SCOPE:
Guideline on the prevention and management of acute rheumatic fever and rheumatic heart disease

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A. Scope and key questions

1. Background

Rheumatic heart disease (RHD) is a disease of poverty. In some children, untreated streptococcal pharyngitis results in a generalised inflammatory illness called acute rheumatic fever (1). Acute rheumatic fever (RF) causes damage to the heart valves, which is often permanent. This is rheumatic heart disease. The first episode of acute rheumatic fever is commonly seen in children 5 to 14 years although recurrent episodes are possible throughout the life course. The disease and its sequelae are easily prevented in countries with high quality health care by treatment of the underlying group A *streptococcus* infection with antibiotics.

The predictors of a poor outcome in the management of RF are overcrowding, poor sanitation and other social determinants of health. Progress in preventing the disease and mortality from the disease closely tracks improvements in social-determinants of health, mainly education and income.

a. Prevalence and global burden of RF/RHD

Rheumatic heart disease affected at least 40 million people and caused an estimated 288 348 deaths in 2019 (cite WHO GHE 2019). Despite it being eradicated in many parts of the world, the disease remains prevalent in sub-Saharan Africa, the Middle East, Central and South Asia, the South Pacific, and among immigrants and older adults in impoverished pockets of high-income countries.

Figure 1 Rheumatic Heart Disease deaths (number) by age, sex and region, GHE 2019

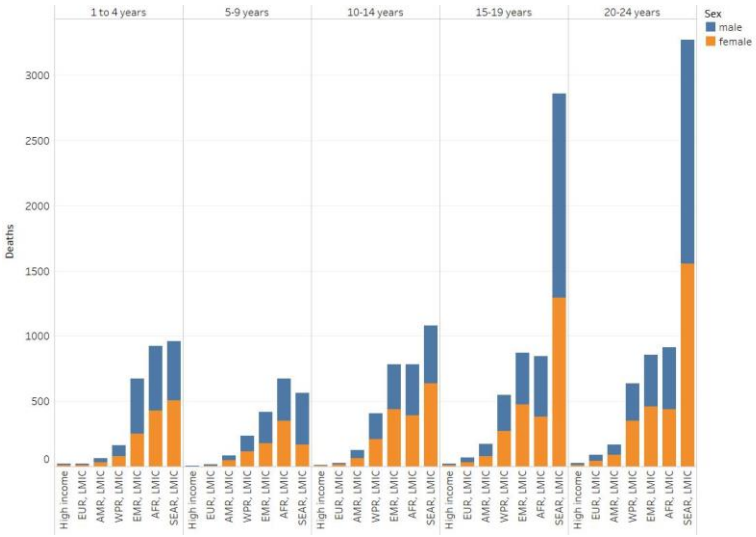
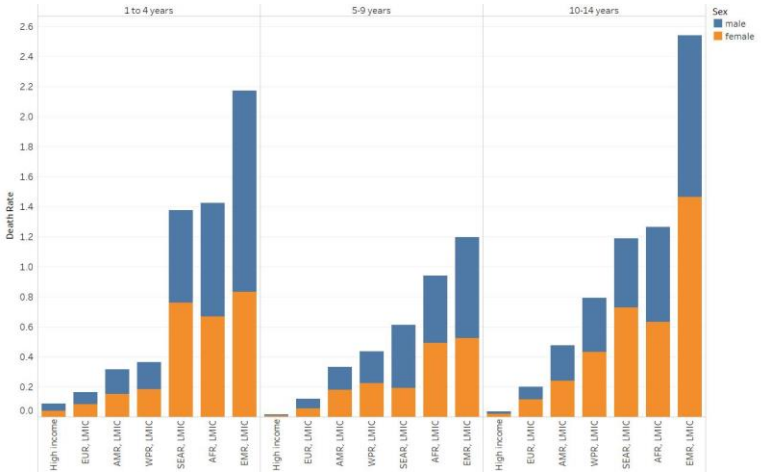


Figure 2 Crude mortality rates (per 100 000) for Rheumatic Heart Disease for 1 to 14-year olds by sex and modified WHO regions, GHE 2019



Countries in these regions have socio-economic inequalities that make it difficult to prevent acute rheumatic fever and these same inequalities make it difficult to manage chronic rheumatic heart disease, which often requires surgery, lifelong treatment and places demands on health systems that are already under pressure. There are also subpopulations within middle and high-income countries where high burdens of RHD still exist. These are in the poorer regions or Brazil and South Africa and also in the indigenous populations of Australia and New Zealand (3).

b. Prevention and management of RF/RHD

There are three levels of prevention of rheumatic heart disease: (1) reducing risk factors such as tackling poverty, improving living standards and increasing access to health (primordial prevention); (2) effective treatment of streptococcal pharyngitis with penicillin (primary prevention of rheumatic fever); and, (3) monthly administration of injections of benzathine benzylpenicillin to patients with previous history of rheumatic fever and/or rheumatic heart disease in order to prevent recurrence of streptococcal pharyngitis and rheumatic fever (secondary prevention).

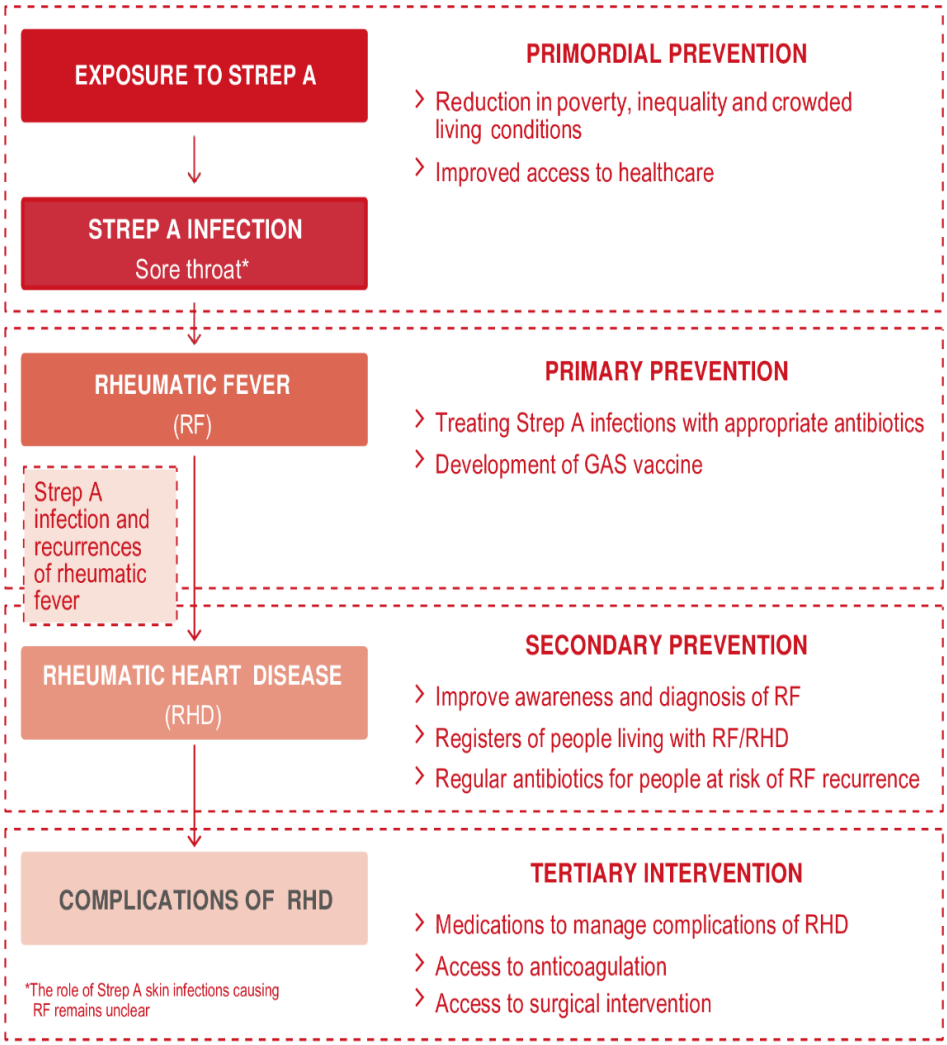
Tertiary intervention pertains to medical and surgical management of the complications of rheumatic heart disease, such as cardiac surgical interventions.

a. Barriers to progress

Most of the observed trends in reduction in the prevalence of rheumatic heart disease globally are due to improved primordial prevention with improved standards of living, expanded access to appropriate care, and rheumatic heart disease programmes as an integrated component of national health systems. The biggest gap in the control and elimination of rheumatic heart disease is in implementing effective primary and secondary prevention measures.

In May 2017, the WHO Executive Board, at its 141st session, adopted resolution EB141.R1 on rheumatic fever and rheumatic disease. A report by the WHO Director-General was presented at the 71st World Health Assembly (WHA71/25) in April 2018 in which WHO committed to “update technical documents and guidelines on identification and clinical management of group A streptococcal pharyngitis, rheumatic fever and rheumatic heart disease, as well as on methods of targeting high-risk groups, early detection and management, including appropriate use of antibiotics.”

Figure 3 Opportunities for intervention for rheumatic fever and rheumatic heart disease (from Wyber et al (4)):



2. Analytic framework/logic model

This guideline aims to provide recommendations on the following aspects of the prevention and management of rheumatic fever and rheumatic heart disease:

a. Primordial prevention: improving living conditions

- Household crowding and bed spacing

b. Primary prevention: Identifying and treating Strep A infection

- Treatment decision-making for suspected bacterial pharyngitis
- Choice of antibiotic(s) for bacterial pharyngitis
- Use of antibiotics for streptococcal skin infection

c. Diagnosis of RF/RHD

- Identification of RF with simplified algorithms
- Use of hand-held echocardiography in the diagnosis of RF/RHD
- Diagnosis of RHD in pregnancy

d. Secondary prevention: prevention of recurrence of rheumatic fever

- Anti-inflammatory treatment in active RF

- Secondary prevention with penicillin – oral or IM BPG
- Secondary prevention in patients with subclinical RHD
- Secondary prevention in patients with severe RHD
- The use of local anaesthetic for administration of IM BPG

The guideline will not include the following aspects of the wider scope of preventing and managing rheumatic fever: medical management and tertiary intervention for rheumatic heart disease (e.g., heart failure, infective endocarditis, surgical intervention); implementing RHD prevention and control programs and service delivery.

3. Key questions

An initial set of key questions (and the components of the questions) to be addressed in the guideline will be the critical starting point for the search for the evidence and formulating the recommendation. The responsible technical officers and the steering group drafted the questions based on the policy and programme guidance needs of Member States and their partners. The population, intervention, control, outcomes (PICO) format was used.

Based on the analytical framework (above), the PICO questions were drafted, and summarized below:

Primordial prevention

- Among populations with different levels of RF/RHD prevalence, does crowding (household and other settings) and other dwelling characteristics affect the incidence or prevalence of streptococcal infection, RF or RHD?

Population	
All populations	
Subgroups	
• By prevalence of RF/RHD: low, medium, high	
Intervention or exposure	**Comparator**
• Crowded (e.g. persons per household; persons per room, bedroom or bed; number of children or siblings; dwelling space or sleeping space per person) or no intervention to ease crowding	• Not crowded or an active intervention to ease crowding in the household (or other setting)
Outcomes	
• Rates of Group A streptococcal infection (incidence and/or prevalence) • Rates of rheumatic fever (incidence and/or prevalence) • Rates of rheumatic heart disease (incidence and/or prevalence) • Acceptability to provider and patient • Feasibility	

Primary prevention

- Among children with sore throat in contexts where laboratory diagnosis or point-of-care testing is not available, what combination of signs and symptoms can identify which patients should receive antibiotics based on the prevalence of RF/RHD?

Population	
• Children* presenting with sore throat in contexts where laboratory diagnosis or point-of-care testing is not available *Children aged 3-15 years old are at greatest risk of bacterial pharyngitis	
Subgroups	
• By prevalence of RF/RHD: low, medium, high	
Intervention	**Comparator**

• Different combinations of signs and symptoms	• Gold standard (laboratory diagnosis or point-of-care test) for bacterial pharyngitis
Outcomes	
• Sensitivity • Positive predictive value • Likelihood of appropriate treatment with antibiotic in timely manner • Rates of rheumatic fever (incidence and/or prevalence) • Rates of rheumatic heart disease (incidence and/or prevalence) • Antibiotic resistance • Antibiotic resistance • Adverse events (any) • Acceptability to provider and patient	

- Among children with suspected or confirmed bacterial pharyngitis, does giving a single dose of intramuscular benzathine penicillin G (IM BPG) compared to giving oral penicillin over several days improve outcomes such as duration or severity of illness?

Population	
• Children with suspected (by clinical decision rule) or confirmed (by laboratory diagnosis or point-of-care test) bacterial pharyngitis	
Subgroups	
• By prevalence of RF/RHD: low, medium, high • By setting, e.g. country income level	
Intervention	**Comparator**
• BPG IM single dose	• Penicillin oral over several days • Other antibiotics
Outcomes	
• Duration of illness, severity of illness, infectivity • Rates of rheumatic fever (incidence and/or prevalence) • Rates of rheumatic heart disease (incidence and/or prevalence) • Morbidity • Anaphylaxis • Antibiotic resistance • Adverse events (any) • Acceptability to provider and patient	

- Among children with streptococcal skin infection, does antibiotic treatment reduce the risk of developing rheumatic fever or rheumatic heart disease?

Population	
• Children with streptococcal skin infection	
Subgroups	
• By prevalence of RF/RHD: low, medium, high • By setting, e.g. country income level	
Intervention	**Comparator**
• Antibiotic treatment of skin infection	• No antibiotic treatment
Outcomes	
• Duration of illness, severity of illness, infectivity • Rates of rheumatic fever (incidence and/or prevalence) • Rates of rheumatic heart disease (incidence and/or prevalence) • Morbidity • Anaphylaxis • Antibiotic resistance	

- Adverse events (any)
- Acceptability to provider and patient

Diagnosis of RF/RHD

- Among patients with suspected rheumatic fever, does using a simplified algorithm compared to use the modified Jones criteria have the same or improved long term outcomes such as likelihood of developing rheumatic heart disease?

Population	
• Patients with suspected rheumatic fever	
Subgroups	
• By prevalence of RF/RHD: low, medium, high	
Intervention	**Comparator**
• Simplified algorithm (not requiring inflammatory markers or confirmation of streptococcal infection) *using non-inferiority analysis	• Modified Jones criteria
Outcomes	
• Sensitivity • Positive predictive value • Likelihood of appropriate treatment in a timely manner • Rates of rheumatic heart disease (incidence and/or prevalence) • Morbidity • Mortality • Adverse events (any) • Acceptability to provider and patient	

- Among patients with suspected rheumatic fever or rheumatic heart disease in contexts where standard echocardiography is not available, does using hand-held echocardiography with simplified criteria or auscultation improve diagnosis of rheumatic heart disease?

Population	
• Patients with suspected rheumatic fever or rheumatic heart disease in contexts where standard echocardiography is not available	
Subgroups	
• By prevalence of RF/RHD: low, medium, high • By severity of RF/RHD	
Intervention	**Comparator**
• Hand-held echocardiography with simplified criteria for rheumatic heart disease with auscultation	• Standard echocardiography (gold standard)
Outcomes	
• Sensitivity • Positive predictive value • Likelihood of appropriate treatment in a timely manner • Rates of rheumatic heart disease (incidence and/or prevalence) • Morbidity • Mortality • Adverse events (any) • Acceptability to provider and patient	

- Among pregnant women in areas with high prevalence of rheumatic heart disease, would the routine use of echocardiography in routine antenatal care compared to not using echocardiography improve maternal, perinatal and neonatal outcomes?

Population	
• Pregnant women in areas with high prevalence of rheumatic heart disease	
Intervention	**Comparator**
• Echocardiography during routine antenatal care	• Routine antenatal care (without echocardiography)
Outcomes	
• Maternal /perinatal/ neonatal morbidity • Maternal /perinatal/ neonatal mortality • Adverse events (any) • Acceptability to provider and patient	

Secondary prevention

- Among patients diagnosed with rheumatic fever, does management which includes anti-inflammatory treatment compared to one which does not include anti-inflammatory treatment result in improved outcomes such as decreases severity of rheumatic heart disease?

Population	
• Patients with rheumatic fever	
Subgroups	
• Pregnancy: pregnant vs not pregnant	
Intervention	**Comparator**
• Management that includes anti-inflammatory treatment	• Management that does not include anti-inflammatory treatment
Outcomes	
• Resolution of carditis • Rates of rheumatic heart disease (incidence and/or prevalence) • Severity of rheumatic heart disease • Morbidity • Mortality • Adverse events (any) • Acceptability to provider and patient	

- Among patients diagnosed with rheumatic fever or rheumatic heart disease, does secondary prophylaxis with benzathine penicillin G compared to using oral penicillin or not giving antibiotics improve outcomes such as recurrence of rheumatic fever and progression of rheumatic heart disease severity?

Population	
• Patients diagnosed with rheumatic fever or rheumatic heart disease	
Subgroups	
• By severity of RHD • Subclinical disease	
Intervention	**Comparator**
• Secondary prophylaxis with benzathine penicillin G	• Oral penicillin • No antibiotic prophylaxis
Outcomes	
• Recurrence of rheumatic fever • Progression or severity of rheumatic heart disease • Morbidity • Mortality	

- Adverse events (any)
- Acceptability to provider and patient

- Among patients prescribed intramuscular BPG for secondary prevention of RHD, is routine management of injection pain using a local anaesthetic associated with improved outcomes?

Population	
Patients prescribed IM BPG for secondary prevention of RHD	
Intervention or exposure	Comparator
• Local anaesthetic for injection pain	• No local anaesthetic for injection pain
Outcomes	
• Patient pain score ratings • Adherence to treatment (regular BPG) • Acceptability to provider and patient Morbidity • Morbidity • Mortality • Adverse events (any)	

These questions will be presented to the GDG for discussion and finalization on in the first meeting of the GDG. The GDG will discuss the relevance of the questions and modify them as needed.

4. Prioritization of outcomes for decision-making

The GDG will score the relative importance of each outcome from 1 to 9 (where 7–9 indicated that the outcome was critical for a decision, 4–6 indicated that it was important and 1–3 indicated that it was not important).

5. Humanitarian and other emergencies

This guideline will be able to support countries to be prepared for health emergencies involving management of RF/RHD. Recommendations will be developed or tailored to the humanitarian setting, depending on the evidence gathered relevant to this context. Expertise within the GDG will also be tapped for perspectives on the humanitarian and emergency context.

B. Systematic review methods

1. Consultation with information specialists

The responsible technical officers will do an initial search for systematic reviews to address each of the key questions. Among the systematic review databases searched were: PROSPERO, Cochrane Library, Epistemonikos and Campbell Collaboration. The steering group reviewed the available systematic reviews for relevance, quality, and timeliness.

In cases when key questions do not have relevant and high quality systematic reviews or for which the systematic reviews are not up-to-date, new or updated reviews will be commissions from the systematic review teams.

The steering group in collaboration with the systematic review team will draft the inclusion and exclusion criteria. Inclusion and exclusion criteria will take into consideration the PICO question as well as (1) the time frame for outcome measures or the duration of the intervention; (2) further specification of setting and subpopulations; (3) study design (i.e. randomized controlled trials only, or various types of nonrandomized experimental or observational studies); (4) publication language; (5) a date range for publications; and additional specifications that are relevant to RF/RHD.

2. Sources for evidence

The search for evidence should as much as possible include studies done in low- and middle-income settings in all WHO regions, in WHO's six official languages and include a search for grey literature. The search strategy and results will be documented and reported, including reasons for exclusion of specific studies.

3. Types of evidence

The quantitative findings for the key questions will be synthesized with a pooled estimate of effect. The results of the systematic reviews will be presented to the GDG, along with an assessment of the confidence in the estimates of effect for the critical and important outcomes.

Qualitative systematic reviews of evidence will be conducted to assess the values and preference of children with chronic pain, and their parents and families in relation to the benefits and harms associated with each intervention, and the acceptability of each of the interventions to health-care staff and key stakeholders.

4. Quality assessment of primary studies

Each study included in a systematic review will be assessed for risk of bias. These will be recorded and will contribute towards the assessment of the overall quality of the evidence. Sources of bias could include: selection bias (e.g. in sequence generation and allocation concealment), performance bias (e.g. blinding of participants and personnel), detection bias (e.g. blinding of outcome assessment), attrition bias (e.g. incomplete outcome data), reporting bias (e.g. selective outcome reporting) and other biases (e.g. contamination of interventions).

5. Assessment of the quality (certainty) of the body of evidence for each outcome

The GRADE profile assessing the quality of the evidence will be prepared for each outcome. The quality of evidence for each outcome will be rated as 'high', 'moderate', 'low', or 'very low' based on a set of criteria including risk of bias, inconsistency, imprecision, indirectness, and publication bias.

The findings of the qualitative reviews will be appraised using the GRADE Confidence in the Evidence from Reviews of Qualitative research (GRADE-CERQual) approach. Overall confidence in the evidence from reviews of qualitative research will be based on four components: methodological limitations of the individual studies; adequacy of the data; coherence of the evidence; and relevance of the individual studies to the review finding.

C. References

1. Watkins DA, Johnson CO, Colquhoun SM, Karthikeyan G, Beaton A, Bukhman G, et al. Global, Regional, and National Burden of Rheumatic Heart Disease, 1990-2015. N Engl J Med. 2017;377(8):713-22.
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4. Wyber R, Johnson T, Perkins S, Watkins D, Mwangi J, La Vincente S, et al. Tools for implementing rheumatic heart disease control programmes (TIPs) handbook, 2nd edition. Geneva, Switzerland: RHD Action.; 2018.