WHO guideline on the prevention and diagnosis of rheumatic fever and rheumatic heart disease

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Abbreviations

ARF	acute rheumatic fever
AHA	American Heart Association
aOR	adjusted odds ratio
AUC	area under curve
aRR	adjusted relative risk
BPG	benzathine penicillin G
CI	confidence interval
CPR	clinical prediction rule
ERG	External Review Group
GAS	group A (beta-haemolytic) *Streptococcus*; *Streptococcus pyogenes*
GDG	Guideline Development Group
GRADE	Grading of Recommendations, Assessment, Development and Evaluation
GRC	WHO Guidelines Review Committee
HIC	high-income country
HHE	handheld echocardiography
IVIG	intravenous immunoglobulin
IM	intramuscular
MCA	Department of Maternal, Newborn, Child and Adolescent Health and Ageing, WHO
MD	mean difference
NPV	negative predictive value
NSAIDS	non-steroidal anti-inflammatory drugs
NYHA	New York Heart Association
OR	odds ratio
PICO	Population, Intervention, Comparator, Outcomes
POC	point-of-care
RADT	rapid antigen detection test
RF	rheumatic fever
RHD	rheumatic heart disease
RCT	randomized controlled trial
RR	relative risk
S. Aureus	*Staphylococcus aureus*
SMD	standardized mean difference
SSSI(s)	skin and skin structure infection(s)
UI	uncertainty interval
WHF	World Heart Federation
WHO	World Health Organization

Glossary

Antibiotic resistance: a subset of antimicrobial resistance that specifically refers to bacteria becoming resistant to antibiotics (medicines that act against bacteria).

Antimicrobial resistance: the ability of bacteria, viruses, fungi and parasites to resist the effects of antimicrobial medicines that kill susceptible organisms or keep them from growing. Antimicrobial resistance predates the use of antimicrobials in human medicine and many bacteria, viruses, fungi and parasites are intrinsically resistant to some antimicrobials. Microorganisms can also acquire resistance by being exposed to antimicrobials. Infection with antimicrobial-resistant pathogens makes infections harder to treat and increases the risk of disease spread, severe illness and death.

Benzathine benzylpenicillin: a long-acting antibiotic for intramuscular administration, also referred to as benzathine penicillin G (BPG). BPG is effective against Streptococcus pyogenes.

Clinical prediction rules: tools that quantify the contribution of history, clinical examination and basic diagnostic tests to classify a patient in terms of the probability of having a target condition or a future health outcome.

Clinically-suspected streptococcal throat infection: Pharyngitis is most frequently viral in origin, and antibiotics are therefore of no benefit. However, when throat infection is bacterial, the most common causative agent is GAS. There are consistent signs and symptoms that make GAS pharyngitis more likely, including the presence of sore throat and fever, and a lack of rhinorrhea or cough. The presence of rhinorrhea or cough are more likely in viral pharyngitis.

Echocardiography: use of ultrasound to investigate the structure and function of the heart, and a sensitive tool for diagnosing valvular pathology.

Standard echocardiography refers to use of fully-functional machines that have become smaller and more portable over time.

Handheld echocardiography involves use of devices that lack some features of fully-functional echocardiography machines, such as spectral Doppler, but retain diagnostic capabilities and are typically much more affordable than full-sized machines.

Guideline development

Certainty of evidence: In the context of evidence syntheses, this phrase refers to the evidence attributes that enable a certain level of confidence that an estimate of an effect or association is correct. In the context of normative or standard-setting product development, the certainty of the evidence determines the level of confidence that the estimates of an effect are adequate to support a particular decision or recommendation (alternative terms: quality of the evidence, confidence in the estimate of effect).

Conflict of interest: A set of circumstances that creates a risk that professional judgement or actions regarding a primary interest will be unduly influenced by a secondary interest; any interest declared by an expert that may affect or reasonably be perceived to affect the expert's objectivity and independence in providing advice. A conflict of interest is of two basic types: financial, and non-financial or intellectual.

Evidence-to-decision frameworks: These are tabular displays of relevant considerations which decision-makers use to make a decision or to formulate a recommendation. Considerations include benefits, harms, acceptability and feasibility of the intervention; equity; resource implications; among others.

GRADE: The Grading of Recommendations, Assessment, Development and Evaluation is a system for assessing the certainty (quality) of a body of evidence and for structuring considerations when formulating recommendations in clinical or public health guidelines.

GRADE evidence tables or GRADE profiles: These are tabular displays of summary measures of effect and the GRADE certainty (quality) assessments of the body of evidence for a specific question (usually defined in Population, Intervention, Comparator and Outcome (PICO) format for questions about interventions).

Guideline Development Group: A multidisciplinary group made up of external individual experts from all WHO regions whose central task is to develop evidence-based recommendations, in addition to formulating the general scope and contents of a guideline. Potential members of the Guideline Development Group are identified by the WHO Steering Group and are selected to encompass the technical skills, diverse perspectives and geographical representation needed. Its membership should be balanced in terms of gender and geography.

Guideline methodologist: an expert in systematic reviews, GRADE and the translation of evidence into recommendations.

Guideline-related research gaps: These represent uncertainties about the facts that arise during the guideline development process and that may affect the recommendation(s). Guideline-related research gaps have various sources, most notably the systematic review(s) and other research or information that supports the domains of the evidence-to-decision framework.

Guiding principle: a high-level normative statement that provides guidance or principles underpinning a recommendation or other normative statement, based on human rights standards or conventions, or on ethics principles.

Steering Group: a group of staff members from relevant WHO departments at all three levels of the Organization, whose work directly deals with or is relevant to the topic of the guideline and who help direct the process of product development.

Systematic review: an objective, reproducible and explicit method of finding answers to specific research questions by searching for and collecting all available studies related to that question, critically appraising relevant primary research, and then analysing and synthesizing the results.

…

Group A *Streptococcus*: also referred to as *Streptococcus pyogenes* or GAS, is a species of beta-haemolytic Gram-positive bacteria that is responsible for a wide range of infections.

Health education: includes a broad range of approaches and may focus on the communication of information concerning the determinants of health, individual risk factors, disease etiology and prognosis, and use of the health care system. Health education can also involve task-based communication designed to support specific behaviours such as medication adherence or focus on transferable skills and knowledge that equip people to make more autonomous decisions relating to their health and to adapt to changing circumstances.

Jones criteria: a set of criteria for diagnosis of rheumatic fever. To establish the diagnosis of rheumatic fever, two major or one major and one minor criteria are required. Last updated in 2015, the Jones criteria remain the standard set of criteria used to diagnose RF.

Latent or subclinical RHD: a previously used term that refers to individuals who have structural or functional lesions of the heart caused by RF but who do not experience clinical manifestations. Since the publication of the *2023 WHF Guidelines for the echocardiographic diagnosis of rheumatic heart disease*, these terms are no longer used.

Pharyngitis: an inflammation of the throat that is most frequently viral in origin, however, when infection is bacterial, the most common causative agent is *Streptococcus pyogenes*, a group A beta-haemolytic *Streptococcus* bacterium. Streptococcal pharyngitis is an important cause of rheumatic fever.

Point-of-care testing: medical diagnostic testing at or near the time and place of patient care, using rapid diagnostic tests.

Populations: In this guideline, "children" refers to people aged 0–9 years, "adolescents" to people aged 10–19 years, "adults" are people 20 years of age and older, and "young adults" refers to people aged 20–39 years.

Prevention of rheumatic fever and rheumatic heart disease

Primordial prevention: aims to avoid episodes of streptococcal infection by addressing poverty, improving living and housing standards including access to clean water and sanitation, reducing crowding, and increasing access to health care.

Primary prevention: can be achieved through the effective diagnosis and prompt treatment of pharyngitis and perhaps superficial skin infections caused by *Streptococcus pyogenes*, a group A beta-haemolytic *Streptococcus* bacterium.

Secondary prevention: involves continuous antibiotic prophylaxis given to patients with a previous history of RF/RHD to prevent a recurrence of RF and the onset of RHD, or when RHD has occurred, to limit its progression to more severe disease.

Rheumatic fever (RF): an autoimmune inflammatory reaction to throat infections or to superficial skin and skin structure infections caused by *Streptococcus pyogenes*, a group A beta-haemolytic *Streptococcus* bacterium. RF may affect the heart (carditis), large joints (arthritis or arthralgia), and sometimes the brain (chorea), skin or subcutaneous tissues. Without prevention, affected individuals may experience repeated episodes of RF.

Rheumatic heart disease (RHD): structural and/or functional changes in the heart caused by damage to the heart valves and heart muscle from the inflammation and scarring caused by one or more episodes of rheumatic fever. RHD is a life-threatening condition.

Risk for rheumatic fever/rheumatic heart disease

- Where reliable epidemiological data are available, populations with low risk are considered as having an RF incidence <2 per 100 000 children (5 to 14 years of age) per year, or an all-age prevalence of RHD of ≤100 per 100 000 population per year.
- Individuals are at low risk for RF/RHD if they come from a setting or population known to experience low rates of RF or RHD as described above.
- Individuals are at moderate/high risk of RF/RHD if they come from a setting or population that is not clearly low risk.

Screening: Screening is the presumptive identification of unrecognized disease or defect by the application of tests, examinations or other procedures which can be applied rapidly. Screening tests sort out apparently well people who probably have a disease from those who probably do not. A screening test is not intended to be diagnostic. Persons with positive or suspicious findings must be referred to their physicians for diagnosis and necessary treatment.

Skin and skin structure infections (SSSIs): are commonly caused by *Staphylococcus aureus*, however, *Streptococcus pyogenes* is also an important cause. There is emerging evidence that streptococcal skin infections are a potential cause of RF, alone or in combination with streptococcal pharyngitis.

***Streptococcus pyogenes*:** a group A beta-haemolytic *Streptococcus* (GAS) bacterium.

Executive summary

Background

Rheumatic heart disease (RHD) is a serious yet preventable public health problem in low- and middle-income countries and in marginalized communities in middle- and high-income countries, including Indigenous populations. RHD is characterized by chronic structural and/or functional changes in the heart, most commonly in the valves, caused by one or more episodes of rheumatic fever (RF). RF is an autoimmune inflammatory reaction to throat infections (pharyngitis) or possibly to superficial skin and skin structure infections (SSSIs) caused by *Streptococcus pyogenes*, a group A beta-haemolytic *Streptococcus* (GAS) bacterium. The first episode of RF is commonly seen in children aged 5 to 14 years. Recurrent episodes are most common within 1 year of the first episode but can occur throughout the life course. RHD most commonly starts in childhood with a diagnostic peak in young adults[1] aged 20 to 39 years. RHD can lead to death or lifelong disability, however, effective early intervention can prevent premature morbidity and mortality.

RHD affected an estimated 55 million people globally and caused 360,000 deaths in 2021 *(1)*. In the twentieth century, the incidence of RF and the prevalence of RHD declined substantially in Europe and North America, and in other high-income settings. However, the gains have not been equitably distributed globally and many regions including sub-Saharan Africa, the Middle East, Central and South Asia, tropical Latin America and the South Pacific continue to have endemic RF and RHD. The prevalence of RHD is estimated to peak between the ages of 20 and 29 years, declines steadily until around 50 years when it then remains relatively stable *(2)*. There is a higher prevalence of RHD among women across nearly all world regions *(2)*.

The prevention of RF/RHD is essential for addressing the significant health, social and economic burdens of RHD. There are four levels of prevention: 1) reducing GAS infections through improvements in housing, living conditions and sanitation (primordial prevention); 2) treatment of GAS throat infections and possibly GAS skin infections (primary prevention of RF); 3) prevention of recurrence of RF through antibiotic prophylaxis (secondary prevention of RHD onset and progression); and 4) treatment of the complications of RHD with medications including anticoagulants, and cardiac interventions including surgery (tertiary prevention).

Scope and target audience

In this guideline, the World Health Organization (WHO) provides evidence-informed recommendations for selected topics relating to RF and RHD. It is not intended to encompass all aspects of the prevention, detection and clinical care of the disease in affected populations and subpopulations. Readers are encouraged to identify high-quality, evidence-informed national and local guidance to complement this guideline.

This guideline encompasses the following:

1. primary prevention of RF and RHD, specifically the identification and treatment of suspected GAS pharyngitis and GAS skin infections;

[1] In this guideline, subpopulations defined by age are: children: up to 9 years; adolescents: 10 to 19 years; adults: 20 years and older; and young adults: 20 to 39 years.

2. secondary prevention of recurrent RF and of RHD, specifically the use of long-term antibiotic prophylaxis, interventions to increase adherence to antibiotic prophylaxis regimes, and screening for early RHD; and
3. management of RF, specifically the treatment of RF with anti-inflammatory drugs.

This guideline is intended for use by a wide range of audiences, including national and local policy-makers and their expert advisers, as well as technical and programme staff at organizations involved in the prevention of RF and RHD, and the identification and care of people with RF or RHD. The guideline may also be used by health workers and their professional societies, and by researchers who are interested in addressing gaps in the evidence.

The audience for this guideline is a global one, across diverse settings with varied perspectives and resources. The content is relevant to all Member States, and in particular countries and regions where populations are at moderate/high risk of RF/RHD.

Methods

These recommendations are based on the most current, high-quality scientific evidence and were formulated following processes and using methods meeting the highest international standards for guideline development, as outlined in the *WHO handbook for guideline development* (2nd edition, 2014) *(3)*. The main steps for the development of WHO guidelines include: 1) establishment of the general scope of the guideline and development of the key questions and a detailed workplan; 2) identification of contributors to the guideline process including the Guideline Development Group (GDG; a diverse panel of technical experts and other stakeholders); 3) assessment of declarations of interest and management of any conflicts of interest of all contributors; 4) conduct of systematic reviews of the evidence to address the key questions; 5) assessment of the certainty (quality) of the body of evidence for critical and important outcomes; 6) formulation of recommendations by the GDG; 7) drafting of the guideline document for review and approval by the GDG followed by targeted peer review; 8) review and approval by WHO's quality assurance body; and 9) publication and dissemination.

Updating

The WHO Secretariat for this guideline will continue to follow advances in the research on the prevention, diagnosis and management of RF and RHD, particularly for questions for which the certainty (quality) of evidence was found to be low or very low. If new evidence emerges or other important considerations arise that may impact the current recommendations, the WHO Department of Maternal, Newborn, Child and Adolescent Health and Ageing (MCA) in Geneva, Switzerland, will coordinate an update of this guideline.

Unless new evidence necessitates an earlier review, at 5 years from publication of this guideline, the MCA Department, along with its internal partners, will conduct systematic reviews of the relevant evidence and appraise the need for updating or revalidating the current guideline. WHO will seek stakeholder input on the scope of the updated guideline, as new interventions and considerations emerge.

Guiding principles

RF and RHD are associated with poverty, residential overcrowding, insufficient access to clean water and sanitation, and barriers to accessing primary health care. The GDG therefore formulated the following guiding principles, which underpin all of the recommendations in this guideline, as well as their adoption, adaptation and implementation in Member States:

1. Programme managers and health workers should work with local authorities and community leaders to ensure adequate living conditions including access to clean water, adequate sanitation and living spaces, housing, and appropriate ventilation in homes and residences.

2. Policy-makers and programme managers should ensure equitable access to screening and treatment services for people with suspected or confirmed GAS infections and RF/RHD. This applies particularly to vulnerable populations living in areas with moderate/high risk of RF/RHD. All people must have access to high-quality services for the prevention, diagnosis and treatment of RF/RHD, as recommended in this guideline.

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2. Global Burden of Disease Collaborative Network. Global Burden of Disease Study 2021 (GBD 2021) Results. Seattle, United States: Institute for Health Metrics and Evaluation (IHME), 2022. Available from https://vizhub.healthdata.org/gbd-results/
3. WHO handbook for guideline development. 2nd ed. Geneva: World Health Organization; 2014. https://www.who.int/publications/i/item/9789241548960

Summary of recommendations

Health education

Recommendation

WHO recommends that health workers provide evidence-based education focused on the relationship between infections of the pharynx and skin potentially caused by group A *Streptococcus* (GAS), and rheumatic fever/rheumatic heart disease (RF/RHD), and thus the importance of treating these infections appropriately, particularly in moderate/high risk settings or populations.

(Conditional recommendation, very low certainty evidence)

Diagnosis of group A streptococcal pharyngitis

No recommendation

WHO, with guidance from the Guideline Development Group (GDG), was unable to make a recommendation at this time on clinical prediction rules (CPRs) or on other sets of signs and symptoms that have sufficient diagnostic accuracy for use in children, adolescents or adults who present with sore throat.

Treatment of group A streptococcal pharyngitis

Recommendation 1

Children, adolescents and adults with sore throat and a positive diagnostic test (either point-of-care (POC) testing or microbial confirmation) for GAS pharyngitis should be treated with antibiotics to prevent RF/RHD.

(Strong recommendation, moderate certainty evidence)

Recommendation 2

In populations at moderate to high risk of RF and RHD and where diagnostic testing to confirm GAS (with either POC testing or microbial confirmation) is not available, children and adolescents with clinically-suspected GAS pharyngitis should be treated with antibiotics to prevent RF/RHD.

(Strong recommendation, very low certainty evidence)

Recommendation 3

For patients with a positive diagnostic test for GAS pharyngitis or with clinically-suspected GAS, WHO recommends penicillin (intramuscular (IM) or oral) as first-line treatment for the prevention of RF/RHD.

(Conditional recommendation, low certainty evidence)

Diagnosis and treatment of skin and skin structure infections

No recommendation

WHO, with guidance from the GDG, was unable to make a recommendation at this time either for or against any specific CPR to be used when GAS skin infection is suspected.

No recommendation

WHO, with guidance from the GDG, was unable to make a recommendation at this time either for or against antibiotic treatment of skin and skin structure infection(s) (SSSIs), whether laboratory-confirmed or clinically diagnosed, for the specific purpose of preventing RF or RHD.

Diagnosis of rheumatic fever

Recommendation

The Jones criteria should be used for RF diagnosis in children, adolescents and adults with suspected RF.

(Strong recommendation, low certainty evidence)

Echocardiography in the diagnosis of rheumatic fever and rheumatic heart disease

Recommendation 1

Among children, adolescents and adults with suspected RF or RHD in settings where standard echocardiography is not available, handheld echocardiography (HHE) can be used for diagnosis of RF-carditis and RHD.

(Strong recommendation, very low certainty evidence for RF-carditis, moderate certainty for RHD)

Recommendation 2

In populations or settings with moderate/high risk of RHD, echocardiographic screening using standard or handheld devices may be considered, to improve early detection of RHD among pregnant women during antenatal care.

(Conditional recommendation, very low certainty evidence)

Recommendation 3

In populations with moderate/high RHD prevalence, echocardiographic screening using standard echocardiography or HHE may be implemented for early detection of RHD among children and adolescents 5 to 19 years of age.

(Strong recommendation, high certainty evidence)

Antibiotic prophylaxis for the prevention of recurrent rheumatic fever

Recommendation 1

Children, adolescents and adults diagnosed with RF or RHD should be prescribed antibiotic prophylaxis to prevent RF recurrence.

(Strong recommendation, moderate certainty evidence)

Recommendation 2

Antibiotic prophylaxis should be prescribed for children and adolescents found to meet minimum criteria for RHD on echocardiography screening to prevent disease progression.

(Strong recommendation, moderate certainty evidence)

Antibiotic prophylaxis may be prescribed for adults 20 years of age and older found to meet minimum criteria for RHD on echocardiography screening.

(Conditional recommendation, very low certainty)

Recommendation 3

Antibiotic prophylaxis should be given to children and adolescents who have advanced RHD to prevent RF recurrence.

(Strong recommendation, very low certainty evidence)

Antibiotic prophylaxis can be given to adults 20 years of age and older who have advanced RHD to prevent RF recurrence based on shared decision-making between the patient and treating health care provider.

(Conditional recommendation, very low certainty evidence)

Recommendation 4

IM benzathine benzylpenicillin (BPG), is the preferred first-line approach to prevent recurrence of RF in patients with prior RF or RHD.

(Strong recommendation, moderate certainty evidence)

Recommendation 5

If an alternative to IM BPG is needed (recommendation 4), oral penicillin is acceptable for RF and RHD prophylaxis.

(Conditional recommendation, moderate certainty evidence)

Good practice statement

Penicillin allergy testing should not be used in patients who have no history of penicillin allergy and who are prescribed IM BPG for secondary prevention of RHD.

Recommendation 6

An oral penicillin test dose may be given prior to IM BPG administration for patients who have a history of mild penicillin allergy; that is, in patients without a prior history of anaphylaxis, angioedema, Steven-Johnson's syndrome or toxic epidermal necrolysis.

(Conditional recommendation, low certainty evidence for immediate allergy and anaphylaxis; very low for delayed allergy)

Recommendation 7

A local anaesthetic may be added to the injectable solution to reduce injection pain in patients who receive IM BPG for secondary prevention of RHD.

(Conditional recommendation, low certainty evidence)

Recommendation 8

Patients who are prescribed antibiotics for secondary prophylaxis of RF or RHD should be supported to improve treatment adherence.

(Strong recommendation, low certainty evidence)

Anti-inflammatory agents for the treatment of rheumatic fever

No recommendation

The GDG was unable to formulate a recommendation. Thus, WHO does not recommend either for or against the use of anti-inflammatory agents for children, adolescents and adults diagnosed with RF to prevent the progression to RHD. These agents include aspirin, non-steroidal anti-inflammatory drugs (NSAIDs), intravenous immunoglobulin and corticosteroids.

1. Introduction

1.1 Rheumatic fever and rheumatic heart disease

Rheumatic heart disease (RHD) is a serious yet preventable public health problem in low- and middle-income countries and in marginalized communities in middle- and high-income countries, including Indigenous populations *(1)*. RHD is chronic structural and/or functional changes in the heart, most commonly in the valves, caused by one or several episodes of rheumatic fever (RF). It most commonly occurs in childhood with a diagnostic peak in young adults, and can lead to death or lifelong disability. Effective early intervention can prevent premature morbidity and mortality from RHD.

RF is an autoimmune inflammatory reaction to throat infections (sore throat or pharyngitis) and possibly to superficial skin and skin structure infections (SSSIs) caused by *Streptococcus pyogenes*, a group A beta-haemolytic *Streptococcus* (GAS) bacterium. RF most often occurs between 10 and 21 days after a GAS infection and most commonly affects the heart (carditis), large joints (arthritis or arthralgia), brain (chorea), and skin and subcutaneous tissues (subcutaneous nodules, erythema marginatum). The first episode of RF is usually seen in children aged 5 to 14 years; recurrent episodes are most common within 1 year of the first episode but can occur throughout the life course.

According to IHME Global Burden of Disease, RHD affected an estimated 55 million people globally in 2021 (95% uncertainty interval (UI): 43-68 million); this represents a 1.7-fold increase in prevalence since 1990 *(2)*. The increase in the absolute numbers of prevalent cases is most likely attributable to population growth and an increase in incidence likely due to increased awareness, increased availability of echocardiography, improved survival in some settings, and to the chronic nature of RHD *(3)*. Incidence increased 1.5-fold between 1990 and 2019, with 2.8 (95% UI: 2.2–3.5) million new cases globally in 2021 *(2)*.

The prevalence of RHD globally is estimated to peak between the ages of 20 and 29 years, years and declines steadily until around 50 years when it then remains relatively stable which may reflect decreasing survival at older ages *(2)*. While the sex distribution is equal under the age of 15 years, in older age groups prevalence is higher in women across nearly all world regions, the reasons for which are unclear *(2)*.

In contrast to the increases in prevalence and incidence over the last three decades, mortality from RHD continues to decrease globally in the twenty-first century. According to WHO Global Health Estimates 2021, age-standardized mortality rate decreased by 28%, between 2000 and 2021 *(4)*. In 2021 the age-standardized death rate was 4.5 per 100 000 population equivalent to 360,000 deaths *(4)*.

The burden of RHD has not been equally distributed across countries and regions. In the twentieth century the incidence of RF and the prevalence of RHD declined substantially in Europe and North America, and in other geographical locations where socioeconomic status rose *(2, 5)*. Declines in RF incidence and RHD mortality over the past century have been attributed to improved sanitation, housing, living conditions, and access to medical care including antibiotics *(4, 6)*, as well as potentially to changes in the epidemiology of GAS infections *(6, 7)*.

The gains in mortality from RHD have also been unequally distributed globally, however, and many regions including sub-Saharan Africa, the Middle East, Central and South Asia and the South Pacific continue to have endemic RF and RHD *(2, 8, 9)*. Populations that are affected by RF and RHD have socioeconomic inequalities that make it difficult to prevent RF and to identify and treat RHD. The latter often requires surgery and lifelong treatment, and places significant demands on health systems. There

are also subpopulations within middle- and high-income countries where RHD still causes a significant burden. Examples include poorer regions of Brazil and South Africa, and the Indigenous populations of Australia, Canada and New Zealand *(9, 10)*.

The economic costs of RF and RHD are significant, particularly in countries with a persistently high prevalence of RHD. The most devastating economic effects are on children and adults in their most productive years. The global cost of deaths due to RHD in 2010 was estimated to be US$ 2200 billion (discounted) or US$ 5400 billion (undiscounted) *(1)*.

1.2 Group A streptococcal infections

GAS infections are caused by *Streptococcus pyogenes*, a species of Gram-positive, aerotolerant bacteria in the genus Streptococcus. *Streptococcus pyogenes* is the predominant species harbouring the Lancefield group A antigen and thus is often referred to as group A *Streptococcus*. GAS, when grown on blood agar, typically produces 2- to 3-mm zones of beta-haemolysis, hence the name "group A (beta-haemolytic) *Streptococcus*" is also used *(11)*.

Infections due to GAS are clinically important for humans, causing diseases ranging from mild superficial skin infections to life-threatening systemic diseases *(12)*. Infections typically begin in the throat or skin. Mild GAS infections include pharyngitis ("sore throat") and localized skin infections (impetigo). Erysipelas and cellulitis are characterized by the spread of *S. pyogenes* in the deep layers of the skin, and necrotizing fasciitis is caused by *S. pyogenes* invasion and multiplication in the fascia. The latter is a life-threatening condition that requires prompt surgical intervention to reduce morbidity and mortality *(12)*. There is emerging evidence that SSSIs caused by GAS are a potential cause of RF, alone or in combination with GAS pharyngitis *(13, 14)*.

Throat infections due to certain strains of GAS can be associated with the release of bacterial toxins, leading to scarlet fever or streptococcal toxic shock syndrome *(12)*. In a small percentage of infections, GAS causes post-infectious syndromes not associated with local bacterial multiplication and pus formation. These autoimmune-mediated complications include RF and acute post-infectious glomerulonephritis, and appear several weeks following the initial streptococcal infection.

GAS remains sensitive to penicillin. Failure of treatment with penicillin is generally attributed to either the local presence of commensal organisms producing beta-lactamase or the failure to achieve adequate antibiotic tissue levels in the pharynx or skin. Certain strains of GAS have developed resistance to other antibiotics including macrolides, tetracyclines and clindamycin *(15, 16)*.

1.3 Risk of rheumatic fever and rheumatic heart disease

The risk of RF and RHD varies across geographical settings and populations *(2, 8, 9)*. In this guideline, we define categories of risk for RF/RHD based on the 2015 statement of the Revised Jones criteria *(17)* as follows:

Low risk of RF/RHD:

- Individuals are at low risk for RF/RHD if they come from a setting or population known to experience low rates of RF or RHD.
- Where reliable epidemiological data are available, populations with low risk are considered as having a RF incidence <2 per 100 000 children (5 to 14 years of age) per year, or an all-age prevalence of RHD of ≤100 per 100 000 population per year.

Moderate/high risk of RF/RHD:

- Individuals not clearly from a low-risk setting or population should be considered at moderate/high risk.

Where the risk is moderate to high, RF/RHD can be considered endemic.

1.4 Prevention and treatment of rheumatic fever and rheumatic heart disease

The prevention of RF/RHD is essential for addressing the significant health, social and economic burdens of RHD *(18)*. There are four levels of prevention of RF/RHD, namely primordial, primary, secondary and tertiary.

- *Primordial prevention* aims to avoid episodes of superficial streptococcal infection by addressing poverty, improving living conditions and housing standards, and increasing access to health care.
- *Primary prevention* of RF can be achieved through the effective diagnosis and prompt treatment of GAS pharyngitis and perhaps of GAS superficial skin infections.
- *Secondary prevention* involves continuous antibiotic prophylaxis given to patients with a previous history of RF/RHD to prevent a recurrence of RF and the onset of RHD, or when RHD has occurred, to limit its progression to more severe disease.
- *Tertiary prevention* focuses on treating and managing the complications of RHD, such as with medications including anticoagulants, and cardiac interventions including surgery.

For countries where there are populations at moderate/high risk of RHD, the public health and clinical strategies should address all aspects of prevention and treatment including improving standards of living and housing; expanding access to appropriate care including services for patients with advanced RHD; ensuring a consistent supply of quality-assured antibiotics for primary and secondary prevention; and improving health literacy. A modelling study developed for the African Union showed that secondary prevention and treatment are cost-saving and avert deaths in the short term, whereas the benefits of primary prevention accrue over a longer period *(18)*. Relevant public health programmes require adequate training, monitoring, surveillance and tracking as integrated components of national health systems – functions that are commonly not well developed in settings with a high burden of RF/RHD. Such programmes should involve a broad range of stakeholders and expertise, including policy-makers, health workers, patients and their caregivers.

1.5 Purpose of the guideline

In this guideline, the World Health Organization (WHO) provides evidence-informed recommendations for primary and secondary prevention and the diagnosis of RF and RHD. These recommendations are based on the most current, high-quality scientific evidence, and were formulated following processes and using methods meeting the highest international standards for guideline development *(19)*.

WHO first released guidelines for the prevention and treatment of RF and RHD in 1954 *(20)*. Subsequently, many countries had striking reductions in disease-specific mortality due to socioeconomic development, the implementation of prevention, screening and treatment programmes, and improvements in health systems *(8)*. Nonetheless, many countries and regions continue to report high prevalences and mortality due to RHD *(2, 9)*, as the reduction of RHD incidence, burden and, ultimately, mortality, occurred unevenly across and within countries.

At its 141st session in May 2017, the WHO Executive Board adopted resolution EB141.R1 on RF and RHD *(21)*. A report by the WHO Director-General was presented at the seventy-first World Health Assembly (WHA71/25) in May 2018 in which WHO committed to "[u]pdate 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" *(1)*. Member States adopted resolution WHA71.14 on Rheumatic Fever and Rheumatic Heart Disease that year *(22)*. A progress report was presented to the seventy-fourth World Health Assembly in 2021 *(23)*, which noted progress in implementing resolution WHA71.14 in the WHO Eastern Mediterranean Region with the development of a regional framework for action on RF/RHD, and a regional expert network. In the WHO Western Pacific Region several countries had established registry programmes for RF/RHD.

This guideline has thus been developed to address key clinical and public health issues related to RF and RHD prevention and diagnosis among children and adults, including pregnant women. The

recommendations are intended to guide WHO Member States and their partners in developing, implementing and sustaining evidence-informed national and local policies, protocols and best practices.

1.6 Scope and target audience

This guideline focuses on selected topics related to the prevention and diagnosis of RF and RHD and covers some treatment aspects. It is not intended to encompass all aspects of prevention, identification and clinical care of affected populations and subpopulations. Such a broad scope was not feasible for WHO to manage at the present time. Readers are encouraged to identify high-quality, evidence-informed national and local guidance to complement this guideline.

This guideline encompasses the following:

1. primary prevention of RF and RHD, specifically the identification and treatment of suspected GAS pharyngitis and GAS skin infections;
2. secondary prevention of recurrent RF and of RHD, specifically the use of long-term antibiotic prophylaxis, interventions to increase adherence to secondary prevention (antibiotic prophylaxis) regimes, and screening for early RHD; and
3. management of RF, specifically the treatment of RF with anti-inflammatory drugs.

This guideline does not address primordial prevention, which focuses on reducing exposure to GAS through decreasing household crowding and by improving living conditions and access to health care. The guideline also does not address tertiary prevention of complications of RHD, which might include medications such as anticoagulants, and cardiac interventions including surgery. The reader is referred to other WHO resources, such as the *WHO Housing and health guidelines* for primordial prevention *(24)*, and to national treatment guidelines for other aspects of RF/RHD management. The World Heart Federation (WHF) makes available expert and evidence-based technical resources that can be used to complement this guideline (https://world-heart-federation.org).

This guideline is intended for use by a wide range of audiences, including national and local policy-makers and their expert advisers, as well as technical and programme staff at organizations involved in the prevention of RF and RHD, and in the identification and care of people with RF or RHD. This guideline may also be used by health workers and their professional societies, and by researchers who are interested in addressing gaps in the evidence.

The audience for this guideline is a global one, across diverse settings with varied perspectives and resources. The content is relevant to all Member States, and in particular to countries and regions where populations are at moderate/high risk of RF/RHD.

2. Methods

The *WHO guideline on the prevention and diagnosis of rheumatic fever and rheumatic heart disease* was developed according to WHO's guidance for guidelines: the *WHO handbook for guideline development* (2nd edition, 2014) *(19)* and meets international standards for evidence-informed guidelines. The main steps for the development of WHO guidelines include: 1) establishment of the general scope of the guideline and development of the key questions and a detailed workplan; 2) identification of contributors to the guideline process; 3) assessment of declarations of interest and management of any conflicts of interest of all contributors; 4) conduct of systematic reviews of the evidence to address the key questions; 5) assessment of the certainty (quality) of the body of evidence for critical and important outcomes; 6) formulation of recommendations; 7) drafting of the guideline document for review and approval by the Guideline Development Group (GDG) followed by targeted peer review; 8) review and approval by WHO's quality assurance body; and 9) publication and dissemination. A brief overview of the processes and methods used is given below; more detailed information is provided in **Web Annex A**.

A broad range of contributors participated in the development of this guideline, including individuals with diverse experiences, expertise and perspectives. Each type of contributor had a well-defined role and was subject to specific WHO policies and procedures: this approach helps to ensure the effectiveness of all contributors and transparency of the process, and to minimize bias.

The WHO Steering Group comprised members from relevant technical units at WHO headquarters, and regional offices were invited to join. This group provided technical guidance and support throughout the development process, as well as project management and administrative support. The Steering Group established the general scope of the guideline and drafted potential key questions which the recommendations might address.

The GDG was responsible for finalizing the scope and key questions and for formulating the recommendations.[1] Members of the GDG came from all WHO regions and from a wide variety of settings. They provided expertise related to RF/RHD, including provision of clinical care, health system and programme management, and experiences with relevant health care. The guideline methodologist supported the WHO Steering Group and the GDG throughout the guideline development process. Systematic review teams were contracted to provide syntheses of the evidence for each key question. The External Review Group (ERG) provided input into the final content and presentation of the guideline. This group was composed of individuals with diverse expertise in the technical aspects and/or in implementation of policies or programmes related to RF and RHD.

WHO requires that all internal and external contributors to its guidelines are thoroughly assessed for conflicts of interest prior to beginning participation in development of the guideline, with reassessment throughout the process. All available information on potential contributors was reviewed by the WHO responsible technical officers and their director. Only after it was determined that no significant conflicts of interest existed, were individuals formally invited to join the GDG or the ERG. External contracts were issued only to individuals and groups with no conflicts of interest.

In response to resolution WHA 71.14 adopted by Member States during the seventy-first World Health Assembly held in May 2018 *(22)*, WHO staff in the Department of Maternal, Newborn, Child and Adolescent Health and Ageing commenced work on this guideline. An initial meeting of the GDG was

[1] See Web Annex A for the list of key questions underpinning the systematic reviews.

held virtually from 26 to 28 July 2021. At this meeting, the GDG established the scope of the guideline and the key questions using the Population, Intervention, Comparator and Outcome (PICO) format (**Web Annex A**), and identified key outcomes. WHO then commissioned a series of systematic reviews of the quantitative evidence on the benefits and harms of relevant interventions (**Web Annex B**).

The commissioned systematic reviews adhered to Cochrane methods and standards *(25)*. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) system *(26)* was used to assess the certainty (quality) of the research evidence included in these reviews. The specific approaches and methods used are described in detail in each review.

The GDG formulated recommendations at a series of virtual meetings held from 8 to 10 March, and on 27 March and 17 April 2023, chaired by a GDG member and facilitated by the guideline methodologist. The GDG was guided by explicit evidence-to-decision considerations *(27)* to ensure a transparent process and comprehensive discussions. Recommendations were based on evidence on the benefits, harms and relative value placed on the outcomes of the intervention, as well as acceptability, feasibility, resource considerations and the potential effects of the interventions on equity across population groups. Human rights conventions and considerations underpin all WHO recommendations.

Each recommendation could be for or against a specific intervention, and either strong or conditional *(26)*. A strong recommendation means the GDG was confident that the desirable effects of adherence to the recommended intervention outweigh the undesirable effects. Most informed people would choose the recommended intervention and policy-makers can adopt the recommended intervention in most situations. A conditional recommendation means that the GDG concluded that the desirable effects of adherence to a recommendation probably outweigh the undesirable effects, but was not as confident. In this latter case, the choices of individuals, programme managers and other decision-makers will vary according to the relative values placed on the outcomes, the acceptability of the intervention and other considerations *(26)*. Policy-makers may require substantial debate and involvement of many stakeholders to make a decision to adopt or adapt a conditional recommendation and to prepare to implement it.

At the virtual meetings, the GDG discussed and agreed upon the recommendations via consensus, meaning that all GDG members in attendance agreed to the final wording and the strength of each recommendation. When consensus could not be reached, voting was the planned default approach. However, voting was never implemented as consensus was always achieved among meeting participants. Only GDG members participated in the consensus process for recommendation formulation, although other meeting attendees could contribute to the discussion (WHO staff, the methodologist, guideline writer and meeting observers). The GDG also formulated two guiding principles, based on human rights standards and ethics principles; no review of human research evidence is needed to make this type of normative statement.

This guideline also contains a list of guideline-related research gaps representing uncertainties about the evidence that arose during the guideline development process and that may affect the recommendation(s). These gaps have various sources, most notably the systematic reviews and other research or information that supports the domains of the evidence-to-decision framework (for example, benefits, harms, acceptability or feasibility of the intervention, and equity, among others), as well as input from the GDG. Presenting these gaps may benefit researchers, funders and other stakeholders with an interest in RHD. Importantly, research that addresses these gaps may improve future evidence-informed guidelines as well as decision-making in Member States and at the local level. The research gaps presented here are not prioritized and they are not intended to be fully comprehensive.

Following the formulation of recommendations by the GDG, the writer drafted the guideline for review and approval by the GDG, and for peer review by the ERG. Once finalized based on the comments received, the guideline underwent a review process by WHO's quality assurance body for guidelines, the Guidelines Review Committee (GRC). Finally, the guideline was prepared for publication and dissemination.

3. Guiding principles

RF and RHD are associated with poverty, residential overcrowding, insufficient access to clean water and sanitation, and barriers to accessing primary health care *(28–31)*. The GDG therefore formulated the following guiding principles, which underpin all of the recommendations in this guideline, as well as their adoption, adaptation and implementation in Member States:

1. Programme managers and health workers should work with local authorities and community leaders to ensure adequate living conditions including access to clean water, adequate sanitation and living spaces, housing, and appropriate ventilation in homes and residences.
2. Policy-makers and programme managers should ensure equitable access to screening and treatment services for people with suspected or confirmed GAS infections and RF/RHD. This applies particularly to vulnerable populations living in areas with moderate/high risk of RF/RHD. All people must have access to high-quality services for the prevention, diagnosis and treatment of RF/RHD, as recommended in this guideline.

4. Recommendations

4.1 Health education

4.1.1 Background

Health education of patients, families and caregivers is important for the prevention and treatment of both communicable and noncommunicable disease. WHO defines health education as "any combination of learning experiences designed to help individuals and communities improve their health by increasing knowledge, influencing motivation and improving health literacy" *(32)*.

Health education includes a broad range of approaches and may focus on the communication of information concerning the determinants of health, individual risk factors, disease etiology and prognosis, and use of the health care system. Health education can also involve task-based communication designed to support specific behaviours such as medication adherence, or focus on transferable skills and knowledge that equip people to make more autonomous decisions relating to their health and to adapt to changing circumstances.

Health education can be implemented in multiple ways such as by community groups, lay or peer counsellors; in schools; as part of media outreach; or through the health care system.

For primary and secondary prevention of RF/RHD, educational interventions have the potential to decrease the disease burden across populations and settings, particularly where the risk of RF and RHD is high.

In this guideline WHO, with the support of the GDG, elected to focus on educational interventions led by health workers. Population-based interventions, such as public advertisements, although potentially important and effective, were considered out of scope; they may be examined in future versions of this guideline.

4.1.2 Recommendation

Recommendation

WHO recommends that health workers provide evidence-based education focused on the relationship between infections of the pharynx and skin potentially caused by GAS, and RF/RHD, and thus the importance of treating these infections appropriately, particularly in moderate/high risk settings or populations.

(Conditional recommendation, very low certainty evidence)

Rationale

Health care worker-led educational interventions focused on RF/RHD increase knowledge among children, adolescents and adults, although the certainty of this body of evidence was very low. If communities are more aware of the relationship between infections of the throat or skin potentially caused by GAS and the risk of RF, the uptake of and adherence to primary prevention measures, such as care-seeking for sore throat or skin infections and adherence to treatment, may be increased.

4.1.3 Remarks

Research evidence identified for this recommendation was sparse and many questions remain unanswered. It was therefore difficult to draw conclusions on critical issues such as optimal

interventions, settings and modes of delivery, and whether the focus should be children or their parents and caregivers.

The link between improving knowledge and optimal health behaviours (for example, seeking appropriate care for a sore throat) could not be ascertained from the systematic review that was commissioned. In addition, the review did not examine educational interventions beyond those delivered by health workers to members of the general public. Thus the potential role of community-level interventions in high-risk regions was not addressed; nor was the education of health workers examined.

4.1.4 Implementation considerations

When implementing health care worker-led educational interventions to augment community members' knowledge of GAS infections and the risk of RF/RHD, the following considerations may be important:

1. Adding to the current demands on health workers creates challenges, thus education on GAS infections needs to be prioritized according to the risk of RF/RHD in the local context, and the competing educational needs of, and demands on, health workers.
2. Training and education programmes for health workers should include information about the causal link between GAS infections and RF/RHD, according to their scope of practice. Continuing education programmes may also address this topic, according to the local context and needs.
3. School-based health education programmes on GAS infections and their relationship to RF/RHD may be considered in areas with moderate/high risk of RF/RHD.
4. Community education on GAS infections and RF/RHD prevention may be incorporated into other public health educational programmes and messages, and delivered in the local setting.
5. Public health agencies and health systems may consider:
    - developing culturally appropriate messaging and materials to promote awareness of the importance of sore throat and skin infections and their link to RF/RHD;
    - partnering with public and private groups working in health education or health promotion to ensure that information on GAS infections and RF/RHD is included;
    - leveraging existing educational content on RF/RHD made available by global or local professional associations and interest groups; and
    - sharing resources, approaches and outcomes with the global community to optimize resource use and dissemination of best practices.

4.1.5 Summary of the evidence

A systematic review of the evidence on RF/RHD educational interventions led by health workers identified four studies, all conducted in areas with high risk of RF/RHD *(33)*. A single cluster-designed randomized controlled trial (RCT) in Brazil compared nurse-led education to tablet-based learning interventions focused on RF/RHD and aimed at schoolchildren. This study reported a similar increase in knowledge about RF/RHD in both groups (increase in mean scores of 23.5% when nurse-led and 23.9% with tablets; moderate certainty evidence; 1301 study participants) *(34)*.

A controlled before-and-after study and a prospective cohort study reported that health worker-led educational interventions resulted in increased knowledge about GAS infections and RF/RHD in India and New Zealand (very low certainty evidence; 696 participants) *(35, 36)*. One study focused on secondary prevention with training of health workers, teachers and (secondarily) pupils in India *(36)*, while the other provided educational sessions on primary prevention along with take-home information sheets to students aged from 12 to 18 years in New Zealand *(35)*.

In another controlled before-and-after study, a multicomponent, health worker-led community educational intervention in New Zealand resulted in increased uptake of primary prevention services,

compared to no intervention. With the educational intervention, 31 more people attended health services per 1000 population (95% CI: 22–44) compared to no intervention (relative risk (RR) 9.99 (95% CI: 7.29–13.67); very low certainty evidence; n=23 610) *(37)*.

4.1.6 Guideline-related research gaps

The following guideline-related research gaps were identified by the GDG:

1. Develop and evaluate community educational interventions focused on the link between GAS infections of the throat or skin and RF/RHD, and the effect of such education on care-seeking behaviour.
2. Develop and evaluate innovative approaches for initiating and scaling up health and care worker-led educational interventions and their effect on the incidence and severity of RF/RHD.
3. Compare the benefits, harms, feasibility, sustainability and cost-effectiveness of various types of educational interventions delivered to the public in a range of settings. Examples include community-based interventions (for example, mass advertising, interventions led by community health workers, public health messaging through radio/television) and health system interventions (for example, patient education in health care facilities or digital information and reminders for health workers).

4.2 Diagnosis of Group A streptococcal pharyngitis

4.2.1 Background

Sore throat (pharyngitis) is a common presenting complaint in primary care *(38, 39)*. Pharyngitis is most frequently viral in origin, however, when infection is bacterial, the most common causative agent is GAS. The global incidence of GAS sore throat episodes among the most commonly affected group – children aged 5–14 years – was estimated at 22.1 (95% CI: 14.7–33.1) episodes per 100 child-years based on pooled data from nine studies conducted between 2000 and 2020, corresponding to 288.6 million episodes per year *(40)*. Determining the causative agent is difficult, however, especially in settings with no or limited access to microbiological diagnostic tools *(41)*. A meta-analysis showed that the prevalence of GAS pharyngitis in patients less than 18 years of age who presented to an outpatient centre with sore throat was 37%, and for children younger than 5 years, it was 24% *(42)*. In adults, GAS pharyngitis typically occurs under 40 years of age, declining steadily with increasing age *(43)*.

The current gold standard for the diagnosis of pharyngitis caused by GAS is microbiological throat culture. Molecular point-of-care (POC) tests may be an alternative gold standard, although there are insufficient data on their diagnostic accuracy in moderate/high-risk RF/RHD settings *(44)*. The diagnostic performance of rapid non-molecular POC testing in these settings is also not known *(45)*.

Clinical prediction rules (CPRs) are tools that quantify the contribution of history, clinical examination and basic diagnostic tests to assess the probability that a patient has a target condition or a future health outcome *(46)*. A number of CPRs have been developed to predict GAS infection in people with a sore throat *(47–53)*. These tools aim to decrease clinicians' uncertainties about managing patients who present with sore throat when microbiological confirmation is not routinely available. For clinicians to confidently use any CPR, it should demonstrate good test performance with external validation in multiple settings or populations *(54)*.

4.2.2 Recommendation

The GDG reviewed the evidence on the diagnostic accuracy of CPRs for GAS pharyngitis, with the intention of making a recommendation on which rule or rules should or might be used for specific populations and settings.

No recommendation

WHO, with guidance from the GDG, was unable to make a recommendation at this time on CPRs or on other sets of signs and symptoms that have sufficient diagnostic accuracy for use in children, adolescents or adults who present with sore throat.

Rationale

Performance of CPRs varies across populations, and none have demonstrated high sensitivity and specificity for detection of GAS pharyngitis across multiple populations. In the absence of a well-validated CPR, WHO does not recommend the use of a specific CPR at this time.

Remarks

The GDG acknowledged the importance of treating GAS pharyngitis to prevent RF/RHD, particularly in moderate/high risk settings, and given the lack of available and affordable microbiological culture and/or POC testing for GAS infections in many such communities.

There are consistent signs and symptoms that make GAS pharyngitis more likely, including the presence of sore throat and fever, and a lack of rhinorrhoea or cough – the latter symptoms are more likely in viral pharyngitis *(47, 55)*. However, in the absence of sufficient evidence of diagnostic accuracy, WHO leaves the decision to use a CPR to national policy-makers.

4.2.3 Summary of the evidence

A systematic review examining studies that either derived or externally validated a CPR for detecting GAS in people with sore throat *(56)* was used to inform the GDG's discussions and decisions. Derivation (model development) studies were included if they examined CPRs with two or more signs or symptoms as predictors, used a prospective study design and multivariable analyses, and were externally validated. Included validation studies assessed the performance of a CPR against the reference standard of microbiological culture of a throat swab or, where the reference standard comprised rapid antigen detection testing (RADT), against microbiological culture or DNA confirmation when the RADT was negative. The review excluded studies where the reference standard was RADT only.

The review identified 24 derivation studies of 24 different CPRs. Of these, seven CPRs were externally validated and were thus included in the systematic review, together with 39 corresponding validation studies. Five of the seven CPRs were derived in high-income countries (United Kingdom, United States of America (USA) or Canada) and the remaining two in Egypt (lower middle income country). Two CPRs were derived in emergency department populations and the remainder in outpatient or general practice populations. Two of the CPRs were derived in adults, three in children and adolescents, and two in mixed populations. Prevalence of GAS in the derivation studies ranged from 14% to 37%.

All seven CPRs included tonsillar exudates and/or swelling as a predictor and six included tender and/or enlarged cervical lymph nodes. Other potential predictors were fever and absence of cough (four CPRs), presence of scarlatiniform rash (one CPR), visit to a health care provider within 3 days (one CPR) and exposure to streptococcal infection (one CPR).

Of the 39 validation studies of the seven CPRs, five reported head-to-head comparisons of four pairs of CPRs in the same study participants. All studies were assessed as having high risk of bias.

Very low certainty evidence from the head-to-head comparisons of the Centor and McIsaac CPRs (two studies) and of the Centor and FeverPain CPRs (one study) favoured the Centor CPR. Very low certainty evidence found that the Centor CPR was equivalent to the Walsh CPR (one study) and that the AbuReesh and Steinhoff 2005 CPRs were equivalent and had poor discriminative ability (one study). Within- and between-study comparisons of the Centor and McIsaac CPR by age group suggested that the Centor CPR may perform better than the McIsaac CPR in older populations (>18 years). However, this finding was not based on a quantitative subgroup analysis and should be interpreted with caution.

The review authors concluded that the comparative diagnostic performance of CPRs to detect GAS infection in people with a sore throat is very uncertain *(56)*. They noted that the potential biases in

the included studies were more likely to underestimate than overestimate the diagnostic accuracy of the CPRs for two reasons. First, the assessment of GAS using microbiological culture as the reference standard is not highly sensitive and hence is likely to underestimate the accuracy. Second, many of the studies were based on medical record assessments of the signs and symptoms used in the prediction rules, rather than actual usage by clinicians. This is likely to have caused a measurement error which underestimated the true accuracy of the CPR.

4.2.4 Guideline-related research gaps

The following guideline-related research gaps were identified by the GDG:

1. Additional studies of CPRs are needed, including:
    - high-quality validation studies (with sufficient sample size) comparing existing CPRs for specific age groups and across multiple settings using GAS culture as the reference standard; and
    - impact testing of CPRs that demonstrate acceptable diagnostic accuracy to determine the effect of use on clinicians' decisions and patient outcomes.
2. New, validated POC tests for the diagnosis of GAS infections are needed that are practical, affordable and fit for purpose in low-resource settings.

4.3 Treatment of group A streptococcal pharyngitis

4.3.1 Background

Given the frequency with which patients present with sore throat in primary care facilities, WHO and the GDG prioritized providing guidance on when to treat patients presenting with pharyngitis with antibiotics. Pharyngitis is most frequently viral in origin and therefore antibiotics are of no benefit. However, when infection is bacterial, the most common causative agent is GAS and antibiotics should be prescribed to prevent suppurative (for example, quinsy, otitis media) and non-suppurative complications (for example, RF/RHD). In high-income countries, these complications are uncommon *(57)*. In a systematic review of 14 RCTs, 82% of study participants presenting with a sore throat and randomly assigned to a control group (placebo or no treatment) were symptom-free without antibiotic treatment at 1 week *(58)*.

Antibiotic treatment can be associated with adverse events such as diarrhoea and skin rash, among others. There is also concern that the large-scale prescription of antibiotics for sore throat may contribute to the global problem of antimicrobial resistance *(59)*. However, these concerns must be weighed against the risk of RF/RHD in moderate/high risk populations. It is thus important for health workers to try to differentiate infections that are viral from those that are likely to be bacterial in origin, and to be strategic in their decisions to treat, and with which drug and for how long.

Determining the causative agent of pharyngitis is often difficult, however. Many and perhaps most populations at moderate/high risk for RF/RHD do not have access to laboratory confirmation of GAS pharyngitis – whether by microbiological culture or POC tests. Thus, establishing definitive confirmation of GAS pharyngitis may not be practical or affordable. It is therefore important to provide guidance as to if and when to treat patients presenting with a sore throat with antibiotics.

4.3.2 Recommendations

Recommendation 1

Children, adolescents and adults with sore throat and a positive diagnostic test (either POC testing or microbial confirmation) for GAS pharyngitis should be treated with antibiotics to prevent RF/RHD.

(Strong recommendation, moderate certainty evidence)

Rationale

There is moderate certainty evidence that antibiotic treatment of confirmed GAS pharyngitis helps to prevent RF/RHD (OR 0.51; 95% CI: 0.28–0.96).

Recommendation 2

In populations at moderate/high risk of RF and RHD and where diagnostic testing to confirm GAS (with either POC testing or microbial confirmation) is not available, children and adolescents with clinically-suspected GAS pharyngitis should be treated with antibiotics to prevent RF/RH.

(Strong recommendation, very low certainty evidence)

Rationale

For RF/RHD prevention, it is important to treat clinically-suspected GAS pharyngitis in children and adolescents in areas with moderate/high risk of RF and RHD with antibiotics to prevent an episode of RF that can induce or aggravate RHD. The first episode of RF is commonly seen in children aged 5 to 14 years and recurrent episodes are most common within 1 year of the first episode.

There is no evidence to support treatment of adults presenting with sore throat to prevent RF/RHD, unless there is a positive diagnostic test (either POC testing or microbial confirmation).

Remarks

There is evidence that a treat-all strategy for children and adolescents presenting with a sore throat reduces the incidence of RF/RHD, especially in moderate/high risk populations. However, there are harms associated with such an approach, including cost, adverse effects from antibiotics, risk of antimicrobial resistance and burden on the health care system. The GDG felt that these harms outweigh the benefits of a treat-all strategy for sore throat, including among populations at high risk for RF/RHD. Therefore, children and adolescents presenting with a sore throat should not receive antibiotic prophylaxis unless GAS pharyngitis is confirmed (Recommendation 1) or clinically suspected in areas with moderate/high risk of RF and RHD (Recommendation 2). GAS pharyngitis is clinically suspected when fever is present, and when rhinorrhoea or cough are absent; viral pharyngitis is more likely when fever is absent and rhinorrhea and cough are present *(47, 55)*.

Recommendation 3

For patients with a positive diagnostic test for GAS pharyngitis or with clinically-suspected GAS, WHO recommends penicillin (intramuscular (IM) or oral) as first-line treatment for the prevention of RF/RHD.

(Conditional recommendation, low certainty evidence)

Rationale

The GDG preferred penicillin to other antibiotics because it has a narrow spectrum of action, no known GAS resistance at the present time, and a lower chance of generating new antimicrobial resistance in the community compared to antibiotics with a broader spectrum. The commissioned systematic review did not, however, report significant differences between penicillin and other antibiotics for resolution of symptoms, with the exception of one comparison that favoured a carbacephem.

4.3.3 Implementation considerations

Considerations and potential activities for the implementation of WHO recommendations on the treatment of GAS pharyngitis to prevent RF/RHD include the following:

1. Guidance on the diagnosis and treatment of pharyngitis for the prevention of RF/RHD should be included in Member States' national health guidelines.
2. While WHO does not recommend a specific CPR for GAS pharyngitis at this time, there are specific signs and symptoms that make GAS pharyngitis more likely. The most consistent of these signs and symptoms is the presence of fever or pharyngeal exudates and the absence of rhinorrhoea and cough (the latter are more likely to be found in viral pharyngitis). When microbial confirmation is not possible, these signs and symptoms can be used to estimate the likelihood that pharyngitis is caused by GAS and thus inform a decision as to whether antibiotic treatment is indicated or not.

3. Governments or national professional standard-setting organizations may provide health workers with simple algorithms to assess pharyngitis, classify the likelihood of bacterial (GAS) infection, and decide whether antibiotic treatment is indicated or not.
4. Health workers should explain to patients with sore throat and their caregivers the rationale for prescribing antibiotics to prevent RF/RHD, or for not prescribing antibiotics when the etiology is unlikely to be bacterial.
5. Antibiotic supply chains, in particular those for oral penicillin and IM benzathine penicillin G (BPG), should be strengthened to ensure availability of treatment for confirmed or suspected GAS pharyngitis in countries and areas at moderate/high risk of RF/RHD.
6. Governments should monitor the emergence of antimicrobial resistance with the treatment of sore throat/pharyngitis, as part of their national antimicrobial resistance and use surveillance system *(60)*.

For additional details on the treatment of pharyngitis, see *The WHO AWaRe (Access, Watch, Reserve) antibiotic book (61)*.

4.3.4 Summary of the evidence

Patients presenting with sore throat

A 2021 Cochrane review *(58)* examined whether children, adolescents and adults who presented to the health care system with complaints of a sore throat should be treated with antibiotics. Twenty-nine RCTs or quasi-RCTs fulfilled the inclusion criteria. A review update commissioned by WHO identified no new studies *(62)*. This review included studies reporting on a total of 15 337 cases of sore throat, including both participants with clinically-suspected and laboratory-confirmed GAS pharyngitis. Most of the studies were conducted in the 1950s; participants ranged in age from <1 year to >50 years. Follow-up varied between 1 and 8 weeks and most studies were conducted in high-income countries.

At day 3, resolution of sore throat was more frequent in participants receiving antibiotic treatment compared to placebo or no treatment (RR 1.56, 95% CI: 1.44–1.69; 16 studies,

3730 participants; moderate certainty evidence). At 1 week, resolution of sore throat symptoms was also more frequent in participants receiving antibiotics (RR 1.09, 95% CI: 1.05–1.12; 14 studies, 3083 participants; moderate certainty evidence), although 81% of participants in the control groups had also recovered by this time.

The overall probability of RF was lower in people treated with antibiotics than those in the control groups (OR 0.36, 95% CI: 0.26–0.50; 17 studies, 12 132 participants; moderate certainty evidence). For every 1000 participants (children, adolescents and adults) treated with antibiotics, there were 12 fewer cases of RF, 15 fewer cases of acute otitis media and 20 fewer cases of quinsy than in the control group. Two cases of acute glomerulonephritis occurred in the control group across the 10 studies that reported this outcome, however, there was no statistically significant difference between antibiotic-treated and control groups (OR 0.07, 95% CI: 0.00–1.32; 10 studies, 5147 participants; low certainty evidence).

Patients with laboratory-proven group A streptococcal infections

An existing Cochrane review *(58)* was updated and used to examine the effectiveness of treatment of children, adolescents and adults with laboratory-confirmed streptococcal pharyngitis. No new studies were identified in the update *(63)*.

At day 3, the resolution of sore throat symptoms was more frequent for GAS-positive patients who received any antibiotic treatment compared to those receiving placebo or no treatment (RR 2.05, 95% CI: 1.81–2.31; 11 studies, 1839 participants; moderate certainty evidence). Similarly, at 1 week, symptom resolution was more frequent in participants receiving any antibiotic compared to placebo or no treatment (RR 1.11, 95% CI: 1.06–1.15; seven studies, 1117 participants; moderate certainty evidence), although in 88% of controls (no treatment or placebo), sore throat symptoms had resolved by 1 week.

There was no statistically significant difference in the probability of acute glomerulonephritis in participants with GAS-positive swabs (OR 0.14, 95% CI: 0–6.82; 3 studies, 1806 participants; very low certainty evidence). This was based on one event reported in the placebo/no-treatment group.

In participants with GAS-positive throat swabs, the probability of progression to RF in those who received antibiotics was half that in those who received placebo or no treatment. The difference was statistically significant (OR 0.51, 95% CI: 0.28–0.96; 7 studies, 3416 participants; moderate certainty evidence). Data on progression to RHD were not reported in the included studies.

For every 100 participants treated with antibiotics, there was one fewer case of RF and three fewer cases of acute otitis media than in the control group. No cases of quinsy were reported in a trial of participants with GAS-positive swabs reporting this outcome.

Data on antimicrobial resistance were poorly reported in the included studies. Only two trials *(64, 65)* conducted sensitivity tests and reported no isolation of penicillin-resistant organisms. Adverse events could not be analysed because of inconsistencies in measurement and reporting across studies The most frequently reported adverse events associated with antibiotic use were diarrhoea, vomiting and rash.

Selection of antibiotics

Two existing, high-quality systematic reviews *(66, 67)* were updated *(62)* to examine the evidence on antibiotic treatment for laboratory-confirmed GAS pharyngitis. The review by Altimimi and colleagues *(67)* included 21 studies and compared short duration oral therapy (2 to 6 days) to 10 days of oral therapy. There was no evidence of clinically important differences in outcomes when different classes of antibiotics were compared to penicillin in adults and children with pharyngitis caused by GAS. Data on the incidence of complications were too few to draw conclusions. No studies compared antibiotics with different administration routes, or different antibiotic treatments for patients with a sore throat as the presenting complaint but without confirmation of GAS.

The second review included 19 studies in patients with confirmed GAS pharyngitis and reported no significant differences in symptom resolution for the various comparisons (low and very low certainty evidence) *(66)*. The single exception was low certainty evidence in children that a carbacephem may be more effective than penicillin. Data on adverse events were too scarce to draw conclusions.

4.3.5 Guideline-related research gaps

The GDG agreed that more research evidence is needed on the benefits and harms of different approaches to GAS treatment including:

1. Develop and test novel strategies in moderate/high risk communities for the primary prevention of RF/RHD. These strategies include involving pharmacies, schools and community health workers in the identification and timely referral and/or treatment of possible GAS infections.
2. Compare different modes of penicillin delivery, dosing schedules and duration of treatment of GAS infection on RF/RHD prevention.
3. Evaluate various approaches to disseminate and implement guidance on appropriate treatment of known or suspected GAS infections, to assess their impact on the incidence of RF and RHD, and their cost-effectiveness.
4. Conduct prospective microbiological studies to understand the impact of primary prevention of RF/RHD on community-wide antimicrobial resistance.
5. Study the benefits and harms of GAS treatment in populations at moderate/high risk of RF/RHD, including the indirect effects of antibiotic treatment such as days of work or school missed, and out-of-pocket expenses, among others.

4.4 Diagnosis and treatment of skin and skin structure infections

4.4.1 Background

Acute bacterial SSSIs are commonly caused by *Staphylococcus aureus* (*S. aureus*), however, GAS is also an important cause. There is emerging evidence that GAS skin infections are a potential cause of RF, alone or in combination with GAS pharyngitis *(13, 68–71)*.

SSSIs represent diseases with a broad spectrum of severity and are generally categorized as purulent (for example, furuncles, bullous impetigo, carbuncles, abscesses), predominantly caused by *S. aureus (72)*. In contrast, skin infections caused by GAS are usually non-purulent *(13)*. Non-purulent SSSIs have a range of clinical presentations, depending on which layers of skin are infected. Those affecting the superficial skin layers include impetigo, pyoderma and erysipelas. Impetigo is highly contagious and is the most common superficial SSSI affecting about 162 million children globally (typically aged 2 to 5 years) at any given time *(73)*. It is particularly prevalent in low-income settings and among Indigenous populations, presenting as non-life-threatening crusty lesions and ecthyma.

GAS can also cause deeper SSSIs such as infections of the subcutaneous tissue (cellulitis) and fascia (necrotizing fasciitis). Furthermore, GAS infections can trigger non-infectious dermal conditions including toxin-mediated, inflammatory and hypersensitivity reactions (scarlet fever, streptococcal toxic shock-like syndrome, erythema nodosum and Henoch-Schönlein purpura, among others *(74, 75)*). These conditions are not considered in this guideline: the indicated clinical and laboratory assessments should be made, followed by appropriate treatment.

GAS skin infections are usually diagnosed clinically. Microbiological culture from the skin is technically challenging and not common practice, even in high-income settings where the technology is readily available. SSSIs are thus treated empirically in most settings.

4.4.2 Recommendations

The GDG examined a systematic review of the evidence on the diagnostic accuracy of combinations of signs and symptoms (CPRs compared to microbiological tests) to identify streptococcal skin infection in children, adolescents and adults.

No recommendation

WHO, with guidance from the GDG, was unable to make a recommendation at this time either for or against any specific CPR to be used when GAS skin infection is suspected.

Rationale

There are currently no CPRs that have high sensitivity for detection of GAS skin infections across multiple populations. Given the absence of a well-validated CPR, the GDG decided there was insufficient evidence to recommend either for or against the use of any CPR for the diagnosis of GAS skin infections at this time.

The GDG also reviewed the evidence on the benefits and harms of treating children, adolescents and adults:

1. with laboratory-confirmed GAS skin infections with antibiotics to prevent RF/RHD; and
2. for GAS skin infections with antibiotics to prevent RF/RHD when laboratory diagnosis is not possible and the diagnosis is based only on clinical assessment.

No recommendation

WHO, with guidance from the GDG, was unable to make a recommendation at this time either for or against antibiotic treatment of SSSIs, whether laboratory-confirmed or clinically diagnosed, for the specific purpose of preventing RF or RHD.

Rationale

No relevant evidence from RCTs in humans was identified in the systematic review to address whether antibiotic treatment of SSSIs versus no antibiotic treatment affects the incidence of RF or RHD. Thus, the GDG did not formulate a recommendation for treatment of SSSIs, either presumed or proven to be caused by GAS, for the specific purpose of RF/RHD prevention.

Remarks

Health workers should treat SSSIs as indicated, based on the signs and symptoms and on relevant laboratory findings. The absence of evidence on the effectiveness of treatment of confirmed or suspected GAS SSSIs to prevent progression to RF/RHD should not affect decision-making when patients with SSSIs present in the clinical setting, to prevent other complications from SSSIs.

4.4.3 Summary of the evidence

A systematic review focused on the diagnostic accuracy of signs and symptoms for GAS skin infections among children, adolescents and adults with suspected bacterial infection *(76)*. Studies with data on subpopulations including children, adolescents, pregnant women and older adults were sought in settings with high and low RF/RHD prevalence (or incidence).

Two studies were identified in the systematic review; both focused on children <18 years of age: a cross-sectional study from Argentina *(77)* and a case-control study from the USA *(78)*. The Argentinian study examined children with symptoms of necrotizing fasciitis and used blood culture as the reference standard. The authors of this study reported a sensitivity of 0.11 (95% CI: 0.05–0.20) and a specificity of 0.94 (95% CI: 0.84–0.98) *(77)* for a set of signs and symptoms. In the second study, Kokx and colleagues *(78)* reported on children with perianal symptoms, using perianal skin cultures as the reference standard. This study reported a sensitivity of 0.91 (95% CI: 0.76–0.98) and a specificity of 1.00 (95% CI: 0.85–1.00).

This body of evidence was assessed as having very low certainty and it did not assess the accuracy of individual signs and symptoms but rather a combination of symptoms. In addition, these studies examined only two specific types of SSSIs and not the broad range of other locations and types of SSSIs caused by GAS.

A systematic review *(63)* did not identify any RCTs examining the effects of antibiotic treatment compared to placebo or no antibiotic treatment among patients with culture-confirmed GAS skin infections. Twelve RCTs compared different antibiotic regimes and their effects on microbial eradication and clinical resolution. However, none of these studies examined the outcomes in relation to severity and duration of GAS SSSIs, progression to RF or RHD, or provider or patient acceptability of treatment regimes.

A systematic review *(79)* identified four RCTs comparing different antibiotic regimens for the treatment of clinically-suspected bacterial skin infections. However, it did not identify any RCTs comparing antibiotic treatment to placebo or no antibiotic treatment to reduce the risk of progression to RF or RHD.

4.4.4 Guideline-related research gaps

The following guideline-related research gaps were identified by the GDG:

1. Determine the role of GAS skin infections in the risk for and pathogenesis of RF and RHD.
2. Examine whether treatment of SSSIs reduces the risk of progression to RF or RHD.

4.5 Diagnosis of rheumatic fever

4.5.1 Background

The accurate diagnosis of RF is essential to all subsequent treatment and follow-up, however, there is no single examination or test to diagnose RF. In 1944, Thomas Duckett Jones developed a diagnostic tool consisting of a set of clinical and laboratory criteria *(80)*. These criteria have undergone a number of modifications over the years: the American Heart Association (AHA) published revised Jones criteria in 1956, 1965, 1984, 1992 and 2015 *(17, 81)*.

The 2015 revision of the Jones criteria for the diagnosis of RF *(17)* (**Table 1**) includes criteria for both the initial episode of RF and for recurrent episodes. A combination of minor and major criteria together with evidence of GAS infection are needed for diagnosis. In addition, there are different criteria for low- versus moderate- or high-risk populations; echocardiography, when available, is used to assess cardiac involvement (clinical or subclinical); and monoarthralgia and low-grade fever are considered minor criteria in moderate- or high-risk populations. The AHA's objective in revising these criteria in 2015 continued to be consistent with the goal of the Jones criteria to favour low sensitivity and high specificity in the diagnosis of RF in low-risk populations, but for the first time considered the need for high sensitivity in moderate- and high-risk settings.

Health workers can find the Jones criteria for diagnosing RF challenging to apply, resulting in both under- and overdiagnosis. Reasons include the lack of specific laboratory or clinical findings, especially in the early stage of disease when there are no clinical signs or symptoms *(82)*; the subjective nature of

Table 1. Revised Jones criteria *(17)*

A. For all patient populations with evidence of preceding GAS infection	
Diagnosis: initial RF	2 Major manifestations or 1 major plus 2 minor manifestations
Diagnosis: recurrent RF	2 Major or 1 major and 2 minor or 3 minor manifestations
B. Major criteria	
Low-risk populations[a]	Moderate- and high-risk populations
Carditisb clinical and/or subclinical	Carditis[b] (clinical and/or subclinical)
Arthritis polyarthritis only	Arthritis (monoarthritis or polyarthritis; polyarthralgia[c])
Chorea	Chorea
Erythema marginatum	Erythema marginatum
Subcutaneous nodules	Subcutaneous nodules
C. Minor criteria	
Low-risk populationsa	Moderate- and high-risk populations
Polyarthralgia	Monoarthritis
Fever (≥38.5 °C)	Fever (≥38.5 °C)
ESR ≥60 mm in the first hour and/or CRP ≥3.0 mg/dL[d]	ESR ≥30 mm/h and/or CRP ≥3.0 mg/dL[d]
Prolonged PR interval, after accounting for age variability (unless carditis is a major criterion)	Prolonged PR interval, after accounting for age variability (unless carditis is a major criterion)

RF, Rheumatic fever; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; GAS, group A *Streptococcus*.

[a] Low-risk populations are those with an acute rheumatic fever (ARF) incidence of ≤2 per 100 000 school-aged children or all-age rheumatic heart disease prevalence of ≤1 per 1000 population per year.

[b] Subclinical carditis indicates echocardiographic valvulitis.

[c] Polyarthralgia should only be considered as a major manifestation in moderate- to high-risk populations after exclusion of other causes *(17)*. As in past versions of the criteria, erythema marginatum and subcutaneous nodules are rarely "stand-alone" major criteria. Additionally, joint manifestations can only be considered in either the major or minor categories but not both in the same patient.

[d] The CRP value must be greater than the upper limit of normal for laboratory. Also, because ESR may evolve during the course of RF, peak ESR values should be used.

Source: adapted from Gewitz et al. (2015) *(17)*.

some of the symptoms; and a lack of access to the component testing in many settings with moderate/high risk of RF/RHD (namely, echocardiography, electrocardiography, streptococcal serology, markers of inflammation) *(83)*. Throat cultures can be associated with a significant false-negative rate, particularly weeks after the acute infection when RF most commonly presents and in settings where antibiotic use is high. Thus, serological testing tends to be favoured *(14)*, but is not readily available.

Advances in understanding the pathophysiology of RF suggest that genetic susceptibility may play an important role *(84–86)*. Furthermore, there is increased interest in diagnostic and prognostic biomarkers to improve and modernize diagnostic testing for RF *(87–91)*. Nonetheless, for low-resource settings, including many areas of moderate/high risk of RF/RHD, diagnostic tests are inaccessible and diagnostic criteria must be as simple, yet as accurate as possible.

The GDG thus prioritized an examination of the potential benefits and harms of simplified sets of diagnostic criteria for RF, particularly for use in high-prevalence countries or in low-resource settings. The question was whether a simplified algorithm could potentially replace the 2015 Jones diagnostic criteria *(17)* in some or all settings.

Recommendation

The Jones criteria should be used for RF diagnosis in children, adolescents and adults with suspected RF.

(Strong recommendation, low certainty evidence)

Rationale

The Jones criteria *(17)* remain the standard set of criteria used to diagnose RF. There is no evidence to support simplified algorithms for RF diagnosis as they may lead to under- and overdiagnosis. Thus WHO does not recommend either for or against the use of any other sets of criteria or algorithms for the diagnosis of RF.

4.5.2 Implementation considerations

In many populations at high risk of RF/RHD it is difficult to implement the Jones criteria *(17)* due to lack of clinical resources and trained personnel. However, WHO recommends that these criteria should be used to the extent possible for RF diagnosis, due to the lack of a validated simpler alternative. The 2015 Jones criteria have a provision for diagnosis of possible RF in settings where the full criteria cannot be evaluated (due to lack of laboratory or echocardiography testing) and suspicion of RF is high.

Where resources are limited, investment in echocardiography, including standard or handheld echocardiography (HHE), might be prioritized over investment in laboratory capacity. For more information, see **section 4.6**.

4.5.3 Summary of the evidence

A systematic review of research evidence *(92)* sought to identify studies comparing a simplified algorithm for RF diagnosis to the 2015 Jones criteria *(17)* or to other diagnostic criteria for RF. Three studies were identified for the review. Simplified diagnostic algorithms using only clinical data at community health centre-level (area under curve (AUC) 0.69, sensitivity 66% and specificity 68%), or with the addition of a 12-lead electrocardiogram and simple laboratory investigations at district-level facilities (AUC 0.76, sensitivity 77%, specificity 67%) have worse performance than models that included the full set of laboratory investigations and echocardiography at national referral hospitals (AUC 0.91, sensitivity 84%, specificity 87%). Using the modified Jones criteria without echocardiography results in important loss of sensitivity (sensitivity 79%, specificity 100%, AUC 0.90). In high-prevalence areas, 2.5 to 5% of children and young adults who do not meet the full modified Jones criteria progress to RHD.

4.5.4 Guideline-related research gaps

The following guideline-related research gaps were identified by the GDG:

1. Develop and test simplified approaches to RF diagnosis, including but not limited to simplified algorithms and biomarkers, which may be more easily integrated into health care systems in settings and populations where there is a moderate/high risk of RF/RHD.
2. Develop and implement an approach to stratify patients with suspected RF by risk of disease based on diagnostic certainty, with pathways for disease management for each risk stratum.
3. Develop accurate criteria for excluding various differential diagnoses to augment the diagnostic accuracy of the 2015 Jones criteria.
4. Develop and test existing diagnostic aids such as user-friendly digital applications ("apps") to facilitate the use of complex sets of criteria by a range of health professionals including frontline workers.

4.6 Echocardiography in the diagnosis of rheumatic fever and rheumatic heart disease

4.6.1 Background

Echocardiography, or the use of ultrasound to investigate the structure and function of the heart, is the most sensitive tool for diagnosing valvular pathology. The 2015 Jones criteria *(17)* include the use of echocardiography for the initial diagnosis of carditis, citing evidence from global studies on the presence of subclinical carditis in RF. In fact, echocardiography has become the gold standard for evaluating patients for rheumatic carditis (during RF) and valvular pathology (during RHD), with more than 25 studies showing superiority in sensitivity and specificity compared to auscultation *(93)*.

Echocardiography is also a powerful tool for case detection of RHD, identifying 12.9 cases per 1000 people (95% CI: 8.9–18.6) in endemic areas, compared to cardiac auscultation (2.9 cases detected per 1000 people; 95% CI: 1.7–5.0) *(94)*. In a systematic review using HHE, the pooled sensitivity and specificity for diagnosis of definite RHD were both >90% when compared to standard echocardiography machines *(95)*.

Over the past decade, echocardiography machines have become smaller and more portable. HHE devices lack some features of fully-functional echocardiography machines, such as spectral Doppler. However, HHE machines retain diagnostic capabilities and are typically much more affordable than full-sized machines *(96)*. Due to both portability and reduced cost, HHE has been investigated extensively for use in RHD diagnosis and screening.

Screening for RHD is potentially a valuable approach to reduce morbidity and mortality from RF/RHD. More than 85% of RHD cases are diagnosed only when advanced disease has developed and cardiac complications are present *(97)*. Yet, RHD most typically evolves over a period of years or even decades, thus providing opportunity for earlier detection and intervention.

Screening is "the presumptive identification of unrecognized disease or defect by the application of tests, examinations or other procedures which can be applied rapidly. Screening tests sort out apparently well people who probably have a disease from those who probably do not" *(98)*.

Screening is not a single test, however – rather it represents a pathway that starts with identification of people at risk for a condition, and proceeds through testing, diagnostic confirmation, treatment and follow-up *(99)*. Effective screening programmes must ensure capacity to diagnose and treat abnormalities identified via a screening test.

In most studies, HHE has been used as a screening tool for RHD, with task-shifting to less experienced providers, simplified protocols and subsequent confirmatory echocardiography by an expert with standard, fully-functional equipment. When available, telemedicine has been extensively utilized for remote diagnosis, improving access to experts. Many of these approaches are not yet standardized,

however. The use of HHE has expanded from clinics and hospital institutions to schools, primary care and other settings, increasing its utilization for POC diagnosis, especially in low-resource settings *(100)*.

Given the high burden of RF and RHD among children and adolescents in moderate- and high-risk settings, screening for RF and RHD using HHE among school-aged children is a potentially effective approach in these settings.

Echocardiography may also play a role in screening pregnant women, identifying valvular changes consistent with RHD even when there is no known history of RF or symptoms of RHD. Pregnancy leads to major changes in the cardiovascular system, including increases in blood volume, heart rate and stroke volume, such that cardiac output increases up to 50% when compared to pre-pregnant levels. These changes can unmask previously unrecognized cardiac disease, or exacerbate clinical symptoms in women with known disease. RHD is a significant burden among pregnant women in low-resource settings *(101, 102)*: 1.5% in a Uganda study, of which only 3.4% had a prior diagnosis *(103)*. Prospective cohort studies have shown that RHD, particularly mitral stenosis, is an independent predictor of maternal and fetal outcomes, thus the identification of such cases is key in global efforts to reduce maternal mortality *(8)*.

Recommendation 1

Among children, adolescents and adults with suspected RF or RHD in settings where standard echocardiography is not available, HHE can be used for diagnosis of RF-carditis and RHD.

(Strong recommendation, very low certainty evidence for RF-carditis, moderate certainty for RHD)

Rationale

There is moderate certainty evidence that HHE can be used by trained health workers to diagnose RHD and its use has been found to be acceptable in populations where this has been studied. The cardiac morphological and functional changes seen during RF overlap those of RHD. One study demonstrated high sensitivity and specificity for HHE in diagnosing RF-carditis compared to auscultation *(104)*. Thus, the GDG concluded that test performance is likely to be similar when using HHE for the diagnosis of RF-carditis, but assessed the certainty of evidence as very low.

Remark

"Standard echocardiography" refers to either stationary or portable fully-functional echocardiography devices, in contrast to POC HHE, which refers to devices that often have limited functionality but high portability.

Recommendation 2

In populations or settings with moderate/high risk of RHD, echocardiographic screening using standard or handheld devices may be considered to improve early detection of RHD among pregnant women during antenatal care.

(Conditional recommendation, very low certainty evidence)

Rationale

RHD is recognized as a major cause of maternal morbidity and mortality and a contributor to adverse fetal outcomes. Many women who have RHD are not aware of their diagnosis, and thus optimal care cannot be provided to mitigate these risks. Additionally, the antenatal period also serves as an important point of contact with the health care system for women, and the diagnosis of RHD during pregnancy may affect future reproductive counselling and decision-making for these women. According to the available evidence, exposure to diagnostic ultrasonography during pregnancy is safe *(105)*.

Remark

"Standard echocardiography" refers to either stationary or portable fully-functional echocardiography devices, in contrast to HHE, which often has limited functionality but high portability.

Recommendation 3

In populations with moderate/high RHD prevalence, echocardiographic screening using standard echocardiography or HHE may be implemented for early detection of RHD among children and adolescents 5 to 19 years of age.

(Strong recommendation, high certainty evidence)

Rationale

As RHD commonly evolves over a period of years or decades, the school-age period and adolescence represent times when early, asymptomatic forms of RHD can be detected and patients can benefit from early intervention.

Studies show that the performance of HHE when used by non-experts and with simple criteria is acceptable for detection of RF-carditis and RHD, with 74% sensitivity and 86% specificity *(106)*.

4.6.2 Implementation considerations

1. Echocardiographic screening programmes should only be undertaken if sufficient resources are available to: i) counsel parents and caregivers as to the importance of follow-up when potential abnormalities are identified on screening; ii) properly diagnose RF/RHD after screening; and iii) provide, at a minimum, secondary antibiotic prophylaxis for patients who are found to have RF/RHD.
2. Screening programmes can rapidly increase the demand for antibiotic prophylaxis where they are employed, therefore health systems adopting screening should ensure reliable supply chains, stock, and training of health workers on indications and administration.
3. Screening programmes should use the 2023 WHF criteria *(107)* for the echocardiographic diagnosis of RHD, or local guidelines, if they exist.
4. HHE machines are a practical and more affordable option for RHD screening, but limited functionality may restrict their use for confirmatory echocardiography. However, most HHE machines now meet the requirements for screening echocardiograms listed in the 2023 WHF criteria *(107)*.
5. Each country should consider the optimal setting for screening programmes (for example, school- or community-based) to maximize uptake and case detection, and minimize resource use in their populations and settings.
6. Where resources are limited, early detection of RHD during antenatal care may be targeted at pregnant women who are mildly symptomatic (for example, with shortness of breath, palpitations, presence of a newly detected murmur) *(108)*.
7. Screening in school-based settings is an efficient approach that can maximize the number of examinations per unit of time. However, screening approaches for children and adolescents need to be customized to meet the needs of the target population, including children who are not enrolled at or not attending school, and who may be at moderate/high risk for RF/RHD.
8. Any country planning to implement echocardiographic screening should also take local context, community knowledge and stigma into consideration and proactively target strategies to reduce harm (for example, community knowledge building, culturally-sensitive counselling, etc.).
9. Any country planning to implement echocardiographic screening by health workers who are not cardiologists or trained sonographers should also invest in workforce training and competency programmes, including continuing education. Telemedicine may be used whenever possible, to improve access.
10. Capacity should be developed alongside screening programmes to provide more comprehensive echocardiographic evaluation to people who are screen-positive, and access to specialist cardiology care for those with more advanced RHD.

4.6.3 Summary of the evidence

WHO commissioned systematic reviews to examine the diagnostic accuracy of HHE and standard echocardiography as well as important outcomes from using these tests to identify people with RF-carditis or RHD *(106)*. The review identified 11 studies with 15 578 participants in total. Two studies examined the diagnostic accuracy of HHE for RHD, while eight examined the use of HHE for screening schoolchildren and adolescents for RHD. One study assessed HHE for diagnosing RF-carditis. The studies were prospective, observational studies, except for one case-control study.

All studies examined only children and adolescents, except one that included a small percentage of participants aged 18 to 25 years, and two studies that included a small number aged 18 to 20 years. All studies were set in high-risk populations, although not necessarily in countries classified as high/moderate risk.

The reference test for all studies was standard echocardiography performed by experts using the 2012 WHF criteria for diagnosing RHD *(109)*. The index test was HHE using a modified version of the 2012 WHF criteria or other simplified echocardiographic criteria. All studies used portable machines: for the index test it was the V-Scan™ device (GE HealthCare), except in one study that used the Lumify S4-1 (Philips Healthcare); and for the reference test it was either the Vivid I, I/Q or Q device (all manufactured by GE HealthCare), or the CX-50 device (Philips Healthcare).

When HHE was compared to standard echocardiography for the diagnosis of RHD, the sensitivity was 0.87 (95% CI: 0.76–0.93), specificity 0.98 (95% CI: 0.71–1.00) and AUC 0.94 (95% CI: 0.84–1.00) (two studies; moderate certainty evidence). In a sub-analysis, diagnostic performance was calculated in patients with definite RHD (AUC 0.99; 95% CI: 0.98–1.00) and in those with borderline RHD (AUC 0.92; 95% CI: 0.79–1.00).

In studies that examined HHE for RHD screening, the sensitivity of HHE in patients with any RHD was 0.79 (95% CI: 0.73–0.84) and specificity 0.85 (95% CI: 0.80–0.89) (seven studies, high certainty evidence); the corresponding AUC was 0.90 (95% CI: 0.85–0.94). In patients with definite RHD the AUC was 0.99 (95% CI: 0.75–1.00), and in those with borderline RHD was 0.88 (95% CI: 0.80–0.99). Time to perform and interpret HHE was not reported in a standard way across studies: it was inferred to be between 2 and 9 minutes for HHE.

Simplified HHE protocols (all used by non-experts) displayed good diagnostic performance for detecting any RHD (minimal or definite) compared to standard echocardiography with complete diagnostic criteria, as used by expert echocardiographers/cardiologists. The sensitivity was 0.78 (95% CI: 0.72–0.84); specificity 0.84 (95% CI: 0.79–0.88) and AUC 0.88 (95% CI: 0.85–0.92) (seven studies; high certainty evidence). The review sought data for other important outcomes including adverse events, patient and provider acceptability, prevention of complications from RHD, and death, but none were identified.

Simplified HHE protocols (all used by non-experts) also displayed good diagnostic performance for detecting any RHD (with minimal or definite echocardiographic criteria) compared to auscultation. One study compared HHE to auscultation for the diagnosis of RF-carditis and reported high specificity (0.99, 95% CI: 0.99–1.00) and low sensitivity (0.17, 95% CI: 0.09–0.28). Two studies compared auscultation to standard echocardiography for diagnosis of or screening for RHD: in one study the sensitivity for diagnosis of definite RHD was 0.09 (95% CI: 0–0.41) and specificity 0.95 (95% CI: 0.87–0.99). In the other study the sensitivity for screening for definite RHD was 0.22 (95% CI: 0.11–0.37) and the specificity 0.91 (95% CI: 0.89–0.93). Based on these findings of low performance, ausculatory screening is no longer recommended.

Pregnant women

A systematic review examined the diagnostic accuracy and outcomes of screening for RHD in the context of antenatal care in areas where there is moderate/high risk of RF/RHD *(110)*. No controlled studies were identified that compared HHE to standard echocardiography for screening for RHD among pregnant women, nor were there any studies that compared screening of pregnant women for RHD

using HHE to routine clinical care. One included study compared HHE to standard echocardiography in a subset of 36 pregnant women and reported a 78% agreement between the two tests *(111)*.

Ten uncontrolled observational studies were identified, five using portable echocardiography or HHE and five using standard echocardiography. The prevalence of RHD varied across studies, ranging from 0.5% to 6.6%. Other cardiac abnormalities (for example, congenital heart disease) were also detected in <1% to 2% of cases. In the largest study *(112)*, 0.4% of 14 275 pregnant women in India who were screened, had RHD.

4.6.4 Guideline-related research gaps

The GDG identified the following guideline-relevant research gaps:

1. Develop and test new approaches for the practical scaling up of RF/RHD screening including use of artificial intelligence for echocardiography acquisition (support for view-finding and image optimization) and interpretation *(113, 114)*.
2. Refine approaches to maximize the impact of screening, including determining the effectiveness of screening through different approaches, such as school-based or community-based approaches.
3. Develop and test models for training non-expert providers to conduct RHD screening, including asynchronous models where a non-expert sends the results to an expert for reading and interpretation of results, and telemedicine.
4. Define the diagnostic accuracy, relative risks and benefits of screening using echocardiography in subpopulations, including children, adolescents, adults and women of childbearing age, in particular focused on the prevention of RHD morbidity and mortality.
5. Examine the diagnostic accuracy and health outcomes of screening in diverse settings such as health care centres and in the community.
6. Assess the optimal periodicity or frequency of screening, and any harm that might have been experienced by individuals who were labelled correctly or incorrectly as having RF/RHD.
7. Evaluate the impact of various integrated RHD screening strategies (such as in antenatal care and in school health services) on RHD morbidity and mortality and on economic outcomes (including cost-effectiveness) in communities where these strategies are employed.

4.7 Antibiotic prophylaxis for the prevention of recurrent rheumatic fever

4.7.1 Background

Given the significant morbidity and mortality associated with recurrent RF and with RHD, preventive interventions are critical, and long-term antibiotic prophylaxis is the standard of care in most regions. Recognizing the importance of this intervention, the GDG examined its benefits and harms, as well as interventions to facilitate its implementation.

Secondary prophylaxis, defined as the "continuous administration of antibiotics to patients with a previous episode of ARF[1] [sic] or already existing RHD" *(115)*, is essential to prevent both the recurrence of RF and its progression to RHD *(116–118)*. IM benzathine benzylpenicillin, or BPG, administered once every 4 weeks, has been demonstrated to be the most effective antibiotic for this purpose and is superior to oral prophylaxis *(117, 119)*.

Severe allergic reactions following administration of penicillin (either oral or IM) are an important consideration with long-term antibiotic prophylaxis. Such reactions include anaphylaxis, angioedema, Stevens-Johnson syndrome and toxic epidermal necrolysis. Severe reactions are infrequent, however. A large-scale prospective study carried out in 1991 by the International Rheumatic Fever Study Group *(120)* with 2736 patient-years, reported allergic reactions to BPG in 3.2% of administrations, with anaphylaxis estimated at 0.2%. The frequency of anaphylactic reactions was calculated at 1.23 per 10 000 injections in a systematic review of pregnant women receiving BPG for prevention of congenital

[1] Acute rheumatic fever.

syphilis *(121)*. A review of patients receiving BPG for RHD prophylaxis reported an overall rate of allergic reactions of 2%, and anaphylactic reactions and fatalities of 0.27% *(122)*. Of 400 children who received BPG in the treatment arm of an RCT in Uganda *(116)*, one had an episode of anaphylaxis and eight a delayed hypersensitivity rash.

Nonetheless, physicians' fear of anaphylaxis has been reported to be one of the major reasons for discontinuation of BPG prophylaxis *(123)*. For example, in some states in India, concerns about adverse reactions have led to the banning of IM BPG *(124)*, and in Israel BPG has been withdrawn and physicians advised to use alternatives *(125)*.

While anaphylaxis and other severe allergic reactions are rare, 5–15% of patients in high-income countries self-report a penicillin allergy *(126)*. However, more than 95% of these patients do not have a true immunologically-mediated allergy and it is very likely that they can tolerate the antibiotic if re-exposed or challenged *(61, 127)*. The GDG therefore examined human research evidence on the frequency of reported and documented penicillin allergy and the potential benefits and harms of testing for allergy.

In addition to allergic reactions, other adverse events associated with IM BPG have been reported, including rash, serum sickness and localized reactions at the injection site such as swelling and severe pain *(122, 128, 129)*. Pain related to IM injection of BPG may limit treatment adherence, particularly in children. There are also data to suggest that patients with severe RHD may be at increased risk of vasovagal reactions in response to the administration of IM BPG, even leading to cardiovascular compromise and death *(122, 129)*. These events may be difficult to distinguish from anaphylaxis, creating additional fear of significant adverse events among health workers, patients and families.

Adherence to secondary prophylaxis regimes thus remains a significant challenge to programmes for the management and control of RF/RHD *(119, 130, 131)*. Data suggest that high rates of adherence (>80% of scheduled injections) are associated with reduced mortality from RHD *(132)*. Adherence to BPG injections prescribed as secondary prophylaxis for RF and RHD is associated with access to health care services; reminder systems; BPG supply; health care staff competence; patient demographic factors including age and number of people per household; interactions among patients, health care staff and health services; and the frequency of IM injections and the duration of secondary prophylaxis *(131)*. Interventions aimed at optimizing adherence to secondary prophylaxis for RHD can focus on one or more aspects related to the health system, social interactions, patient and provider behaviours, injection pain, and the education and training of health workers and patients *(119, 130)*.

While once-per-month administration of IM BPG provides advantages for long-term secondary prophylaxis *(133)*, interventions to optimize long-term adherence are needed. The GDG thus focused on two interventions to address long-term adherence: local anaesthetics to potentially reduce pain from IM BPG injections, and public education regarding RF and RHD prevention.

4.7.2 Recommendations

WHO makes the following recommendations regarding long-term antibiotic prophylaxis for the prevention of recurrent RF and the prevention of RHD or its worsening.

Recommendation 1

Children, adolescents and adults diagnosed with RF or RHD should be prescribed antibiotic prophylaxis to prevent RF recurrence.

(Strong recommendation, moderate certainty evidence)

Rationale

The available evidence consistently shows that patients who receive antibiotic prophylaxis after an episode of RF are less likely to have a recurrent episode of RF than those who do not receive prophylaxis. Additionally, the GDG considered that decreasing recurrent RF is an important factor in reducing the severity and progression of RHD *(116, 132, 134)*.

Recommendation 2

Antibiotic prophylaxis should be prescribed for children and adolescents found to meet the minimum criteria for RHD on echocardiographic screening to prevent disease progression.

(Strong recommendation, moderate certainty evidence)

Antibiotic prophylaxis may be prescribed for adults 20 years of age and older found to meet the minimum criteria for RHD on echocardiographic screening.

(Conditional recommendation, very low certainty)

Rationale

Evidence shows that children and adolescents who meet the minimum echocardiographic criteria on echocardiographic screening without other manifestations according to the Jones criteria *(17)* benefit from antibiotic prophylaxis to prevent RF and progression of RHD *(135)*. One recent high-quality RCT reported a reduction in risk of RHD progression among children with preclinical RHD detected through echocardiographic screening who were prescribed IM BPG every 28 days for antibiotic prophylaxis compared to those who were not prescribed prophylaxis *(116)*.

For adults, the evidence was of very low certainty, therefore WHO issues a conditional recommendation for this age group. Data suggest that secondary antibiotic prophylaxis may not be as effective in adults as in children and adolescents. Thus, for adults meeting the echocardiographic criteria for RHD, the decision whether to start antibiotic prophylaxis should be made after a discussion between the provider and the patient, weighing the risks and benefits.

Remarks

Echocardiographic screening can detect early signs of RHD and is a gateway to its rapid diagnosis. The 2023 WHF guidelines for the echocardiographic diagnosis of RHD provide guidance on diagnostic criteria and staging *(107)*.

Recommendation 3

Antibiotic prophylaxis should be given to children and adolescents who have advanced RHD to prevent RF recurrence.

(Strong recommendation, very low certainty evidence)

Antibiotic prophylaxis can be given to adults 20 years of age and older who have advanced RHD to prevent RF recurrence based on shared decision-making between the patient and treating health care provider.

(Conditional recommendation, very low certainty evidence)

Rationale

Although there are very few high-quality studies supporting the use of antibiotic prophylaxis in preventing mortality or cardiac complications in advanced RHD, recurrent RF is strongly associated with worsening RHD. Affected patients are at high risk of clinical complications that require medical or surgical interventions that are often not available in many RHD-endemic settings. Thus avoiding recurrent RF is a priority.

Adults have a lower risk of GAS and are likely to be further from their primary episode of RF. Consequently, the risk–benefit assessment may be different from that in children and adolescents. Decisions regarding antibiotic prophylaxis should thus be made through shared decision-making between the adult patient and their health care provider.

Recommendation 4

IM BPG is the preferred first-line approach to prevent recurrence of RF in patients with prior RF or RHD.

(Strong recommendation, moderate certainty evidence)

Rationale

A limited number of studies report fewer RF recurrences among patients who receive IM BPG prophylaxis compared to oral penicillin (moderate certainty evidence). The GDG also considered additional factors in their decision, including a higher likelihood of adherence to IM BPG, low rates of serious adverse events, and the current greater global availability and lower cost of IM BPG compared to oral penicillin.

Recommendation 5

If an alternative to IM BPG is needed (Recommendation 4), oral penicillin is acceptable for RF and RHD prophylaxis.

(Conditional recommendation, moderate certainty evidence)

Rationale

Multiple studies comparing oral penicillin to no prophylaxis show fewer RF recurrences among patients who receive oral prophylaxis (moderate certainty of evidence). Additionally, the GDG considered that in situations where there are patient or provider barriers to the provision of IM BPG, oral penicillin is more effective than no prophylaxis.

Good practice statement

Penicillin allergy testing should not be used in patients who have no history of penicillin allergy and who are prescribed IM BPG for secondary prevention of RHD.

Rationale

A single, negative penicillin allergy test may lead to a false sense of security for patients and health workers. Although rare, allergic reactions, including anaphylaxis, can occur at any time. *The WHO AWaRe (Access, Watch, Reserve) antibiotic book (61)* also recommends against routine skin testing before prescribing a beta-lactam antibiotic (for example, penicillin and amoxicillin) in children or adults.

Recommendation 6

An oral penicillin test dose may be given prior to IM BPG administration for patients who have a history of mild penicillin allergy, that is in patients without a prior history of anaphylaxis, angioedema, Steven-Johnson's syndrome or toxic epidermal necrolysis.

(Conditional recommendation, low certainty evidence for immediate allergy and anaphylaxis; very low for delayed allergy)

Rationale

Penicillin prophylaxis is superior to alternative antibiotic prophylaxis in terms of effectiveness and from an antibiotic stewardship perspective. Therefore it is important to avoid unnecessarily excluding patients from receiving penicillin prophylaxis, as overdiagnosis of penicillin allergy is common. No data were identified on the diagnostic performance of allergy testing or its impact on complication rates in the context of RF/RHD prophylaxis. A systematic review *(136)* of the diagnostic accuracy of penicillin allergy testing among patients reporting a penicillin/beta-lactam allergy noted high specificity and negative predictive value (NPV), but low sensitivity for both skin testing and immunoglobulin E (IgE) quantification. There is also low certainty evidence that oral testing has a lower risk of minor allergic reactions than skin testing.

Recommendation 7

A local anaesthetic may be added to the injectable solution to reduce injection pain in patients who receive IM BPG for secondary prevention of RHD.

(Conditional recommendation, low certainty evidence)

Rationale

Adherence to secondary prophylaxis improves outcomes for patients with RHD. A low-quality study suggests that patients accept and prefer to use pain reduction techniques. Low certainty evidence indicates that adding lidocaine to the injectable solution reduces pain immediately post-injection, with no harms reported and no change in serum penicillin concentrations.

Recommendation 8

Patients who are prescribed antibiotics for secondary prophylaxis of RF or RHD should be supported to improve treatment adherence.

(Strong recommendation, low certainty evidence)

Rationale

There is low certainty evidence that patients who feel more supported have better adherence to long-term antibiotic prophylaxis. Quantitative and qualitative evidence suggest that many different types of patient support interventions (nurse-led interventions, appointment reminders, recall/reminder systems, improved access to clinics, support from peers) may improve adherence to secondary prophylaxis. Despite the low certainty of the body of evidence on benefits, the GDG felt that patients should receive support, given the benefits of secondary prophylaxis for RF/RHD and the low risk of harms from such interventions.

Remark

The choice of alternative antibiotics for those with confirmed penicillin allergy should consider resistance patterns in the setting. Macrolide antibiotics (erythromycin, roxithromycin, azithromycin and clarithromycin) are favoured alternatives in people with adverse reactions to beta-lactams due to their tolerability and dosing regimen. Thus, if most *S. pyogenes* isolates remain susceptible, macrolides are an acceptable second-line option *(137)*.

4.7.3 Implementation considerations

The GDG formulated a number of considerations for end-users when implementing WHO's recommendation on long-term antibiotic prophylaxis for prevention of recurrent RF or progression of RHD.

Long-term antibiotic prophylaxis: education and training

1. There is limited evidence to guide decisions on duration of therapy. For the present time, programme managers and health workers should follow their national and professional society guidelines or refer to documentation made available by global authoritative bodies such as the WHF.
2. Improved health worker education is needed on:
    - the signs, symptoms and consequences of RF. This may lead to increased case detection with subsequent provision of appropriate care to patients;
    - the availability and safety of antibiotic prophylaxis to prevent progression of RHD and the importance of adherence to long-term prophylaxis;
    - the low risk of adverse side-effects from secondary RF prophylaxis;
    - optimal administration of IM penicillin, including the use of techniques to distract the client or minimize pain;
    - the low risk of serious side-effects related to IM penicillin; and
    - the recognition and care of patients who have an allergic reaction, including anaphylaxis.

3. Improved community education is needed about the signs, symptoms and consequences of RF. This may lead to increased case presentation.
    — Optimal strategies for education may vary by location and should be designed in consultation with patients and the community. They can be informed by past experiences of using educational strategies for other health-related conditions.
4. Patient and caregiver education is needed on:
    — the rarity and manageability of penicillin allergy; and
    — options for pain reduction with IM penicillin.

The WHO AWaRe (Access, Watch, Reserve) antibiotic book (61) provides additional information on allergies to antibiotics, and on antibiotic stewardship.

Long-term antibiotic prophylaxis: health system organization and optimization

1. Governments and concerned stakeholders should work with manufacturers to ensure continuous availability of quality-assured BPG at community and primary care levels in affected countries.
2. Managers at health care centres should ensure that appropriate antibiotics are available, together with supplies for treating adverse drug reactions including anaphylaxis.
3. Health system strengthening, including tracing individuals who do not adhere to prophylaxis regimens may be needed to deliver antibiotic prophylaxis at scale to a large number of children and adolescents.
4. Health workers should take a careful history of allergic reactions to drugs including penicillin when planning treatment and management.
5. Emergency kits for treating anaphylaxis should be available in all settings where IM BPG is administered.
6. Technical capacity for RF diagnosis in health care centres needs to be augmented, including, for example, laboratory testing, electrocardiography and echocardiography.
7. Registries of secondary prophylaxis for RF and RHD should be implemented, maintained and evaluated. Registry-based care may provide a strategy for organizing patient-level support, and providing critical data on health system performance and on the benefits and harms of prophylaxis in specific populations.

Long-term antibiotic prophylaxis: patient and drug selection

1. The staging of RHD detected by echocardiography was updated by the WHF in 2023 *(107)* and provides criteria for stages A–D ranging from mild (stages A/B) to advanced (stages C/D) RHD.
2. In adults, decisions regarding antibiotic prophylaxis should be made jointly by the patient and their health care provider. The relevant issues include weighing the risk of acquiring GAS infection (for example, due to regular exposure to or care of children), time since last RF episode (the highest risk of recurrence is in the first year after RF), the number of RF recurrences (a higher number of recurrences correlates with a higher risk of another recurrence), and the availability of advanced care and surgery should the patient have a RF recurrence with acute worsening of heart valve disease.
3. Oral penicillin may be prescribed as an alternative when IM penicillin delivery is not optimal or possible for individual patients. This includes, for example, patients with severe RHD who have multiple comorbidities, those who experience severe injection pain leading to discontinuation of prophylaxis, and individuals who have difficulty accessing health care facilities.
4. Oral penicillin is appropriate when there is a strong patient preference for oral as compared to IM prophylaxis.

5. Prophylaxis with oral penicillin is also appropriate when the health system is not able to deliver IM penicillin (for example, owing to problems with drug supply or inadequate health worker training) or to respond to possible adverse events with IM delivery.
6. Oral penicillin is appropriate in situations where the risk of recurrent RF is considered low (for example, patient is 40 years of age or older), but this decision should be made jointly by the patient and their health workers.
7. Oral penicillin may be considered when a patient has severe valvular heart disease, in particular severe mitral or aortic stenosis or decreased left ventricular systolic function, as there is concern that these patients may experience sudden fatal, cardiac events related to IM injection *(129)*.
8. Given that a high proportion of patients with isolated mild aortic regurgitation or isolated mild mitral regurgitation will show regression of echocardiographic findings *(116)*, it may be reasonable to discontinue antibiotic prophylaxis in children with normal echocardiography after 1 to 2 years.

4.7.4 Guideline-related research gaps

The GDG identified a number of guideline-related research gaps concerning long-term antibiotic prophylaxis, including:

1. Examine the benefits and harms of secondary antibiotic prophylaxis, particularly the effect on RHD onset and progression among subpopulations (for example, adults, children, disease severity groups, clinical- versus screening-detected disease). This will inform future recommendations about dosing and duration of prophylaxis for these subgroups.
2. Develop and test new antibiotic formulations and approaches to delivery to improve acceptability and feasibility of continuous antibiotic prophylaxis to prevent RHD progression, morbidity and mortality. This includes testing of modern oral penicillin preparations (phenoxymethylpenicillin (Pen v™)) as compared to IM BPG.
3. Develop and test new strategies to support patients, families and health workers to ensure optimal adherence to secondary antibiotic prophylaxis including approaches such as mobile and digital health tools and peer-to-peer support.
4. Conduct high-quality studies to further our understanding of adverse events related to IM BPG, identify groups with the highest risk, and develop and test mitigation strategies to reduce these risks.
5. Assess the benefits and harms of penicillin allergy testing, and seek answers to the following questions:
   - Does allergy testing help prevent anaphylaxis and/or deaths?
   - Should all patients be tested for penicillin allergy or only those at high risk of severe adverse events?
   - Is skin testing the best option?
   - What is the cost-effectiveness of penicillin allergy testing? Does it differ for specific subpopulations?
6. Further examine the risk factors for RHD and RHD progression, including identification of patients who are most likely to benefit from secondary antibiotic prophylaxis considering sociodemographic, clinical and especially echocardiographic variables.

4.7.5 Summary of the evidence

Long-term antibiotic prophylaxis

Several systematic reviews were commissioned to inform the set of recommendations on long-term antibiotic prophylaxis for the prevention of recurrent RF and of RHD. One systematic review *(135)* identified 11 studies (4104 participants; 8 RCTs and 3 quasi-randomized studies) that provided evidence on the benefits and harms of long-term antibiotic treatment for secondary prevention of RF

recurrence (and progression to RHD). Seven studies were performed in the outpatient setting, two in an inpatient or dedicated convalescent home setting and one in schools. Nine studies were in high-income countries. Most studies focused on children (<18 or 19 years of age). One study included only patients with early or echo-detected RHD *(116)*; two others reported approximately 50% of participants with RHD.

Much of the evidence identified is historical, from studies published over 50 years ago. These studies had poorly defined populations, diagnoses were made in the absence of echocardiography, the distribution of disease severity in participants was unknown and randomization was problematic. The majority of included studies were assessed as having high risk of bias.

Pooled analysis of six trials demonstrated that antibiotic prophylaxis (oral or IM) was superior to no antibiotics in reducing the risk of recurrence of RF (RR 0.39, 95% CI 0.22–0.69, 6 studies, 1721 participants, moderate certainty evidence). Similarly, five trials compared oral antibiotics to no antibiotic, and pooled analysis showed that antibiotics are likely to reduce the risk of recurrence of RF (RR 0.32, 95% CI: 0.13–0.79, 5 studies, 727 participants, moderate certainty evidence).

Compared to no antibiotic prophylaxis, IM BPG reduced the risk of progression of RHD in individuals with early RHD *(116)*, but there was no evidence that this can be achieved in late-stage RHD *(138)*. Antibiotics (oral or IM) did not decrease all-cause mortality. Rates of delayed hypersensitivity or allergic reaction, and of local reactions to injection were significantly higher than in controls (P<0.05). Rates of anaphylaxis and adverse events were elevated with antibiotic treatment compared to no treatment, however, confidence intervals were wide and crossed the null value (1.0).

Four trials compared IM to oral administration of antibiotic prophylaxis: the pooled analysis showed that IM BPG is likely to reduce the risk of recurrence of RF by approximately 90% when compared to oral antibiotics in count data (RR 0.07, 95% CI: 0.02–0.26, 2 studies, 395 participants, low certainty evidence) and rate data (rate ratio 0.12, 95% CI: 0.04–0.33, 769 participants, moderate certainty evidence). When used in a clinic setting IM BPG can reduce the risk of poor adherence when compared to oral administration (RR 0.1, 95% CI 0.06–0.22, 2 trials, 577 participants, low certainty evidence). The available evidence did not demonstrate a statistically significant reduction in all-cause mortality between the two modes of administration, however.

There was evidence that children and adolescents are more likely to refuse IM antibiotics than oral alternatives. The included studies did not report rates of anaphylaxis, obstetric complications, diarrhoea or vomiting. Compared to oral penicillin, IM BPG was associated with local reactions to injection in approximately 10% of included participants *(139)*. One study demonstrated extremely low rates of true penicillin allergy among 535 children receiving IM penicillin *(140)*.

Data on the optimal frequency of antibiotic administration varied across studies. A systematic review suggested that IM penicillin administered every 2 weeks may lead to reduced RF recurrence (RR 0.52, 95% CI: 0.33–0.83) and fewer GAS throat infections (RR 0.60, 95% CI: 0.42–0.85) than 4-weekly injections, although this is based on only one study *(117)*. Evidence from another included study suggested that 3-weekly IM penicillin injections reduced GAS throat infections (RR 0.67, 95% CI: 0.48–0.92) compared to 4-weekly IM penicillin *(141)*. A more recent study suggests that weekly administration may be optimal *(142)*. The optimal duration of long-term antibiotic prophylaxis is unclear as follow-up periods varied across studies from 8 months to 6 years.

Prevalence of penicillin allergy

The GDG examined recent reviews of the incidence of severe allergic reactions to penicillin. A review *(122)* of allergic reactions following BPG administration for RHD prophylaxis where most of the patients had moderate-to-severe RHD and heart failure reported a rate of anaphylaxis of 0.27% (95% CI: 0.16–0.41%) and a death rate of 0.13% (95% CI: 0.06–0.24%).

A meta-analysis of 112 primary studies *(143)* and 26 595 participants with a penicillin allergy label who underwent drug provocation testing reported a pooled frequency of severe reactions of 0.06% (95% credible interval (CrI): 0.0–0.13%; I2 57.9%). Eighty-six per cent of the 93 observed severe reactions were anaphylaxis (0.03%, 95% CrI: 0–0.04%; I2 44.2%). No patients had a subsequent fatal reaction.

Another systematic review *(144)* examined the prevalence of immediate adverse reactions to beta-lactam antibiotics, particularly penicillin derivatives, in patients scheduled for skin testing or oral challenge. These authors reported a higher prevalence of immediate allergic reactions among adults (7.78%, 95% CI: 6.53–9.04%) than children 1.98% (95% CI: 1.35–2.60%).

Penicillin allergy testing

A systematic review *(136)* of the diagnostic accuracy of penicillin allergy testing among patients reporting a penicillin/beta-lactam allergy included a meta-analysis of 20 studies on skin testing and a meta-analysis of 11 studies on specific IgE quantification. In both meta-analyses the reference standard was drug challenge among patients reporting a penicillin/beta-lactam allergy. However, this review excluded studies in patients with specific diseases, including RF.

Both tests had high specificity and NPV but low sensitivity. The specificity of skin tests was 96.8% (95% CI: 94.2–98.3%) and the sensitivity was 30.7% (95% CI: 18.9–45.9%) with moderate discriminative capacity (AUC/c-statistic 0.686; 20 studies). The specificity of specific IgE quantification was 97.4% (95% CI: 95.2–98.6%) and the sensitivity 19.3% (95% CI: 12.0–29.4%) with low discriminative capacity (AUC/c-statistic 0.420; 11 studies) *(136)*.

The commissioned systematic review addressed the safety of direct oral drug challenge versus skin testing followed by drug administration in patients with suspected penicillin allergy *(145)*. Immediate allergic reactions of minor severity were observed in a minority of patients and occurred less frequently with direct oral drug challenge: 2.3% versus 11.5% (RR=0.25, 95% CI: 0.15–0.45, 5 studies; low certainty evidence). No cases of anaphylaxis or deaths were observed in the included studies.

In the setting of secondary prophylaxis of RF, no data were identified on the diagnostic performance of allergy testing or the effectiveness of allergy testing in reducing complication rates.

Local anaesthetic injection for pain relief

The commissioned systematic review *(146)* identified three cross-over RCTs and one qualitative study, all from communities with moderate/high prevalence of RF/RHD. The three RCTs compared the effect on injection pain of administering BPG diluted with lidocaine hydrochloride 1% to BPG diluted with sterile water for the delivery of secondary prophylaxis in 117 children and young people (ages 10 to 19 years) with RF and/or RHD. This review suggested that there is an improvement in pain sensation immediately post-injection with BPG diluted with lidocaine compared to sterile water (standardized mean difference (SMD) −1.57, 95% CI: −2.25 to −0.90, low certainty evidence). However, there was no significant difference in pain score at 2 to 4 hours post-injection (very low certainty evidence). No adverse events were reported.

A qualitative study explored the experiences, acceptability, barriers and facilitators of injection pain among 29 Aboriginal children and young people in Australia with RF receiving monthly injections of IM BPG together with 59 health workers' experiences administering such injections *(147)*. Data were collected using observations in addition to semi-structured or unstructured interviews, with thematic analysis of responses. Some patients felt that they were now "used to" the pain or that they did not find it painful any more. Most patients stated that the injection pain was difficult to bear and this was a significant barrier to their adherence to the prescribed treatment.

Most health workers agreed with the experiences described by their patients, expressing degrees of sorrow about the injections and reluctance to administer them. Some patients showed ability to negotiate injection pain with clinicians, such as accepting an offer of local anaesthetic, while some other patients demonstrated either lack of ability or opportunity to negotiate. Most health workers faced challenges and uncertainty about determining patients' preferences for pain control measures. Many patients found it difficult to comprehend and accept pain reduction measures as they were not consistently offered (including local anaesthetics mixed with the injection, oral paracetamol, the application of cold externally, warming the injectable solution, among others). All outcomes of this study were assessed as very low certainty evidence.

Interventions to improve treatment adherence

A commissioned systematic review *(148)* examined a broad range of interventions aimed at promoting adherence to antibiotic prophylaxis for RF and RHD, including patient support groups, psycho-educational interventions, communication/integration with health and social care professionals, registry-based care, care and support plans, case management, follow-up support and multi-component interventions. These interventions were compared to either no intervention or to a different intervention.

This systematic review *(148)* identified eight studies: one RCT, two cross-sectional studies and five qualitative studies. The included RCT *(149)* compared a nurse-led intervention (one-to-one teaching of patients, doubt clarification, and reminder calls and text messages from health workers to receive their BPG injections) to usual care (regular work-up, treatment prescriptions and an educational pamphlet) in patients who were prescribed secondary antibiotic prophylaxis for RHD. The nurse-led intervention improved treatment adherence (number of prescribed BPG injections) and reduced the frequency of RHD symptoms. However, this study was small and had very serious limitations.

No data were identified on morbidity, mortality or acceptability of interventions to providers or patients, or on adverse events. No studies were identified that examined psycho-educational interventions (for example, skills building, self-help, self-management/coping skills support), registry-based care or multicomponent interventions.

In one of the included studies, several factors were associated with poor adherence to secondary prophylaxis, defined as receipt of <80% of the annual prescribed BPG injections *(150)*: patient residence in rural settings (adjusted odds ratio (aOR) 6.8, 95% CI: 1.9–24.4); no or mild RHD symptoms (New York Heart Association (NYHA) classification of heart failure I or II) (aOR 12.6, 95% CI: 2.5–63.0); patient residing >30 km from the health facility (aOR 5.5, 95% CI: 1.2–26.7); and being on antibiotic prophylaxis for more than 5 years (aOR 1.2, 95% CI: 1.1–3.2).

Another included study *(133)* reported an association between patient adherence to secondary antibiotic prophylaxis for RF or RHD (defined as receiving >80% of the annual prescribed BPG injections) and absence of prior hospital admissions (aOR 26.2, 95% CI: 2.6–269.7) and a single prior hospital admission (aOR 50.1, 95% CI: 2.9–873.8).

The main findings of the five qualitative studies included in the systematic review were:

1. In patients who were prescribed secondary prophylaxis for RHD, lack of support from peers led to intermittent or non-adherence.
2. Reminder and recall systems were considered important for adherence.
3. Poor availability of experienced health workers was a barrier to adherence, while establishing relationships between health workers and patients led to improved uptake of long-term antibiotic prophylaxis.
4. A shared understanding of individual roles (health workers, patients, relatives, peer supporters) enabled treatment adherence.
5. Poor access to health clinics was a barrier to adherence; availability of alternative modalities to access treatment improved adherence.

4.8 Anti-inflammatory agents for the treatment of rheumatic fever

4.8.1 Background

RF is an inflammatory condition caused by an autoimmune mechanism whereby autoantibodies and T cells react against streptococcal cell wall components and, through molecular mimicry, human antigens *(74)*. This immune-mediated insult can affect the heart (carditis), the main joints (arthritis), and sometimes the brain, skin or subcutaneous tissues *(151)*. RHD refers to the chronic structural and functional changes in the myocardium and valves due to RF-induced inflammation and scarring *(117)*. Given that RF and RHD are the result of both infection and inflammation, anti-inflammatory agents, in

addition to antibiotic treatment, have been used for treatment of RF. They include corticosteroids (for example, prednisone), non-steroid anti-inflammatory drugs (NSAIDs) such as aspirin, and intravenous immunoglobulin (IVIG) *(152)*.

4.8.2 Recommendation

The GDG reviewed the evidence on the benefits and harms of anti-inflammatory agents for the treatment of RF to prevent the development of RHD.

No recommendation

The GDG was unable to formulate a recommendation. Thus, WHO does not recommend either for or against the use of anti-inflammatory agents for children, adolescents and adults diagnosed with RF to prevent the progression to RHD. These agents include aspirin, NSAIDs, IVIG and corticosteroids.

Rationale

It is currently unknown whether the addition of anti-inflammatory agents to antibiotics is beneficial in children, adolescents and adults diagnosed with RF with regard to progression to RHD, or severity of carditis or valvular lesions. Based on low and very low certainty evidence, aspirin, NSAIDs, IVIG and corticosteroids were neither more beneficial nor more harmful than placebo in children, adolescents and adults diagnosed with RF.

One RCT reported that prednisone may be more harmful than placebo for the outcome of progression to RHD, however, both CIs overlapped the null value of 1.0 (very low certainty evidence). One study suggested that hydrocortisone may reduce progression to RHD compared to aspirin (low certainty evidence). The GDG noted that there was uncertainty regarding the definition of progression to RHD used in the included studies and long-term follow-up was lacking.

The GDG acknowledged that corticosteroids may improve general symptoms of RF *(17, 153)*. However, they also considered the potential adverse effects of anti-inflammatory agents in their deliberations. Naproxen is associated with liver toxicity *(154)* and corticosteroids are known to have many adverse side-effects *(155)*.

The GDG thus determined that the body of evidence did not support a recommendation either for or against the use of corticosteroids, NSAIDs or IVIG in any age group to treat RF and prevent the progression to RHD.

4.8.3 Implementation considerations

In global practice today, corticosteroids are commonly given as adjunct therapy in patients who present with moderate or severe carditis in the context of RF. However, more data are needed to support this practice as outlined below. For resolution of symptoms (for example, joint pain), health workers may use their discretion according to applicable guidelines and local practice. However, there are insufficient data to recommend corticosteroids for prevention of RHD or its progression.

4.8.4 Guideline-related research gaps

The GDG identified a number of guideline-related research gaps concerning long-term anti-inflammatory agents including:

1. Conduct high-quality, adequately powered, RCTs using existing anti-inflammatory and immunomodulatory medications that are promising candidate drugs for patients with RF or RHD.
2. Discover and validate diagnostic and prognostic biomarkers of RF and RHD for the purpose of improving diagnostic testing and identifying novel mechanisms of the disease and new therapeutic targets.

4.8.5 Summary of the evidence

The commissioned review included 10 RCTs (1243 participants in total) examining the benefits and harms of anti-inflammatory agents for RF or RHD *(156)*. Interventions included prednisone (five RCTs), cortisone (three), hydrocortisone (two), methylprednisolone (one), dexamethasone (one), corticotropin (one), aspirin (seven), naproxen (one), and IVIG (one). Most studies were from the USA; two studies were performed in high-prevalence countries (Brazil and South Africa).

Comparisons with statistically significant results ($P<0.05$) included a small RCT reporting clinical improvement in NYHA functional class and left ventricular ejection fraction, and reduction of left ventricular end-systolic dimension with oral prednisone compared to intravenous methylprednisolone (all outcomes low certainty evidence). One study suggested that hydrocortisone may reduce progression to RHD compared to aspirin (RR 0.43, 95% CI: 0.19–0.97, low certainty evidence).

An RCT reported that prednisone may be more harmful than placebo for the outcome of progression to RHD (RR 1.68, 95% CI: 0.91–3.12, very low certainty evidence) and mortality (RR 0.84, 95% CI: 0.06–12.42, very low certainty evidence).

5. Monitoring and evaluation

Monitoring and evaluation will be built into the dissemination and implementation process to provide data and information on uptake, implementation and impact of this guideline. In collaboration with the monitoring and evaluation team of the WHO Department of Maternal, Newborn, Child and Adolescent Health and Ageing, the data on country- and regional-level adoption of the recommendations will be monitored and evaluated in the short-to-medium term in WHO Member States, through the WHO sexual, reproductive, maternal, newborn, child and adolescent health (SRMNCAH) policy survey *(157)*. This survey is conducted every 4 years.

6. Dissemination, adaptation and updating

As this is a global guideline, Member States are expected to adapt the recommendations to their setting, taking into account feasibility, resource availability and other considerations at the national and subnational level. WHO regional and country offices can assist with the adaptation processes.

When planning to implement the recommendations in this guideline, Member States and other end-users need to ensure that the necessary policies, regulations, infrastructure and personnel are in place. This is necessary in order to provide accessible, high-quality health services for primary and secondary prevention of RF and RHD, including timely and appropriate identification and treatment of suspected or confirmed GAS pharyngitis and skin infections. In addition, there are a number of important considerations for end-users as they implement these recommendations.

The WHO Secretariat for this guideline will continue to follow developments in the research on prevention, diagnosis and management of RF and RHD, particularly for questions for which the certainty of evidence was found to be low or very low. If new evidence emerges or other important considerations arise that may impact the current recommendations, the Department of Maternal, Newborn, Child and Adolescent Health and Ageing will coordinate an update of this guideline, following the procedures outlined in the WHO handbook for guideline development (2nd edition) *(19)*.

Unless new evidence necessitates an earlier review, at 5 years from publication of this guideline, the Department of Maternal, Newborn, Child and Adolescent Health and Ageing at the WHO headquarters in Geneva, Switzerland, together with its internal partners, will conduct systematic reviews of the relevant evidence and appraise the need for updating or revalidating the current guideline. WHO will seek stakeholder input on the scope of the updated guideline, as new interventions and considerations emerge.

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Annex 1.

Guideline contributors

The following individuals contributed to development of the *WHO guideline on the prevention and diagnosis of rheumatic fever and rheumatic heart disease*. Persons who contributed to the WHO guideline did so in an individual capacity: they do not represent any Member State or government, or any organization or entity with which they may be affiliated.

WHO seeks to ensure that all contributors to its guidelines are free of any interests that might conflict with Member States' interests. The WHO Steering Group and the Director of the WHO Department of Maternal, Child and Adolescent Health and Ageing assessed declarations of interests, curricula vitae and other information from all potential contributors and determined that there were no conflicts of interest among these individuals prior to issuing invitations for involvement. Interests were reassessed throughout the guideline development process in order to identify any changes in interests that needed reassessment for conflicts of interest.

Table A1.1 Members of the Guideline Development Group

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F, female; M, male.

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AFR, African Region; AMR, Region of the Americas; EMR, Eastern Mediterranean Region; EUR, European Region; F, female; M, male; SEA, South-East Asia Region; WPR, Western Pacific Region.

[a] Participated in the first meeting of the Guideline Development Group as a member, but was unable to participate in subsequent meetings to review the evidence and develop the recommendations.

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