entire population of a geographical region, administrative area or community in which specific diseases are highly endemic; or (iii) the entire population of a country. These three types of coverage are referred to as (i) programme coverage, (ii) geographical coverage and (iii) national coverage, respectively. Adequate treatment coverage for schistosomiasis is defined by WHO as treating ≥ 75% of the target population.

Executive summary

Human schistosomiasis is a chronic parasitic disease caused by infection with blood flukes (trematode worms) of the genus *Schistosoma*. The disease is a public health problem in tropical and subtropical regions of Africa, Asia, the Caribbean and South America. Approximately 779 million people are at risk of acquiring the infection *(1)*. Some 236.6 million people required preventive chemotherapy in 2019 *(2)*. Schistosomiasis is a neglected tropical disease (NTD), a diverse group of diseases and conditions that affect predominantly low-income populations worldwide.

In response to resolutions adopted by the World Health Assembly and in line with the Organization's 13th General Programme of Work 2019–2023, WHO supports Member States to expand access to prevention, diagnosis, treatment and care interventions for NTDs as a contribution towards the achievement of universal health coverage by 2030.

In 2020, WHO published a new road map to guide action against NTDs during the decade 2021–2030. The road map targets the elimination of schistosomiasis as a public health problem by 2030 and the interruption of schistosome transmission in humans in selected countries by 2030. Attainment of these targets will contribute to progress towards Sustainable Development Goal 3: "ensure healthy lives and promote well-being for all at all ages". The WHO strategy to control and eliminate human schistosomiasis includes preventive chemotherapy of at-risk groups, access to improved drinking-water, and improved sanitation, hygiene education, environmental management and snail control.

This WHO guideline[1] was developed in accordance with the WHO handbook for guideline development (2014). A guideline steering group was established to formulate the key questions to be addressed in the guideline using the population, intervention, comparator and outcome (PICO) format and to prioritize outcomes. The PICO questions were reviewed by a guideline development group (GDG) and then used to systematically retrieve, appraise and synthesize the evidence, formulate the recommendations, and plan for dissemination and implementation of the guideline. All policy recommendations were formulated through consensus based on the judgements of the GDG, informed by the evidence and by the expertise and experience of its members; on the one occasion when consensus was not reached, members adopted a voting process. The external review group commented on the final draft of the guideline but could not alter the recommendations made by the GDG.

[1]A WHO guideline is any document developed by WHO containing recommendations for clinical practice or public health policy. A recommendation tells the intended end-user of the guideline what he or she can or should do in specific situations to achieve the best health outcomes possible, individually or collectively. It offers a choice among different interventions or measures having an anticipated positive impact on health and implications for the use of resources. Recommendations help the user of the guideline to make informed decisions on whether to undertake specific interventions, clinical tests or public health measures, and on where and when to do so. Recommendations also help the user to select and prioritize across a range of potential interventions.

Goal and objectives of the guideline

The goal of this guideline is to provide evidence-based recommendations to countries in their efforts to accomplish schistosomiasis morbidity control and elimination as a public health problem, and to move towards interruption of transmission. The recommendations contained herein will help countries to implement national schistosomiasis control and elimination programmes and support efforts to verify the interruption of transmission.

The specific objectives are to provide guidance on:

- prevalence thresholds, target age groups and frequency of preventive chemotherapy for schistosomiasis;
- establishment of water, sanitation and hygiene (WASH) and snail control activities to support control and elimination of schistosomiasis;
- use of diagnostic tests in humans in low transmission areas and for moving to, and evaluating the interruption of transmission of schistosomiasis;
- tools for the assessment of *Schistosoma* spp. infection in snail hosts; and
- diagnostic tests for the assessment of schistosomiasis infection in animal reservoirs of infection

The current guideline updates and supersedes previous schistosomiasis-related recommendations contained in the following WHO publications:

- Schistosomiasis: progress report 2001–2011 and strategic plan 2012–2020. Geneva: World Health Organization; 2013
- Preventive chemotherapy in human helminthiasis: coordinated use of anthelminthic drugs in control interventions: a manual for health professionals and programme managers. Geneva: World Health Organization; 2006
- Prevention and control of schistosomiasis and soil-transmitted helminthiasis: report of a WHO Expert Committee. Geneva: World Health Organization; 2002 (WHO Technical Report Series, No. 912)
- The control of schistosomiasis: second report of the WHO expert committee. Geneva: World Health Organization, 1993 (WHO Technical Report Series, No. 830)
- Elimination of schistosomiasis from low-transmission areas: report of a WHO informal consultation, Brazil. Geneva: World Health Organization; 2008
- Helminth control in school-age children: a guide for managers of control programmes, second edition. Geneva: World Health Organization; 2011

Rationale for developing the guideline

This guideline is warranted for the following reasons.

1. Previous implementation guidelines for schistosomiasis were based mainly on expert opinion.
2. There was no previously published guidance on the evaluation of the interruption of schistosomiasis transmission.
3. Resolution WHA65.21 on elimination of schistosomiasis, adopted by the Sixty-fifth World Health Assembly in 2012, called on WHO to prepare guidance for Member States in order to determine when to embark on elimination programmes where appropriate and to provide tools to document progress.
4. Schistosomiasis remains a significant public health problem in many countries. Preventive chemotherapy has been demonstrated to deliver benefits to affected communities but is still not readily accessible by all. By providing a revised guideline, the intention is to empower and support health ministries and local communities to extend the use of preventive chemotherapy in order to support wider target populations in their efforts to control and eliminate this disease.
5. From a patient and a public health perspective, there is no acceptable level of schistosomiasis morbidity. The approaches recommended in this revised guideline are designed to eliminate morbidity from schistosomiasis, but this will require sustained effort.
6. Recent impact assessment surveys *(3–8)* have shown that the prevalence of schistosomiasis infection determined using parasitological techniques has dropped to low levels in some countries. New guidance is therefore required for countries that need to move from morbidity control towards elimination as a public health problem *(9–13)*.
7. Sensitive diagnostic tools have been developed for use in humans, animals and snail intermediate hosts *(14–18)*. Guidance is needed for their use, in particular the thresholds for their utilization in low transmission areas.

Target audience

The key audiences for this guideline are policy-makers, national NTD control programmes and national NTD task forces in health ministries, regional programme review groups and implementation partners.

This guideline is intended as a reference document for all stakeholders, including WHO, pharmaceutical manufacturers of preventive chemotherapy medicines, donor organizations, nongovernmental organizations and academic institutions.

The following groups will be empowered and impacted by the guideline:

- residents of communities in which schistosomiasis is endemic;
- visitors and tourists to schistosomiasis-endemic areas;
- distributors of medicines during preventive chemotherapy;

- district or other administrative level focal points for preventive chemotherapy in the health ministry;
- national NTD programme managers and NTD coordinators in endemic countries;
- national pharmacovigilance agencies in endemic countries;
- national medicine regulatory authorities;
- ministries of education and the environment;
- manufacturers of preventive chemotherapy medicines; and
- donor organizations that support schistosomiasis control and elimination programmes.

Limitations

This guideline is based on the best evidence available to the GDG in 2021. For many questions that the guideline set out to answer, the evidence base was limited. Evidence is in any event subject to change. The guideline will therefore be updated accordingly as new evidence emerges.

Summary of recommendations

Recommendation 1

In endemic communities with prevalence of *Schistosoma* spp. infection ≥ 10%, WHO recommends annual preventive chemotherapy with a single dose of praziquantel at ≥ 75% treatment coverage in all age groups from 2 years old, including adults, pregnant women after the first trimester and lactating women, to control schistosomiasis morbidity and advance towards eliminating the disease as a public health problem.

Strong recommendation

Certainty of evidence: moderate

Implementation considerations

- Prevalence of infection is defined as the percentage of individuals of all ages in a population targeted for treatment who are infected with any species of *Schistosoma*. The strategy of preventive chemotherapy does not differ by *Schistosoma* species.
- The prevalence threshold of 10% is based on estimation by parasitological microscopy, using duplicate Kato–Katz smears from one stool sample for intestinal schistosomiasis, predominantly *S. mansoni* and *S. japonicum*, and single 10 mL urine filtration for urogenital schistosomiasis due to *S. haematobium*.
- The point-of-care circulating cathodic antigen test can be used to determine prevalence of *S. mansoni*; 30% prevalence by this test is to be considered equivalent to 10% prevalence by the Kato–Katz technique.
- Routine monitoring for effective coverage and evaluation of the impact of the intervention (using repeat population-based surveys conducted after five rounds of preventive chemotherapy, or more frequently with a mid-term evaluation after three rounds) should be integral parts of preventive chemotherapy programmes, to help inform the decision on changing the strategy and continuing or stopping the programme.
- Expanded preventive chemotherapy programmes pose a greater theoretical risk to the development of drug resistance. Evidence of the potential emergence of reduced praziquantel efficacy in response to increased drug use is rarely reported; thus, continued vigilance to monitor drug efficacy over time through efficacy surveys is imperative to detect any emergence of drug resistance.

- Routine monitoring for safety of the intervention should also be an integral part of preventive chemotherapy programmes.
- Preventive chemotherapy in preschool-aged children (pre-SAC) is appropriate for those aged ≥ 2 years. Younger children, aged < 2 years, may be considered for treatment on an individual clinical basis. The medication for children aged < 2 years should be an oral disintegrating tablet formulation (under development) that is easily administered, disintegrates in the mouth and, ideally, has a sweet taste and smell; if paediatric formulations are not available, praziquantel crushed in soft food may be used for individual case treatment only.
- Available evidence does not differentiate approaches to infection with the different species of *Schistosoma*.
- The 10% prevalence threshold for intervention will expand eligibility for preventive chemotherapy programmes and necessitate a larger global supply of praziquantel than that currently available via donation schemes (estimated at 300 million tablets annually at the time of publication of this guideline).
- Community mapping of the epidemiology of schistosomiasis can reduce the need for praziquantel, as treatment can be better targeted to communities and at-risk regions.
- Ensuring high coverage is essential for preventive chemotherapy and may require incentivization of local community drug distributors.
- Public health awareness campaigns are necessary to ensure high coverage in preventive chemotherapy programmes and to address concerns about adverse events from medication.

Recommendation 2

In endemic communities with prevalence of *Schistosoma* spp. infection < 10%, WHO suggests one of two approaches based on programmatic objectives and resources: (i) where there has been a programme of regular preventive chemotherapy, to continue the intervention at the same or reduced frequency towards interruption of transmission; or (ii) where there has not been a programme of regular preventive chemotherapy, to use a clinical approach of test-and-treat, instead of preventive chemotherapy targeting a population.

Conditional recommendation

Certainty of evidence: very low

Implementation considerations

- Close epidemiological monitoring (sentinel sites surveys or mid-term evaluation every 3 years) should be established to monitor *Schistosoma* spp. prevalence, especially in settings in which the prevalence was previously ≥ 10% or with a history of preventive chemotherapy with praziquantel if reducing the frequency of preventive chemotherapy with praziquantel.

Recommendation 3

In endemic communities with prevalence of *Schistosoma* spp. infection ≥ 10% that demonstrate lack of an appropriate response to annual preventive chemotherapy, despite adequate treatment coverage (≥ 75%), WHO suggests consideration of biannual (twice yearly) instead of annual preventive chemotherapy.

Conditional recommendation

Certainty of evidence: very low

Implementation considerations

- Lack of an appropriate response should be defined as a less than one-third relative reduction in prevalence comparing the baseline prevalence survey and a repeat prevalence survey completed after 2 years of annual preventive chemotherapy. The intervening period should include a minimum of two rounds of preventive chemotherapy to all at-risk groups at adequate treatment coverage (≥ 75%). The relative reduction in prevalence can be estimated as follows: [(prevalence at baseline − prevalence at year 3)/(prevalence at baseline)]. Alternative definitions could consider absolute changes in prevalence of infection, or changes in average intensity of infection (defined as egg concentrations in stool or urine).
- The timing of prevalence surveys should consider the seasonality of transmission to ensure that prevalence is measured at the same point in each seasonal transmission cycle.
- Communities suspected to be "persistent hot spots" or of high endemicity (defined as areas with baseline prevalence ≥ 50% in school-aged children (SAC) are encouraged to conduct early prevalence surveys (after two annual rounds of preventive chemotherapy) to inform any decision on the use of biannual treatment.
- Biannual preventive chemotherapy should be prioritized in areas of higher prevalence (defined as areas with baseline prevalence ≥ 50% in SAC and persistent hot spot settings already achieving high levels of coverage of annual preventive chemotherapy without appropriate response. In settings of moderate prevalence (defined as areas with prevalence 10–49% in SAC), annual treatment may be sufficient.
- Routine monitoring for effective treatment coverage should be an integral part of preventive chemotherapy programmes, with attention to ensuring that annual treatment achieves high coverage (≥ 75%) before any decision to move to biannual treatment.

- There is currently a lack of evidence to inform recommendations on the duration of biannual treatment. As an interim measure, 3 consecutive years of biannual preventive chemotherapy is suggested, followed by implementation of an impact survey to assess if it should be continued or reduced in frequency.
- Biannual treatment programmes will require a larger global supply of praziquantel than that currently available via donation schemes (estimated at 300 million tablets annually at the time of publication of this guideline).
- Biannual treatment programmes should have administrations spaced out equally throughout the year (approximately 6 months between treatments).

Recommendation 4

WHO recommends that health facilities provide access to treatment with praziquantel to control morbidity due to schistosomiasis in all infected individuals regardless of age, including infected pregnant excluding the first trimester, lactating women and pre-SAC aged < 2 years. The decision to administer treatment in children under 2 years of age should be based on testing and clinical judgement.

Strong recommendation

Certainty of evidence: moderate

Implementation considerations

- Pregnancy status should be assessed by discretely questioning the individual herself. If she is uncertain, a negative urine-based pregnancy test can be requested before the treatment is administered.
- The medicine for children aged < 2 years should be an oral formulation (currently under development) that is easily administered, disintegrates in the mouth and, ideally, has a sweet taste and smell; if paediatric formulations are not available, praziquantel crushed in soft food may be used for individual case treatment only.

Recommendation 5

WHO recommends WASH interventions, environmental interventions (water engineering and focal snail control with molluscicides) and behavioural change interventions as essential measures to help reduce transmission of Schistosoma spp. in endemic areas.

Strong recommendation

Certainty of evidence: low

Implementation considerations

- WASH interventions are expected to provide modest benefits in limiting *Schistosoma* transmission, but these benefits extend also to reducing risk for multiple infectious diseases.
- Behavioural change interventions should be implemented from the start of any preventive chemotherapy programme.
- Coordination and joint planning between programmes for control of schistosomiasis and WASH are essential. Inclusion of WASH in the schistosomiasis strategy will require mapping and sharing of epidemiological information alongside WASH coverage to ensure prioritization of water and sanitation services to areas that are endemic for schistosomiasis.
- Similarly, schistosomiasis education and health programme delivery should include inputs to WASH programme design, collaboration on behavioural change interventions and integration of behavioural change promotion.
- Where persistent hot spots of transmission emerge during the course of preventive chemotherapy campaigns, control of intermediate host snail populations should be prioritized especially if the programme is already achieving high levels of treatment coverage.
- Co-implementation of snail control with mass treatment campaigns is expected to hasten achievement of WHO goals for morbidity control and elimination as a public health problem.
- Snail control will be essential to ultimately eliminate local transmission, in combination with WASH interventions.
- Sensitization and public health awareness campaigns will be necessary to ensure high acceptance of snail control interventions.
- Development of snail control programmes will require a larger and less expensive global supply of molluscicides.
- Skilled and dedicated snail control workers will be essential to the success of snail control initiatives.
- Deworming should be delivered together with promotion of health and hygiene to reduce transmission by encouraging healthy behaviours such as proper disposal of faeces.

Recommendation 6

In communities approaching the interruption of transmission (defined as having no autochthonous human cases reported for 5 consecutive years), WHO suggests a verification framework that consists of:

1. Testing for *Schistosoma* infection in humans with a diagnostic that has high sensitivity and specificity. This may require the use of a two-step diagnostic process starting with a high sensitivity test confirmed with a second, high specificity test.
2. Testing for *Schistosoma* infection in snails with a diagnostic that has high sensitivity and specificity. This may require the use of a two-step diagnostic process starting with a high sensitivity test confirmed with a second, high specificity test.
3. Testing for *Schistosoma* infection in non-human mammalian hosts, as applicable, with a diagnostic that has high sensitivity and specificity. This may require the use of a two-step diagnostic process starting with a high sensitivity test confirmed with a second, high specificity test.

Conditional recommendation

Certainty of evidence: low

Implementation considerations

- The eventual predictive performance of the sampling of humans, snails and non-human mammalian hosts to identify settings that have eliminated transmission will depend upon the sampling strategy, with decisions on sample size, geographical zone and timespan for sampling.
- Future work could consider a two-step verification of *Schistosoma* infection status in humans with a first highly sensitive test (for example, serology) and a second confirmatory highly specific test (for example, miracidia hatching test).
- Sampling and diagnostic tools in snail populations and in non-human mammalian hosts should be considered when interruption of transmission is the public health goal and is suspected based on recent epidemiological surveys in human populations.
- The magnitude of the contribution of non-human mammalian hosts to transmission of schistosomiasis remains understudied, especially for species other than *S. japonicum*.

1. Introduction

Human schistosomiasis is an acute and chronic parasitic disease caused by infection with blood flukes (trematode worms) of the genus *Schistosoma*. The disease has been reported from 78 countries *(2)*. Estimates suggest that at least 236.6 million people required preventive treatment worldwide in 2019 *(2)*. Schistosomes are transmitted when people and/or infected animal host species contaminate freshwater sources with their excreta (faeces and/or urine) containing parasite eggs, which hatch in water. People become infected when the larval forms (cercariae) of the parasite – released after multiplication within freshwater snails – penetrate the skin during contact with infested water and develop into adult schistosomes in the human body. Adult worms live in the blood vessels where the females release eggs after coupling with male worms. Some of the eggs are evacuated in the faeces or urine to continue the parasite's life cycle; others become trapped in body tissues, stimulating immune reactions that can progressively damage organs.

In 2001, the Fifty-fourth World Health Assembly adopted resolution WHA54.19 on schistosomiasis and soil-transmitted helminth infections, officially endorsing:

> *as the best means of reducing mortality and morbidity and improving health and development in infected communities, the regular treatment of high-risk groups, particularly school-age children, and ensured access to single-dose drugs against schistosomiasis and soil-transmitted helminth infections in primary health care services, complemented by the simultaneous implementation of plans for basic sanitation and adequate safe water supplies (19).*

This approach, now defined as "preventive chemotherapy", is the core public health strategy used to control and eliminate schistosomiasis. The resolution also urged Member States:

> *to sustain successful control activities in low-transmission areas in order to eliminate schistosomiasis and soil-transmitted helminth infections as a public health problem, and to give high priority to implementing or intensifying control of schistosomiasis and soil-transmitted helminth infections in areas of high transmission while monitoring drug quality and efficacy (19).*

The goal of these activities was to achieve a minimum target of regular administration of preventive chemotherapy to at least 75%, and of up to 100% of all SAC at risk of morbidity by 2010.

In 2002, a WHO expert committee formulated recommendations to translate the resolution into operational guidance *(20)*. The strategy had as its goal control of morbidity through large-scale mass chemotherapy campaigns with praziquantel, using thresholds of prevalence to categorize at risk-populations and to determine the frequency of the intervention. In 2006, the strategy was revised to include at-risk groups

(for instance, fishermen, car washers, farmers of irrigation fields) and entire communities living in highly endemic areas. It is at this time that the concept of preventive chemotherapy was introduced *(21)*.

Evaluation of the effect of the resolution showed that the target of treating at least 75% of all SAC in 2010 was not reached *(22)*, partly because the necessary free-of-charge, quality-assured medicines and resources for implementation were not available. Indeed, in 2010, only 30 of 52 countries requiring preventive chemotherapy had implemented mass treatment campaigns; overall, 34.8 million people were treated worldwide during 2006–2010. In the WHO African Region, treatment coverage ranged from 4% in Nigeria, the country estimated to account for 24.5% of the global population requiring preventive chemotherapy for schistosomiasis, to 27.5% in Ghana *(22)*.

In 2012, the Sixty-fifth World Health Assembly adopted resolution WHA65.21 on elimination of schistosomiasis, noting the progress made to control schistosomiasis and calling on Member States to intensify control towards elimination of transmission where appropriate *(23)*.

Also in 2012, the first road map *(24)* and the London Declaration *(25)* on NTDs were published, renewing emphasis on control of schistosomiasis. Commitments were pledged by various partners. Merck KGaA (Darmstadt) committed to increasing the supply of praziquantel, the main medicine used to treat schistosomiasis, to reach 250 million tablets per year in 2015, equivalent to 100 million treatments for SAC. Other donors, such as the United States Agency for International Development, the United Kingdom Department for International Development (now Foreign, Commonwealth and Development Office) and World Vision, committed to supporting countries in which schistosomiasis is endemic with both praziquantel for treatment and funding for implementation. The 2012 road map set targets to reach at least 75% treatment coverage of SAC in 2020, and to eliminate the disease in some WHO regions.

The strategy to control and eliminate human schistosomiasis is based on preventive chemotherapy, or "large-scale preventive treatment against helminthiases and trachoma with safe, single-dose, quality-assured medicines" alone or in combination in medicine packages to prevent morbidity and interrupt transmission *(21)*. Preventive therapy through mass treatment of targeted groups should be repeated regularly over several years in order to reduce levels of infection and prevent morbidity, especially the development of irreversible pathology in adulthood.

The previous guidance on control of schistosomiasis morbidity was based on the recommendations of a WHO Expert Committee in 2002 *(20)*. In 2012, it was updated to reflect additional strategies, namely treatment in low prevalence areas and treatment of special "at-risk" groups *(22)*.

This current guideline is valid for supporting morbidity control and elimination as a public health problem for *Schistosoma* spp. (including *S. mansoni*, *S. japonicum*, *S. mekongi*, *S. guineensis*, *S. intercalatum* and *S. haematobium*).[1] In order to interrupt transmission, additional strategies must be implemented; the current guideline offers recommendations on these.

[1] In many communities where *Schistosoma haematobium* is identified in humans by urine filtration, a proportion of the parasites may be hybrid parasites, arising from coinfection with and pairing between *S. haematobium* and other *Schistosoma* species more normally found in domestic and wild animals. While these hybrid parasites are unlikely to be important in terms of the effectiveness of the use of praziquantel to treat infection in humans, they may become more significant when interventions move towards the target of interruption of transmission. The zoonotic nature of *S. japonicum* and *S. mekongi* is well established. Evidence is accumulating to support the contribution of wild animals to the transmission of *S. mansoni* to humans.

1.1 Assessment of conflicts of interest

All GDG members (as well as the external review group) completed and submitted WHO declaration of interests and confidentiality agreement forms before the initial GDG teleconference. The declarations submitted by each member were reviewed and assessed for any conflict of interest that warranted action in accordance with standard WHO procedures, and were cleared by the Office of Compliance, Risk Management and Ethics.

In accordance with WHO policy on conflicts of interest and in order to strengthen public trust and transparency, the Guideline Steering Group posted the names and brief biographies of all GDG members on the WHO website 10 weeks before the GDG meeting, to allow the public to comment on any competing interests that may have gone unnoticed or that may not have been reported during earlier assessments. No conflicts of interest that could have compromised the experts' objectivity and independence in providing advice to WHO in formulating these recommendations were detected.

Annex 1 gives a complete list of all contributors to the guideline and their professional affiliations. The declarations of interest and their management are summarized in **Annex 2**.

1.2 Methods used to develop the guideline

The guideline panel followed the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach *(26)* to develop the guideline. The evidence-informed recommendations were drafted at a meeting of the GDG (Geneva, 26–28 November 2018) in which the systematic reviewers presented the evidence and the guideline methodologist facilitated the discussion and consensus process. After the 2018 physical meeting, the systematic reviews were updated to integrate additional data. The GDG held several virtual meetings, created sub-working groups and maintained interaction via email. At the last meeting of the entire GDG (September 2020), decisions on the recommendations and their strength and, where appropriate, the implementation considerations or remarks to be attached to each recommendation, were generally reached by discussion and consensus. When consensus could not be reached, members of the GDG adopted a voting process.

1.2.1 Rating the certainty of evidence

The GRADE approach starts by rating the certainty of the evidence (that is, the reliability of the estimates). Randomized trials start with a rating of high, whereas non-randomized studies start with a rating of low. This initial level of certainty of evidence can be increased or decreased based on several factors.

In GRADE, the certainty of evidence is rated as high, moderate, low, or very low. These four levels describe the trustworthiness of estimates of effect of the intervention on each outcome. High certainty implies that future research is less likely to change the current estimates (**Annex 3** provides a detailed description). A judgement about the certainty in net benefit (across all outcomes) is then made.

When recommending annual preventive chemotherapy with praziquantel, the certainty of evidence was complex and consisted of several components with varying levels of evidence (including high certainty of evidence supporting

the antiparasitic and pharmacodynamics of praziquantel; low certainty of evidence supporting the selection of a certain prevalence threshold; and variable certainty of evidence supporting the effectiveness of and adherence to implementation programmes). As a result, a global judgement about the certainty of evidence was made across these various sources of data. Indirect evidence was considered, particularly for the recommendation on WASH interventions (recommendation 5). The certainty of evidence about WASH interventions was low for schistosomiasis but was high for other infectious diseases, thus supporting a strong recommendation.

1.2.2 Applying the evidence-to-decision framework

After rating the certainty of the evidence, the guideline panel makes decisions by applying the evidence-to-decision framework developed by the GRADE Working Group. This framework incorporates factors other than the certainty of evidence, such as the balance of benefits and harms; cost and resources; relevant values and preferences; availability, acceptability and feasibility of the intervention; and the impact on health equity. On the basis on this framework the recommendations are graded as either strong or weak (also called "conditional"). A strong recommendation implies that the guideline developers believe that all or almost all informed people would make the recommended intervention. Conversely, guideline panels make a conditional recommendation when they believe that most informed people would choose the recommended course of action, but a substantial number may not. Typically, a strong recommendation is developed from evidence of moderate or high certainty, although not always *(27)*. The overarching principles followed in the evidence-to-decision framework of this guideline were (i) to place the highest value on prevention of morbidity from and elimination of schistosomiasis; and (ii) to place more weight in the framework on the feasibility factor by making the recommendations easy to implement by programmes with varying infrastructures, resources and personnel.

1.2.3 Systematic reviews supporting the guideline

The GDG commissioned specific systematic reviews and identified several published ones. The systematic reviews used in this guideline addressed the following topics:

- impact of preventive chemotherapy against schistosomiasis on disease morbidity in key population age groups *(28)*;
- optimal prevalence threshold for preventive chemotherapy against schistosomiasis to control morbidity *(29)*;
- frequency of praziquantel for preventive chemotherapy to control morbidity *(30)*;
- safety of praziquantel for preventive chemotherapy against schistosomiasis in at-risk populations *(31)*;
- chemical-based snail control against schistosomiasis in at-risk communities *(32)*;
- WASH interventions and schistosomiasis in at-risk populations *(33)*;
- diagnostic tools for *Schistosoma* infection in humans to verify elimination of transmission *(34)*;
- diagnostic tools for detection of *Schistosoma* in snails and the environment to verify elimination of transmission *(35)*; and
- diagnostic tools for *Schistosoma* infection in non-human animal hosts to verify elimination of transmission *(36)*.

1.2.4 Linkage of systematic reviews to recommendations

Recommendation 1
Systematic reviews: 1, 2, 3, 4, 7

- Systematic review 1 provided evidence to support the strategy of preventive chemotherapy in reducing the prevalence of *Schistosoma* spp. infection (moderate to high certainty of evidence) and the associated disease morbidity by age group (low certainty of evidence).
- Systematic review 2 summarized evidence to support the choice of a threshold of 10% prevalence of *Schistosoma* spp. infection to initiate preventive chemotherapy (very low certainty of evidence).
- Systematic review 3 provided evidence to support the frequency of annual preventive chemotherapy (moderate certainty of evidence).
- Systematic review 4 provided evidence to support the safety of praziquantel for preventive chemotherapy and treatment in children aged ≥ 2 years, adults, pregnant women after the first trimester and lactating women (moderate certainty of evidence).
- Systematic review 7 provided evidence to support the use of either parasitological or point-of-care circulating cathodic antigen tests to define the prevalence threshold (moderate certainty of evidence).

Recommendation 2
Systematic review: 2

- Systematic review 2 summarized evidence to support the choice of a threshold of 10% prevalence of *Schistosoma* spp. infection to initiate preventive chemotherapy; therefore, when the baseline prevalence of *Schistosoma* spp. is below this threshold, a strategy of test-and-treat was recommended (very low certainty of evidence).

Recommendation 3
Systematic review: 3

- Systematic review 3 provided evidence on the frequency of annual preventive chemotherapy, and evidence that escalation to twice yearly (biannual) preventive chemotherapy may be needed in settings with limited response to annual treatment (moderate certainty of evidence)..

Recommendation 4
Systematic review: 4

- Systematic review 4 provided evidence to support the safety of praziquantel for treatment of children aged ≥ 2 years, adults, pregnant women after the first trimester and lactating women. In children aged ≤ 2 years, limited data exist, thus requiring clinical judgement (moderate certainty of evidence).

Recommendation 5
Systematic review: 5, 6

- Systematic review 5 provided evidence on the effectiveness of chemical-based snail control as a strategy to reduce the prevalence of *Schistosoma* spp. infection (low certainty of evidence).
- Systematic review 6 provided evidence on the effectiveness of WASH interventions to reduce the prevalence of *Schistosoma* spp. (low certainty of evidence).

Recommendation 6

Systematic reviews: 7, 8, 9

- Systematic review 7 provided evidence on diagnostic tools in humans (moderate certainty of evidence).
- Systematic review 8 provided evidence on diagnostic tools in snails (low certainty of evidence).
- Systematic review 9 provided evidence on diagnostic tools in non-human animal hosts (low certainty of evidence).

2. Background on human schistosomiasis

2.1 Epidemiology

Human schistosomiasis is a chronic parasitic disease that results from infection by trematode worms of the genus *Schistosoma*. Six species of *Schistosoma* are responsible for the two major forms of the disease (intestinal and urogenital schistosomiasis).*S. mansoni*, *S. japonicum*, *S. mekongi*, *S. guineensis* and *S. intercalatum* cause intestinal schistosomiasis and *S. haematobium* causes urogenital schistosomiasis.

S. japonicum and *S. mekongi* are highly zoonotic species, involving transmission between human and animals *(37, 38)*. *S. mansoni* infects rodents and non-human primates, although the zoonotic contribution to human disease is unknown *(39–41)*. *S. haematobium* can hybridize successfully with livestock schistosome species and perpetuate transmission to humans *(42, 43)*. Likewise, hybridized livestock *Schistosoma* species can also infect humans *(44, 45)*. Schistosomiasis is a mainly rural disease but is also found also at the periphery of urban areas, where it often affects people engaged in agriculture and fishing, as well as those involved in domestic chores such as washing clothes.

The disease principally affects impoverished populations who are either unaware of its transmission potential from the water sources they use, or who are unable to avoid contact with infested water because of their profession (agriculture, fishing), embedded recreational behaviours (swimming and playing in water) or due to lack of a reliable source of safe water *(37, 46)*.

Adult worms of *S. mansoni, S. japonicum, S. mekongi, S. guineensis* and *S. intercalatum* live in the blood vessels surrounding the intestines; *S. haematobium* adults live in the urinary venous plexus. Male and female worms copulate and produce between 50 and several hundred eggs per day (up to thousands for *S. japonicum*) some of which exit the host by transitioning through the gut or bladder wall and are excreted with host faeces or urine.

Miracidia (the first free-swimming larval stage) emerge from the eggs that hatch when they reach fresh water. For the next 6–12 hours, miracidia actively seek intermediate host snails of specific species. *S. mansoni* infects snail species of the genus *Biomphalaria*; *S. japonicum* infects *Oncomelania* spp.; *Bulinus* species are hosts of *S. haematobium*, *S. guineensis* and *S. intercalatum*. The intermediate hosts of *S. mekongi* are of the genus *Neotricula*. Each miracidium invades the soft tissues of the snail and develops into a mother sporocyst. After a period of multiplication of 3–7 weeks in the snail, the cercariae emerge as a free-swimming larval stage capable of infecting humans or other animal reservoir hosts. One miracidium can develop into as many as 100 000 cercariae. Cercariae, which can live up to 48 hours in freshwater, can penetrate the skin of the definitive host (that is, the host in which the parasites mature to the adult stage) and

transform into schistosomula that migrate through the lungs to the liver where they reach maturity. After 4–12 weeks, male and female worms may pair and move via the blood vessels to their final position, where they begin to produce eggs. An average schistosome pair produces eggs for 2–5 years, although some may survive for decades *(37, 47)*. An active *S. mansoni* infection was diagnosed in a soldier who had left an endemic area of Angola 40 years previously *(47)*.

The course of schistosome infection in humans can be divided into three phases: migratory, acute, and chronic. During the migratory phase, cercariae penetrate and migrate through the skin. This phase is often asymptomatic, but sensitized patients may experience transient dermatitis and, occasionally, pulmonary lesions and pneumonitis. The acute phase (during which Katayama syndrome may occur) is characterized by hypersensitivity responses, including serum sickness due to immune complex formation, resulting in pyrexia, fatigue, aches, lymphadenopathy, gastrointestinal discomfort, intestinal pain, diarrhoea with blood and mucous in faeces, asthenia and weight loss. Laboratory tests may show leucocytosis with eosinophilia. The chronic phase occurs in subsequent months in response to the cumulative deposition of schistosome eggs in tissues and the host reactions that develop against them. Not all the eggs laid by female worms successfully exit the host: many are swept away in the circulation and become trapped in organs where they elicit strong granulomatous responses. Eggs become surrounded by inflammatory cells forming the characteristic granuloma, which may coalesce to form larger granulomatous reactions (polyps). The encapsulated eggs die and eventually calcify or are destroyed. The resulting effects on host organs and tissues are manifold. Symptoms of intestinal schistosomiasis include intestinal polyposis, abdominal pain, diarrhoea, glomerulonephritis, pulmonary arteritis, and cardiovascular problems including heart failure and periportal fibrosis. Portal hypertension can lead to hepatomegaly, splenomegaly and ascites. Infections with *S. haematobium* often cause haematuria, pain when urinating, hydronephrosis and progressive disruption of the bladder wall, and may increase the risk of carcinoma *(48)*. Eggs, particularly in infections of heavy intensity, are sometimes scattered within almost all tissues and organs, including the nervous system (brain and especially the spinal cord), testes, ovaries, skin and eyes *(49)*.

Control of the disease also entails interrupting the cycle of transmission of infection. Ensuring safe water supplies and reducing contact with infected water sources, whether for work, daily chores (**Fig. 1**) or recreation (**Fig. 2**), is the long-term solution to the prevention of urogenital schistosomiasis. WASH education is therefore a critical component of an integrated control and elimination strategy *(33)*.

Holistic, layered approaches beyond medical interventions will be the most effective. Poverty, gender inequality, human rights and access to education, which undermine women and girls' access to SRHR, must also be addressed.

2.2 Control and elimination strategies

An integrated schistosomiasis control strategy, combining large-scale preventive chemotherapy, provision of potable water, improved sanitation, hygiene, education, snail control and environmental modification, can lead to interruption of schistosomiasis transmission (elimination) *(50, 51)*. Countries remain at various stages of control and elimination (see **Table**).

Table. Status of mass drug administration in countries and territories endemic for schistosomiasis in 2020

MDA not started	MDA started but not at scale or irregular	MDA expanded to all endemic IUs	Evaluation needed to verify interruption of transmission	Mapping needed to determine the current situation
Equatorial Guinea South Africa	Botswana Brazil Central African Republic Chad Congo Gabon Guinea-Bissau Namibia Nigeria Sao Tome and Principe Somalia South Sudan Venezuela (Bolivarian Republic of) Zambia	Benin Burkina Faso Burundi Cambodia Cameroon Côte d'Ivoire Democratic Republic of the Congo Eritrea Eswatini Ethiopia Egypt Gambia Ghana Guinea Indonesia Kenya Liberia Lao People's Democratic Republic Madagascar Malawi Mali Mauritania Mozambique Niger Philippines Rwanda Senegal Sierra Leone Sudan Togo United Republic of Tanzania Uganda Yemen Zimbabwe.	Antigua and Barbuda Dominican Republic China Guadeloupe Iraq Islamic Republic of Iran Japan Jordan Mauritius Martinique Montserrat Morocco Oman Puerto Rico Saudi Arabia Syrian Arab Republic Saint Lucia Suriname Tunisia.	Algeria Djibouti India Lebanon Libya Malaysia Myanmar Thailand Turkey.
2	15	34	19	9
51 countries requiring preventive chemotherapy				

IU: implementation unit; MDA: mass drug administration.

Based on the experience of several countries, an intensified control programme leading to elimination of schistosomiasis can be divided into five phases: (i) morbidity control; (ii) elimination as a public health problem; (iii) interruption of transmission (elimination); (iv) post-transmission surveillance; and (v) verification of elimination. As a programme progresses from one phase to another, its objectives should be modified, with scaled-up activities, including appropriate public health interventions (snail control and environmental management, WASH, One Health) and a robust surveillance system to reach the specified goal. It may take a country 13– 50 years to achieve interruption of transmission from launching the first group of interventions for morbidity control, and will require multiple interventions (not only preventive chemotherapy) that are implemented effectively, sustained, uninterrupted and have strong political commitment and investment *(7, 22, 52)*.

There is no "one-size-fits-all" intervention scenario that can guarantee the elimination of schistosomiasis because the disease is epidemiologically distinct throughout its geographical distribution. Key species and ecological differences affect transmission dynamics, disease pathology, occurrence of reservoir hosts, habitat of intermediate snail hosts and the age pattern at which individuals acquire and resolve infection, as well as patterns of exposure to infection. In addition, some countries have advanced schistosomiasis control or elimination programmes, while others have yet to start programmes using the recommended strategies. Integration of activities to control or eliminate schistosomiasis with existing preventive chemotherapy programmes to control or eliminate other NTDs should therefore be considered. During the phases of morbidity control and elimination as a public health problem, treatment for schistosomiasis may be coordinated with preventive chemotherapy for lymphatic filariasis, onchocerciasis, soil-transmitted helminthiases and trachoma *(21)*.

Summary of evidence and rationale for recommendations

3. Implementing preventive chemotherapy based on prevalence of infection

To recommend preventive chemotherapy with praziquantel, the GDG considered evidence about three topics: effectiveness of praziquantel on schistosomiasis morbidity; optimal prevalence threshold; and frequency of the intervention. These three types of evidence supported the three recommendations summarized below. Overall, the certainty of evidence of the effect of preventive chemotherapy on schistosomiasis was moderate to high, while it was very low for the selection of threshold and for the test-and-treat strategy.

3.1 Recommendations

Recommendation 1

In endemic communities with prevalence of *Schistosoma* spp. infection ≥ 10%, WHO recommends annual preventive chemotherapy with a single dose of praziquantel at ≥ 75% treatment coverage in all age groups from 2 years old, including adults, pregnant women after the first trimester and lactating women, to control schistosomiasis morbidity and advance towards eliminating the disease as a public health problem.

Strong recommendation

Certainty of evidence: moderate

Implementation considerations

- Prevalence of infection is defined as the percentage of individuals of all ages in a population targeted for treatment who are infected with any species of *Schistosoma*. The strategy of preventive chemotherapy does not differ by *Schistosoma* species.
- The prevalence threshold of 10% is based on estimation by parasitological microscopy, using duplicate Kato–Katz smears from one stool sample for intestinal schistosomiasis, predominantly *S. mansoni* and *S. japonicum*, and single 10 mL urine filtration for urogenital schistosomiasis due to *S. haematobium*.

- The point-of-care circulating cathodic antigen test can be used to determine prevalence of *S. mansoni*; 30% prevalence by this test is to be considered equivalent to 10% prevalence by the Kato–Katz technique.
- Routine monitoring for effective coverage and evaluation of the impact of the intervention (using repeat population-based surveys conducted after five rounds of preventive chemotherapy, or more frequently with a mid-term evaluation after three rounds) should be integral parts of preventive chemotherapy programmes, to help inform the decision on changing the strategy and continuing or stopping the programme.
- Expanded preventive chemotherapy programmes pose a greater theoretical risk to the development of drug resistance. Evidence of the potential emergence of reduced praziquantel efficacy in response to increased drug use is rarely reported; thus, continued vigilance to monitor drug efficacy over time through efficacy surveys is imperative to detect any emergence of drug resistance.
- Routine monitoring for safety of the intervention should also be an integral part of preventive chemotherapy programmes.
- Preventive chemotherapy in pre-SAC is appropriate for those aged ≥ 2 years. Younger children, aged < 2 years, may be considered for treatment on an individual clinical basis. The medication for children aged < 2 years should be an oral disintegrating tablet formulation (under development) that is easily administered, disintegrates in the mouth and, ideally, has a sweet taste and smell; if paediatric formulations are not available, praziquantel crushed in soft food may be used for individual case treatment only.
- Available evidence does not differentiate approaches to infection with the different species of *Schistosoma*.
- The 10% prevalence threshold for intervention will expand eligibility for preventive chemotherapy programmes and necessitate a larger global supply of praziquantel than that currently available through donation programmes (estimated at 300 million tablets annually at the time of publication of this guideline).
- Community mapping of the epidemiology of schistosomiasis can reduce the need for praziquantel, as treatment can be better targeted to communities and at-risk regions.
- Ensuring high coverage is essential for preventive chemotherapy and may require incentivization of local community drug distributors.
- Public health awareness campaigns are necessary to ensure high coverage in preventive chemotherapy programmes and to address concerns about adverse events from medication.

Recommendation 2

In endemic communities with prevalence of *Schistosoma* spp. infection < 10%, WHO suggests one of two approaches based on programmatic objectives and resources: (i) where there has been a programme of regular preventive chemotherapy, to continue the intervention at the same or reduced frequency towards interruption of transmission; or (ii) where there has not been a programme of regular preventive chemotherapy, to use a clinical approach of test-and-treat, instead of preventive chemotherapy targeting a population.

Conditional recommendation

Certainty of evidence: very low

Implementation considerations

- Close epidemiological monitoring (sentinel sites surveys or mid-term evaluation every 3 years) should be established to monitor *Schistosoma* spp. prevalence, especially in settings previously endemic with ≥ 10% prevalence or with a history of preventive chemotherapy with praziquantel if reducing the frequency of preventive chemotherapy.

Recommendation 3

In endemic communities with prevalence of *Schistosoma* spp. infection ≥ 10% that demonstrate lack of an appropriate response to annual preventive chemotherapy, despite adequate treatment coverage (≥ 75%), WHO suggests consideration of biannual (twice yearly) instead of annual preventive chemotherapy.

Conditional recommendation

Certainty of evidence: very low

Implementation considerations

- Lack of an appropriate response should be defined as a less than one-third relative reduction in prevalence comparing the baseline prevalence survey and a repeat prevalence survey completed after 2 years of annual preventive chemotherapy. The intervening period should include a minimum of two rounds of preventive chemotherapy to all at-risk groups at adequate treatment coverage (≥ 75%). The relative reduction in prevalence can be estimated as follows: [(prevalence at baseline − prevalence at year 3)/(prevalence at baseline)]. Alternative definitions could consider absolute changes in prevalence of infection, or changes in average intensity of infection (defined as egg concentrations in stool or urine).

- The timing of prevalence surveys should consider the seasonality of transmission to ensure that prevalence is measured at the same point in each seasonal transmission cycle.
- Communities suspected to be persistent hot spots or of high endemicity (defined as areas with baseline prevalence ≥ 50% in SAC are encouraged to conduct early prevalence surveys (after two annual rounds of preventive chemotherapy) to inform any decision on the use of biannual treatment.
- Biannual preventive chemotherapy should be prioritized in areas of higher prevalence (defined as areas with baseline prevalence ≥ 50% in SAC and persistent hot spot settings already achieving high levels of coverage of annual preventive chemotherapy without appropriate response. In settings of moderate prevalence (defined as areas with prevalence 10– 49% in SAC), annual treatment may be sufficient.
- Routine monitoring for effective treatment coverage should be an integral part of preventive chemotherapy programmes, with attention to ensuring that annual treatment achieves high coverage (≥ 75%) before any decision to move to biannual treatment.
- There is currently a lack of evidence to inform recommendations on the duration of biannual treatment. As an interim measure, 3 consecutive years of biannual preventive chemotherapy is suggested, followed by implementation of an impact survey to assess if it should be continued or reduced in frequency.
- Biannual treatment programmes will require a larger global supply of praziquantel than that currently available via donation schemes (estimated at 300 million tablets annually at the time of publication of this guideline).
- Biannual treatment programmes should have administrations spaced out equally throughout the year (approximately 6 months between treatments).

3.2 Rationale

3.2.1 Impact of preventive chemotherapy on schistosomiasis morbidity in key population age groups

Overall results of evidence on the relationship between preventive chemotherapy against schistosomiasis and disease morbidity in key population age groups

1. Preventive chemotherapy with praziquantel reduces the prevalence and intensity of infection and may improve some morbidity outcomes in SAC; additional evidence may support benefits in pre-SAC, older adolescent and adult populations.

2. The majority of data on preventive chemotherapy and morbidity outcomes are of low or very low certainty and focus on SAC. Data for adult populations are derived from studies for all age groups; insufficient data are available for *S. japonicum* and *S. mekongi*, thus requiring extrapolation from other *Schistosoma* species.

3. The benefit of preventive chemotherapy in key age groups will differ based on setting-specific epidemiology and morbidity outcomes; the benefit of treating all age

groups is likely greater in settings of moderate and high prevalence (prevalence ≥ 10%).

4. There may be more benefits to community-wide than school-based preventive chemotherapy on overall transmission in the community. There is a likely benefit of community-wide treatment on morbidity in pre-SAC, adolescent and adult populations.

Considerations in formulating the recommendations

Certainty of evidence. The overall certainty of the evidence for the effect of preventive chemotherapy on schistosomiasis prevalence was moderate, while the certainty of the effect on reducing morbidity in key age groups was low or very low.

Balance of benefits and harms. The morbidity and mortality caused by schistosomiasis are well described, with a clinical presentation that is distinct by parasite species, human age group and duration of infection *(53)*. Schistosomiasis, depending on the causative species, can present with various pathologies ranging from malnutrition, anaemia and infertility, to liver and kidney failure, increased risk of cancer and death *(53)*. The chronic sequelae of schistosomiasis are thought to be related to cumulative exposure, meaning that both the intensity of infection and its duration are important. The key benefit of preventive chemotherapy is treatment of reversible pathology, prevention of future pathology and potential reductions in community transmission. However, some disease processes during schistosomiasis are irreversible and are not improved by medicine. While the current evidence remains limited, sufficient data exist to support the benefits of preventive chemotherapy, with improvements in human health across all age groups; most of the evidence is available from studies of SAC *(28, 54, 55)*. The likely health benefits are dependent on age , local transmission ecology and other context-specific factors. Furthermore, the health benefit is expected to be greatest in settings of moderate and high prevalence (≥ 10%) where larger numbers of infections of moderate or heavy intensity are found. People with heavy-intensity infections are more likely to manifest severe morbidity from the disease. The evidence demonstrates that community-wide, and even school-based preventive chemotherapy, can lower prevalence in non-target populations such as adults and children just entering school *(56, 57)*, presumably through lowering village-level egg output and thus transmission.

Evidence of severe potential harms of preventive chemotherapy in key age groups remains rare. A review of safety trials with praziquantel across a range of age groups, including pre-SAC, found that mild transient adverse effects (for example, abdominal pain, nausea) were relatively common, although persistent or moderate and severe adverse events were uncommon *(58– 66)*. People with heavy-intensity infections also had a higher incidence of mild adverse events, although they would also be those expected to benefit most from treatment *(59, 60)*. Consideration of harm is most important in relation to people who are not infected, and who therefore have a risk of adverse events without the prospect of any benefits to health (although lower risk of adverse events than infected individuals). There are case reports describing serious adverse effects, although the causality remains unclear. Finally, there remains a reasonable concern around choking or aspiration during administration of medication, as for any medication delivered in tablet form, especially in younger pre-SAC *(67)*.

Values and preferences. The GDG agreed that there was little variability in the value that populations assigned to the treatment of different age groups in treatment programmes

to control schistosomiasis. There was a paucity of literature demonstrating age-specific differences in value of treating key age groups, although there may be a modest preference for treating children.

Acceptability. Preventive chemotherapy against schistosomiasis is generally widely accepted by policy-makers, health workers, teachers involved in deworming programmes and, usually, by communities at risk of schistosomiasis *(68, 69)*. Many countries have national schistosomiasis control programmes, although their focus has been historically on SAC. Any lack of acceptability of preventive chemotherapy in the treated population is ascribed to low and variable levels of knowledge, concern for side-effects and lack of perceived benefit. There is no clear evidence to support a differential acceptability of preventive chemotherapy by age group. In general, significant gaps still exist in knowledge about schistosomiasis and the damaging health effects associated with infection. The understanding of infection and associated disease will vary across age groups and should be addressed when tailoring programmes of engagement, educating and empowering communities, shaping interventions and securing support for participation in multi-year preventive chemotherapy programmes.

Resource implications. The GDG agreed that the inclusion of all at-risk age groups for preventive chemotherapy against schistosomiasis would provide a favourable ratio of resources relative to the expected benefit.

A review of the costing literature yielded an average cost of delivering treatment per child of US$ 0.50 and per-community member of US$ 1.50 *(9)* (which would include pre-SAC, adolescents and adults). This cost was reduced with increasing size of the treated population due to economies of scale. These estimates included procurement and distribution of medicines, training and supervision of teachers, and monitoring. The additional cost of praziquantel depends on whether or not it was donated and on the average number of pills per person given the need for weight-based dosing. The overall cost was driven largely by the delivery of medication rather than the medication itself.

A review of the literature considering cost–effectiveness concluded that the strategy of community-wide preventive chemotherapy across all age groups, compared with treatment of SAC alone, met conventional measures of cost–effectiveness in many scenarios *(9, 70, 71)*. Treatment of only SAC would also be cost-effective with lower total resource utilization, but would limit the total avertable disease burden *(9, 70, 71)*. The cost–effectiveness of treating all age groups would be increased if applied in settings of moderate and high prevalence (≥ 10%). Thus, the choice of prevalence thresholds to guide the frequency of praziquantel can improve the efficiency of resource utilization.

Equity. The GDG agreed that preventive chemotherapy across all age groups would yield greater reductions in schistosomiasis disease burden and improve equity.

Schistosomiasis is a disease that disproportionately affects poor, vulnerable people who are unable to routinely access health services. Historically, treatment has focused on SAC, which neglects the remainder of the population who carry a substantial disease burden, namely pre-SAC, older adolescents and adult populations. Preventive chemotherapy applied across all key age groups would improve equity significantly by treating the disease burden in the entire at-risk population, thus providing better control of the overall disease burden. However, careful programmatic design and delivery would be essential to ensure that access to medicines is provided equitably to reach the entire at-risk population and avoid repeated treatment of more easily accessed population

subsets (for instance, children in school, more wealthy individuals) that could instead decrease equity. Early engagement in establishing a partnership with the community can ensure their empowerment and assistance in shaping operational aspects of schistosomiasis programmes and address any unintended consequences that may impact equity.

Feasibility. The GDG agreed that preventive chemotherapy across all age groups is technically feasible. Community-wide mass drug administration (MDA) programmes for schistosomiasis and other NTDs have been implemented in some countries for many years.

The feasibility of preventive chemotherapy with praziquantel would be specific to the at-risk age group. For treatment of SAC, school-based delivery systems would be appropriate. Historically, these have been successful and readily supported by ministries of health and education. For children not attending schools (including pre-SAC), older adolescents and adults, community-based distribution channels are required. Community-based treatment has been used successfully for other NTD programmes. A systematic review in which community-based, school-based and combined delivery platforms were studied found that combined school-based and community-based strategies obtained the highest levels of coverage *(72)*. The importance of community drug distributors in community-based strategies is described in section 3.2.2).

Overall, during its deliberations the GDG took into particular consideration the following evidence that resulted in the recommendations:

- This summarized evidence supported the decision to include all ages, 2 years or older, in preventive chemotherapy programmes, including adults, pregnant women after the first trimester and lactating women.
- There is a moderate level of evidence that preventive chemotherapy reduces the prevalence of *Schistosoma* spp. infection, and evidence of low certainty that treatment may cause some reduction in disease morbidity in all age groups; this relationship is heterogenous across age groups and epidemiological settings. The moderate certainty of evidence found in recommendation 1 is based on the evidence of moderate to high certainty about the role of preventive chemotherapy in reducing infection prevalence, but is downgraded due to the evidence of lower certainty about the benefit to health outcomes.
- SAC infected with *Schistosoma* benefit significantly from treatment with praziquantel in curing infection or reducing worm burden. Treatment in such individuals may confer benefits in terms of reducing weight deficits and other morbidities.
- Pre-SAC, adolescents and adult populations infected with Schistosoma benefit significantly from treatment with praziquantel, which may cure the infection or reduce worm burden, and may have modest benefits on some related morbidities.
- Preventive chemotherapy with praziquantel is generally well tolerated in all age groups, with only mild transient adverse events.
- Preventive chemotherapy with praziquantel is normally well accepted among children, parents, teachers, health workers and members of the community, is technically feasible and remains a cost-effective intervention, even with community-wide treatment.

- Settings of moderate and high prevalence with higher frequency of moderate and heavy intensity infections were considered a priority for preventive chemotherapy programmes.
- Preventive chemotherapy across all age groups rather than treating SAC alone would improve equity and treat substantial morbidity, but programmes need to ensure high coverage in the highest risk group of SAC.

3.2.2 Optimal prevalence threshold for preventive chemotherapy to control morbidity

Overall results of evidence on the prevalence threshold for preventive chemotherapy against schistosomiasis and need for complementary strategies

1. Based on meta-regression estimates, the reduction in prevalence associated with one year of school-based preventive chemotherapy against *S. mansoni* was 33% and against *S. haematobium* was 46%, which can be extrapolated to project the effect of various preventive chemotherapy strategies on infection prevalence.

2. Models of *Schistosoma* transmission demonstrate community-wide treatment achieved greater prevalence reductions than school-based treatment alone, with no modelled scenario achieving elimination.

3. Cost–effectiveness modelling designed to identify the optimal prevalence threshold to initiate preventive chemotherapy against schistosomiasis estimated a prevalence threshold of 5% for annual treatment of SAC (compared with no preventive chemotherapy) and 15% for annual treatment of the entire community (compared with SAC alone).

4. The prevalence threshold of 10% prevalence by Kato–Katz is estimated to be comparable to 30% prevalence by point-of-care circulating cathodic antigen test.

5. The available evidence does not identify the optimal prevalence threshold for stopping preventive chemotherapy programmes, but there may be a point at which test, treat, track, test and treat may become more acceptable and efficient.

6. Ensuring high treatment coverage is essential for preventive chemotherapy programmes and may require incentivization of local community drug distributors.

Considerations in formulating the recommendations

Certainty of evidence. The overall certainty of the evidence supporting the effectiveness of preventive chemotherapy against schistosomiasis is at least moderate; for the choice of an optimal prevalence threshold it is very low, given that it is supported by observational data and modelling studies alone.

Balance of benefits and harms. The balance of benefits and harms is related to the selection of the prevalence threshold below which to initiate preventive chemotherapy. The morbidity and mortality caused by schistosomiasis are well documented. Generally, a higher prevalence threshold would be more restrictive with treatment. In this scenario, only higher prevalence settings would receive preventive chemotherapy, which would

withhold treatment from people who would benefit from treatment in lower prevalence settings, although this approach would have a lower overall cost. Conversely, a lower prevalence threshold would generally expand treatment. In this scenario, a higher total number of people would benefit, although this approach would have a higher overall cost. The health benefit of preventive chemotherapy is expected to be greatest in higher prevalence settings where there are a larger number of people with infections of moderate or heavy intensity. There would be diminishing health utility returns achieved by treating progressively lower prevalence settings. In the drive towards the interruption of transmission, intervention strategies will need to be adapted to direct treatment to those who have most to gain from it and are most likely to contribute to ongoing transmission of the infection.

The potential harms related to the selection of a prevalence threshold at which to initiate preventive chemotherapy is largely based upon the proportion of the population likely to be given medicine who are not infected. With a lower prevalence threshold, a greater proportion of the population given medicine will be uninfected, meaning they would not benefit from treatment but are subjected to any risks of the medicine. For this reason, the safety profile of the medicine is important, especially in people who are not infected and who therefore bear the risk of adverse events without benefit. Safety trials of praziquantel across a range of age groups, including pre-SAC, demonstrate that it is well tolerated, with moderate and severe adverse events being uncommon *(58– 66)*.

Values and preferences. The GDG opined that populations disregard the fact that MDA is initiated depending on the relationship of local infection prevalence to a WHO-defined threshold.

A systematic review of the literature on values and preferences towards schistosomiasis and control measures in sub-Saharan Africa, as well as similar studies from the Americas and Asia, found generally low and variable levels of knowledge about both disease and interventions, especially among younger children *(73–76)*. While many populations recognized schistosomiasis as a cause of disease and as harmful to health, understanding about transmission of infection and control measures was generally lower and variable by age, gender and level of education *(75)*. Some studies further documented a relationship between concern about side-effects or lack of perceived benefit and poor uptake of preventive chemotherapy *(77, 78)*. Therefore, the value that a population assigns to preventive chemotherapy may be related to the prevalence threshold; specifically, there would be less value assigned to it in lower prevalence settings where disease is less common. In general, significant gaps still exist in knowledge about schistosomiasis and health effects, which likely affect preferences towards and acceptability of preventive chemotherapy and treatment of key age groups. If at-risk communities are to be empowered to contribute effectively to decisions on control and elimination of schistosomiasis, then efforts will be required to address the gaps in their knowledge.

Acceptability. Preventive chemotherapy against schistosomiasis is generally widely accepted by policy-makers, health workers and teachers involved in deworming programmes *(68, 69)*. Many countries have national schistosomiasis control programmes, although historically their focus has been on SAC. There is no clear evidence to support the view that the choice of a prevalence threshold at which to initiate preventive chemotherapy will differentially affect acceptability. Prior to any intervention. the target population should be provided with information on schistosomiasis and its

potential impacts on their health and well-being. Ideally, communities should endorse the proposed interventions before programmes are initiated. Programme managers should maintain a regular dialogue with the target community to identify and address any potential concerns. Giving praziquantel with food, such as bread, biscuits, juices or porridge, should be encouraged as this can increase acceptability and lower the incidence and severity of adverse effects.

Resource implications. The GDG agreed that identifying the optimal prevalence threshold at which to initiate preventive chemotherapy requires balancing the ratio of resources to the expected health benefit.

A review of the evidence is consistent with the conclusion that a lower prevalence threshold would likely result in expanded treatment and a larger public health impact, but higher overall cost and lower cost–effectiveness. Conversely, the selection of a higher prevalence threshold would generally result in a more favourable ratio of resources relative to expected health benefit, but smaller public health impact. A review of the costing literature yielded an average cost of delivering treatment per child of US$ 0.50 and per-community member of US$ 1.50, which was reduced with increasing size of the treated population due to economies of scale *(70)*.

Based on balancing resources and expected benefits to human health, the optimal prevalence thresholds can be estimated. In line with the recommendation that all age groups receive treatment, the prevalence threshold will be selected for community-wide treatment with the alternative being no preventive chemotherapy. Notably, the cost–effectiveness of the intervention will often be improved if it is applied in higher prevalence settings with larger overall effectiveness. Notably, there were uncertainties and setting-specific differences that affect the optimal prevalence threshold for a given context, including the economic status, epidemiology, and assumptions on cost and disability.

Equity. The consideration of equity is important for any intervention against schistosomiasis. The GDG agreed that preventive chemotherapy at a lower prevalence threshold would yield greater reductions in schistosomiasis disease burden, improve treatment access and improve equity. The GDG recognized that any strategy for the control and elimination of schistosomiasis must be delivered against the wider consideration of the social determinants of health and well-being and a rights-based approach that respects education and confidentiality.

Schistosomiasis is a disease that disproportionately affects poor, vulnerable populations and those with restricted access to health services. Preventive chemotherapy applied across all key age groups would improve equity by addressing the disease burden in all at-risk populations and providing better control of overall disease burden. Extending access to treatment at a lower prevalence threshold would also improve access to treatment for many impoverished people who remain infected. However, careful programmatic design and delivery would be essential to ensure that access to medicines is provided equitably to reach all at-risk populations and avoid repeated treatment of easily accessed populations (for instance, children in school, the wealthy) that could instead worsen equity.

In any community where preventive chemotherapy is successful, and programmes are beginning to move towards the elimination of transmission, the intervention may bring

little direct benefit to some individuals who carry very low levels of infection or who are not infected. This aspect is an inevitable consequence of any approach involving preventive chemotherapy. Programme managers should therefore monitor the situation and be ready to adjust their strategies in response at the earliest possible time. The safety profile of praziquantel is good, so any risks to uninfected individuals who take the medicine are minimal.

Feasibility. The GDG agreed that preventive chemotherapy at most prevalence thresholds is technically feasible. The various delivery modes that could be used to reach at-risk populations are described in section 3.2.1. Many ongoing community-wide programmes for other NTDs that target elimination are operating in settings of low prevalence, underscoring the feasibility of a preventive chemotherapy programme at most prevalence thresholds for schistosomiasis. As programmes are ongoing, attention is needed to ensure that coverage remains high given the risk of non-compliance and treatment fatigue.

Where school-based approaches are not possible, an important dimension of the feasibility of preventive chemotherapy for NTDs, including schistosomiasis, is the front-line delivery in communities of praziquantel to infected individuals and those who discharge this role. Different countries have adopted different approaches, in line with the local context. Most programmes have involved people designated as health care workers, primary health care workers, community health workers and community drug deliverers (collectively referred to as community drug distributors) *(79, 80)*.

The duties and responsibilities associated with the roles of community drug distributors vary from programme to programme and may not always be well-defined. Any training offered to them may be sporadic *(80)*. Generally, they may be expected to educate the community about schistosomiasis, keep census information up to date, safely distribute drugs, encourage communities to accept annual rounds of treatment, monitor individual compliance and treatment coverage and record any adverse side-effects of treatment.

Achieving 75– 100% treatment coverage is largely dependent on the intrinsic and extrinsic motivation of community drug distributors, many of whom are unpaid volunteers and yet discharge their duties and responsibilities at a significant opportunity cost to themselves. The long-term success and sustainability of preventive chemotherapy and progress towards elimination will continue to require the continued contribution of community drug distributors. Instigating programmes based on a 10% prevalence threshold will place ever greater demands on them, potentially impacting their performance and jeopardizing the success of the programme *(81)*. Rather than supporting equity, the demands on community drug distributors that result in reduced performance could reduce equity. It is essential therefore that consideration is given to finding better ways to support, train and incentivize this critical human element of praziquantel delivery.

In making their decisions on the use of these interventions and their interrelation with specific prevalence thresholds, the GDG considered the following.

- The evidence identified in these systematic reviews indicated that preventive chemotherapy reduces the prevalence of *Schistosoma* spp. infection (moderate certainty of the evidence) (see **Annex 4.1.1**).

- The application of observational studies from the Schistosomiasis Consortium for Operational Research and Evaluation (SCORE) programme supported the need for a prevalence threshold in the range of 10– 25% to adequately reduce the prevalence of schistosomiasis.
- The identification of the optimal prevalence threshold balances resource utilization and expected health benefit. A single prevalence threshold was chosen to ensure logistical ease of implementation in diverse settings.
- The cost–effectiveness of modelling finds the optimal prevalence threshold to be estimated at 5– 10% if only considering community-wide treatment with the alternative being no preventive chemotherapy.
- People across all age groups infected with *Schistosoma* spp. benefit significantly from treatment with praziquantel to cure infection or reduce worm burden, and it may have benefits in reducing the incidence of related morbidities.
- Preventive chemotherapy with praziquantel effectively reduces overall prevalence of *Schistosoma* spp. and likely has the benefit of reducing associated disease burden.
- Preventive chemotherapy with praziquantel is well tolerated across all age groups and *Schistosoma* species, with only transient, mild adverse events reported such as abdominal pain, headache and dizziness; adverse events in non-infected persons are uncommon.
- Pregnant women in the first trimester should be excluded from preventive chemotherapy in harmonization with guidance for other NTDs suitable for preventive chemotherapy that are co-implemented, such as soil-transmitted helminthiases, and the limited number of pregnant women in the first trimester included in available safety studies.
- Preventive chemotherapy with praziquantel is well accepted among children, parents, teachers, health workers and members of the community, is technically feasible and remains a cost-effective intervention, even with community-wide treatment. Giving praziquantel with food, such as bread, biscuits, juices or porridge, can increase acceptability and lower the incidence and severity of adverse effects.

3.2.3 Frequency of preventive chemotherapy with praziquantel

Overall results of evidence on the effect of frequency of praziquantel for preventive chemotherapy against schistosomiasis

1. In most endemic communities where the prevalence of infection with *Schistosoma* spp. is 10% or higher, WHO recommends annual preventive chemotherapy with praziquantel.

2. In settings of high prevalence (≥ 50%) or persistent hot spots, biannual (twice a year) preventive chemotherapy with praziquantel may be more effective than

annual treatment at reducing the prevalence of infection, intensity of infection and prevalence of infections of heavy intensity.

3. Moderate quality data on the increased frequency of preventive chemotherapy exist only for *S. haematobium*, but this conclusion is expected to extend to *S. mansoni* and *S. japonicum*.

4. Biannual preventive chemotherapy with praziquantel may be more cost-effective than annual treatment, especially in high prevalence settings.

5. Identification of persistent hot spot communities will require follow up surveys to detect a lack of prevalence reduction after multiple years of high treatment coverage with preventive chemotherapy. Based on published work, the GDG determined that a reasonable definition for "persistent hot spot" communities includes those with a less than one-third relative reduction in baseline prevalence after 2 years of annual preventive chemotherapy.

Considerations in formulating the recommendations

Certainty of evidence. Certainty of evidence. The overall certainty of evidence for the effect of biannual versus annual preventive chemotherapy against schistosomiasis on critical parasitological outcomes was moderate when considering data for *S. haematobium*, and low or very low when considering data for *S. mansoni* (due to limited sample size from two studies).

Balance of benefits and harms. The morbidity and mortality of schistosomiasis are well documented, as previously discussed. Biannual administration of praziquantel through preventive chemotherapy may provide more benefit in the treated community (for those that are infected) by both reducing infection intensity and curing those who are infected, relative to the administration of annual of treatment in some cases. This benefit is expected to be greatest in high prevalence (≥ 50%) settings where larger numbers of infections of moderate or heavy intensity are found, or in persistent hot spot communities with high transmission dynamics and high reinfection rates in which prevalence cannot be reduced without more frequent treatment. While studies linking preventive chemotherapy with direct benefits to health continue to be limited and have remained somewhat controversial, sufficient evidence exists to support the view that treatment of schistosomiasis through preventive chemotherapy does improve human health *(54, 55, 82)*. Importantly, no direct benefit is expected for those in the community who are uninfected. They may be in the majority in many settings.

Safety trials with praziquantel have shown that it is well tolerated *(58–65)*. The risk of adverse events is summarized in **Annex 4.2**.

Values and preferences. The GDG agreed that there was little variability in the value that populations assigned to interventions to control schistosomiasis (see previous discussion of values and preferences).

Acceptability. Preventive chemotherapy against schistosomiasis is generally widely accepted by policy-makers, health workers and teachers involved in deworming programmes *(68, 69)*. Many countries have national schistosomiasis control programmes.

The acceptability of preventive chemotherapy has been previously discussed, and more frequent treatment (twice annually) is not expected to change this.

Resource implications. The GDG agreed that more frequent biannual (treatment twice a year) preventive chemotherapy against schistosomiasis in at-risk populations would provide a favourable ratio of resources relative to the expected benefit.

A review of the literature concluded that a strategy of biannual preventive chemotherapy against schistosomiasis in at-risk populations, compared with annual treatment, either school-based or community-wide, met conventional measures for cost–effectiveness in many scenarios *(9, 70, 71)*. In comparison, proposals for a selective test-and-treat strategy would be more resource intensive since this approach would require clinic visits, diagnostic screening and treatment; a selective approach may also be less effective given the imperfect sensitivity of helminth diagnostics that could miss infections.

The cost–effectiveness of biannual preventive chemotherapy would be increased if applied in higher prevalence settings; therefore, the choice of prevalence thresholds to guide frequency of praziquantel can improve the resource efficiency. A cost–effectiveness analysis which estimated the efficient thresholds for school-based and community-wide annual and biannual preventive chemotherapy found that in settings with schistosomiasis prevalence greater than 30%, biannual preventive chemotherapy delivered to the entire at-risk community was cost-effective *(9)*.

Equity. The GDG agreed that more frequent preventive chemotherapy would yield greater reductions in schistosomiasis disease burden and could improve equity.

Schistosomiasis is a disease that disproportionately affects the poor, vulnerable and those unable to obtain health services. More frequent preventive chemotherapy that provides better control of overall disease burden could yield improved equity by especially benefiting the marginalized populations that are most affected. However, careful programmatic design and delivery would be essential to ensure that drug access is provided equitably to reach all at-risk populations and to avoid repeated treatment of more easily accessed populations (for instance, children in school, the wealthy) that could instead decrease equity.

Feasibility. The GDG agreed that biannual preventive chemotherapy with praziquantel is technically feasible. Annual programmes for schistosomiasis have been ongoing in many countries, and biannual preventive chemotherapy programmes exist for other NTDs.

During its deliberations, the GDG considered the following evidence that resulted in the recommendations:

- This summarized evidence supported the selection of the frequency of annual preventive chemotherapy for recommendation 1, with the further recommendation to switch to biannual preventive chemotherapy in communities that lack appropriate response in prevalence for recommendation 3. There is low to moderate certainty of evidence to support biannual treatment, although considerably less certainty on when it is needed.
- The settings that may benefit from biannual versus annual treatment may be those that lack an appropriate response to annual preventive chemotherapy, which could

be defined by a less than one-third relative reduction in prevalence (range of values given to account for various epidemiological settings and baseline prevalence) comparing the baseline prevalence survey and a repeat prevalence survey completed after 2 years of annual preventive chemotherapy. This is based on data that this change may predict a persistent hot spot that would benefit from biannual treatment. The relative reduction in prevalence can be estimated as follows: [(prevalence at baseline − prevalence at year 3)/(prevalence at baseline)].The intervening period should include a minimum of two MDA rounds to all at-risk groups at adequate treatment coverage (≥ 75%). Alternative definitions could consider absolute change in prevalence in infection, or change in average intensity of infection (defined as egg concentration in stool or urine).

- Biannual preventive chemotherapy may be more effective than annual treatment for settings at risk for *S. haematobium* in reducing prevalence and intensity of infection, especially in high prevalence (≥ 50%) settings and persistent hot spot communities.
- There is very low certainty of evidence on the effectiveness of biannual preventive chemotherapy on *S. mansoni* or *S. japonicum* species, although the effectiveness of biannual preventive chemotherapy is expected to be comparable to the estimated effectiveness in *S. haematobium*.
- Data from SCORE demonstrate that before preventive chemotherapy is used it is difficult to predict which settings will be persistent hot spots and require intensified preventive chemotherapy.
- Preventive chemotherapy with praziquantel of annual or biannual frequency is generally well tolerated in all age groups, with only mild transient adverse events.
- Whether given at annual or biannual frequency, preventive chemotherapy with praziquantel is well accepted among children, parents, teachers, health workers and members of the community, is technically feasible and remains a cost-effective intervention, even with community-wide treatment.
- High prevalence settings (defined as areas with baseline prevalence of infection of 50% and above in SAC were considered a priority for biannual preventive chemotherapy programmes.

4. Safety of praziquantel for treatment of schistosomiasis

4.1 Recommendations

Recommendation 4

WHO recommends that health facilities provide access to treatment with praziquantel to control morbidity due to schistosomiasis in all infected individuals regardless of age, including infected pregnant excluding the first trimester, lactating women and pre-SAC aged < 2 years. The decision to administer treatment in children under 2 years of age should be based on testing and clinical judgement.

Strong recommendation

Certainty of evidence: moderate

Implementation consideration

- Pregnancy status should be assessed by discretely questioning the individual herself. If she is uncertain, a negative urine-based pregnancy test can be requested before the treatment is administrated.
- The medicine for children aged < 2 years should be an oral formulation (currently under development) that is easily administered, disintegrates in the mouth and, ideally, has a sweet taste and smell; if paediatric formulations are not available, praziquantel crushed in soft food may be used for individual case treatment only.

4.2 Rationale

Overall results of evidence on the safety of praziquantel for treatment of schistosomiasis in at-risk populations

1. Treatment with praziquantel is well tolerated with only transient, mild adverse events such as abdominal pain, headache and dizziness.

2. Treatment with praziquantel is well tolerated across all age groups, when treating any Schistosoma species, and in uninfected persons.

Considerations in formulating the recommendations

Certainty of evidence. The overall certainty of evidence for the safety of praziquantel for treatment of schistosomiasis in at-risk populations was moderate.

Balance of benefits and harms. The morbidity and mortality of schistosomiasis are well documented, as previously described. Any infected individual should be treated, regardless of age. The potential harms described for preventive chemotherapy with praziquantel are based upon adverse events from giving the medicine both to those who are infected (who benefit) and those who are uninfected (who do not benefit). The evidence synthesized demonstrates the safety of praziquantel, with documented transient, mild adverse events such as abdominal pain, headache, dizziness and diarrhoea *(83, 66, 84, 85)*; persistent mild, moderate and severe adverse events were uncommon *(59– 66)*. People with infections of high intensity also had a higher incidence of mild adverse events, but would also be expected to benefit most from treatment *(59, 60)*. The concern for harm is of greatest consequence in people who are not infected but are nevertheless treated, given the public health approach of preventive chemotherapy, and therefore bear a risk of adverse events without immediate personal benefit (although with lower risk of those adverse events than among those who are infected at the time of treatment). Case reports of more serious adverse effects exist, although causality remains uncertain. Given the limited number of pregnant women at first trimester included in the available study *(86)* and on the basis of exercising maximum precaution, the GDG decided to recommend exclusion of pregnant women in the first trimester from preventive chemotherapy campaigns even though the study did not report risk on adverse pregnancy outcomes. There remains a poorly characterized concern for treatment with praziquantel when a person has another concurrent infection such as neurocysticercosis, although associated adverse effects have not been noted in practice. Patients with neurocysticercosis are treated routinely with doses of praziquantel (for example, 50 mg/kg per day for 10 consecutive days) that are many times higher than those used in annual MDA programmes for schistosomiasis, suggesting the drug is well tolerated in such individuals. However, out of an abundance of caution, in areas co-endemic for *Taenia solium*, MDA with praziquantel should not include people with signs compatible with neurocysticercosis, such as seizures, and active surveillance should be conducted and include post-MDA neurological side-effects. Finally, there remains a concern around choking or aspiration during administration of medications, especially in younger children, with that concern rising where treatments are more frequent and total doses are higher *(67)*.

Values and preferences. The GDG agreed that there was likely variability in the value that populations assigned to safety of praziquantel used in preventive chemotherapy programmes to control schistosomiasis. Some people may be more averse to experiencing adverse effects than others. Yet, as far as we know, these adverse events are generally not serious, and well-informed individuals will likely place high value on treating people infected with schistosomiasis and accept the trade-off of experiencing transient mild symptoms related to treatment in order to reduce prevalence and morbidity (see previous discussion of values and preferences).

Acceptability. When the status of infection is proven, in health facility-based treatment the need for treatment tends to overcome the fear of any potential side-effects.

Preventive chemotherapy against schistosomiasis is generally widely accepted by relevant stakeholders, as previously discussed.

Resource implications. The GDG agreed that the implementation of routine treatment in health facilities, and preventive chemotherapy with praziquantel against schistosomiasis in at-risk populations, would both carry a favourable ratio of required resources relative to expected benefit. This would require the heath system to make praziquantel available for treatment of infected individuals in health facilities of endemic areas. A review of the literature concluded that a strategy of preventive chemotherapy against schistosomiasis has favourable cost–effectiveness *(9, 70, 71)*.

Equity. The GDG agreed that more preventive chemotherapy with praziquantel would yield greater reductions in schistosomiasis disease burden and could improve health equity.

Schistosomiasis is a disease that disproportionately affects poor, vulnerable populations and those who are unable to obtain health services. For this reason, the medication used to treat this infection in a public health programme is necessarily required to have a robust safety profile. Given high efficacy and typically mild, transient adverse events, individual treatment or preventive chemotherapy with praziquantel would likely provide better control of individual- or population-level disease burden that could yield improved equity by benefiting especially the marginalized populations that are most affected.

Feasibility. The GDG agreed that individual treatment and preventive chemotherapy with praziquantel are both technically feasible. Annual preventive chemotherapy programmes for schistosomiasis have been ongoing in many countries for a number of years.

The feasibility of preventive chemotherapy with praziquantel would depend upon the at-risk population of interest. For treatment of SAC, school-based delivery systems would be appropriate, which are supported by ministries of health and education. For children not attending schools, adolescents and at-risk adults, community-based distribution channels are required. The medications have been administered through preventive chemotherapy programmes without the presence of a medical doctor and without significant adverse reactions being documented. The favourable safety profile of praziquantel ensures easier feasibility of administration. Part of the praziquantel remaining after MDA could be allocated for routine treatment of infected individuals presenting to health facilities of endemic areas.

Overall, the decision-making process of the GDG was informed by the following considerations:

- The evidence assessed indicated that use of praziquantel is safe in children aged 2 years and older, as well as in adults, pregnant women after the first trimester and lactating women, as indicated in recommendation 1. However, due to data limitations in children aged under 2 years, the GDG determined that clinical judgement should be exercised in these cases, as outlined in recommendation 4.
- People across all age groups infected with *Schistosoma* spp. benefit significantly from treatment with praziquantel to cure the infection or reduce worm burden and other schistosomiasis-related morbidities.

- Preventive chemotherapy with praziquantel is well tolerated, with typically transient mild adverse events reported such as abdominal pain, headache and dizziness.
- Preventive chemotherapy with praziquantel is well tolerated across all age groups, in pregnant women, in treatment across *Schistosoma* species, and in those who are not infected with *Schistosoma*.
- Preventive chemotherapy with praziquantel is well accepted among children, parents, teachers, health workers and members of the community, is technically feasible and remains a cost-effective intervention.

5. WASH and snail control interventions

5.1 Recommendations

Recommendation 5

WHO recommends WASH interventions, environmental interventions (water engineering and focal snail control with molluscicides) and behavioural change interventions as essential measures to help reduce transmission of Schistosoma spp. in endemic areas.

Strong recommendation

Certainty of evidence: low

Implementation considerations

- WASH interventions are expected to provide modest benefits in limiting Schistosoma transmission, but these benefits extend also to reducing risk for multiple infectious diseases.
- Behavioural change interventions should be implemented from the start of any preventive chemotherapy programme.
- Coordination and joint planning between programmes for control of schistosomiasis and WASH are essential. Inclusion of WASH in the schistosomiasis strategy will require mapping and sharing of epidemiological information alongside WASH coverage to ensure prioritization of water and sanitation services to areas that are endemic for schistosomiasis.
- Similarly, schistosomiasis education and health programme delivery should include inputs to WASH programme design, collaboration on behavioural change interventions and integration of behavioural change promotion.
- Where persistent hot spots of transmission emerge during the course of preventive chemotherapy campaigns, control of intermediate host snail populations should be prioritized especially if the programme is already achieving high levels of treatment coverage.
- Co-implementation of snail control with mass treatment campaigns is expected to hasten achievement of WHO goals for morbidity control and elimination as a public health problem.

- Snail control will be essential to ultimately eliminate local transmission, in combination with WASH interventions.
- Sensitization and public health awareness campaigns will be necessary to ensure high acceptance of snail control interventions.
- Development of snail control programmes will require a larger and less expensive global supply of molluscicides.
- Skilled and dedicated snail control workers will be essential to the success of snail control initiatives.
- Deworming should be delivered together with promotion of health and hygiene to reduce transmission by encouraging healthy behaviours such as proper disposal of faeces.

5.2 Rationale

5.2.1 WASH interventions and schistosomiasis in at-risk populations

Evidence on the impact of WASH on schistosomiasis

1. Access to improved WASH may reduce prevalence of schistosomiasis.

2. The relationship between improved WASH and schistosomiasis was heterogeneous, and suggests the importance of contextual factors on the potential impact of these interventions.

3. The majority of data linking access to WASH and schistosomiasis are of low or very low certainty of evidence, mostly cross-sectional surveys.

4. Although the evidence used to inform this recommendation was based on two systematic reviews published in 2013 and 2015, no relevant data warranting the revision of this recommendation have emerged; therefore, the systematic reviews are valid and applicable.

Considerations in formulating the recommendations

Certainty of evidence. The overall certainty of evidence for the effect of improved WASH interventions on critical outcomes of prevalence of schistosomiasis was low or very low. This is partially due to the complexity involved in designing randomized-controlled trials focused on the WASH practices specific to a pathogen (for example, *Schistosoma*), and other design and methodological challenges.

Balance of benefits and harms. The morbidity and mortality caused by schistosomiasis are well documented, ranging from malnutrition, anaemia and infertility, to liver and kidney failure, cancer and death *(53)*. More effective suppression of *Schistosoma* infection and reinfection is likely to provide benefit in the treated community by reducing intensity and duration of infection in at-risk populations. The results from the meta-analysis support the concept that the addition of interventions to improve WASH may decrease prevalence of schistosomiasis, as mediated through reduced contact with

cercaria-infested water, via prevention of faecal or urinary contamination of water bodies. Notably, WASH interventions will likely have other desirable effects on communities by reducing other excreta-related infections, such as diarrhoeal disease, typhoid fever and soil-transmitted helminth infections. In addition, there may be potential benefits in terms of child growth and social and mental well-being *(46, 87, 88)*. To achieve these goals, WASH interventions should be implemented in a way that maximizes health impacts, according to the principles set out in WHO guidelines related to water and sanitation *(89– 92)*.

The potential harm from using a WASH focus would be any lost resources when the intervention is not implemented appropriately. For example, failure at any step of the sanitation chain (from point of generation to final disposal or use) can result in contamination with human excreta with consequent ongoing transmission.

Values and preferences. The GDG agreed that there was little variability in the value that populations assigned to WASH interventions to control schistosomiasis.

In general, significant gaps still exist in knowledge about schistosomiasis and its impacts on health. Knowledge of WASH impacts on health are likely greater. The use of WASH to supplement schistosomiasis control efforts may further increase the value of and preference for WASH interventions. The gaps in knowledge about schistosomiasis and health effects may affect preferences and acceptability of WASH interventions, although evidence suggests that health awareness is not always the main determinant for adoption of safer WASH behaviours and is highly context specific.

Acceptability. WASH interventions are generally well accepted by the community, although there is large variation in WASH programmes and their acceptance. Generally, when WASH is designed and delivered in a way that responds to cultural, social and economic contexts, as well as the needs and preferences of individuals, households and communities, these WASH programmes are well accepted. However, if the intervention is not implemented with consideration of the above and in line with the WHO guidelines *(89– 92)*, acceptability of services may be reduced (for example, lack of sinks and showers near water supplies, inadequate privacy and safety of the toilet facilities or use of hardware or technologies that do not meet user preferences), resulting in a lack of uptake of services and lack of use (including reverting to open defecation).

Resource implications. WASH interventions often require high resource utilization, both for building infrastructure as well as for continued operation and maintenance. Water supply and sanitation services are often implemented and financed outside the health sector, involving a multitude of stakeholders. This includes different government ministries (for instance, infrastructure, public works), municipalities, utilities and households, etc. Health authorities should contribute resources towards coordination with key WASH stakeholders, training of health staff on environmental health expertise, monitoring systems and development of robust behaviour change approaches. These costs should be considered in comparison with the likely benefits over the medium to long term, and across both schistosomiasis and other infectious

diseases where health benefits may be derived. As settings reduce the overall disease burden of schistosomiasis, the unit cost per treatment becomes more expensive and these environmental and behavioural factors will be needed. There are no formal cost-effectiveness studies of WASH interventions on schistosomiasis.

Safe WASH access and practices are generally associated with a reduced risk of schistosomiasis but have higher resource needs *(93, 94)*. Environmental and behavioural factors will be needed to phase out preventive chemotherapy and snail control while preventing rebound of infection. This transition could potentially be resource-saving in the long term.

Equity. Schistosomiasis tends to affect the poorest and most vulnerable communities which also lack access to basic WASH services, tend to be affected by other excreta-related infections, and are less likely to be able to afford the cost of treatment and other economic consequences of ill health and poor well-being. Improving access to and use of WASH among communities that are most affected by schistosomiasis is thus likely to improve equity. Interventions should consider availability, accessibility, and quality of safe water and sanitation services.

Feasibility. The GDG agreed that reduction of *Schistosoma* transmission via WASH interventions may be a valuable complementary strategy to preventive chemotherapy and potentially technically feasible in some settings. WASH to address schistosomiasis is likely to be most feasible through better coordination and joint planning between schistosomiasis control programmes and ongoing WASH programmes, including through sharing and mapping of epidemiological information alongside WASH coverage, providing inputs to WASH programme design, collaborating on behaviour change interventions and integrating behaviour change promotion within delivery of schistosomiasis/education/health programmes.

Overall, during its deliberations the GDG took into particular consideration the following evidence that resulted in the above recommendation.

- The evidence assessed supported the recommendation for the effectiveness of WASH interventions as a complementary measure to reduce the prevalence of schistosomiasis. While the certainty of evidence was low, the strong strength of the recommendation is influenced by the many indirect benefits of WASH across other infectious diseases and aspects of health.
- There are low-quality data (from multiple observational studies) to indicate that higher levels of WASH access and practices are associated with reduced risk of Schistosoma infection.
- WASH activities are likely resource intensive, but may be more feasible by coordinating with other ongoing WASH programmes.

5.2.2 Chemical-based snail control in at-risk communities

Overall results of evidence on the relationship of chemical-based host snail control against schistosomiasis in at-risk communities

1. Chemical-based snail control may reduce the prevalence and incidence of schistosomiasis, with additional effectiveness when combined with preventive chemotherapy.

2. The majority of data on snail control and epidemiological outcomes are of low or very low quality, often from un-controlled studies.

3. The relationship of snail control and reductions in prevalence and incidence was heterogeneous by setting and water type, although it did not appear to depend on baseline prevalence.

4. The addition of molluscicide to preventive chemotherapy is expected to be cost-effective in both low- and high-prevalence settings.

Considerations in formulating the recommendations

Certainty of evidence. The overall certainty of evidence for the effect of molluscicides-based snail control on critical outcomes of prevalence and incidence was low or very low when considering data for *S. haematobium* and *S. mansoni*. There were insufficient data to provide estimates for *S. japonicum*.

Balance of benefits and harms. The morbidity and mortality of schistosomiasis is well documented as discussed previously. The results from the meta-analysis support the view that the addition of snail control may reduce prevalence and incidence of schistosomiasis.

A systematic review of the safety of the most commonly used chemical molluscicide (niclosamide) has found broadly minimal risk to humans and the environment, provided the application is appropriately dose-limited, informed and supervised *(95)*. Niclosamide is harmful to fish, amphibia, certain insect larvae and, in higher doses, to aquatic vegetation, although these effects are generally short lived *(96–98)*. The evidence supports the conclusion that niclosamide is not toxic to livestock. While niclosamide for snail control is not likely to result in human ingestion, this chemical is considered safe for humans, as it is an approved human drug for treatment of tapeworm infection, and is also considered safe for use during pregnancy *(99)*. Because niclosamide decays quickly, over 24 hours, animals that can rapidly move away from an area of application may return in a matter of days *(100)*. Focal application of niclosamide at human-water contact sites can further reduce any deleterious environmental effects of snail control, while still maximizing potential benefits on *Schistosoma* transmission *(101)*.

Values and preferences. The GDG agreed that there was some variability in the value that populations assigned to interventions to control schistosomiasis. While studies are

limited, there is likely a concern by the population about snail control and effects on the environment.

Acceptability. Limited studies suggest a high degree of acceptance of niclosamide-based snail control in test communities *(97, 102)*. Policy-makers, health workers and teachers involved in schistosomiasis control programmes may have varying concerns about the environmental impact of niclosamide on local flora and fauna. The acceptability of snail control is likely related to levels of knowledge about molluscicide. The acceptability of snail control interventions among the population is generally considered to be higher with sensitization and other awareness and educational campaigns prior to implementation; these educational campaigns often include supplementary information on the importance of water and hygiene.

Resource implications. The GDG agreed that the implementation of snail control with preventive chemotherapy against schistosomiasis in at-risk populations would require consideration of the favourable ratio of resources relative to expected benefits but may prove relatively cost-effective in some settings.

A review of the costing literature and recent experience in Zanzibar *(98)* yielded an average cost of delivering molluscicide per village of US$ 379. This estimate included procurement and distribution of capital equipment and supplies, training and supervision of snail control field workers, and monitoring. Modelling studies of mass drug treatment combined with snail control, using summary estimates of impact taken from the meta-analysis, indicated that incremental cost–effectiveness for adding snail control in an endemic African area meets the conventional definition for being highly cost-effective *(103)*. In both low- and high-prevalence settings, community-wide MDA with additional snail control reduced total disability by an additional 40% compared with school-based MDA alone. The optimally cost-effective scenario included the addition of snail control to MDA in more than 95% of simulations *(103)*.

Equity. The GDG agreed that more effective transmission control via snail control interventions would yield greater reductions in schistosomiasis disease burden and could improve equity.

Schistosomiasis is a disease that disproportionately affects the poor, vulnerable and those unable to obtain health services. Interventions that provide better control of overall disease burden could yield improved equity by especially benefiting the marginalized populations that are most affected. However, careful programmatic design and delivery would be essential to ensure that snail control is provided equitably in order to reach all at-risk populations and to avoid repeated treatment of easily accessed populations (for instance, more wealthy communities) that could instead worsen equity.

Feasibility. The GDG agreed that reduction of *Schistosoma* transmission via snail control is technically feasible in some settings. Programmes for schistosomiasis control are now ongoing in many countries, but many of the recently implemented programmes may not have experience with molluscicide-based snail control. There may be opportunities for integration into existing vector control programmes for malaria, and changes in resource utilization based on scale of programmes. Capacity-building (for snail identification and control implementation) and coordination among relevant ministries (health, education, water, roads, and agriculture) will be essential to obtain optimal results. WHO has

developed technical manuals to build capacity of programmes in utilizing molluscicides *(104)* and guidelines for their evaluation *(105, 106)*.

Overall, during its deliberations the GDG took into consideration the following aspects that resulted in the formulation of this recommendation.

- The evidence assessed supported the recommendation for the effectiveness of WASH interventions as a complementary measure to reduce the prevalence of schistosomiasis. While the certainty of evidence was low, the strong strength of the recommendation is influenced by the many indirect benefits of WASH across other infectious diseases and aspects of health.
- The body of evidence on the effectiveness of focal snail control supported the use of this intervention as a complementary measure to reduce the prevalence of schistosomiasis.
- There are low-quality data (from multiple studies) to indicate that well-informed implementation of chemical-based molluscicide for control of intermediate host snails of *Schistosoma* spp. can reduce local prevalence and incidence of human infections.
- There are very low-quality data on the necessary frequency of molluscicide application. These indicate a broad range of potential intervals, reflecting the variation in local ecology of snail habitats.
- The additional benefit of adding molluscicide to preventive chemotherapy to further reduce morbidity from schistosomiasis is expected to be cost–effective in both low- and high-prevalence settings.

6. Verification of interruption of transmission

6.1 Recommendation

Recommendation 6

In communities approaching the interruption of transmission (defined as having no autochthonous human cases reported for 5 consecutive years), WHO suggests a verification framework that consists of:

1. Testing for *Schistosoma* infection in humans with a diagnostic that has high sensitivity and specificity. This may require the use of a two-step diagnostic process starting with a high sensitivity test confirmed with a second, high specificity test.
2. Testing for *Schistosoma* infection in snails with a diagnostic that has high sensitivity and specificity. This may require the use of a two-step diagnostic process starting with a high sensitivity test confirmed with a second, high specificity test.
3. Testing for *Schistosoma* infection in non-human mammalian hosts, as applicable, with a diagnostic that has high sensitivity and specificity. This may require the use of a two-step diagnostic process starting with a high sensitivity test confirmed with a second, high specificity test.

Conditional recommendation

Certainty of evidence: low

Implementation considerations

- The eventual predictive performance of the sampling of humans, snails and non-human mammalian hosts to identify settings that have eliminated transmission will depend upon the sampling strategy, with decisions on sample size, geographical zone and timespan for sampling.
- Future work could consider a two-step verification of *Schistosoma* infection status in humans with a first highly sensitive test (for example, serology) and a second confirmatory highly specific test (for example, miracidia hatching test).
- Sampling and diagnostic tools in snail populations and in non-human mammalian hosts should be considered when interruption of transmission is the public health goal and is suspected based on recent epidemiological surveys in human populations.

- The magnitude of the contribution of non-human mammalian hosts to transmission of schistosomiasis remains understudied, especially for species other than *S. japonicum*.

6.2 Rationale

6.2.1 Diagnostic tools for detection of Schistosoma infection in humans to verify elimination of transmission

Overall results of evidence on tools for diagnosis of Schistosoma infection in humans

1. There is good evidence to support the continued use of conventional tools of Kato–Katz and point-of-care circulating cathodic antigen tests to detect *S. mansoni* and of urine microscopy for *S. haematobium* to support epidemiological surveillance in areas of moderate or high prevalence, despite the low sensitivity for low intensity (light) infections seen with urine and stool microscopy.

2. There is insufficient evidence to support using new diagnostic methods beyond the conventional tools of microscopy of Kato–Katz smears or urine filtration, or point-of-care circulating cathodic antigen tests, for epidemiological surveillance.

3. Further work is needed to characterize the sensitivity and specificity of immunological and molecular diagnostic tools for human schistosomiasis.

Considerations in formulating the recommendations

Certainty of evidence. The overall certainty of evidence for the accuracy of tools to diagnose Schistosoma infections in humans was moderate; there were no data for the assessment of the accuracy of any diagnostic tool to predict elimination.

Balance of benefits and harms. The use of diagnostic tools for human *Schistosoma* infections has substantial benefits to clinical care and public health. In the public health setting, diagnostics that are sensitive, specific and resource efficient would improve the identification of people with schistosomiasis, especially those with infections of light intensity that may be missed by less sensitive methods, and guide optimal public health decisions. More sensitive diagnostics would be of particular importance in the setting of verifying transmission elimination or estimation of prevalence in low prevalence settings. The evidence supports the benefit of conventional tools of Kato–Katz and point-of-care circulating cathodic antigen tests for *S. mansoni* and of urine microscopy for *S. haematobium* that broadly meet these criteria, even though the stool and urine microscopy assays are of low sensitivity for detection of light infections.

There is the potential for harm with diagnostic tools for human *Schistosoma* infections, mainly if the tool lacks adequate sensitivity. This adverse outcome could include missing a diagnosis that affects a clinical decision or, in the public health setting, by producing a biased estimate of the prevalence resulting in a potentially suboptimal public health decision. If the diagnostic tool was applied to verifying elimination of transmission, poorly sensitive diagnostics may misclassify a setting as having interrupted transmission, when in reality the setting remained endemic for schistosomiasis. This would result in withholding preventive chemotherapy and other interventions against schistosomiasis

from people who would benefit from treatment and risk rebound of disease in the population. Alternatively, a poorly specific diagnostic could misclassify a setting as being persistently endemic that would subject the population to continued interventions and utilize resources without expected benefit. The evidence supports the use of the conventional tools of Kato–Katz and point-of-care circulating cathodic antigen tests for *S. mansoni* and of urine microscopy for *S. haematobium*, although given the low sensitivity of the microscopy assays for detecting infections of light intensity, there remains some risk of harm in these domains.

Values and preferences. The GDG agreed that there was little variability in the value that populations assigned to diagnostic tools for human schistosomiasis.

Conventional methods for diagnosis of schistosomiasis have been around for decades and are well accepted, including Kato–Katz for *S. mansoni* and urine microscopy for *S. haematobium*. More recently, point-of-care circulating cathodic antigen testing was introduced for diagnosis of *S. mansoni* and has been gradually adopted *(15, 107)*. Therefore, it is reasonable to assume that if new diagnostic methods provided value in accuracy or resource efficiency, this diagnostic would be well valued by public health officials and populations affected by schistosomiasis alike.

Acceptability. Conventional Kato–Katz and point-of-care circulating cathodic antigen diagnostic tests for *S. mansoni* and urine microscopy for *S. haematobium* are well accepted in guiding decision-making in schistosomiasis programmes *(68, 69)*. The acceptability of human diagnostics for schistosomiasis is likely related to the level of knowledge about the disease. New diagnostics would require education and discussion, and exchange with local health workers and national decision-makers before being adopted. Generally, it is reasonable to assume that if new diagnostic methods provided value in accuracy or resource efficiency, they would be well accepted by public health officials and populations affected by schistosomiasis alike.

Resource implications. The GDG agreed that continued use of conventional Kato–Katz and point-of-care circulating cathodic antigen diagnostic tools for *S. mansoni* and urine microscopy for *S. haematobium* have a favourable ratio of resources relative to the expected benefit. These conventional tools remain relatively low cost, although they require some technical expertise. In the future, if new diagnostic tools were sensitive, specific and resource efficient, they could enable improved detection of schistosomiasis to aid verification of transmission elimination, which would inform the cessation of several interventions against schistosomiasis and provide significant financial and human resource savings. Put simply, the magnitude of cost of the parasitological and point-of-care circulating cathodic antigen tests is significantly lower relative to current immunological and molecular testing counterparts.

Equity. The GDG agreed that choice of human diagnostic tools for schistosomiasis would have only minimal implications for equity.

Schistosomiasis is endemic in populations that disproportionately affect poor and vulnerable populations and those who are unable to obtain health services, therefore any tool that improves diagnosis or public health intervention against this disease has some implication to improve equity. New diagnostic tools for schistosomiasis that are more sensitive, specific, and resource efficient may improve equity through better

diagnosis in humans, especially in lower prevalence settings, and would support efforts to verify elimination.

Feasibility. The GDG agreed that using current diagnostic tools for schistosomiasis is feasible.

Conventional methods for diagnosis of schistosomiasis have been available for decades and are widely implemented in large population surveys, underscoring their feasibility. There is insufficient evidence to support the feasibility of using any new method beyond the conventional tools for diagnosis, Kato–Katz and point-of-care circulating cathodic antigen tests for *S. mansoni* and urine microscopy for *S. haematobium*, for mapping and monitoring of schistosomiasis in humans. Specifically, newer molecular techniques lack consistent data on sensitivity and specificity, are not available in commercially ready forms, and often rely on challenging laboratory and technical requirements. Future work is still needed to further characterize many molecular techniques including approaches based on polymerase chain reaction (PCR) and loop-mediated isothermal amplification (LAMP), which are produced in commercially available forms.

Overall, during its deliberations the GDG took into consideration the following aspects that resulted in the formulation of this recommendation:

- This summarized evidence supported the need for a test with high sensitivity and specificity for diagnosis of *Schistosoma* spp. in humans, which, based on the review, may require two separate tests.
- Conventional tools for diagnosis of human schistosomiasis of Kato–Katz for *S. mansoni* and urine microscopy for *S. haematobium* have low sensitivity and excellent specificity.
- Conventional diagnostic tools in humans are well accepted, low cost and feasible given their widespread implementation.
- New diagnostic tools, such as molecular-based and immunological diagnostics, lack sufficient data on sensitivity and specificity, and their utility is further limited by challenges with feasibility and resource implications.

6.2.2 Diagnostic tools for detection of Schistosoma in snails and the environment to verify elimination of transmission

Overall results of evidence on tools for detection of Schistosoma in snails and the environment

1. Conventional methods of snail shedding and crushing techniques are specific for detection of *Schistosoma* to genus level in snails and generally more feasible, but may lack sensitivity in detection.

2. Newer methods of LAMP are more sensitive for detection of *Schistosoma* in snails. They may allow for a sampling pooling strategy to improve resource efficiency but they are more technically challenging.

3. Although more evidence is needed to support molecular-based diagnostics for detection of *Schistosoma* in snails, techniques such as LAMP, eDNA (environmental

DNA) and qPCR (quantitative PCR) hold considerable promise for sensitivity and specificity.

4. The relationship between detection of *Schistosoma* in snails and ongoing transmission remains unclear and requires further elucidation.

5. Future work is needed to design a surveillance strategy using a defined diagnostic tool to identify the optimal snail sampling, geographical zone, timescale and resource utilization to predict verification of elimination.

Considerations in formulating the recommendations

Certainty of evidence. The overall certainty of evidence for the diagnostic accuracy of tools to detect *Schistosoma* in snails was low; there were no data for accuracy of any diagnostic tool to predict elimination.

Balance of benefits and harms. The use of diagnostic tools to identify *Schistosoma* in snails has substantial potential benefit to public health. Diagnostic tools that are sensitive, specific and resource efficient would improve the identification of snails harbouring *Schistosoma*, which may provide useful insights into ongoing transmission that are otherwise difficult to detect and would guide optimal public health decisions. The successful identification of geographical regions previously endemic for schistosomiasis, which have now eliminated ongoing transmission, could allow national programmes to cease regular preventive chemotherapy programmes. This would provide substantial savings in cost and general resource utilization (for instance, community health workers, public health staff) by stopping a programme that would provide no expected health benefit. Notably, the unique added value of diagnostic tools in snail populations to provide these resource benefits holds true only if these tools were superior to conventional surveys in human populations in terms of diagnostic accuracy or resource usage. The snail detection tools may also have application in post-elimination surveillance programmes or if reservoir hosts are believed to play a significant role in transmission.

More sensitive diagnostic tools would be of particular importance in the setting of verifying transmission elimination. The evidence supports the benefit of conventional tools of snail shedding and crushing techniques that are highly specific for detection of *Schistosoma* in snails and generally more feasible, as well as newer methods of LAMP, eDNA and qPCR that are more sensitive, although more challenging to implement given requirements for expensive, sophisticated laboratory infrastructure.

There is potential for harm with diagnostic tools for *Schistosoma* in snail populations, mainly if the tools lack adequate sensitivity. This adverse outcome could occur in the public health setting by producing a biased estimate of the prevalence of *Schistosoma* in snails, resulting in a suboptimal public health decision. If the diagnostic tool was applied to verifying elimination, poorly sensitive diagnostics might misclassify a setting as having eliminated transmission of schistosomiasis, when in reality the setting remained endemic for schistosomiasis; this would result in withholding therapy with praziquantel to people who would otherwise benefit from treatment and potentially allow the disease to rebound. Alternatively, a poorly specific diagnostic could misclassify a setting as being persistently endemic, which would subject the population to continued and unnecessary preventive chemotherapy campaigns and utilize resources without expected benefit. The evidence supports the use of conventional tools of snail

shedding and crushing techniques as well as newer methods of LAMP, eDNA and qPCR, although sometimes, given their low sensitivity, there remains some risk for harm in these domains.

Values and preferences. The GDG agreed that there was little variability in the value that populations assigned to diagnostic tools for *Schistosoma* in snail populations. The risk threshold of an endemic populations for misclassification of whether a setting has "eliminated" transmission (corresponding to the diagnostic tool and surveillance strategy) remains unclear. Historically, public health programmes have remained conservative, which would underscore the importance of a high sensitivity test and a high certainty of estimate.

Acceptability. Conventional human diagnostics to estimate prevalence are well accepted to guide preventive chemotherapy programmes *(68, 69)*. However, the acceptability of using diagnostic tools in snail populations as well as their implications for verifying elimination has not been studied. However, epidemiological surveys in non-human populations have been used in public health decision-making in cases of other infectious diseases, such as with xenomonitoring for other tropical diseases or mosquito-borne illnesses *(108)*. Additionally, recent advances in eDNA approaches have provided evidence for its utility in the detection of schistosomiasis from aquatic settings in Madagascar *(109)*, the United Republic of Tanzania *(110)* and the Philippines *(111)*. Generally, it is reasonable to assume that if new diagnostic methods provided value in public health decision-making or resource efficiency, that this diagnostic would be well accepted by the public health officials and populations affected by schistosomiasis. This would require discussion and exchange with local health workers and national decision-makers.

Resource implications. The GDG agreed that the diagnostic tools for *Schistosoma* in snail populations to verify elimination could, in future, potentially provide a favourable ratio of resources relative to expected benefit, if certain conditions are met.

The surveillance strategy to deploy a diagnostic tool in snail populations, including the optimal snail sampling, geographical zone and timescale, remains unclear and would determine overall resource utilization. Furthermore, many detection tools differ substantially based on their reliance on laboratory equipment and reagents, technical expertise and time intensiveness. The conventional tools of snail shedding and crushing techniques as well as newer methods of LAMP or using hand-held qPCR machines are likely to yield the lowest cost. Overall, the short-term resource utilization of these surveys is likely to be substantial.

Theoretically, these diagnostic tools in snail populations could guide a decision to correctly classify regions as having eliminated transmission, paired with a verification survey. This would allow for cessation of several interventions against schistosomiasis that would release significant funding and deliver human resources savings. These benefits are entirely predicated on the predictive ability for this snail diagnostic-based approach to correctly classify regions as having eliminated transmission or not; a misclassification could have deleterious resource implications. Most notably, if diagnostic tools misclassified a setting as having eliminated schistosomiasis, when in reality the setting remained endemic for the disease, this would result in withholding interventions from communities that would benefit from them, with significant resource implications

if this allows rebound of disease, which would negate prior public health resource investment and progress.

Equity. The GDG agreed that using snail diagnostic tools to verify elimination of schistosomiasis might have only minimal implications to equity.

Schistosomiasis is endemic in populations that disproportionately affect poor, vulnerable populations and who those unable to obtain health services. The successful implementation of snail diagnostic tools to verify elimination of schistosomiasis would potentially yield resource savings that could be allocated to other public health priorities. The surplus of public health funding would likely improve equity by addressing other pressing issues.

Feasibility. The GDG agreed that using snail diagnostic tools to verify elimination of schistosomiasis would be technically challenging.

Conventional methods for detection of *Schistosoma* in snail populations have been around for decades and are widely used but are labour intensive, underscoring their uncertain feasibility. Newer diagnostic tools such as LAMP are likely to be even more challenging to implement given larger reliance of laboratory equipment and reagents, technical expertise and time intensiveness, but are undergoing rapid development and offer promise. Their feasibility will also be dictated by the surveillance strategy to deploy a diagnostic tool in snail populations, including the optimal snail sampling, geographical zone and timescale. Further data are required on diagnostic accuracy and field validation of both conventional and molecular techniques, and further elucidation of the sampling schemes needed to predict elimination of transmission.

Overall, during its deliberations the GDG took into consideration the following aspects that resulted in the formulation of this recommendation:

- This summarized evidence supported the need for a high sensitivity and specificity test for diagnosis of *Schistosoma* spp. in snails, which, based on the review, may require two separate tests.
- Conventional methods of snail shedding and crushing techniques are highly specific for detection of *Schistosoma* to genus level in snails and are generally more feasible, accepted and low cost, but lack sensitivity in detection.
- Newer methods such as LAMP are more sensitive for detection of *Schistosoma* in snails, which may allow for a sampling pooling strategy for resource efficiency but are more technically challenging and have a higher cost.
- Pooling of snail samples (especially for small snail species) provides many advantages to improve diagnostic yield but requires a highly sensitive diagnostic tool and further investigation.
- The final predictive performance of snail diagnosis to predict elimination of transmission and the associated acceptability, feasibility and resource implications remains unclear.

6.2.3 Diagnostic tools for detection of Schistosoma infection in non-human animal hosts to verify elimination of transmission

Overall results of evidence on tools for detection of Schistosoma in non-human animal hosts

1. The parasitological technique of formalin-ethyl acetate sedimentation, the miracidia hatching test and the molecular technique of PCR to diagnose *Schistosoma* infections in non-human animal hosts have reasonable sensitivity and very high specificity, although further validation and standardization of these techniques is necessary.

2. There are generally limited data on sensitivity and specificity of new parasitological, immunological and molecular techniques for detection of *Schistosoma* in non-human animal hosts and further work is needed.

3. There have been, until recently, limited data on the relative contribution of non-human animal hosts such as bovines, rats, pigs and dogs to transmission of schistosomiasis, especially for species other than *S. japonicum*, and further work is needed.

4. Future work is needed to design a surveillance strategy using a defined diagnostic tool (or tools) to identify the optimal sampling of non-human, animal hosts, geographical zone, timescale and resource utilization to validate verification of elimination.

Considerations in formulating the recommendations

Certainty of evidence. The overall certainty of evidence provided within the systematic review for the diagnostic accuracy of tools for detection of *Schistosoma* in non-human animal hosts was low; there were no data for the value of diagnostic tool to verify interruption of transmission.

Balance of benefits and harms. The use of diagnostic tools to identify *Schistosoma* in non-human animal hosts has substantial potential benefit to public health. Diagnostic tools that are sensitive, specific and resource efficient would improve the identification of non-human animal hosts with *Schistosoma* infection, which may provide useful insights into ongoing transmission that is otherwise difficult to detect, and would guide optimal public health decisions. The successful identification of geographical regions previously endemic for schistosomiasis, which have now eliminated ongoing transmission, could allow national programmes to cease regular preventive chemotherapy programmes. This would provide substantial savings in cost and general resource utilization (for instance, community health workers, public health staff) by stopping a programme that would provide no expected health benefit. Notably, the added value of diagnostic tools in non-human animal hosts is in providing additional information for verification of interruption of transmission than surveys in human populations alone. These tools could also provide further insights into the role of local animals in the transmission cycle for schistosomiasis in a given setting. The detection tools for use in non-human animal hosts may also have application to post-elimination surveillance programmes. More sensitive diagnostic tools would be of particular importance when verifying elimination of transmission. The evidence supports the benefit of the parasitological techniques of the formalin-ethyl acetate sedimentation and the miracidia hatching test, combined with

molecular PCR techniques to diagnose the species and/or genotype of *Schistosoma* infections in non-human animal hosts.

There is potential for harm with diagnostic tools for *Schistosoma* in non-human animal hosts, mainly if the tool lacks adequate sensitivity and/or specificity. This adverse outcome could occur in the public health setting by producing a biased estimate of the prevalence of *Schistosoma* in non-human animal hosts, resulting in a suboptimal public health decision. If the diagnostic tool was applied to verifying elimination, poorly sensitive diagnostics may misclassify a setting as having eliminated transmission, when in reality the setting remained endemic for schistosomiasis; this would result in decreased surveillance among communities that could benefit from treatment, and potentially allow the disease to rebound. Alternatively, a poorly specific diagnostic could misclassify a setting as being persistently endemic, which would subject the population to continued interventions and utilize resources without expected benefit. The evidence supports the benefit of parasitological technique of formalin-ethyl acetate sedimentation, the miracidia hatching test and the molecular technique of PCR to diagnose Schistosoma infections in non-human animal hosts, given the low sensitivity of the miracidia hatching technique alone, and/or the lack of species/genotype identification without PCR; however, given their low sensitivity, there remains some risk for harm in these domains.

Values and preferences. The GDG recognized the lack of clarity about population values and their variability regarding diagnostic methods in non-human animal hosts for schistosomiasis.

Acceptability. Conventional human diagnostics to estimate prevalence are well accepted to guide preventive chemotherapy programmes *(68, 69)*. However, the acceptability of using diagnostic tools in non-human animal reservoirs, especially to verify elimination, has not been studied. The acceptability of diagnostics in animals is likely based upon the level of understanding and discussion about the role of non-human animal hosts in transmitting schistosomiasis. Generally, it is reasonable to assume that if new diagnostic methods provided value in public health decision-making or resource efficiency, that this diagnostic would be well accepted by the public health officials and populations affected by schistosomiasis. This would require discussion and exchange with local health workers and national decision-makers.

Resource implications. The GDG agreed that the diagnostic tools for *Schistosoma* in non-human animal hosts to verify elimination could potentially, in the future, have a favourable ratio of resources relative to expected benefit if certain conditions are met.

The surveillance strategy to deploy a diagnostic tool in non-human animal hosts, including the optimal animal hosts, geographical zone and timescale, remains unclear and would determine overall resource utilization. Furthermore, many detection tools differ substantially in resource implications based on their reliance on laboratory equipment and reagents, technical expertise and time intensiveness. The tools of formalin-ethyl acetate sedimentation, the miracidia hatching test and molecular technique of PCR are likely to require substantial short-term resource utilization for surveys.

Theoretically, diagnostic tools in non-human animal hosts could guide a decision to correctly classify regions as having eliminated transmission. This would allow for the cessation of several interventions against schistosomiasis that would provide significant funding and human resources savings. However, the contribution of non-human animal

hosts in the transmission of *S. japonicum* and other *Schistosoma* species remains heterogeneous by setting. Furthermore, without species- and, potentially, strain-detection through PCR to identify shared transmission, the interpretation of positive tests for schistosomiasis in animals may be limited, and therefore the benefits and cost-effectiveness remain to be elucidated.

Equity. The GDG agreed that using diagnostic tools in non-human animal hosts might have only minimal implications to equity, but would be most relevant to verification of interruption of transmission.

Schistosomiasis is endemic in populations that disproportionately affect poor, vulnerable population and those who are unable to obtain health services. Therefore, any tool that improves knowledge of this disease may have implications for improving equity. The flexibility offered by the release of this public health funding would likely improve equity by addressing other pressing issues.

Feasibility. The GDG agreed that using diagnostic tools in non-human animal hosts, especially to verify schistosomiasis elimination, would be technically challenging.

Conventional methods for detection of *Schistosoma* in non-human animal hosts have limited data and are not widely implemented, underscoring their uncertain feasibility. Newer diagnostic tools such as molecular or immunological tests are likely to be even more challenging to implement given high resource requirements and further commercial development. The parasitological technique of formalin-ethyl acetate sedimentation, the miracidia hatching test and the molecular technique of PCR are the best supported, based on evidence for accuracy and potential for feasibility, although they are still labour intensive and have expensive requirements for laboratory infrastructure and expertise. Finally, the interpretation of a positive parasitological test alone in the setting of a verification of elimination survey, without corresponding molecular identification to demonstrate shared species/strain transmission, remains unclear, and future work elucidating the general contribution of non-human animal hosts to transmission, especially for species other than *S. japonicum*, is warranted. Likewise, future work is needed on the diagnostic tests themselves and their role in a future verification of elimination survey, as the paucity of this data limits the current feasibility.

Overall, during its deliberations the GDG took into consideration the following aspects that resulted the formulation of this recommendation:

- This summarized evidence supported the need for a high-sensitivity and high-specificity test for diagnosis of *Schistosoma* spp. in non-human animal hosts, which, based on the review, may require two separate tests.
- The parasitological technique of formalin-ethyl acetate sedimentation, the miracidia hatching test and the molecular technique of PCR to diagnose *Schistosoma* infections in non-human animal hosts have reasonable sensitivity, although further validation and standardization of these techniques is necessary to determine feasibility and resource utilization.
- There is generally limited data on sensitivity and specificity of new parasitological, immunological and molecular techniques for detection of *Schistosoma* in non-human animal hosts, and further work is needed.
- The final predictive performance of detection of *Schistosoma* in non-human animal hosts to predict elimination of transmission and the associated acceptability, feasibility and resource implications remain unclear.

7. Dissemination, implementation and evaluation of the guideline

The guideline will be produced as electronic (PDF) and print versions and translated into appropriate United Nations languages. The web-based version of the guideline will be posted on the WHO website. It will be disseminated through a broad network of international partners, including WHO country and regional offices, health ministries, WHO collaborating centres, universities, other United Nations agencies and nongovernmental organizations.

Derivative products (1–2 page brochures /infographics) and computer and smartphone applications highlighting the various recommendations will also be developed. The guideline will be promoted during workshops and scientific congresses. Toolkits and manuals will be developed to facilitate understanding and implementation of the guideline. The guideline will be promoted during global and regional webinars, workshops and scientific congresses.

Manuals will be developed to facilitate understanding and implementation of the guideline, particularly for mapping and impact assessment surveys as well as for surveys and procedures for verifying interruption of schistosomiasis transmission.

The guideline can be adapted at regional and national levels to reflect local circumstances and resource considerations.

Appraisal of the guideline will be measured through the use of the recommendations for the requests of medicine for mass treatment, the increase of the treatment of the new age groups included in MDA campaigns (pre-SAC, adults, and pregnant and lactating women), the increase of the implementation of the other recommended strategies (use of molluscicides by the country programmes, WASH and behavioural change communication, for example).

An online survey will be conducted through WHO regional and country offices and through selected respondents of other user groups (for instance, professional societies, donors, nongovernmental organizations) 2 years after publication of the guideline in order to gauge utilization in-country and whether any of its recommendations have been implemented or have influenced policy decisions.

Evidence will be reviewed 5 years after the date of publication and the need for updating of recommendations determined. This may be done earlier if the evidence should significantly alter before then.

8. Future research needs

Discussions among the members of the GDG and the external review group highlighted the limited evidence available in some areas of knowledge, meriting further research on control and elimination of schistosomiasis, particularly in the following areas:

- studies to define indicators for measuring disease morbidity when moving towards elimination of schistosomiasis as a public health problem;
- studies on optimal strategies for equitable treatment of diverse occupational groups such as fishermen, farmers, irrigation workers and car washers;
- study on compliance of individuals taking praziquantel in areas where transmission has been reduced;
- new diagnostics are urgently needed for diagnosis of *Schistosoma* spp. The current methods of Kato–Katz and urine microscopy have very limited sensitivity, which further acts as a limiting factor for developing new diagnostics in humans;
- quality control, monitoring and evaluation for the performance and the quality of the diagnostic tests;
- effectiveness of praziquantel in treatment and prevention of female and male genital schistosomiasis;
- implication of zoonotic transmission of all *Schistosoma* species, but especially *S. haematobium* and *S. mansoni*, on the interruption of the transmission and need for treatment of animals in endemic areas;
- monitoring drug efficacy to detect any emergence of drug resistance;
- studies on the safety of praziquantel during first trimester of pregnancy, with appropriates sample sizes;
- development of a vaccination for people and animals to prevent reinfection and reduce transmission;
- strategies for treatment in low prevalence areas that do not require MDA;
- research on better diagnostic tests in animals and snails;
- operational research on persistent hot spots: identification and control response;
- studies on the optimum treatment coverage in age groups for morbidity control according to transmission archetypes;
- studies on seasonal targeting of interventions;
- comparison of test-and-treat versus MDA;

- circumstances for tailoring strategies to include biannual treatment, snail control and WASH;
- contribution of hybrid schistosomes to transmission and diagnosis;
- further operational research in settings that treat school-based compared with community-wide treatment;
- WASH- determination of optimal approaches for joint implementation in highly endemic regions; and
- development and evaluation of new and environmentally friendly molluscicides.

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Annex 2. Summary of declarations of interests and their management

Name	Declared interests	Management of conflicts of interest
Guideline development group		
Fernando Schemelzer M. Bezerra	None declared	Not applicable
Daniel Colley	Employment at University of Georgia (USA) and research support from BMGF (US$ 23 million for 9 years) and NIH (US$ 3.5 million for 8 years)	The assessment concluded that no financial interests (resulting from funding sources) and employment that could directly affect, or could appear to affect, the professional judgement of the expert were identified.
Fiona Fleming	Research support from United Kingdom Department for International development [now Foreign, Commonwealth and Development Office] (UK£ 35 million) and University of Georgia (BMGF, US$ 1.8 million)	The assessment concluded that no financial interests (resulting from funding sources) that could directly affect, or could appear to affect, the professional judgement of the expert were identified.
Paul Hagan	Advisory board member of BMGF-funded SCORE (travel reimbursement from University of Georgia/SCORE (US$ 1100 per visit). Member of GSA board; no funding of any kind	These competing interests are not considered to pose any risk to this guideline development process or to reduce its credibility. The assessment concluded that no financial interest (resulting from funding source) that could directly affect, or could appear to affect, the professional judgement of the expert was identified.
Mamoun Homeida	None declared	Not applicable
Narcis Kabatereine	None declared	Not applicable
Fatma Kabole	Research support for the Zanzibar schistosomiasis elimination project (US$ 60 000-120 000/year from Natural History Museum London/ BMGF)	The assessment concluded that no financial interest (resulting from funding source) that could directly affect, or could appear to affect, the professional judgement of the expert was identified.

Charles H. King	Senior scientist, part-time employment in SCORE; US$ 56 000/ year and research support from BMGF (US$ 500 000/year in 2016)	The assessment concluded that no financial interests (resulting from funding source) and employment that could directly affect, or could appear to affect, the professional judgement of the expert was identified.
Margaret A. Mafe	None declared	Not applicable
Nicholas Midzi	None declared	Not applicable
Francisca Mutapi	None declared	Not applicable
Joseph Mwanga	None declared	Not applicable
Reda Ramzy	None declared	Not applicable
Allen Ross	None declared	Not applicable
Fadjar Satrija	Consultant for schistosomiasis elimination in Indonesia (US$ 24 329) and grant for a study on schistosomiasis transmission in Indonesia (US$ 13 510)	The assessment concluded that no financial interest (resulting from funding source) that could directly affect, or could appear to affect, the professional judgement of the expert was identified.
Russell J. Stothard	None declared	Not applicable
Mamadou Souncalo Traoré	None declared	Not applicable
Jürg Utzinger	Member of the Children Without Worms task force	This competing interest is not considered to pose any risk to this guideline development process or to reduce its credibility as the focus is schistosomiasis. The assessment concluded that no interests that could directly affect, or could appear to affect, the professional judgement of the expert was identified.
Joanne P. Webster	None declared	Not applicable
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BMGF: Bill & Melinda Gates Foundation; GSA: Global Schistosomiasis Alliance; NIH: National Institutes of Health (USA); NSF: National Science Foundation (USA); SCORE: Schistosomiasis Consortium for Operational Research and Evaluation..

Annex 3. GRADE quality of evidence (certainty of evidence)

⊕⊕⊕⊕ High quality (certainty) evidence

- We are very confident that the true effect lies close to that of the estimate of effect.

⊕⊕⊕⊙ Moderate quality (certainty) evidence

- We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

⊕⊕⊙⊙ Low quality (certainty) evidence

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

⊕⊙⊙⊙ Very low quality (certainty) evidence

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

Source: Balshem H, Helfand M, Schünemann HJ, Oxman AD, Kunz R, Brozek, et al. GRADE guidelines: 3. Rating the quality of evidence. J Clin Epidemiol. 2011; 64(4):401-6. doi:10.1016/j.jclinepi.2010.07.015.

Annex 4. Evidence review, PICO questions and GRADE summary tables

Annex 4.1 Implementing preventive chemotherapy based on prevalence of infection

A4.1.1 Impact of preventive chemotherapy on schistosomiasis morbidity in key population age groups

The primary evidence that informed the recommendation on defining age groups to be targeted with preventive chemotherapy against schistosomiasis was drawn from one commissioned systematic review and meta-analysis *(1)* that examined the association between schistosomiasis and disease morbidity in key age groups, utilizing data from an estimated 319 observational and randomized studies. The guideline development group (GDG) also considered various data sources including recent meta-analyses *(2–4)*, observational studies outside the review, modelling studies and cost-effectiveness analyses. Key aspects considered include disease morbidity in key population age groups, and considerations on targeting key age groups in preventive chemotherapy programmes.

The systematic review and meta-analysis underpinning the recommendation assessed the relationship between preventive chemotherapy with praziquantel for *Schistosoma* infections in key age groups of preschool-aged children (pre-SAC), school-aged children (SAC) and adult populations, with various parasitological and morbidity outcomes *(1)*. The review's search criteria included all study types, including randomized trials and observational studies (including those without a control group), but excluded case reports and case series. Included studies measured the parasitological outcomes of prevalence and intensity of infection (measured through eggs in stool or urine), clinical morbidity (e.g. hepatomegaly, splenomegaly, periportal fibrosis, urogenital tract lesions, haematuria, proteinuria, hydronephrosis, anaemia), self-reported symptoms (e.g. diarrhoea, abdominal pain, blood in urine), and "subtle" morbidity (e.g. losses in cognitive ability, school attendance). The review also included discussion of the broader literature, including other recent meta-analyses and modelling studies contributing to the evidence base.

The review's authors searched the PubMed database. They further reviewed the reference lists of systematic reviews identified to address the topic of morbidity in schistosomiasis, as well as the reference lists of selected studies. The last search for evidence was done in July 2018, with later evidence incorporated in February 2019.

The review identified an estimated 319 observational and randomized studies that met the inclusion criteria for the meta-analysis. This included 27 randomized controlled

trials and 292 observational (controlled and uncontrolled cohort studies, controlled and uncontrolled repeated cross-sectional studies) studies. The studies mostly included settings with *Schistosoma mansoni* (*n*=153) or *S. haematobium* (*n*=166), with some data for *S. japonicum* (*n*=12). The preventive chemotherapy strategies used to reduce infection-related morbidity outcomes represented in this study were mostly targeted at SAC (*n*=20) or the entire population (*n*=16), with some studies targeting pre-SAC alone (*n*=6) or adults (*n*=4). The outcomes reported were parasitological (*n*=319) or morbidity (*n*=46 studies) related. Of these studies, the majority were from high prevalence settings (defined as prevalence > 50%; *n*=99 studies), while n=210 were from moderate prevalence settings (defined as prevalence 10–50%); the remainder were from low prevalence settings (defined as prevalence < 10%).

In the meta-analysis, preventive chemotherapy was associated with reductions across parasitological and morbidity outcomes. The data were examined in sub-group analyses for four age groups: (i) SAC; (ii) pre-SAC; (iii) adults; and (iv) all age groups.

In SAC, preventive chemotherapy was associated with reduced *S. mansoni* prevalence [70%; 95% confidence interval (CI): 63–77%, *n*=38 studies] and *S. haematobium* prevalence [67%; 95% CI: 57–74%, *n*=47 studies], as well as reduction in the prevalence of haematuria [60%; 95% CI: 37–75%, *n*=10 studies], proteinuria [64%; 95% CI: 41–78%, *n*=5 studies], anaemia [30%; 95% CI: 21–27%, *n*=2 studies], right-sided hepatomegaly [57%; 95% CI: 18–78%, *n*=2 studies] and urinary tract lesions [63%; 95% CI: 44–76%, *n*=5 studies]. The reviews showed no measurable reductions in the prevalence of blood in stool, diarrhoea, hepatomegaly, splenomegaly, urinary bladder pathology or portal vein changes.

In pre-SAC, preventive chemotherapy was associated with reduced *S. mansoni* prevalence [39%; 95% CI: 28–48%, *n*=120 studies], *S. haematobium* prevalence [75%; 95% CI: 70-80%, *n*=145 studies], and proteinuria [90%; 95% CI: 65–97%, *n*=1 study]. There was no measurable reduction in urinary tract pathology; data were lacking for morbidities such as blood in stool, periportal fibrosis, diarrhoea, haematuria, hepatomegaly, urinary bladder lesions, anaemia, splenomegaly and portal vein changes.

In adults, preventive chemotherapy was associated with reduced *S. mansoni* prevalence [79%; 95% CI: 70–86%, *n*=15 studies] but data were lacking for *S. haematobium*. There was no meaningful reduction in the prevalence of urinary bladder pathology or urinary tract lesions or periportal fibrosis in adults, and no data were available for other age groups. In all age groups (including adults), reductions were noted in the prevalence of *S. mansoni* [44%; 95% CI: 26–57%, *n*=19 studies] and *S. haematobium* [68%; 95% CI: 37–84%, *n*=6 studies], as well as proteinuria [75%; 95% CI: 38–90%, *n*=2 studies], blood in stool [74%; 95% CI: 51–86%, *n*=4 studies], splenomegaly [56%; 95% CI: 35–70%, *n*=3], and urinary tract lesions [74%; 95% CI: 51–86%, *n*=3 studies]. There were no measurable reductions in the prevalence of diarrhoea, hepatomegaly, periportal fibrosis or portal vein changes. Data were lacking for haematuria, anaemia and upper urinary tract pathology.

The certainty of evidence supporting an effect on reducing prevalence is moderate. For the effect on morbidity outcomes, it is low. Furthermore, of the morbidity outcomes, the necessary stratification by age group and *Schistosoma* species further limited the

number of available studies and provided more imprecise estimates. Extrapolation across these subgroups was required for decision-making.

The GDG considered additional analyses on the disease burden from schistosomiasis in pre-SAC (5, 6) and on the safety and efficacy of praziquantel in young children *(7, 8)*. Other systematic reviews and meta-analyses that have examined the relationship between preventive chemotherapy and morbidity outcomes were also considered *(2–4)*. In the first meta-analysis, the authors used data from randomized trials for preventive chemotherapy with albendazole or mebendazole against soil-transmitted helminthiases and schistosomiasis *(6)*. The authors focused on pre-SAC and SAC. The analysis relevant to the present study was from a subgroup analysis that examined preventive chemotherapy for schistosomiasis alone in an unspecified age group on outcome of weight, height, and cognition. The key finding was that preventive chemotherapy for schistosomiasis together with albendazole or mebendazole may slightly increase weight (0.41 kg, 95% CI: −0.20, 1.01; *n*=1 study), with no change in height and low certainty of evidence *(2)*. Treatment with praziquantel had no effect upon cognition, with moderate certainty of evidence *(4)*. The key limitation in this study was the shortage of available data with the inclusion of only one randomized trial for the analysis with weight.

In the second meta-analysis, the authors used data from largely observational studies and some randomized trials on preventive chemotherapy in SAC or all age groups (including adults) *(2)*. In this study, for chemotherapy with praziquantel against *S. mansoni* and *S. haematobium*, there were associated reductions in hepatomegaly, splenomegaly, periportal fibrosis, diarrhoea and blood in stool, with very low certainty of evidence; when examining data on *S. haematobium*, there were associated reductions in haematuria, proteinuria, and bladder and urinary tract lesions, with very low certainty of evidence *(2)*. Notably, there were clear associated correlations between magnitude of decreased morbidity and reduction in egg counts (marker of infection intensity in schistosomiasis). The key limitation of this study is the inclusion of very low quality data.

In the third meta-analysis, the authors used data from largely observational studies and some randomized trials for chemotherapy with praziquantel and other medicines in SAC and adolescents *(3)*. In this study, two groups of children were compared: (i) children infected with *Schistosoma* or those who did not receive praziquantel; and (ii) children not infected with *Schistosoma* or those who did receive praziquantel. Based on this comparison using mostly observational data, children with *Schistosoma* infection who were not treated had associated reductions in school attendance, scholastic achievement, learning and memory, without changes in reaction time or intelligence. The key limitation of this study is the inclusion of very low quality data, and a comparison of groups that is likely to be confounded. This limits the interpretability of the findings.

Differences between these meta-analyses were attributable to differences in the study inclusion criteria. Specifically, the proportion of observational and uncontrolled studies was markedly different between the meta-analyses. Given the risk of residual confounding from observational studies, the positive findings of preventive chemotherapy on health in the meta-analyses are reliant largely on observational data, while overall null effects were described in the meta-analysis that was reliant only on

randomized controlled trials. This suggests that many associations between preventive chemotherapy and improved health may not be robust.

There are many complexities to consider when interpreting the morbidity data. First, effectiveness in treating a given age group requires both reversing acute pathology and also reducing cumulative infection burden that will prevent future morbidity. Second, the optimal decision on age group targeting for preventive chemotherapy will be related to *Schistosoma* prevalence. Specifically, higher prevalence settings experiencing greater disease morbidity will likely have larger potential benefits from wider treatment across age groups and effects on transmission *(9, 10)*, but many of these settings were not captured in previous trials or observational data. Third, many of the study outcomes do not directly measure morbidity but rather more intermediate measures of pathology. Finally, the measurement of the relationship between preventive chemotherapy and disease outcomes remains complex given the mix of acute reversible and chronic irreversible pathologies, different Schistosoma species and the consideration of epidemiological complexities of transmission that may limit the ability to detect generalized findings; these include subtle morbidity and urogenital manifestations in vulnerable populations.

There remain additional complexities in considering the ideal age groups to be targeted for preventive chemotherapy against schistosomiasis, including implications on transmission and local epidemiology. The age groups included in preventive chemotherapy may affect the overall community transmission of *Schistosoma*. The aim of preventive chemotherapy programmes is not only to reduce morbidity in those infected but also to reduce ongoing transmission, to prevent new or heavy intensity infections that lead to morbidity. The evidence for targeting SAC compared with entire communities in mass drug administration (MDA) remains mixed. Recent mathematical modelling studies that compared school and community-based MDA have found many scenarios where community-wide treatment confers larger impacts on transmission and reduction in prevalence across age groups *(11–13)*. Conversely, the Schistosomiasis Consortium for Operational Research and Evaluation (SCORE) randomized trials have recently compared various schedules for school and community-based MDA on *Schistosoma* prevalence over a 5-year period in a multi-country study in selected epidemiological settings *(14–16)*. They found that all treatment strategies produced similar effects on *Schistosoma* prevalence (prevalence selectively measured in SAC). Notably, some of the SCORE studies found evidence of reduced adult prevalence associated with all strategies, including school-based MDA in which adults were not treated, suggesting meaningful reductions in overall community transmission using this approach. These trials had some limitations including a lower treatment coverage in the community-wide strategy (notably, differentially lower coverage in SAC within community-wide strategies, with SAC being the age group in which prevalence was measured), differing baseline prevalence, paucity of measurement in older age groups and selection of study sites, with specified ranges of prevalence that may not reflect the situation in many other communities. However, the SCORE trials suggest that community-wide MDA in selected epidemiological scenarios may not confer great advantage, though it is likely to reduce prevalence in adolescent and adult age groups through direct treatment effects. A review of the literature on cost–effectiveness concluded that the strategy of community-wide preventive chemotherapy across all age groups compared with targeted treatment of SAC alone met conventional measures of cost–effectiveness in many scenarios *(9, 12, 17)*, with much of this benefit

being derived from the treatment of infection in older age groups not accessed by approaches involving school-based preventive chemotherapy. Broader literature on trials of community-wide MDA have demonstrated substantial reductions in prevalence and transmission across age-groups, but not achieving interruption of transmission even with complementary interventions *(18)*. A recent multi-country sentinel site observational study of schistosomiasis control programmes demonstrated reductions in prevalence in SAC across programmes with school-based preventive chemotherapy *(19)*.

Ultimately, the relationship between preventive chemotherapy against schistosomiasis and morbidity varies across morbidity outcomes, age groups and different epidemiological settings. The limited data available from high-quality studies prevents generation of meaningful inferences in many key outcomes and age groups. The totality of evidence supports preventive chemotherapy in SAC based on parasitological and some morbidity outcomes. There is also low-certainty evidence to support inclusion of pre-SAC, adolescent and adult populations in preventive chemotherapy programmes to improve parasitological and some morbidity outcomes.

Finally, broader treatment across all age groups raises the theoretical concern for the development of drug resistance. Data are limited to support clinically meaningful drug resistance, although some recent evidence demonstrated potential emergence of reduced praziquantel efficacy in response to increased drug pressure *(20)*. Ongoing, close monitoring for detection of emergence of drug resistance will be critical, and further guidance and surveillance will be needed.

PICO question

Population	Any population group or individuals including pre-SAC (aged ≤ 4–59 months), SAC including adolescents (aged ≥ 72 months), adults and entire population in endemic settings
Intervention	MDA or preventive chemotherapy with praziquantel
Comparator	No preventive chemotherapy
Outcome	Parasitological and health outcomes

GRADE summary table of the findings

Outcomes	Groups	Relative effect OR (95% CI)	Sample size (studies)	Certainty of the evidence (GRADE)
Prevalence of *S. mansoni* infection	Pre-SAC	0.61 (0.52–0.72)	130 784 (120)	⨁⨁⨁⊙ Moderate[1]
	SAC	0.30 (0.23–0.37)	68 892 (35)	⨁⨁⨁⊙ Moderate[1]
	Adults	0.21 (0.14–0.30)	21 468 (15)	⨁⨁⨁⊙ Moderate[1]
	All ages	0.56 (0.43–0.74)	54 424 (19)	⨁⨁⨁⊙ Moderate[1]
Prevalence of *S. haematobium* infection	Pre-SAC	0.25 (0.20–0.43)	21 634 (145)	⨁⨁⨁⊙ Moderate[1]
	SAC	0.33 (0.26–0.43)	19231 (47)	⨁⨁⨁⊙ Moderate[1]
	All ages	0.32 (0.16–0.63)	5500 (6)	⨁⨁⨁⊙ Moderate[1]
Blood in stool	Pre-SAC	1.09 (0.70–1.70)	308 (1)	⨁⊙⊙⊙ Very low[2]
	SAC	0.95 (0.72–1.26)	518 (1)	⨁⊙⊙⊙ Very low[2]
	All ages	0.26 (0.14–0.49)	1783 (4)	⨁⊙⊙⊙ Low[3]
Diarrhoea	Pre-SAC	0.93 (0.63–1.45)	427 (1)	⨁⊙⊙⊙ Very low[2]
	All ages	1.25 (0.15–10.09)	1635 (4)	⨁⊙⊙⊙ Very low[2]
Haematuria	SAC	0.40 (0.25–0.63)	10.981 (11)	⨁⨁⨁⊙ Moderate[1]
	Adults	0.28 (0.16–0.49)	271 (1)	⨁⨁⨁⊙ Moderate[1]
	All ages	0.28 (0.64–1.30)	493 (1)	⨁⨁⨁⊙ Moderate[1]
Anaemia	Pre-SAC	0.98 (0.77–1.26)	571 (1)	⨁⊙⊙⊙ Very low[2]
	SAC	0.70 (0.63–0.79)	3170 (2)	⨁⊙⊙⊙ Low[3]
Proteinuria	Pre-SAC	0.10 (0.03–0.35)	117 (1)	⨁⊙⊙⊙ Very low
	SAC	0.36 (0.22–0.59)	2861 (7)	⨁⊙⊙⊙ Very low[3]
Right-sided hepatomegaly	Pre-SAC	0.43 (0.22–0.82)	1408 (2)	⨁⊙⊙⊙ Very low[2]
	Adults	0.64 (0.35–1.15)	192 (1)	⨁⊙⊙⊙ Very low
	All ages	1.09 (0.45–2.64)	821 (2)	⨁⊙⊙⊙ Very low[2]

Left-sided hepatomegaly	SAC	0.82 (0.52–1.28)	4338 (5)	⨁⊙⊙⊙ Very low[2]
	Adults	0.93 (0.78–1.92)	535 (1)	⨁⊙⊙⊙ Very low[2]
	All ages	1.43 (0.64–3.92)	2664 (5)	⨁⊙⊙⊙ Very low[2]
Hepatomegaly no specific lobe	SAC	0.00 (0.00–0.01)	840 (1)	⨁⊙⊙⊙ Very low[2]
	All ages	1.01 (0.71–1.44)	2054 (3)	⨁⊙⊙⊙ Very low[2]
Splenomegaly	SAC	0.83 (0.58–1.19)	2514 (5)	⨁⊙⊙⊙ Very low[2]
	Adults	0.51 (0.12–2.24)	478 (1)	⨁⊙⊙⊙ Very low[2]
	All ages	0.56 (0.42–0.79)	2955 (7)	⨁⊙⊙⊙ Very low[2]
Periportal fibrosis	SAC	0.37 (0.27–0.51)	510 (1)	⨁⊙⊙⊙ Very low[3]
	Adults	0.83 (0.42–1.64)	2041 (3)	⨁⊙⊙⊙ Low[2]
	All ages	0.93 (0.53–1.64)	3223 (8)	⨁⊙⊙⊙ Low[2]
Urinary bladder lesions	SAC	0.63 (0.33–1.20)	6198 (8)	⨁⊙⊙⊙ Low[2]
	Adults	1.00 (0.22–4.55)	763 (3)	⨁⊙⊙⊙ Low[2]
	All ages	0.26 (0.14–0.49)	1132 (3)	⨁⊙⊙⊙ Low[1]
Urinary tract pathology	Pre-SAC	1.06 (0.61–1.855)	122 (1)	⨁⊙⊙⊙ Very low[2]
	SAC	0.37 (0.24–0.56)	4454 (5)	⨁⨁⨁⊙ Moderate[1]
	Adults	0.81 (0.53–1.23)	150 (1)	⨁⊙⊙⊙ Very low[2]
	All ages	0.56 (0.22–0.59)	222 (1)	⨁⨁⨁⊙ Moderate[1]
Portal vein change	SAC	0.41 (0.10–1.71)	335 (2)	⨁⊙⊙⊙ Very low[2]
	Adults	0.59 (0.48–0.71)	921 (1)	⨁⊙⊙⊙ Very low[2]
	All ages	0.68 (0.31–1.51)	507 (3)	⨁⊙⊙⊙ Very low[2]
Portal vein change	SAC	Not pooled	442 (2)	⨁⊙⊙⊙ Low

CI: confidence interval; GRADE: Grading of Recommendations, Assessment, Development and Evaluation; OR: odds ratio; pre-SAC: preschool-aged children; SAC: school-aged children.

[1] Downgraded for concerns about risk of bias. The studies had a mix of randomized, nonrandomized and before and–after designs; however, the results were consistent across study designs.

[2] Downgraded for concerns about risk of bias and for severe imprecision.

[3] Downgraded for concerns about risk of bias and imprecision.

A4.1.2 Optimal prevalence threshold for preventive chemotherapy for morbidity control

The primary evidence to support the recommendation on the optimal prevalence threshold for preventive chemotherapy came from one commissioned systematic review and meta-analysis *(21)* and a cost–effectiveness analysis *(9)*. The GDG also considered various other data sources including programmatic data, observational studies outside the review and modelling studies.

The review searched PubMed and LILACS from 1978 to 31 March 2021, with no language restrictions, using pretested search terms, and also the Cochrane Infectious Diseases Group Specialized Register, CENTRAL (The Cochrane Library 2021), mRCT, Hinari, Africa Journals Online and Google Scholar. The last search was performed in March 2021.

The systematic review estimated the prevalence reduction associated with one year of preventive chemotherapy with praziquantel *(21)*. The authors compiled observational studies and randomized trials that provided data at two time points, in populations participating in a preventive chemotherapy programme using praziquantel. They then applied estimated prevalence ratio reductions to predict the effect of preventive chemotherapy programmes over time. They identified 34 observational and randomized studies that met the inclusion criteria, including data from populations infected with *S. mansoni* and *S. haematobium*. Based on the meta-regression, the authors estimated an annual reduction of *S. mansoni* prevalence by 22% (prevalence ratio [PR]: 0.78; 95% CI: 0.577, 0.79) and annual reduction in *S. haematobium* prevalence by 26% (PR: 0.74; 95% CI: 0.73, 0.75). The preventive chemotherapy strategies represented were mostly targeted at SAC. The authors used the data to make transmission projections under various strategies, including: (i) SAC alone; ii) pre-SAC and SAC; and (iii) community-wide treatment across all age groups. The projections demonstrated greater prevalence reductions with expanded community-wide treatment, without any scenario achieving complete elimination of transmission following 10 years of annual treatment.

The cost–effectiveness analysis *(9)* estimated the optimal prevalence thresholds for preventive chemotherapy with various strategies against schistosomiasis. In this study, the authors used an age-stratified statistical model to project *Schistosoma* transmission under various intervention strategies, with associated estimations of total cost and averted disease burden (measured in disability-adjusted life years). The authors tested various frequencies of preventive chemotherapy programmes targeting: (i) SAC alone; and (ii) community-wide treatment across all age groups. Using conventional thresholds of cost–effectiveness for a low-income country, annual preventive chemotherapy targeting SAC was recommended at a prevalence threshold of 5% (95% uncertainty interval [UI]: 1.7, 5.2%), and annual community-wide treatment was recommended at a prevalence threshold of 15% (95% UI: 7.3, 18.5). The selection of the optimal cost–effective threshold was sensitive to changes in setting-specific differences, such as economic threshold (willingness-to-pay, measured in US$ per averted disability-adjusted life year), epidemiology, and assumptions on cost and disability.

The prevalence threshold for preventive chemotherapy is based upon stool examination with Kato–Katz smears for intestinal schistosomiasis, and urine filtration and microscopy

for urinary schistosomiasis. For *S. mansoni*, the point-of-care circulating cathodic antigen diagnostic test provides an alternative to Kato-Katz smears. To convert the optimal prevalence threshold estimated by Kato-Katz to a prevalence estimated by the point-of-care diagnostic test, a published analysis *(22)* was used. The authors compiled 30 datasets with individual-level data on *S. mansoni* with results from both tests, and estimated that 5% prevalence by Kato–Katz was comparable to 20% prevalence by circulating cathodic antigen; similarly, 10% prevalence by Kato–Katz was comparable to 30% prevalence by circulating cathodic antigen *(22)* (**Annex 6**).

There remain key complexities in identification of the optimal prevalence threshold for preventive chemotherapy. First, the choice of threshold is fundamentally a problem of balancing resource utilization with expected benefit on human health, and not a question that can be readily addressed by traditional forms of evidence such as randomized control trials. For example, a lower prevalence threshold would result in a larger number of treated people and, presumably, a larger health impact; however, there would be a higher overall cost for medicines and their delivery. Conversely, a higher prevalence threshold would restrict treatment to fewer people and have a smaller health impact, although it would also have a lower overall cost. The optimal balance of resource utilization with expected health benefit guided the decision on the threshold set out in this guideline. Second, the prevalence threshold depends on the preventive chemotherapy strategy, mainly the age group targeted and the frequency of the programme; based on a previous recommendation, all age groups > 2 years will be recommended to receive preventive chemotherapy. Third, the optimal prevalence threshold will be different among settings based on epidemiology, existing public health platforms and delivery costs, variable coverage and other contextual health systems factors. Therefore, the identification of a prevalence threshold is largely designed to be generalizable but will necessarily fail to capture setting-specific differences. Fourth, the prevalence threshold is specific to the diagnostic tool used to estimate prevalence. Fifth, the current evidence does not include "adaptive" strategies that can modify the preventive chemotherapy strategy in response to the measured effectiveness of the strategy on prevalence, such as "persistent hot spot" settings that remain as high-risk communities despite repeated treatment *(11)*. Recent randomized trials of preventive chemotherapy strategies against schistosomiasis have identified these persistent hot spot settings, where more intensive strategies may be needed *(23–25)*. This suggests that such strategies may need to be re-evaluated after a period of time to determine the need for intensification. Sixth, the available evidence does not identify the optimal prevalence threshold for stopping preventive chemotherapy programmes. Finally, there are insufficient data to support a test-and-treat strategy except in settings where preventive chemotherapy is not recommended, in part due to the more intensive resource requirements relative to the strategy and the requirement for a highly sensitive diagnostic test.

Historically, WHO recommended that preventive chemotherapy programmes use praziquantel (40–60 mg/kg) as a single dose given annually. This dosing regimen had been informed by a randomized trial that compared 40 mg/kg and 60 mg/kg and found them to have equivalent outcomes *(26)*. A larger body of literature has examined two-dose administration and varying dosing, which may have a role in achieving better

efficacy in some settings. However, current evidence supports single-dose administration to balance efficacy and operational feasibility. The dose administered is determined now using the praziquantel dose pole, by which height approximates the person's weight, giving a colour code for the number of pills required to provide the recommended dose/kg.

Preventive chemotherapy has been central to the success of the majority of programmes that have eliminated schistosomiasis as a public health problem and that are now in the process of interrupting transmission or are awaiting verification that they have reached this goal (see **Table**). In each of these countries, the core elements of the control and elimination strategies have been varying combinations of (i) reducing adult worms and eggs with preventive chemotherapy; (ii) eliminating intermediate snail hosts (iii) reducing contamination of water and, more rarely, (iv) preventing human infection through sanitation and hygiene. Most such programmes have had some degree of community education and engagement.

Programmes in these countries have been successful because of sustained political will and determination to achieve the goal of elimination, even though severe morbidity due to infection had been eliminated. When severe morbidity is controlled as a result of a sustained preventive chemotherapy programmes, there is a possibility that countries shift their focus and divert resources to other public health problems, risking 'bounce-back' – an increase in transmission, infection and disease in the community, rather than continuing the push towards elimination of schistosomiasis transmission.

Evidence from countries awaiting verification of interruption of transmission is that preventive chemotherapy has been a major component of their success. WHO therefore recommends that preventive chemotherapy continues to be a key component of programmes that have reduced prevalence to < 10%, and that this should be reinforced by having praziquantel readily available in health centres for infected people of all ages. It is recognized that programmes will need flexibility to take account of regional and local variations when progressing to this stage.

For communities with baseline prevalence of *Schistosoma* < 10% and no previous history of praziquantel MDA, preventive chemotherapy can be provided at a reduced frequency of once every 2 or 3 years with the aim of reducing endemicity, preventing any rebound in infection prevalence and sustaining efforts towards interruption of transmission. In

these settings, clinical studies also support access to praziquantel treatment for infected people in a test-and-treat strategy, including in pre-SAC *(27)*.

Based on all available data and considering uncertainty and other factors (see **Annex 4.5**), the GDG reached a consensus on recommending a threshold of 10% parasitological (Kato–Katz or urine filtration) prevalence.

PICO question

Population	Entire population or subgroups (pre-SAC, SAC and adults including pregnant and lactating women) infected with any of the schistosome species or non-infected, living in endemic areas, who received praziquantel during a preventive chemotherapy or MDA programme
Intervention	Praziquantel at a single oral dose (≥ 40 mg/kg) or in combination with albendazole, mebendazole, pyrantel pamoate or levamisole (for soil-transmitted helminthiases), or albendazole plus either ivermectin or diethylcarbamazine citrate (for lymphatic filariasis), artemisinin-based combination therapies (for malaria) or azithromycin [Zithromax] (for trachoma)
Comparator	WHO recommended prevalence thresholds (for low, moderate and high endemicities)
Outcome	Primary outcomes ▪ Post-MDA prevalence of infection or percentage reduction at follow-up ▪ Post-MDA intensity of infection or percentage reduction of egg count at follow-up ▪ Post-MDA transmission or percentage reduction in transmission at follow-up Secondary outcomes ▪ Compliance and acceptance of the intervention by the population ▪ Cost-effectiveness of the prevalence threshold selected for preventive chemotherapy ▪ Cost-effectiveness of the diagnostic criteria selected for preventive chemotherapy

GRADE summary table of the findings

Outcomes	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	Sample size (studies)	Certainty of the evidence (GRADE)
	Without preventive chemotherapy	With preventive chemotherapy			
1-year prevalence reduction of *S. mansoni* infection in SAC (annual SBT; 0–1 year)	8155/45 510 (17.9%)	5047/40 563 (12.4%)	PR=0.56 (0.46–0.69)	45 510 (14)	⨁⨁⨁⊙[1]
4-year prevalence reduction of *S. mansoni* infection in SAC (annual SBT; 0–4 years)	3936/17 745 (22.2%)	1196/9738 (12.3%)	PR=0.25 (0.11–0.59)	17 745 (5)	⨁⨁⨁⊙[1]
Annual prevalence reduction of *S. mansoni* infection in SAC (annual SBT; threshold > 5%; follow-up: range 1–7 years)			PR=0.78 (0.77–0.79)	123 045 (20)	⨁⨁⨁⊙[1]
1-year prevalence reduction of *S. haematobium* infection in SAC (annual SBT; 0–1 year)	6582/20 040 (32.8%)	3027/17 828 (17.0%)	PR=0.38 (0.28–0.52)	20 040 (8)	⨁⨁⨁⊙[1]
4-year prevalence reduction of *S. haematobium* infection in SAC (annual SBT; 0–4 years)	1387/6274 (22.1%)	949/4680 (20.3%)	PR=0.38 (0.28–0.52)	6724 (2)	⨁⨁⨁⊙[1]
Annual prevalence reduction of *S. haematobium* infection in SAC (annual SBT; threshold > 5%; follow-up: range 1–7 years)			PR=0.74 (0.73–0.75)	106 912 (13)	⨁⨁⨁⊙[1]

GRADE: Grading of Recommendations, Assessment, Development and Evaluation; PR: prevalence ratio; SAC: school-aged children; SBT: school-based treatment. .

[1] Mostly observational studies with a large effect size.

A4.1.3 Modelling evidence

A 5-year treatment programme with praziquantel (40 mg/kg per treatment) against schistosomiasis and albendazole (400 mg per treatment) against soil-transmitted helminthiases at 75% treatment coverage.

Annual preventive chemotherapy against schistosomiasis	Highly cost-effective in treatment of SAC at a prevalence threshold of 5% (95% uncertainty interval 1.7–5.2%)
	Highly cost-effective in community-wide treatment at a prevalence of 15% (7.3–18.5%)

A4.1.4 Frequency of preventive chemotherapy with praziquantel

The primary evidence that formed the recommendation on frequency of preventive chemotherapy against schistosomiasis in at-risk populations came from one meta-analysis *(28)* utilizing data from two randomized trials *(29, 30)*. The GDG also considered data from observational studies, modelling studies and cost-effectiveness analyses.

The systematic review underpinning the recommendation assessed variable frequencies of preventive chemotherapy with praziquantel for *Schistosoma* infections in at-risk populations and their effect on prevalence and intensity of infection *(28)*. The review's search criteria identified randomized trials and quasi-randomized trials comparing biannual with annual preventive chemotherapy using praziquantel in at-risk populations for schistosomiasis. The analyses included measured the parasitological outcomes of prevalence and intensity of infection in at-risk populations, including SAC, older adolescents and adults. The review also included a discussion of the broader literature examining the optimal frequency of praziquantel dosing, including observational studies, modelling studies and cost-effectiveness analyses.

The review's authors searched the Cochrane Central Register of Controlled Trials (CENTRAL), Cochrane Infectious Diseases Specialized Register, the Cochrane Library, MEDLINE, Google Scholar, conference proceedings, metaRegister of Controlled Trials (mRCT), World Health Organization International Clinical Trials Registry Platform and reference lists. In addition, the authors of the study contacted individual researchers and organizations for relevant published and unpublished data and information on ongoing trials. The last search for evidence was done in September 2020.

The review identified three cluster-randomized controlled trials that met the inclusion criteria. The first trial enrolled 240 SAC (aged 5–14 years) from four villages in Senegal endemic for *S. haematobium* (baseline, 35% prevalence) and *S. mansoni* (baseline, 24% prevalence), and randomized villages to annual or biannual school-based preventive chemotherapy with praziquantel with the main outcome of prevalence and infection intensity at one year *(30)*. The second trial *(29)* enrolled 22 372 participants (aged 5–50 years, although parasitological outcomes were predominately measured in those aged 9–12 years) from 225 villages in Niger endemic for *S. haematobium* (baseline, moderate prevalence < 25%, and high prevalence > 25%), with the main outcome being change in prevalence, infection intensity and prevalence of heavy-intensity infections at 5 years. In this second trial, villages were randomized to: (i) biannual or annual school-based treatment in moderate prevalence areas; (ii) biannual or annual school-based treatment

in high prevalence areas; and (iii) biannual or annual community-wide treatment in high prevalence areas.

The third study *(31)* included 377 primary-school children (aged 7–19 years) with confirmed *S. mansoni* infection, who were enrolled and randomized to receive praziquantel (40 mg/kg) at baseline and at 6 months or at baseline only.

In terms of the effect of twice-yearly treatment on prevalence of *S. haematobium* infection, the first trial *(29)* showed reduction from baseline over 5 years (statistically significant only in areas with high starting prevalence). The second trial *(30)* showed a significant reduction of 10.8% vs 35% ($P < 0.001$ In terms of the intensity of *S. haematobium* infection, there was a nonsignificant reduction in the first trial, whereas the second trial showed significant reduction in intervention villages and a nonsignificant increase in the control villages. There was a nonsignificant prevalence reduction of 16% for *S. mansoni*. The evidence was of moderate certainty for *S. haematobium* and low for *S. mansoni* (perhaps due to the limited sample size).

The findings of this systematic review are driven largely by a single cluster-randomized trial, providing evidence for settings endemic for *S. haematobium (29)*. Notably, this trial had a sufficiently large sample size and was assessed to have minimal bias across the five domains: selection bias (random sequence generation, allocation concealment), detection bias (blinding of outcome assessment), attrition bias (incomplete outcome data), reporting bias (selective outcome reporting) and other biases. However, blinding may not have been performed. The key limitations in this evidence were that data were generated from a single setting, endemic only for *S. haematobium* (and not for other *Schistosoma* spp.); parasitological outcomes were measured in a narrow age group (aged 9–12 years); and outcomes were parasitological with no measures of direct health outcomes.

The evidence from settings endemic for *S. mansoni* is provided by two small cluster-randomized trials of low to very low quality and with high risk of bias *(30, 31)*. Therefore, conclusions on the effects of biannual vs annual praziquantel for *S. mansoni* (or *S. japonicum*) are limited by paucity of data. However, while *Schistosoma* species have differences in biology and transmission, this paucity of data may require extrapolation of the higher quality data for *S. haematobium* to the expected benefits of biannual treatment for the other *Schistosoma* species. This extrapolation is supported by a systematic review of observational data that found comparable treatment outcomes for *Schistosoma* species; in this study, repeat doses of praziquantel (distinct from biannual treatment) may have significantly reduced the prevalence and infection intensity, with benefits greater for *S. mansoni* infection than for *S. haematobium*.

Ultimately, the effect of biannual compared to annual preventive chemotherapy will be related to *Schistosoma* prevalence, where higher prevalence settings experience greater benefits from biannual than annual treatment. Modelling studies indicate that increasing frequency of preventive chemotherapy PC against schistosomiasis from annual to biannual would reduce the prevalence of infection, infection intensity, and also be highly cost-effective. This conclusion is especially true in higher prevalence settings *(9, 11, 12, 32)*. Furthermore, modelling studies found that in addition to more frequent treatment,

the inclusion of adolescents and adults in treatment programmes in settings with high prevalence may be highly cost-effective.

There is mixed evidence to guide selection of criteria for when biannual rather than annual preventive chemotherapy confers greater prevalence reductions. The evidence suggests targeting higher prevalence settings or persistent hot spot communities that fail to respond to annual preventive chemotherapy. In some modelling studies, higher baseline prevalence (suggesting a higher force of infection) was associated with greater benefit from more frequent treatment. The recent SCORE randomized trial determined that persistent hot spots (that is, communities with *Schistosoma* prevalence that failed to decrease after repeated preventive chemotherapy) may benefit from biannual treatment but were difficult to identify from starting prevalence alone.

Some studies have proposed various operational definitions of a persistent hot spot community, based upon the response to preventive chemotherapy *(33)*. In recent analyses, the best predictor amongst potential persistent hot spot community for likely benefit from biannual preventive chemotherapy has been relative change in prevalence after 2–3 years of preventive chemotherapy *(25, 33)*. The exact choice for the threshold relative change in infection prevalence is imperfect and probably varies by baseline prevalence and epidemiological setting. For example, a setting that changes from 40% to 20% absolute infection prevalence (50% relative reduction) over two annual rounds of preventive chemotherapy is likely responding to treatment and may not require biannual treatment. Conversely, a setting that changes from 40% to 35% absolute infection prevalence (13% relative reduction) over two annual rounds of preventive chemotherapy is likely not responding to annual treatment and may require biannual treatment. An alternative to using relative prevalence reduction may be change in absolute prevalence of infection or change in average intensity of infection (defined as egg concentration in stool or urine). Based on published data, the GDG determined that < 30% relative reduction in prevalence (when comparing the baseline prevalence to a repeat prevalence estimate generated after 2 years of annual preventive chemotherapy with ≥ 75% treatment coverage) suggests a hot spot.

PICO question

Population	Pre-SAC (4–59 months of age), SAC, and adults
Intervention	Biannual treatment with praziquantel
Comparator	Annual treatment with praziquantel
Outcome	▪ Prevalence of schistosomiasis infection ▪ Intensity of schistosomiasis infection ▪ Prevalence of high-intensity schistosomiasis infection

GRADE summary table of the findings

Outcomes	Anticipated absolute effects (95% CI)		Relative effect	Sample size (studies)	Certainty of the evidence (GRADE)
	With annual PZQ treatment	With biannual PZQ treatment			
Prevalence of *S. haematobium* infection	117.8 per 1000	80.5 per 1000 (65.6–97.4)	The first trial showed reduction from baseline over 5 years (statistically significant in areas with high starting prevalence). The second trial showed significant reduction 10.8% vs. 35% (p < 10–3).	22 372 (two cluster RCTs)	⨁⨁⨁⊙ Moderate[1]
Prevalence of high intensity *S. haematobium* infection	8.2 per 1000	4.99 per 1000 (0.63–9.36)	Non-significant reduction in the first trial. In the second trial, significant reduction in the intervention villages and non-significant increase in the control villages.	22 372 (two cluster RCTs)	⨁⨁⨁⊙ Moderate[1]
Prevalence of *S. mansoni* infection	317.1 per 1000	266.9 per 1000	0.84 (0.67–1.06)	583 (one study)	⨁⨁⊙⊙ Low[2]
Prevalence of high intensity *S. mansoni* infection	8.3 per 1000	0 per 1000	3.0 (0.12–72.9)	240 (one cluster RCT)	⨁⊙⊙⊙ Very Low[2]
Intensity of *S. haematobium* infection			MD –1.09 (–1.21 to –0.97)	2190 (one cluster RCT)	⨁⨁⨁⊙ Moderate[1]

GRADE: Grading of Recommendations, Assessment, Development and Evaluation; MD: mean difference; PZQ: praziquantel; RCT: randomized controlled trial

[1] Study design is cluster RCT. Downgraded for concerns about risk of bias.

[2] Downgraded for concerns about risk of bias and for severe imprecision

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Annex 4.2 Safety of praziquantel for treatment of schistosomiasis

The primary evidence that formed the recommendation on safety of praziquantel for preventive chemotherapy against schistosomiasis in at-risk populations is one systematic review *(1)*. Other recently published systematic reviews *(2–5)* were examined in parallel, and the GDG also considered various datasets from observational studies.

The systematic review underpinning the recommendation assessed the safety of praziquantel in the key age groups of pre-SAC, SAC, adolescents, and adults including pregnant and lactating women *(1)*. The review's search criteria included studies of all types. It recorded adverse events categorized as serious and non-serious events. The review also included discussion of the broader literature.

The review's authors searched the MEDLINE, EMBASE and LILACS, Cochrane Infectious Diseases Group Specialized Register, CENTRAL (The Cochrane Library 2018), mRCT, Hinari and Africa Online Journals, and contacted individual researchers and organizations for relevant published and unpublished data and information on ongoing trials. The last search for evidence was made in October 2018. The review identified 3196 studies through searches from the aforementioned electronic databases and 155 from other sources, of which 131 studies were included in the review.

In the review, the principal finding was that praziquantel was associated with mild transient adverse events, most commonly abdominal pain (16.5%, 33 550 participants; 75 studies), headache (13.2%, 25 986 participants; 68 studies), vomiting (7.8%, 27 801 participants; 66 studies), nausea (7.6%, 19 009 participants; 56 studies), diarrhoea (4.8%, 18 595 participants; 59 studies), dizziness (3.8%, 20,716 participants; 61 studies), fever (2.6%, 23,096 participants; 36 studies), pruritus (2.8%, 16 247; 34 studies), anorexia (1.3%, 10 580 participants; 17 studies) and somnolence (1.2%, 12 805 participants; 23 studies). While normally well tolerated with only mild adverse events, there are rare reports of severe adverse events including serious anorexia (5 events out of 10 580 participants treated), severe vomiting (1 event out of 27 801 treated), severe nausea (9 events out of 19 009 treated) and severe diarrhoea (2 events out of 18 595 participants treated). Children tend to experience more events than adults for the same dose of praziquantel, but do not have adverse events of greater severity. The few studies included in the review that assessed safety in pregnancy (particularly fetal outcomes) and during lactation did not find any major events; however, the number of women in the first trimester of pregnancy included in the data was low. The overall certainty of evidence for these associations was moderate. The data included in the review had a large sample size and were likely at low or moderate risk of bias.

Multiple other systematic reviews and a recent randomized trial provide data on the safety of praziquantel in various age groups and for treatment of different *Schistosoma* species *(1–6)*. In the Cochrane Collaboration systematic reviews for *S. mansoni* and *S. haematobium*, the authors compiled data from randomized controlled trials that reported adverse events *(4, 5)*. The data suggest that treatment with praziquantel is associated infrequently with transient mild adverse events, most commonly abdominal pain, headache, dizziness, muscle and joint pain, diarrhoea, and fatigue. These studies did not report differences in moderate or severe events for those who received treatment. While data were not often age-stratified, there was no clear association

between adverse events and age. Data on monitoring and reporting of adverse event were generally considered to have moderate quality.

In a recently updated systematic review for *S. mansoni* and *S. haematobium*, the authors compiled data from observational and randomized studies that reported adverse events *(2, 3)*. The compiled data similarly suggest that praziquantel is associated with transient mild adverse events, most commonly drowsiness, abdominal pain, headache, fatigue, nausea, dizziness, weakness and diarrhoea. Similar to the previous studies, this systematic review did not identify differences in moderate or severe events for those who received treatment, and there was not clear evidence for age-based differences.

Recent trial data suggest that treatment is safe and well tolerated in children aged 2–5 years *(6)*.

Two randomized placebo-controlled trials have documented the safety of administering praziquantel in pregnant and breastfeeding women *(7, 8)*. In the first trial, in Uganda, 2507 pregnant women living in settings endemic for *S. mansoni* were randomized to praziquantel and albendazole or a placebo, with no differences found in outcomes of birth weight, perinatal mortality or congenital anomalies; however, few women in the first trimester of pregnancy were included in the study *(7)*. In the second trial in the Philippines, 370 pregnant women (at 12–16 weeks gestation) infected with *S. japonicum* were enrolled and randomized to praziquantel or placebo, with no differences found in outcomes of birth weight, abortion, fetal death in utero, congenital anomalies or adverse events (headache, malaise, dizziness).

PICO question

Population	Pre-SAC, SAC, and adults including pregnant and lactating women or entire communities in endemic areas infected with any of the following schistosome species: *S. haematobium, S. mansoni, S. japonicum, S. intercalatum, S. guineensis* and *S. mekongi* or non-infected individuals who received praziquantel during preventive chemotherapy or MDA
Intervention	▪ Praziquantel given at a dose of 40 mg/kg, 50 mg/kg, 60 mg/kg or ≥70 mg/kg ▪ Praziquantel co-administered with albendazole, mebendazole, pyrantel pamoate or levamisole (for soil-transmitted helminthiases), or albendazole plus either ivermectin or diethylcarbamazine citrate (for lymphatic filariasis), or artemisinin-based combination therapies (for malaria)
Comparator	Placebo; no praziquantel treatment; other anti-schistosomal drugs
Outcome	▪ Adverse events

GRADE summary table of the findings

Outcomes	Anticipated absolute effects[a] (95% CI)		Relative effect (95% CI)	Sample size (studies)	Certainty of the evidence (GRADE)
	Without preventive chemotherapy	With preventive chemotherapy			
Serious adverse events[a]	0	0	No data	75 985 (108)	⨁⨁⨁⊙ Moderate[1]
Dizziness	2 per 100	19 per 100	3.8% (3.54–4.06%)	20 716 (61)	⨁⨁⊙⊙ Low[2]
Abdominal pain	4 per 100	66 per 100	16.5% (16.1–16.9%)	33 550 (75)	⨁⨁⊙⊙ Low[2]
Headache	3 per 100	39 per 100	13.2% (12.79–13.61%)	25 986 (68)	⨁⨁⊙⊙ Low[2]
Diarrhoea	2 per 100	10 per 100	4.8% (4.49–5.11%)	18 595 (59)	⨁⨁⊙⊙ Low[2]

CI: confidence interval; GRADE: Grading of Recommendations, Assessment, Development and Evaluation.
[a] Includes stillbirth, congenital anomalies, premature birth or events requiring hospitalization.
[1] It is likely that serious adverse events are rare with praziquantel and are similar to those in the control group since none have been reported in such a large sample.
[2] Increased risk of bias: many of the included studies were not randomized. Increased risk of bias: some symptoms such as diarrhoea, headache and abdominal pain are common and caused by other schistosomes or other infections rather than by the medications given.

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Annex 4.3 WASH and snail control interventions

A4.3.1 WASH interventions and schistosomiasis in at-risk populations

The primary evidence that underpinned the recommendation on the relationship of water, sanitation and hygiene (WASH) interventions and schistosomiasis in at-risk populations is contained in two published meta-analyses *(1, 2)*, utilizing data from 52 observational studies published in 2013 and 2015. We searched for an update; however, no major review on WASH and schistosomiasis has been published since then.

The first systematic review assessed the relationship between access to safe water and sanitation with Schistosoma infection *(1)*. The review search criteria included all study types, including cross-sectional studies. The review authors searched PubMed, Web of Science, Embase and the Cochrane Library, and also reviewed the bibliographies of identified references. The last search for evidence was done in December 2013. The authors identified 44 eligible studies including 54 datasets comparing access to safe water and infection with *S. mansoni* (*n*=35), *S. haematobium*, (*n*=17) and *S. japonicum* (*n*=2), 24 datasets comparing access to adequate sanitation and infection with *S. mansoni*, and 12 datasets comparing access to adequate sanitation and infection with *S. haematobium*. They found no eligible studies on sanitation and *S. japonicum*, or on hygienic practices. The included studies were all observational, mostly being based on cross-sectional surveys. In the meta-analysis, safe water and adequate sanitation were associated with reduced odds of being infected with *Schistosoma*, with the limitation that the data were derived only from non-randomized studies. The key findings were that safe water supply was associated with lower odds of *Schistosoma* infection (OR [odds ratio]: 0.53, 95% CI: 0.47, 0.61) and adequate sanitation was associated with lower odds of *S. mansoni* (OR: 0.59, 95% CI: 0.47, 0.73) and *S. haematobium* (OR: 0.69, 95% CI: 0.57, 0.84).

The second systematic review assessed the relationship between access to improved sanitation and *Schistosoma* infection *(2)*. The review's authors searched PubMed, Web of Science, Embase and the Cochrane Library, and followed the search strategy outlined by the previous meta-analysis *(1)*. The last search for evidence was done in December 2015. The authors identified 30 eligible studies, 22 of which were also identified in the Grimes paper *(1)*. Studies were conducted in Sub-Saharan Africa (*n*=13) and South America (*n*=12), predominantly in Brazil for *S. mansoni*. Most studies were conducted in rural contexts (*n*=19). Included studies were all observational, cross-sectional surveys. In the meta-analysis, sanitation was associated with lower odds of infection with *S. mansoni* (OR: 0.61, 95% CI: 0.50, 0.74; *n*=23) and *S. haematobium* (OR: 0.69, 95% CI: 0.58, 0.81; *n*=10). The included data were from predominantly non-randomized studies at increased risk of bias. Finally, the relationship between WASH interventions and schistosomiasis may be non-linear, meaning that changes in WASH exposures may not yield proportional changes in schistosomiasis incidence *(3)*.

Despite limitations in the evidence, based on the life cycle of *Schistosoma* infection, access to improved WASH is likely still necessary to reduce transmission and eventually achieve elimination. For example, safe water supplies for drinking and for domestic activities (e.g. laundry and bathing) can reduce or prevent human contact with contaminated surface water. Safe sanitation systems can prevent excreta (urine and faeces) from contaminating snail-infested water bodies, which can drive overall transmission. Some *Schistosoma* species have animal reservoirs which contribute to human infection (e.g. *S. japonicum* and water buffalo) and there are emerging animal

livestock–human hybrids, such as a *S. haematobium–S. bovis* hybrid. Thus, preventing animal contact with surface water is also crucial. Many factors are ultimately necessary for improvements to WASH to be successful, including ensuring that improvements are maintained over time, are adopted throughout the population through behavioural change and address key routes of transmission (e.g. contact with fresh water).

Collaboration between WASH and neglected tropical disease (NTD) programmes is likely critical to control and eliminate schistosomiasis and other infectious diseases of poverty. The WHO global strategy on WASH and NTDs 2015–2020 has outlined an approach to share information, undertake joint planning and monitoring, and increase the evidence base for intervention design in order to accelerate and sustain disease control and overall health and well-being *(4)*. It is supported by several practical tools to support collaboration on the ground *(5)*. WHO guidelines are relevant to schistosomiasis control efforts, including the guidelines for drinking-water quality *(6)* recreational water use *(7, 8)* and sanitation and health *(9)*.

PICO question

Population	Population of all ages
Intervention	▪ Safe water sources included those described as 'closed' rather than 'open', 'piped water', 'drinking water' or 'cistern' in the home, 'clean' rather than 'river or lake', 'adequate', 'public supplies', 'treated', or 'safe'. Wells were considered safe except in South America. The category of 'non-use of water from ponds or irrigation wells' was also included on the assumption that it refers to the water used for most or all domestic water needs. ▪ Adequate sanitation included '(pit) latrine', 'flush toilet', 'sewer connection' or 'sewerage, 'cesspool' or 'septic tank'.
Comparator	'Unsafe water sources' 'Inadequate sanitation'
Outcome	Schistosomiasis as defined as infection with any human schistosome, assessed through the presence of eggs in the urine or stool (*S. mansoni, S. haematobium, S. japonicum*).

GRADE summary table of the findings

Outcomes	Relative effect (95% CI)	Sample size (studies)	Certainty of the evidence (GRADE)
Safe water supply			
S. haematobium	OR 0.57 (0.45–0.71)	33 214 12 studies	⨁⨁⊙⊙ Low[1]
S. mansoni	OR 0.53 (0.45–0.63)	41 165 28 studies	⨁⨁⊙⊙ Low[1]
S. japonicum	OR 0.37 (0.30–0.46)	11 406 2 studies	⨁⨁⊙⊙ Low[1]
Adequate sanitation			
S. haematobium	0.69 (0.57–0.84)	28 023 8 studies	⨁⨁⊙⊙ Low[1]
S. mansoni	0.59 (0.47–0.73)	35 453 18 studies	⨁⨁⊙⊙ Low[1]

CI: confidence interval; GRADE: Grading of Recommendations, Assessment, Development and Evaluation; OR: odds ratio.
[1] Studies were non-randomized and some were cross-sectional..

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A4.3.2 Chemical-based snail control in at-risk communities

The primary evidence that formed the recommendation on the relationship of chemical-based snail control methods and schistosomiasis prevalence and incidence in at-risk populations is contained in a published meta-analysis *(1)* that utilized data from 63 observational, before and after field trials performed from 1953–1992. The recommendation also considered uncontrolled observational data from 47 snail control studies, and recommendations from transmission modelling work, combined with cost–effectiveness analyses *(2)*.

The systematic review underpinning the recommendation evaluated evidence on the impact of chemical-based host snail control methods on local prevalence and incidence of schistosomiasis across all age groups *(1)*. The review search criteria included all study types, including non-randomized trials and quasi-experimental trials, including observational studies comparing pre-post outcomes after snail control interventions. Studies were not excluded for having concurrent preventive chemotherapy programmes. The included studies measured prevalence outcomes in either SAC or children and adults, and reported incidence in cohorts or from prevalence estimation among the very youngest age class of children (aged ≤ 5 years), indicative of ongoing transmission given their very young age. The review also included discussion of the broader literature examining the optimal frequency of molluscicide treatment, including observational studies of snail repopulation over time, modelling studies and cost–effectiveness analyses.

The review's authors searched PubMed, Google Scholar, Web of Science, SCIELO and African Journals Online, as well as other resources such as WHO technical reports and archived files at Case Western Reserve University (Cleveland (OH), USA) and SCORE. Study references were reviewed if relevant and available (including grey literature) for inclusion in the meta-analysis. The last search for evidence was done in October 2014. Eligible studies included published or unpublished molluscicide field trials performed before January 2014 involving host snails for *S. mansoni* or *S. haematobium*, with a primary focus on the use of niclosamide as the molluscicide intervention.

The review identified 63 observational studies that met the inclusion criteria for the meta-analysis, involving data on *S. mansoni* or *S. haematobium* across all age groups from Africa, South America, the Caribbean and the Islamic Republic of Iran. Studies of S. japonicum snail control were reviewed but did not provide sufficient data on human outcomes to be included in the meta-analysis. The predominant study types included in this review were observational, comparing local incidence or prevalence of *Schistosoma* infection in at-risk human populations before and after chemical-based snail control (with or without concurrent preventive chemotherapy). The authors observed large variability in molluscicide dosing. The treatment intervals varied from 3 to 52 weeks depending on location, water source and type of application. Reporting on the effectiveness of molluscicide treatment and the duration of its effects also varied widely among studies; as a result, these snail reduction data were not amenable to meta-analysis, as had been done for the niclosamide trials in China *(3, 4)*.

In the meta-analysis, among 35 studies reporting on the relationship of snail control to human prevalence, the random effects meta-analysis indicated that, on average, odds

of prevalence of infection were reduced 77% (odds ratio [OR] = 0.23, 95% CI: 0.17, 0.31) during the course of molluscicide, with increased impact if the molluscicide was combined with drug therapy, and a progressively greater impact over time. In 17 studies reporting local incidence, risk of new infection was reduced 64% (risk ratio [RR] = 0.36 95% CI: 0.25, 0.5), but concurrent preventive chemotherapy did not appear to influence the incidence effects. Graphical summaries are presented in *(1)*.

The relationships between snail control and schistosomiasis prevalence or incidence were heterogeneous. The observed prevalence reduction with snail control was smaller where snail control was used alone (OR 0.47, 95% CI: 0.28, 0.80), and greater among studies where snail control was combined with community-based treatment programmes (OR 0.16, 95% CI: 0.12, 0.23). There were no clear differences in the impact of snail control between *S. mansoni* and. *S. haematobium* endemic locations. Other observed heterogeneities included that snail control treatment of natural water sites had greater overall impact than treatment of irrigation systems, and that the baseline local prevalence of infection did not have a clear effect on the size of prevalence reductions obtained during a molluscicide programme. The observed incidence reduction was greater in areas with natural water sources as compared with irrigation schemes (RR 0.36 vs 0.55). However, there was no apparent difference in incidence reduction effect when drug treatments were included in the control programmes (RR for snail control alone was 0.33 vs 0.32 for snail control plus community drug treatment).

The principal findings of this systematic review are dominated by low- and very low-certainty evidence with high risk of bias, often from uncontrolled studies, which limits their interpretability. The majority of studies had high risk of bias across six domains: (i) selection bias (random sequence generation, allocation concealment), (ii) performance bias (blinding of participants/personnel), (iii) detection bias (blinding of outcome assessment), (iv) attrition bias (incomplete outcome data), (v) reporting bias (selective outcome reporting) and (vi) other biases. Generally, included papers reported research performed in the pre-1990s era; more recent literature was not available. Snail control has not been a widely adopted practice, which has probably reduced research activity on this topic; additional research on focal snail control has been conducted within SCORE, demonstrating that this intervention may have a role *(5)*. Most reported studies involved a single intervention site, studies were non-randomized and, for the most part, the comparison of intervention effects involved historical rather than concurrent comparison data. In studies in which concurrent untreated comparison sites were monitored, the risk of baseline differences between treated and untreated areas was often high *(6)*, thus relationships observed between snail control and reductions in prevalence and incidence may not be fully related to the snail control intervention. There was also a high degree of heterogeneity among the studies included in the meta-analysis: the Higgins and Thompson I^2 statistic was 99.9 for prevalence studies, and 93.2 for incidence studies.

PICO question

Population	SAC, children and adults Subgroups ▪ *S. mansoni* ▪ *S. haematobium* ▪ Geographical regions ▪ Local dominant water exposure (irrigation vs natural)
Intervention	Chemical-based molluscicide at water contact sites, the sites of transmission Subgroups ▪ Snail control alone ▪ Snail control with screening of local human population and treatment of egg-positive subjects ▪ Snail control with mass treatment of SAC or SAC and adults
Comparator	No intervention, or comparison to pre-intervention historical data from the treated zone
Outcome	Pre/post change in odds of local Schistosoma prevalence in SAC or total population Pre/post change in risk of local Schistosoma incidence in pre-SAC, SAC, selected adults or total population

GRADE summary table of the findings

Outcomes	Relative effect (95% CI)	Sample size (studies)	Certainty of the evidence (GRADE)
All ages			
Prevalence of infection	OR of having infection after implementation = 0.193 (95% CI: 0.144–0.258)	998 126 (21)	⨁⨁⊙⊙ Moderate[1]
Incidence of infection	RR of infection after implementation = 0.526 (95% CI: 0.386–0.716)	4320 (8)	⨁⨁⊙⊙ Moderate[1]
SAC			
Prevalence of infection	OR of having infection after implementation = 0.365 (95% CI: 0.172–0.774)	400 698 (14)	⨁⨁⊙⊙ Moderate[1]
Incidence of infection	RR of infection after implementation = 0.311 (95% CI: 0.226–0.427)	2310 (7)	⨁⨁⊙⊙ Moderate[1]

CI: confidence interval; GRADE: Grading of Recommendations, Assessment, Development and Evaluation; OR: odds ratio; RR: risk ratio; SAC: school-aged children.
[1] Non-randomized studies; upgraded due to a large effect size.

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Annex 4.4 Verification of interruption of transmission

A4.4.1 Diagnostic tools for *Schistosoma* infection in humans to verify elimination of transmission

The primary evidence that supported the recommendation on diagnostic tools for Schistosoma infection in humans in the context of verification of transmission elimination was captured by a recent systematic review and meta-analysis *(1)*. The recommendation also considered various studies that incorporated quantitative and qualitative aspects of appraising these diagnostic tools.

The systematic review assessed a wide range of diagnostic tools for detection of *Schistosoma* infection in humans. For *S. mansoni*, the review used Kato–Katz as the reference standard to evaluate CCA (circulating cathodic antigen), CAA (circulating anodic antigen), FLOTAC, SmCTF-RDT, PCR (polymerase chain reaction) and ELISA (enzyme-linked immunosorbent assay). These methods use samples of faeces, urine and blood to detect the presence of eggs, antigen or antibody, respectively. For *S. haematobium*, the review included urine filtration and microscopy as the reference standard to evaluate proteinuria reagent strips, haematuria reagent strips, ELISA, LAMP (loop-mediated isothermal amplification) and indirect hemagglutination assay (IHA). These methods use urine samples to detect the presence of eggs or sequelae of disease (i.e. proteinuria or haematuria). Many techniques for diagnosis of Schistosoma included molecular techniques requiring various laboratory procedures such as antibody assays for detection of schistosome antigens with ELISA or amplification of schistosome DNA with PCR.

The review search criteria included any study that applied a method for diagnosis of *Schistosoma* in human populations. The authors included analyses that reported key outcomes of diagnostic performance for each tool, mainly sensitivity and specificity; the review also included evaluation of study bias and challenges with applicability of study conclusions. The review authors searched PubMed, EMBASE, the Cochrane Library, LILACS and Africa-Wide Information databases. The last search for evidence was done in February 2021.

In the meta-analysis, 17 techniques for diagnosing S. mansoni and S. haematobium infections in humans were identified outside of the reference tests. The overall certainty of evidence was moderate.

For diagnosis of *S. mansoni* using 2, 4 or 6 Kato–Katz tests as the reference standard, CCA1 was estimated to have a sensitivity of 64% (95% CI: 41–83%, *n*=4 studies), 85% (95% CI: 76–92%, *n*=9 studies), 81% (95% CI: 54–95%, *n*=4 studies) and a specificity of 66% (95% CI: 43–84%), 62% (95% CI: 50–74%), 63% (95% CI: 43–80%) respectively. There was a paucity of data on CAA, although a single study estimated a sensitivity of 96% (95% CI: 79–100%, *n*=1 study) and a specificity of 65% (95% CI: 60–70%, *n*=1 study) in reference to Kato–Katz. The SmCTF-RDT was estimated to have a sensitivity of 87% (95% CI: 30–99%, *n*=4 studies) and a specificity of 35% (95% CI: 14–63%, *n*=4 studies) in reference to Kato–Katz. The remaining diagnostics, including many molecular-based

methods such as ELISA and PCR-based assays, lacked sufficient data from which to draw informative conclusions.

For diagnosis of *S. haematobium* using urine microscopy as the reference standard, haematuria reagent strips were estimated to have a sensitivity of 86% (95% CI: 58–98%, *n*=5 studies) and a specificity of 86% (95% CI: 73–96%); proteinuria reagent strips were estimated to have a sensitivity of 72% (95% CI: 24–96%, *n*=3 studies) and a specificity of 86% (95% CI: 48–99%). The remainding identified diagnostics, including many molecular-based methods such as ELISA and PCR-based assays, lacked sufficient data from which to draw informative conclusions. The overall certainty of evidence for the accuracy of tools to diagnose Schistosoma infections in humans was moderate.

The key limitation of the meta-analysis was the use of an imperfect test as the reference 'gold standard' (Kato–Katz for *S. mansoni,* urine microscopy for *S. haematobium*). The analysis was further limited by the availability of data from relatively few studies. The reference diagnostic tests used in the analysis have notoriously low sensitivity, which precluded adequate estimation of diagnostic characteristics for a new test with superior sensitivity. Specifically, if a diagnostic test was included with superior sensitivity to the imperfect reference standard, the new diagnosis would be penalized by being assigned a low estimated specificity. Notably, many of the included diagnostic tests in the analyses lacked commercially available forms, and many molecular methods often required intensive laboratory facilities, resources and expertise. The study further lacked rigorous evaluation of CCA, including the role of trace positive in representing true infection; importantly, this topic was investigated by WHO in a systematic review that treated trace positives as true infections *(2)*. The specificity of many parasitological diagnostics will likely differ by setting and be related to disease prevalence; reagent strips for proteinuria or haematuria and diagnostics that are dependent on egg burden (which is related to transmission intensity) will be affected in this way. The study also did not include analyses for *S. japonicum*.

Recent reviews and meta-analyses provide data on the sensitivity and specificity of CCA and other point-of-care diagnostic tests for schistosomiasis *(3, 4*). A Cochrane meta-analysis of the sensitivity and specificity of point-of-care tests for schistosomiasis *(4)* estimated that CCA for diagnosis of *S. mansoni* had a sensitivity of 89% and specificity of 55%, assuming that CCA is a more sensitive test than the reference test, stool microscopy. A second study estimated conversion rates between prevalence estimated by Kato–Katz and CCA *(3)*. The authors compiled 30 datasets with individual-level data on S. mansoni with Kato–Katz and CCA, and estimated that 5% prevalence by Kato–Katz was comparable to 20% prevalence by CCA; similarly, 10% prevalence by Kato–Katz was comparable to 30% prevalence by CCA *(3)*. Notably, different versions of the CCA test were used for these studies.

The review demonstrates the specifications of diagnostic tools for *Schistosoma* infections in humans. While many point-of-care, molecular and immunological methods

show promise, analyses have been unable to identify a new diagnostic tool that is clearly superior to the routinely used conventional methods.

PICO question

Population	Adults and children (pre-SAC and SAC) living in endemic areas who have received elimination interventionss
Intervention	▪ CCA1 → Circulating cathodic antigen urine cassette assay v1 (5) ▪ CCA2 → Circulating cathodic antigen urine cassette assay v2 ▪ CAA → Circulating anodic antigen urine cassette assay ▪ FLOTAC ▪ SmCTF-RDT → *S. mansoni* cercarial transformation fluid rapid diagnostic test ▪ Sm DNA PCR → *S. mansoni* DNA detection by PCR ▪ SWAP ELISA soluble adult worm antigen preparation-specific IgG ELISA ▪ IgM ELISA → IgM antibodies against a fraction of *S. mansoni* adult worm antigen ▪ IgG ELISA → IgG antibodies against a fraction of *S. mansoni* adult worm antigen ▪ Anti IgG RDT Sh → Anti-human IgG antibody rapid diagnostic test ▪ Proteinuria → Proteinuria reagent strips ▪ Haematuria → Haematuria reagent strips ▪ AWE-SEA Elisa → *S. mansoni* adult worm extract and *S. mansoni* soluble egg antigen ELISA ▪ LAMP → loop-mediated isothermal amplification ▪ IHA → indirect hemagglutination assay ▪ Colorimetric test → Macroscopic haematuria by colorimetric test ▪ rSP13-ELISA → recombinant proteins SjSP-13-based ELISA kit
Comparator (reference tests)	▪ Double KK → Duplicate Kato–Katz smears ▪ Quadruple KK → Quadriplicate Kato–Katz smears ▪ Sextuple KK → Sextuplicate Kato–Katz smears ▪ Duplicate KK → Duplicate Kato–Katz smears ▪ Triplicate KK → Triplicate Kato–Katz smears ▪ Urine filtration → Urine filtration and microscopy ▪ Urine microscopy → Urine filtration and microscopy
Outcome	Performance of the tests: sensitivity, specificity, positive predictive value, negative predictive value Disease prevalence with the reference test and with the index test

GRADE summary table of the findings

Outcomes[a] (reference)	Diagnostic estimates (95% CI)	Sample size (studies)	Certainty of the evidence (GRADE)[b]
CCA1 *(5)*	Vs 2 KK: Se=64% Sp=66% Vs 4 KK: Se=85% Sp=62% Vs 6 KK: Se=81% Sp=63%	788 (4) 4173 (9) 1441 (4)	⨁⨁⨁⊙ Moderate[1]
CCA2	Vs 2 KK: Se=59% Sp=87% Vs 4 KK: Se=46% Sp=88%	100 (2) 100 (1)	⨁⨁⨁⊙ Moderate[1]
CAA	Vs 4 KK: Se=89% Sp=60% Vs urine microscopy: Se=70% Sp=46%	377 (1) 265 (1)	⨁⨁⨁⊙ Moderate[1]
FLOTAC	Fresh vs 3KK: Se=65% Sp=70% 10d vs 3KK: Se=88% Sp=64% 30d vs 3KK: Se=93% Sp=61%	112 (1) 112 (1) 112 (1)	⨁⨁⨁⊙ Moderate[1]
SmCTF-RDT	Vs 4 KK: Se=87% Sp=35% Vs urine microscopy: Se=62% Sp=38%	291 (4) 117 (1)	⨁⨁⨁⊙ Moderate[1]
Sm DNA PCR	Vs 2 KK: Se=96% Sp=32%	89 (1)	⨁⨁⨁⊙ Moderate[1]
SWAP ELISA	Vs 6 KK: Se=83% Sp=55%	482 (1)	⨁⨁⨁⊙ Moderate[1]
IgM ELISA	Vs 3 KK: Se=92% Sp=91%	137 (1)	⨁⨁⨁⊙ Moderate[1]
IgG ELISA	Vs 3 KK: Se=88% Sp=66%	247 (1)	⨁⨁⨁⊙ Moderate[1]
Anti IgG RDT Sh	Vs urine microscopy: Se=47% Sp=19%	160 (1)	⨁⨁⨁⊙ Moderate[1]
Proteinuria reagent strips	Vs urine microscopy: Se=72% Sp=86%	3324 (4)	⨁⨁⨁⊙ Moderate[1]
Haematuria reagent strips	Vs urine microscopy: Se=86% Sp=86%	4862 (6)	⨁⨁⨁⊙ Moderate[1]
AWE-SEA ELISA	Vs 4 KK: Se=94% Sp=64%	247 (2)	⨁⨁⨁⊙ Moderate[1]
LAMP	Vs 3 KK: Se=87% Sp=50% Vs urine microscopy: Se=66% Sp=79%	110 (1) 94 (1)	⨁⨁⨁⊙ Moderate[1]

IHA	Vs 3 KK: Se=81% Sp=7%	203 (2)	⨁⨁⨁⊙ Moderate[1]
Colorimetric test	Vs urine microscopy: Se=52% Sp=67%	1279 (1)	⨁⨁⨁⊙ Moderate[1]
rSP13-ELISA	Vs 27 KK: Se=88% Sp=64%	1371 (1)	⨁⨁⨁⊙ Moderate[1]

[a] Anti IgG RDT Sh: anti-human IgG antibody rapid diagnostic test; AWE-SEA ELISA: *S. mansoni* adult worm extract and *S. mansoni* soluble egg antigen; ELISA CAA: circulating anodic antigen urine cassette assay; CCA1: circulating cathodic antigen urine cassette assay v1; CCA2: circulating cathodic antigen urine cassette assay v2; Colorimetric test: macroscopic haematuria by colorimetric test; ELISA: enzyme-linked immunosorbent assay; IgG ELISA: IgG antibodies against a fraction of *S. mansoni* adult worm antigen; IgM ELISA: IgM antibodies against a fraction of *S. mansoni* adult worm antigen; IHA: indirect haemagglutination assay; KK: Kato-Katz; LAMP: loop-mediated isothermal amplification; rSP13-ELISA: recombinant proteins SjSP-13-based ELISA kit; se: sensitivity; SmCTF-RDT: *S. mansoni* cercarial transformation fluid rapid diagnostic test; Sm DNA PCR: *S. mansoni* DNA detection by PCR; sp: specificity; SWAP ELISA: soluble adult worm antigen preparation-specific IgG ELISA.
[b] GRADE: Grading of Recommendations, Assessment, Development and Evaluation.
[1] The certainty of the diagnostic accuracy estimates is limited because the gold standard test is imperfect; therefore, certainty was rated down due to risk of bias. Estimates were judged to be sufficiently precise for most comparisons.

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A4.4.2 Diagnostic tools for detection of Schistosoma in snails and the environment to verify elimination of transmission

The primary evidence that formed the recommendation on tools to detect *Schistosoma* in snails to verify transmission elimination for schistosomiasis was extracted from a systematic review and meta-analysis *(1)*. The GDG also considered various studies that incorporated both quantitative and qualitative aspects of appraising these diagnostic tools.

The systematic review underpinning the recommendation assessed a wide range of diagnostic tools for detection of *Schistosoma* in snails. The review included conventional methods of direct shedding, snail crushing and water-based detection methods, as well as newer methods of PCR, ELISA, DNA hybridization and LAMP. The most conventional method, that of direct shedding, involved isolating a relevant sample of snails, placing them in a small volume of water, and observing visually for schistosome cercariae being released from the snails and being "shed" into the water. Snail-crushing techniques involved direct light microscopy of crushed snails to visualize schistosome cercariae. The molecular methods of PCR, ELISA and LAMP involved creating aqueous extractions from snail samples, and then applying various laboratory procedures such as antibody assay for detection of schistosome antigens with ELISA or amplification of schistosome DNA with PCR.

The review search criteria included any study that applied a method for detection of *Schistosoma* in snails or water bodies. The included analyses reported key outcomes for each tool of diagnostic performance with sensitivity and specificity; the review also included evaluation of study bias, quality, consistency, cost and species differentiation, and included a discussion of the practical strengths and limitations of each method.

The review's authors searched the PubMed, Web of Science, Google Scholar, China Academic Journals Full-text Database and ResearchGate, and reference lists. They further contacted individual experts for relevant unpublished data and ongoing studies. The last search for evidence was done in September 2020. A total of 119 studies were included in the review.

In the meta-analysis, 25 techniques for diagnosing *Schistosoma* in snails or in the water were identified. Of these, only a minority had sufficient data on diagnostic performance to be considered in the meta-analysis; these techniques included direct shedding, ELISA, PCR and LAMP. The sensitivity of direct shedding was estimated to be 25–100% (*n*=12 studies), ELISA was 88–100% (*n*=7 studies), conventional PCR was 100% (*n*=36 studies), quantitative PCR was 93% (*n*=1 study) and LAMP was 97–100% (*n*=16 studies). The data on specificity of these techniques were generally lacking, although they were often reported as 90–100%. The overall certainty of evidence for diagnostic accuracy estimates was mostly low or very low. Studies often lacked a true reference standard for adequate measurement of sensitivity and specificity, did not have standardization of approaches or implementation in real-world settings, and often required advanced laboratory facilities, resources and expertise. Furthermore, the key outcomes were sensitivity and specificity for the detection of *Schistosoma* in snails, while the broader question of the sensitivity and specificity required to predict elimination of transmission, which would also include sampling schemes and future studies, was not addressed. The interpretability of the diagnostic characteristics of these techniques was further limited

due to lack of data across Schistosoma species and snail types, and generally poor validation of the techniques.

The review demonstrates the specifications of diagnostic tools for *Schistosoma* in snails, with the best evidence for conventional methods of snail shedding and crushing techniques as well as the newer method based on LAMP. Generally, diagnostic tools require further development, characterization and validation in the field setting. Future work is also needed to understand the sampling strategies necessary to provide the relevant information, i.e. verification of elimination in formerly endemic settings.

PICO question

Population	Snail populations and aquatic environment in settings endemic for schistosomiasis Subgroups ▪ by snail populations ▪ by aquatic environment
Intervention	Diagnostic tool for detection of *Schistosoma* Subgroups ▪ by diagnostic tool including parasitological, immunoassay and molecular test
Comparator	Snail shedding/crushing (reference standard)/no diagnostic in snail population
Outcome	▪ Sensitivity of *Schistosoma* infection status ▪ Specificity of *Schistosoma* infection status

GRADE summary table of the findings

	Anticipated relative effects			
Outcomes	**Sensitivity**	**Specificity**	**Number of studies**	**Certainty of the evidence (GRADE)**
Direct shedding	Insufficient data	25–100%	12	⨁⨁◯◯ Low[1]
Snail crushing	Insufficient data	Insufficient data	6	⨁⨁◯◯ Low[1]
ELISA/immune-detection	100%	88–100%	7	⨁◯◯◯ Very low[1,2]
Biochemical analysis	Insufficient data	Insufficient data	2	⨁◯◯◯ Very low[1,2]
DNA hybridization/ DOT BLOT	Insufficient data	100%	5	⨁◯◯◯ Very low[1,2]
Conventional PCR	90–100%	100%	36	⨁◯◯◯ Low
PCR with restriction digestion	Insufficient data	Insufficient data	2	⨁◯◯◯ Very low[1,2]
RAPD PCR	Insufficient data	Insufficient data	1	⨁◯◯◯ Very low[1,2]
Repeat sequence PCR	Insufficient data	Insufficient data	7	⨁◯◯◯ Very low[1,2]
Nested PCR	Insufficient data	80–92%	5	⨁◯◯◯ Very low[1,2]
Multiplex PCR	70%	Insufficient data	6	⨁⨁◯◯ Low[1]
qPCR	80–85.7%	93%	17 (1)	⨁⨁◯◯ Low[1]
FRET-PCR	100%	Insufficient data	5	⨁⨁◯◯ Low[1]
LAMP	86.67– 94%	96.7–100%	16	⨁⨁⨁◯ Moderate[1]
Microfluidics LAMP	Insufficient data	Insufficient data	1	⨁◯◯◯ Very low[1,2]

Recombinase polymerase amplification	Insufficient data	Insufficient data	1	⨁⊙⊙⊙ Very Low[1,2]
Filtering then direct examination of filter	Insufficient data	30–93.75 %	6	⨁⊙⊙⊙ Very Low[1,2]
Sentinel rodents	Insufficient data	Insufficient data	11	⨁⊙⊙⊙ Very Low[1,2]
Sentinel snails	Insufficient data	Insufficient data	5	⨁⊙⊙⊙ Very Low[1,2]
Environmental DNA	53–95%	75–95%	2	⨁⨁⨁⊙ Moderate[1,2]
ddPCR	100%	Insufficient data	2	⨁⊙⊙⊙ Very Low[1,2]
Cercariae traps	Insufficient data	Insufficient data	4	⨁⊙⊙⊙ Very Low[1,2]
Robotics	Insufficient data	Insufficient data	1	⨁⊙⊙⊙ Very Low[1,2]
Oligochromatic dipstick	Insufficient data	Insufficient data	2	⨁⊙⊙⊙ Very Low[1,2]
Filtration then molecular characterization	Insufficient data	50%	1	⨁⊙⊙⊙ Very Low[1,2]

ddPCR: droplet digital PCR; FRET-PCR: fluorescence resonance energy transfer PCR; GRADE: Grading of Recommendations Assessment, Development and Evaluation; LAMP: loop-mediated isothermal amplification; qPCR: quantitative PCR; PCR: polymerase chain reaction; RAPD DNA: random amplified polymorphic DNA..
[1] Serious concerns about risk of bias (rated down once or twice).
[2] Imprecision

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A4.4.3 Diagnostic tools for *Schistosoma* infection in non-human animal hosts to verify elimination of transmission

The primary evidence that formed the recommendation on diagnostic tools for *Schistosoma* infection in non-human animal hosts to verify transmission elimination of schistosomiasis is derived from a systematic review and meta-analysis *(1)*. The GDG also considered various studies that incorporated both quantitative and qualitative aspects of appraising these diagnostic tools, and their application under endemic settings.

The systematic review underpinning the recommendation assessed a wide range of diagnostic tools for detection of *Schistosoma* in non-human animal hosts, predominantly *S. japonicum*. The review included diagnostics using parasitological, immunological and molecular techniques. The parasitological tests used fecal samples and included Kato–Katz, miracidia hatching test and formalin-ethyl acetate sedimentation technique. The immunological assays used serum samples and included a colloidal gold immuno-chromatography assay, indirect hemagglutination assay and enzyme-linked immunosorbent assay. Finally, the molecular tools used fecal samples and included the PCR. Many techniques, including the parasitological ones, required multiple sample preparation steps and laboratory infrastructure. The immunological and molecular methods required extensive laboratory reagents, laboratory procedures, and technical expertise.

The review was structured to include any study that applied two or more methods for detection of *Schistosoma* in non-human animal hosts. A search term for "rodent" was not included. The authors included analyses that reported diagnostic performance with various metrics, including sensitivity and agreement (Cohen's kappa) relative to a reference standard. The review also included evaluation of each study, and discussion of practical strengths and limitations of each method.

The review's authors searched PubMed, Web of Science, Science Direct, China National Knowledge Infrastructure, Wanfang Database for Chinese Literature, the World Health Organization's Library Database, Food and Agriculture Organization, and World Organisation for Animal Health. The last search for evidence was done in August 2019; no language restrictions were applied.

In the systematic review, 14 techniques for diagnosing *Schistosoma* in non-human animal hosts were identified from 19 studies. Of these, only a subset had sufficient data on diagnostic performance to be considered in the meta-analysis. The majority were studies that assessed *S. japonicum*, and included samples from common animal reservoirs such as cattle and other bovines, including buffalo. The primary meta-analysis used PCR as the reference standard, and estimated the sensitivity of the parasitological techniques Kato–Katz, miracidia hatching test, and formalin-ethyl acetate sedimentation. With PCR as the reference standard, the sensitivity of the miracidia hatching test was estimated to be 23% (95% CI: 0, 54%), Kato–Katz was 27% (95% CI: 0, 62%), and formalin-ethyl acetate sedimentation was estimated to be 85% (95% CI: 67, 100%). There were no data on specificity for these tests within those studies included in the systematic review. The second analysis evaluated diagnostic agreement with Cohen's kappa between immunological techniques – primarily colloidal gold immunochromatography assay and indirect hemagglutination assay – and conventional miracidia hatching test. There was substantial agreement between the miracidia hatching test and colloidal gold immuno-

chromatography (kappa 0.5–0.7) and indirect hemagglutination (kappa 0.55–0.75) assays. The overall certainty of evidence supporting the diagnostic accuracy estimates was low.

The key limitation of the meta-analysis of parasitological techniques was that the data included were few and from studies judged to have a high risk of bias. There were insufficient data for meta-analysis of immunological and molecular techniques. The analysis was limited by a lack of a true gold standard; PCR was used as the reference standard, although the inherent imperfect test characteristics obscured interpretation of the study results. Furthermore, specificity estimates were not generated within this meta-analysis – although subsequent research on diagnostics, not included in this meta-analysis, has provided initial sensitivity/specificity estimates for diagnostic tests for schistosomiasis in both wildlife (mini-FLOTAC, versus autopsy as pseudo-gold standard) *(2)* and domestic livestock (miracidial hatching test, duplicate Kato–Katz, autopsy) *(3)* in Africa. Finally, potentially pertinent non-human hosts, notably rodents, were not included in the systematic review search terms, despite increasing evidence that wild rodents may serve as key reservoir or spillover hosts for ongoing human transmission and/or recrudescence for both *S. japonicum* in Asia *(4)* and other human schistosome species in Africa *(5–7)*. There are also limitations with the diagnostic techniques themselves, as some parasitological techniques can be labour-intensive with high demands for laboratory infrastructure and expertise. Finally, the correct interpretation of a positive parasitological test in the setting of a verification of elimination survey, unless complementary molecular analyses to species and/or genotype level are also performed, remains unclear, as does the magnitude of contribution of non-human animal hosts to transmission of schistosomiasis, especially for species beyond *S. japonicum*.

The review demonstrated some evidence to support the parasitological technique of formalin-ethyl acetate sedimentation or molecular technique of PCR to diagnose *Schistosoma* infections in non-human animal hosts, although further validation and standardization of these techniques are necessary. The next step will be the development and validation of these diagnostic techniques within the framework of the verification of elimination surveys.

PICO question

Population	Non-human animal hosts in areas endemic for schistosomiasis ▪ domestic and wild animal hosts including buffalo, cattle, goat, sheep, pig, rabbit, rodent and chimpanzee
Intervention	Diagnostic technique for detection of *Schistosoma* infections, including parasitological, immunological and molecular techniques
Comparator	None
Outcome	Sensitivity and specificity Cohen's kappa estimate

GRADE summary table of the findings

Outcomes	Diagnostic and agreement estimates (95% CI)	Hosts	Sample size (studies)	Certainty of the evidence (GRADE)
Kappa estimate (MHT)[a]				
GICA	0.61 (0.52, 0.70)	Goat/ buffalo/ cattle	314/197/162 (1)	⨁⊙⊙⊙ Very low[1,2]
IHA	0.65 (0.56, 0.74)	Goat/buffalo/ cattle	314/197/162 (1)	⨁⊙⊙⊙ Very low[1,2]
T-DIGFA	0.99 (0.95, 1.0)	Cattle	140 (1)	⨁⊙⊙⊙ Very low[1,2]
ELISA	0.56 (0.46, 0.64)	Cattle	110 (1)	⨁⊙⊙⊙ Low[1,2]
PAPS	0.97 (0.96, 0.97)	Cattle	4217 (1)	⨁⊙⊙⊙ Very low[1,2]
Kappa estimate (qPCR)[b]				
MHT	0.0 (0.0, 0.02)	Rodent/dog/ goat/buffalo/ cattle	76/52/145/10/10 (2)	⨁⊙⊙⊙ Low[1,2]
KK	0.03 (0.0, 0.08)	Dog/cattle/ carabao/buffalo	52/10/44/81 (3)	⨁⊙⊙⊙ Low[1,2]
FED-SD	0.68 (0.44, 0.88)	Cattle/carabao/ Buffalo	48/105/44 (2)	⨁⊙⊙⊙ Low[1,2]
Sensitivity estimate (qPCR)[b]				
MHT	0.01 (0.0, 0.05)	Rodent/dog/ goat/buffalo/ cattle	76/52/145/10/10 (2)	⨁⨁⊙⊙ Moderate[1,2]
KK	0.06 (0.0, 0.21)	Dog/cattle/ carabao/buffalo	52,10;44;81 (3)	⨁⨁⊙⊙ Moderate[1,2]
FED-SD	0.89 (0.65, 1.0)	Cattle/carabao/ bovine	48,105; 44 (2)	⨁⨁⊙⊙ Moderate[1,2]

ELISA: enzyme-linked immunosorbent assay; FEA-SD: formalin-ethyl acetate sedimentation technique; GICA: gold immuno-chromatography assay; GRADE: Grading of Recommendations Assessment, Development and Evaluation; IHA: indirect hemagglutination assay; KK: Kato–Katz; MHT: miracidia hatching test; PAPS: polyaldehyde polystyrene immunization microspheres; PCR: polymerase chain reaction; qPCR: quantitative PCR.

[a] MHT was used as a reference test;

[b] qPCR was used as a reference test.

[1] Imprecision

[2] Risk of bias.

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Annex 4.5 Assessment of the choice of the 10% threshold for preventive chemotherapy

Criteria (reference)	5% prevalence threshold		10% prevalence threshold		Comment
	In support of	Against	In support of	Against	
Independent modelling study conducted in one country (Côte d'Ivoire) in four communities for morbidity control *(1)*	Annual school-based PC is cost-effective above a 5% prevalence threshold (95% UI: 1.7–5.2%).		Annual community-based PC is cost-effective above a 15% prevalence threshold (95% UI: 7.3–18.5%).		
Systematic review and meta-analysis *(2)*	N/A	N/A	N/A	N/A	Data and analysis used did not directly address identification of optimal prevalence thresholds, only relative reductions in prevalence.
Modelling study *(2)*	"Recommend 5% prevalence threshold with community-wide treatment"	"Model fit can be improved with further calibration with meta-regression result"	N/A	N/A	
Diagnostic test *(3)*	CCA diagnostic more sensitive for *S. mansoni* than egg-detection diagnostics in low endemic settings. 5% prevalence by KK was comparable to 30% prevalence by CCA for *S. mansoni*	Egg detection diagnostics perform poorly at low levels of prevalence and intensity. Lack of more sensitive diagnostic for *S. haematobium* to detect 5% without the need for large sample sizes.	Egg detection methods may perform "good enough" at this level of prevalence. 10% prevalence by KK was comparable to 30% prevalence by CCA for *S. mansoni*	Egg detection methods may still underperform where 10% prevalence is the threshold. Lack of more sensitive diagnostic for *S. haematobium* to detect 5% without the need for large sample sizes.	CCA test is recommended only for *S. mansoni*.
Transmission context					For both 5% and 10% where endemic equilibrium is this level of prevalence, or below, a different set of intervention strategies will be required than for a setting where transmission has been driven down to this prevalence.

Public health impact	More infected individuals would be treated Larger public health impact	More resources for delivery and PZQ required	Fewer resources for delivery and PZQ required	Fewer infected individuals would be treated Smaller public health impact	The health benefit of PC is expected to be greatest in higher prevalence settings where larger numbers of moderate or heavy infections reside, and there would be diminishing returns on health utility by treating lower prevalence settings.
Potential harms		Lower prevalence threshold, a greater proportion of the uninfected population would be given PZQ	Higher prevalence threshold, a reduced proportion of the uninfected population would be given PZQ (than 5% threshold)		
Values and preferences		There would be less value assigned to PC by at-risk communities, in lower prevalence settings where disease is less common			
Acceptability		There could be less compliance with PC in areas with very low prevalence			There is no clear evidence to support the view that the choice of a prevalence threshold to initiate PC will differentially affect acceptability.
Resources and drug implications		More required than for 10% threshold Higher overall cost Lower cost-effectiveness, but this is dependent on the time horizon and expected outcome	Less required than for 5% threshold Lower overall cost than 5% threshold Higher cost-effectiveness, but this is dependent on the time horizon and expected outcome		Drug implication for PZQ and resources of prevalence thresholds may be significant, but decision on threshold should be independent.

Equity	PC at a lower prevalence threshold would yield greater reductions in schistosomiasis disease burden, improve treatment access, and improve equity				Careful programmatic design and delivery would be essential to ensure drug access is provided equitably to reach all at-risk populations and avoid repeated treatment of easily accessed populations (e.g. children in school, the wealthy) that could instead worsen equity.
Feasibility		Implementation will be delayed by reviews of implementation units' endemicity status in countries	Fast update of the Joint Application Package forms for medicine requests and reporting		PC at most prevalence thresholds is technically feasible and currently ongoing in many countries.

CCA: circulating cathodic antigen; KK: Kato-Katz; N/A: not available; PC: preventive chemotherapy; PZQ: praziquantel; SR: systematic review; UI: uncertainty interval.

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Annex 5. Classes of intensity of schistosome infection

Intensity of infection	*S. mansoni*[a]	*S. haematobium*
Light	1-99 epg	< 50 eggs: /10 mL urine
Moderate	100-399 epg	
Heavy	≥ 400 epg	≥ 50 eggs/10 mL urine or visible haematuria)

epg: eggs per gram.
[a] Applies also to other species that cause intestinal schistosomiasis.

Source: Adapted from Prevention and control of schistosomiasis and soil-transmitted helminthiasis: report of a WHO Expert Committee. Geneva: World Health Organization; 2002 (WHO Technical Report Series, No. 912).

Annex 6. Estimated equivalent prevalence of point-of-care circulating cathodic antigen to single and duplicate slide Kato-Katz and suggested equivalent prevalence threshold for *Schistosoma mansoni*

Kato-Katz	POC-CCA Traces/1+/2+/3+	Suggested threshold	1+/2+/3+	2+/3+
Single				
1%	5-30%	10%	3-10%	1%
5%	10-30%	20%	5-15%	5%
10%	20-40%	30%	15-25%	10%
25%	35-70%	50%	30-50%	25%
50%	> 75%	75%	> 60%	50%
Duplicate				
1%	5-25%	10%	3-10%	1%
5%	10-35%	20%	5-15%	5%
10%	15-40%	30%	10-20%	5-10%
25%	30-70%	45%	25-40%	15-25%
50%	> 60%	60%	> 50%	> 40%

Source: Barenbold O, Garba A, Colley DG, Fleming FM, Haggag AA, Ramzy RMR, et al. Translating preventive chemotherapy prevalence thresholds for *Schistosoma mansoni* from the Kato–Katz technique into the point-of-care circulating cathodic antigen diagnostic test. PLoS Negl Trop Dis. 2018;12(12):e0006941.

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