Review

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Detection and management of latent rheumatic heart disease: a narrative review

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Abstract

Rheumatic heart disease (RHD) is a public health concern in many developing nations around the world. Early detection of latent or subclinical RHD can help in reversing mild lesions, retarding disease progression, reducing morbidity and mortality, and improving the quality of life of patients. Echocardiography is the gold-standard method for screening and confirming latent RHD cases. The rates and determinants of progression of latent RHD cases as assessed by echocardiography have been found to be variable through studies. Even though latent RHD has a slow rate of progression, the rate of progression of its subtype, 'definite' RHD, is substantial. A brief training of nonexpert operators on the use of handheld echocardiography with a simplified protocol is an important strategy to scale up the screening program to detect latent cases. Newer advancements in screening, such as deep-learning digital stethoscopes and telehealth services, have provided an opportunity to expand screening programs even in resource-constrained settings. Newer studies have established the efficacy and safety profile of secondary antibiotic prophylaxis in latent RHD. The concerned authorities in endemic regions of the world should work on improving the availability and accessibility of antibiotic prophylaxis.

Keywords: disease screening, echocardiography, rheumatic heart disease, secondary prophylaxis

Introduction

Rheumatic heart disease (RHD) is a chronic sequela resulting from multiple episodes of acute rheumatic fever (ARF) at a young age, leading to progressive valve damage and potential heart failure. RHD is a chief cause of morbidity and mortality in developing countries in sub-Saharan Africa and South Asia. The incidence of RHD has dropped significantly in high-income nations due to improvements in hygiene and sanitation, living conditions, and access to quality medical care. However, RHD remains a significant public health problem in low-income and middle-income countries, and it affects an estimated 33 million people worldwide[1,2].

HIGHLIGHTS

- Echocardiographic screening is the gold-standard of diagnosis of latent rheumatic heart disease.
- The rates of progression and regression of latent disease along with its determinants are variable.
- The use of handheld echocardiography with a simplified protocol by nonexpert operators is an important strategy to scale up the screening program.
- Secondary antibiotic prophylaxis has a proven efficacy on retarding the progression of latent rheumatic heart disease.

Early detection of RHD is critical for reversing mild lesions, preventing disease progression, reducing the morbidity and mortality, and improving quality of life[3,4]. However, early detection continues to be challenging because RHD is often asymptomatic in its early stages. Latent RHD or subclinical RHD is defined as a case with echocardiographic evidence of RHD in an asymptomatic person discovered during echocardiographic screening[5]. The prevalence of latent RHD has been reported to be five to ten times higher than clinical RHD[6,7]. The significant burden of latent disease, particularly observed in young populations aged 5–16 years, can pose a significant hurdle to the socioeconomic progress of developing nations[1,8]. Even though most cases of latent RHD are mild, studies have shown that about two-thirds of children with latent definite RHD could already have significant valvular abnormalities, mostly affecting the mitral valve (MV) and aortic valves (AV)[9]. The severity of these valvular abnormalities in RHD is an independent predictor of

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disease progression, and adverse outcomes such as death and heart failure[10].

Recent technological advances in echocardiography and other diagnostic modalities, the development of novel and modified diagnostic criteria, and the expansion of screening programs with the help of nonexpert operators have the potential to improve detection rates of latent RHD. Despite this, a significant number of challenges to detecting latent RHD cases still exist. Since there is a variable association between episodes of sore throat, ARF, and the occurrence of RHD, the true burden of latent RHD can be determined through active case finding and disease screening on a large population scale. The recurrence of ARF has been found to be linked with a lack of adherence to prophylactic measures. Additionally, individuals who experience a recurrence of ARF tend to have more severe valve regurgitation and higher rates of monoarthritis[11].

Studies have not been able to determine the true burden of latent RHD in communities owing to the need for huge amounts of skilled manpower, portable screening equipment, and sufficient funding. Likewise, newer innovations in RHD detection that are expected to solve these problems are either not fully verified in their efficacy or widely accepted yet by experts. The mainstay of the management of latent RHD is the use of benzathine penicillin G (BPG) as a secondary prophylaxis for a prolonged duration to prevent repeat attacks of ARF[12,13]. Though the use of secondary prophylaxis has been historically controversial, novel studies on the use of secondary prophylaxis in latent RHD have brought significant new evidence to the literature. The purpose of this narrative review is to provide an overview of the current methodology of RHD diagnosis, advancements in disease screening, and the management of latent RHD, as well as a brief discussion of future directions.

Methods

A comprehensive search of electronic databases, including PubMed, Embase, and Google Scholar, from January 2000 to April 2023 was conducted. The search strategy was developed in consultation with a medical librarian and included relevant keywords and subject headings. The search terms used included 'asymptomatic rheumatic heart disease', 'latent rheumatic heart disease', 'subclinical rheumatic heart disease', 'silent rheumatic heart disease', 'echocardiography', 'telemedicine', 'artificial intelligence', 'machine learning', 'deep learning', 'secondary prophylaxis', 'antibiotic prophylaxis', and 'benzathine penicillin G'. The PubMed search was conducted with the appropriate MeSH terms and the Embase search was performed using Emtree terms. Boolean operators 'OR' and 'AND' were used as required between the MeSH and Emtree terms to identify the relevant articles in each database. The search was extended to include conference proceedings in journals, preprints, and thesis repositories. We also searched the reference list of each of the included studies to identify other potential articles of interest. The last search was completed on 30 April 2023.

The selection process involved an assessment of the abstracts and the major findings of the studies using the following inclusion criteria: any English language article published in a peer-reviewed journal that reported on the diagnosis and treatment of latent RHD. We excluded studies that focused on clinically detected RHD, other valvular heart disease, or congenital heart disease, animal studies, case reports, and articles with inaccessible full texts. Duplicate articles were removed using the Endnote 20.0.1 library. This narrative review study did not require ethics approval or the informed consent of the participants.

Findings and discussion

Use of echocardiography in the detection of latent RHD

Echocardiographic screening has globally revolutionized the detection of RHD over the past decade. A wealth of studies has extensively investigated the burden of RHD in endemic countries around the world, mostly through school-based screening programs[14–21]. Community-based studies have been conducted that have shown a much higher prevalence of RHD among late teens and young adults when compared to school-going children[6,22,23]. The pooled prevalence of latent RHD screened and confirmed by echocardiography alone in South Asia was 18.28 per 1000, according to a meta-analysis by Lamichhane *et al*.[2] On the other hand, the pooled RHD prevalence was 2.79 per 1000 when auscultation was used to screen for cases and echocardiography was subsequently used to confirm the diagnosis. This data demonstrates the well-known disadvantage of the low sensitivity and low specificity of auscultation-based screening for asymptomatic RHD[7,24,25]. Since many cases would be missed in the first round of screening with auscultation, a two-step screening design of auscultation followed by echocardiography is not advisable.

Echocardiography is the gold-standard method for screening and confirming latent RHD cases. Following the development of the World Heart Federation (WHF) 2012 criteria, a homogeneity in the reporting of the prevalence of RHD has been observed in the literature. The WHF guidelines classify a patient without a history of ARF through echocardiography into three groups: (1) normal; (2) borderline RHD; and (3) definite RHD[26]. The details of the WHF 2012 criteria have been provided in Figure 1.

Progression and regression of latent RHD

The course of latent RHD is highly variable. Latent RHD can either remain stable, progress to a severe condition, or regress to a less severe form or even a normal state. The progression of RHD implies either a change in classification from borderline to definite RHD or a worsening of the severity of valve lesions in cases of definite RHD. A case may be reclassified from borderline to definite RHD because of (a) the development of a new pathological regurgitation on a morphologically abnormal valve, (b) the occurrence of new morphological changes in a previously unaffected valve, or (c) the occurrence of significant mitral stenosis[27,28].

So far, a number of longitudinal cohorts of children with latent RHD have been described[15,22,28–36]. The results from these studies unequivocally demonstrate that latent RHD exhibits a diverse range of diagnoses and outcomes. The median follow-up duration for these cohorts ranges from 2 to 7 years. The first study on the dynamics of valvular lesions in latent RHD was conducted by Paar and colleagues in 2010[22]. They used WHO 2005 criteria of classification of RHD into 'definite', 'probable', and 'possible' cases. With a median interval of 5.7 months, Paar *et al*. conducted subsequent follow-up examinations to evaluate any alterations in

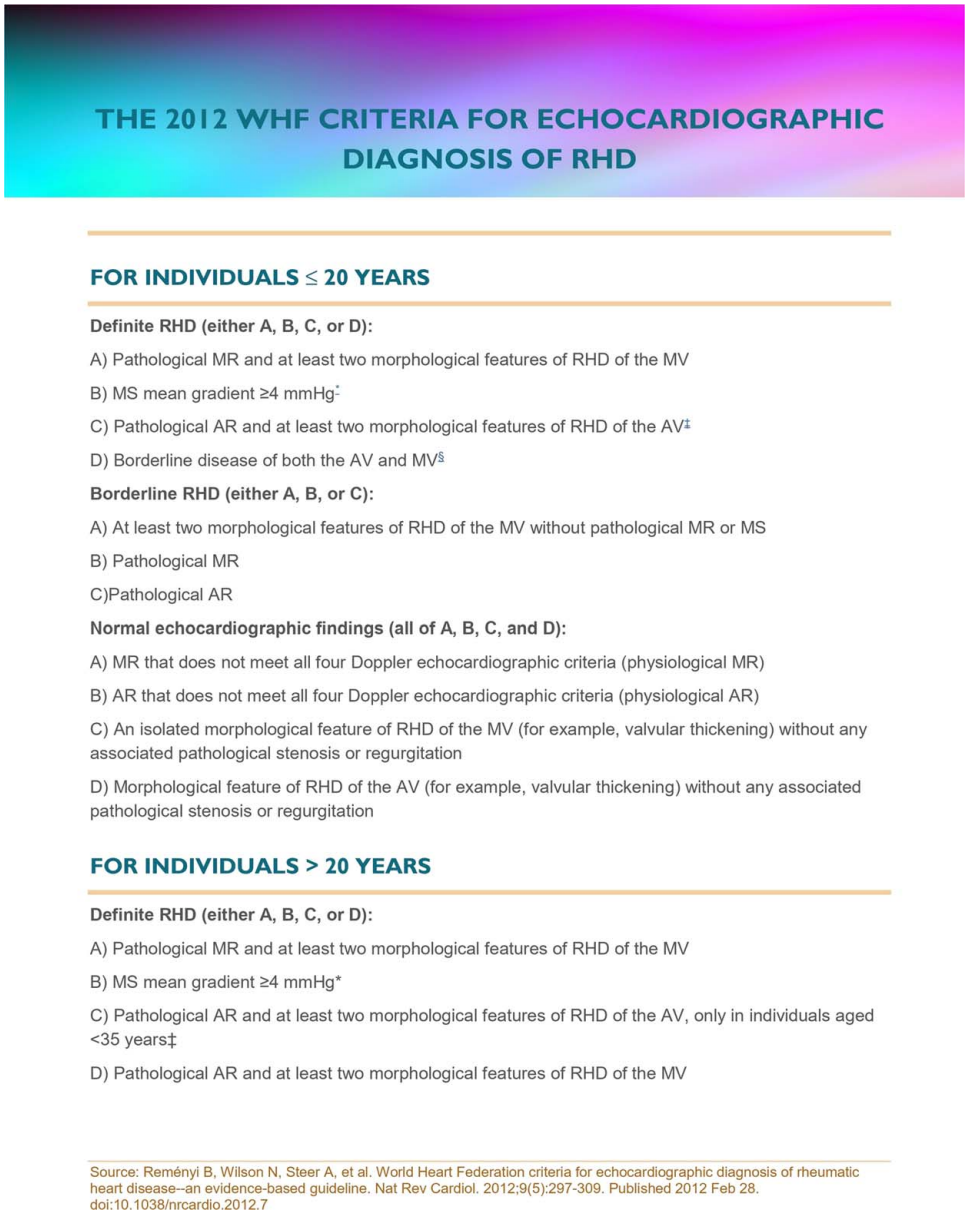

Figure 1. The 2012 WHF criteria for echocardiographic diagnosis of rheumatic heart disease.

the clinical and echo-Doppler findings among 'possible' or 'probable' RHD. The majority of the subjects (58%) that were initially categorized as 'possible' RHD exhibited little or no change during this follow-up. On the other hand, ~9% of the sample exhibited the presence of a murmur indicative of MR. This particular manifestation was also found to be associated with structural irregularities in the MV, leading to a reclassification of these subjects into the 'definite' category of RHD. Likewise, among the individuals who were categorized as 'possible' RHD, 14% exhibited a progression of anatomical changes or a deterioration in mitral regurgitation (MR). One-third of patients in this study with 'possible' RHD on the first examination no longer met the diagnostic criteria and were reclassified as 'normal' on the subsequent follow-up. In regards to 'probable' RHD cases, 12.5% of patients progressed to definite RHD, whereas 25% of them reverted back to a normal state[22].

The RHEUMATIC study in India followed up on the progression of valvular lesions in 100 children with a mean interval of 15.4±6.6 months. They observed the progression of valvular lesions in only 4% of the children. A significant majority of children; 68%, had no change in their lesions whereas 28% of them showed a decrease in grade of MR by at least one[15]. Similarly, Remond *et al.* reported that progression was observed in 19.7% of all cases and 3.6% of borderline cases of latent RHD diagnosed with echocardiography. Furthermore, it was demonstrated that children with borderline RHD of the MV, as opposed to the AV, are subject to an increased susceptibility for the progression of valvular lesions. The progression rates among

borderline RHD cases with lesions in MV and AV were 39 and 10%, respectively[29].

In a study conducted by Zühlke *et al*., a total of 55 cases were meticulously reviewed after a median duration of 60 months, employing the widely recognized WHF criteria. Out of 10 individuals diagnosed with definite RHD, it was observed that two cases transitioned to a borderline RHD classification, while one case demonstrated complete resolution and returned to a normal echocardiography finding. Among the cohort of 34 individuals with borderline RHD, it was observed that 20% of the cases exhibited progression to definite RHD, while 59% were determined to be within the normal range. A significant portion of the typical cases involved adults who were categorized using the WHF definitions for individuals aged over 20 years. It is important to note that the WHF definitions do not encompass the borderline category. Consequently, the proportion of individuals exhibiting objective improvements in echocardiography may have been comparatively lower[36]. Another study by Engelman *et al*. with a mean follow-up duration of ~2 years, 78% persisted or progressed and 21% improved in the diagnostic category. The borderline RHD cases showed a notable level of heterogeneity, as evidenced by the varying outcomes observed within this group. Specifically, the findings indicated that 24% of individuals diagnosed with borderline disease progressed to develop moderate or severe, definite RHD, while 12% of individuals demonstrated a normalization of their condition over the duration of the study period[30]. These findings are expected to closely resemble the natural progression of echocardiographic findings due to the minimal utilization of antibiotic prophylaxis within the cohort.

The disease is said to be stable when the classification of the disease as 'definite' or 'borderline' stays the same in subsequent screenings. When the disease has progressed or remained stable, the outcome is considered 'unfavorable'. Indeed, unfavorable outcomes generally include a worsening diagnostic category, the persistence of definite RHD, or the development or worsening of valve regurgitation or stenosis. The rates of progression and regression of RHD have varied among numerous studies. The precise number of individuals with latent RHD who may develop clinically significant illness, as well as the rate at which this progression occurs, and the potential impact of early identification on outcomes, are still not definitively understood. However, the data on disease progression could be a good indicator for deciding who should be prescribed prophylaxis once a more solid consensus is achieved. In addition, monitoring the progression or regression of the disease after providing prophylaxis is of great importance to understanding the efficacy of BPG in all subtypes of latent RHD. The rates of progression and regression of latent RHD identified in studies conducted as per the WHF criteria have been provided in Table 1 and Table 2, respectively. Beaton *et al*. found that worsening MR was the reason behind the progression of more than half of the cases with RHD[28].

A wide range of rates of progression and regression of latent RHD lesions among different studies has led to unclear conclusions. In addition, comparing the rate of disease progression poses its own challenges due to the variability of the definition of disease progression, the variety of outcomes, and the inclusion of children with differing severity levels of RHD. Gutman *et al*. reported that the pooled prevalence rate for progression per year of latent RHD was 5% per year. Likewise, the prevalence rate of borderline latent RHD progression was 2% per year. A significant increase in the risk of progression of valvular disease in the latent group (relative risk = 3.57) compared with controls was also observed in the same meta-analysis. The rate of regression of latent RHD was 15% per year[37]. This shows that even though latent RHD has a slow rate of progression, the rate of progression of latent definite RHD is substantial. An inconsistency in reporting the progression of definite RHD is another challenging aspect of the assessment of disease course today. There is a need for a unified criteria-based grading of the progression of lesions with definite RHD. To quantify the prediction of the unfavorable outcomes of latent RHD, a simplified scoring system has been devised and tested in a study by Bechtluff *et al*.[32] Bechtluff and colleagues used the simplified score of Nunes *et al*.[38], which was found to be a significant predictor of unfavorable outcomes in latent RHD at a two-year follow-up (hazard ratio = 1.197).

The determinants of the progression of RHD have been studied in a handful of studies with contradictory outcomes. Demographic characteristics such as age and gender have been variably associated with the progression of latent RHD. One study reported that a young age was a risk factor for latent disease persistence or progression[39]. Furthermore, children of increasing age and older children had lower odds of disease persistence and progression[28,35]. On the contrary, Shrestha *et al*.[34] could not find such an association with the age of the patient. The role of sex in the risk of disease progression was not significant[31,34,40]. Socioeconomic factors like overcrowding have been found to be associated with disease progression[17]. While another study on borderline cases did not show an association between

Table 1

Rates of progression of latent rheumatic heart disease (WHF criteria) over the duration of each study.

References	Total RHD cases progression %	Definite RHD %	Definite RHD stable %	Borderline RHD %	Borderline RHD stable %	Average follow-up duration
Kotit *et al*.[35]	19.4	17.4	39.1	23.1	38.5	42.1 ± 12.9 months (R = 18–60)
Sanyahumbi *et al*.[33]	N/A	N/A	55	3	51	2 years
Beaton *et al*.[28]	46.1	26.2[a]	28.6[a]	9.8	43.9	2.4 years (R = 1.1–5.9)
Shrestha *et al*.[34]	N/A	N/A	55.6	17.6	23.5	1.9 years (IQR = 1.1–4.5)
Beaton 2014[39]	N/A	N/A	N/A	10	49	25 months (7–25)
Remond 2015[29]	19.7	N/A	N/A	23.6	N/A	R = 2.5–5 years
Bertaina *et al*.[31]	N/A	N/A	N/A	8	60	23 months (IQR = 20.5–33.0)
Bechtlufft *et al*.[32]	N/A	N/A	48.1	17.1	28.8	29 ± 9 months (11–48)
Zuhlke 2016[52]	N/A	N/A	70	20.6	20.6	60.8 months (IQR = 51.3–63.5)

R, range; IQR, inter-quartile range.

[a]only mild definite cases.

Table 2

Rates of regression of latent rheumatic heart disease (WHF criteria) over the duration of study.

References	Total RHD cases regression %	Definite RHD %	Borderline RHD %	Prophylaxis %	Average follow-up duration
Kotit *et al.*[35]	41.67	43.5	38.5	83.3[a]	42.1 ± 12.9 months (R = 18–60)
Sanyahumbi *et al.*[33]	45.83	45.5	45.9	100[b], 18[b]	2 years
Beaton *et al.*[28]	46.1	45.2[c]	46.3	84.7[a]	2.4 years (R = 1.1–5.9)
Shrestha *et al.*[34]	32.1	27.8	41.2	58.3[a]	1.9 years (IQR = 1.1–4.5
Beaton 2014	N/A	N/A	42	85.3[8]	25 months (7–25)
Bertaina *et al.*[31]	N/A	N/A	32	24[a]	23 months (IQR = 20.5–33.0)
Bechtlufft *et al.*[32]	N/A	N/A		6.6[b]	29 ± 9 months (11–48)
Zuhlke 2016	52.3	30	58.8	4.6[a]	60.8 months (IQR = 51.3–63.5)

[a]Percentage of patients adherent to the prophylaxis (80% or more doses).
[b]Percentage of patients who received prophylaxis.
[c]only mild definite cases.
R, range; IQR, inter-quartile range.

overcrowding and the course of the disease. Likewise, other factors such as socioeconomic status, number of siblings, and type of school enrollment had no association with the disease[31,34]. Besides, a higher antistreptolysin (ASO) titer at the diagnosis has been identified as one of the risk factors for latent disease persistence or progression, according to Beaton *et al.*[39]; however, other inflammatory markers like C-reactive protein (CRP) and Erythrocyte sedimentation rate (ESR) had no association with the progression of disease.

The morphological characteristics of the valve lesion at the time of initial diagnosis have an inconsistent association with the unfavorable outcomes in the patients. Remond *et al.*[29] observed a significant association between the progression of borderline cases and lesions of MVs. Another study from Uganda also observed significant associations between the nature of valvular lesions and unfavorable outcomes. A patient with aortic insufficiency is 5.37 times more likely to suffer from disease progression when compared to patients without aortic insufficiency. Likewise, the presence of pathological AR, restricted leaflet motion, and excessive leaflet motion have been associated with an increased risk of unfavorable outcomes in latent RHD[28]. The same study suggested that children with mild, definite RHD were more likely to show disease progression than children with borderline cases. Additionally, Beaton and colleagues reported that increased numbers of morphological abnormalities in affected patients increase the likelihood of disease persistence and progression[39]. Alternatively, Zuhlke *et al.*[10] reported no association between morphological abnormalities of the valve and the progression or persistence of the disease. Bertaina *et al.*[31] also reported a lack of association between disease course and the presence of regurgitation findings in echocardiography.

Most echocardiographic screening reveals a larger borderline population and a smaller definite RHD population[33,41]. Generally, the majority of borderline cases are diagnosed with the presence of isolated pathological MR[42]. Hunter *et al.* described that interscallop separation of the posterior MV leaflet is a normal finding that can cause isolated pathological MR. This finding indicates a potentially large number of misclassified borderline RHD cases that utilized echocardiographic screening. The study also emphasized that a mechanistic evaluation of pathological MR is essential since interscallop separation has been identified as the underlying mechanism of MR in up to 70.5% of borderline cases[43]. The addition of this evaluation to WHF echo-screening criteria can potentially reduce the number of false positive cases and cut down on the huge cost and labor burden of screening programs.

Advances in screening of latent RHD

Echocardiography has undergone recent innovation, which has improved accessibility for a larger population, even in resource-constrained settings. One such advancement is the birth of a portable handheld echocardiography (HHE) machine. Numerous studies have used the HHE to estimate the burden of latent RHD in different populations[10,40,44–47]. Telford *et al.* conducted a meta-analysis that showed that the HHE had good accuracy for the detection of definite RHD, modest accuracy for the detection of any RHD, and poor accuracy for the detection of borderline RHD. The pooled sensitivity and specificity of HHE for the detection of latent RHD were 81.56 and 89.75%, respectively[48]. However, the HHE was found to overestimate MV morphological abnormalities. Additionally, the specificity for anterior leaflet thickness greater than 3 mm and restricted leaflet motion was 66.7 and 79%, respectively[40]. Although the HHE has poor accuracy for the detection of borderline disease, it might still be important for definite RHD detection in endemic regions due to its high sensitivity and specificity. The HHE has also been found to be a more cost-effective strategy than standard echocardiography in two studies[49,50]. However, its lack of spectral Doppler imaging capabilities, shorter battery life, and vulnerability to overheating on prolonged use are some of its innate technical disadvantages.

Another advancement in screening is the use of a deep-learning digital stethoscope. Ali *et al.* published a protocol for using a digital stethoscope to collect phonocardiographic and echocardiographic data from RHD-positive cases in order to train a deep neural network to diagnose and classify the diseases into subtypes based on the WHF criteria. This innovation is supposed to overcome the disadvantages of current echocardiography screening, like costliness and the need for specially trained staff[51]. A similar modality of computer-assisted auscultation was utilized by Zuhlke with a sensitivity and specificity of 4 and 93.7%, respectively[52]. Owing to the poor sensitivity of this method, it has not been used for the screening of latent RHD since.

Screening by nonexpert operators

Severe valvular abnormalities of RHD can only be managed with advanced surgical or catheterization procedures in well-equipped

centers. These health services may not always be accessible or affordable, particularly in developing nations where the burden of RHD is high. If RHD could be detected in its early stages before the valvular abnormalities became severe, secondary prophylaxis could stop the disease progression and even lead to regression in some cases[12]. This strategy of secondary prevention in RHD has been found to be a cost-effective method of tackling the disease burden on a global scale. Hence, there is a need to expand screening programs to reach as many people as possible to improve case detection and secondary prophylaxis coverage. Briefly trained nonexperts like nurses, medical students, biotechnicians, and primary healthcare workers have been deployed to improve the coverage of screening programs in many studies[41,44,53–55].

Focused RHD screening by nurses trained for 8 weeks was found to have a sensitivity of 84.2% and a specificity of 85.6% in the Fijian population[54]. A substantial agreement has been achieved between cardiologists and nurses on the assessment of MR and AR in the same screening program[56]. Three other studies have utilized HHE with briefly trained nonexperts, demonstrating a sensitivity ranging from 74 to 84% and a specificity ranging from 79 to 92%[44,53,55].

Along with focused training programs on standard comprehensive echocardiography, simplified criteria and single-view echo-screening protocols have been devised to enable nonexpert operators to use echocardiography machines. Mirabel *et al.* decided that a combination of two parameters, MR greater than or equal to 2 cm or any AR, could be used as a cutoff in an abbreviated protocol[55]. Furthermore, Lu *et al.*[57] settled on combining MR greater than or equal to 1.5 cm or any AR as the best strategy with acceptable diagnostic accuracy. Meanwhile, Beaton *et al.*[53] showed that upon increasing the MR cutoff point from 1.5 to 2 cm, the sensitivity would drastically reduce from 83 to 44%. A number of simplified protocols only measure the regurgitation jet length and exclude the morphological characteristics of the valves. This can lead to missing out of isolated morphological abnormalities that can be present in early RHD[38]. Single-view screening protocols have demonstrated sensitivity as high as 100% and specificity as high as 94%[38,45,58,59]. A single-view protocol takes about 1.2 min per child, which is significantly less than a multiview protocol. Such a quick assessment can be considered in large screening programs with the limited availability of expert cardiologists. Screening a large number of children in an endemic region means early diagnosis, which in turn can save more children from morbidity and premature mortality[60].

Another potential approach to screening for RHD is demonstrated by the innovative use of telehealth solutions in Brazil, which has enabled efficient communication between echocardiography experts and nonexperts who were involved in screening patients and obtaining the images[41]. This modality of 'task-shifting' to nonexperts is also expected to be a sustainable and low-cost strategy for the detection of latent RHD[61]. The training of the nonexperts in focused echo-screening has been variable in the studies. There is a need for standardized training and learning modules for them to improve their diagnostic accuracy while maintaining consistency among screening programs[13].

Efficacy of secondary antibiotic prophylaxis

RHD patients who are either borderline or definite and are at risk of ARF should get monthly prophylaxis. A BPG injection every 4 weeks is usually suggested for secondary prevention in these patients[5]. The efficacy of BPG as a secondary prophylaxis in latent RHD has remained doubtful for a long time. Interestingly, a study by Remond *et al.*[29] even showed that the use of BPG was independently associated with disease progression. A similar association between BPG use and unfavorable outcomes has been reported in a prospective study among Ugandan children[28]. These paradoxical findings can be attributed to the methodological bias of the studies. The patients who received secondary prophylaxis in these nonexperimental studies were chosen at the doctor's discretion. It is suggested that the doctors may have prescribed BPG to children who were more vulnerable to the disease due to multiple risk factors or those who had a more severe presentation of valvular disease. This bias has been eliminated in a recent randomized controlled trial, GOAL, conducted by Beaton and colleagues in Uganda. This trial showed a significant reduction in the proportion of progression in RHD cases among those who received BPG every 4 weeks for 2 years when compared to those who did not receive any prophylaxis. However, no significant differences in regression rate were observed in this trial[62]. Another cluster randomized trial conducted in Nepal reported a 71% reduction in the prevalence of latent RHD among the cases who underwent echocardiographic screening followed by antibiotic prophylaxis[4]. Recently, Shrestha *et al.* reported that a majority of children who showed regression in definite RHD cases had received prophylaxis. These studies have added to the body of evidence on the efficacy of prophylaxis among screening-detected cases in reducing the burden of latent RHD. This strategy should be implemented in endemic regions to retard disease progression, reverse subclinical valvular lesions, and check the transmission from infectious reservoirs.

Adherence to secondary antibiotic prophylaxis

Adherence to antibiotic prophylaxis is vital to prevent future infections and recurrent attacks of ARF. The threshold for optimal adherence to prophylaxis has commonly been 80% of the recommended doses of BPG. Hence, the factors affecting adherence to the treatment should be assessed and addressed accordingly. A study from Nepal reported that demographic factors such as age, sex, type of school enrollment, and socioeconomic status of the patient and their family had no effect on adherence to the treatment[34]. On the other hand, increasing age and time since diagnosis were associated with decreased adherence in Fijian patients. Meanwhile, urban Fijian residents were 3.36 times more likely to be adherent than rural residents[63]. In the case of Ugandan patients, young age, latent disease status, and limited education were the strongest predictors of optimal adherence[64]. These studies likely lack generalizability because they were conducted in populations of people with unique traditions and cultures. A study from Egypt identified waiting times in clinics as a deterrent to obtaining a BPG injection in their setting. The adherent patients were found to have a better understanding of the disease and the consequences of missed BPG doses than those who were nonadherent[65]. This demonstrates the importance of educating the patient about all aspects of BPG injection, as the patient's knowledge about the disease and

secondary prophylaxis may be directly linked to adherence to the treatment.

Safety of secondary antibiotic prophylaxis

There is a lack of abundant evidence on the safety profile of antibiotic prophylaxis in the current literature. According to the GOAL trial, severe adverse events following BPG use were seen in 0.2% of its recipients. The common adverse events of BPG use are local side effects such as injection site pain and swelling, minor allergies, etc. About 63% of the patients reported mild adverse events like pain, limping, and localized leg swelling after injection. Additionally, 1.7% of patients reported a delayed hypersensitivity rash associated with BPG[62]. Furthermore, the uptake of antibiotic prophylaxis for a long period of time can cause significant psychological trauma for the patients and their caregivers[66,67].

Newer possibilities in the medical management of RHD

With the rise of molecular medicine, an entirely new understanding of disease pathogenesis has emerged. Signaling pathways are considered crucial underlying mechanisms in the occurrence and development of several diseases. Numerous drugs that exert their pharmacological effects by acting on the signaling pathways of multiple diseases have been produced and accepted. There have been no effective drugs for the prevention or treatment of RHD, despite the identification of numerous pathways involved in disease pathogenesis. To date, six major signaling pathways have been identified and discussed in the literature. The study of the pathways has also identified potential intervention targets that could be used for the treatment of RHD.

The pathways involved in the occurrence and pathogenesis of RHD are the RhoA/Rho-associated protein kinase (RhoA/ROCK) signaling pathway[68], the mitogen-activated protein kinase (MAPK) signaling pathway[69], Protein kinase B(AKT)/S6 kinase (S6K) signaling pathway[70,71], TGF-β1/Smad signaling pathway[72], Wnt signaling pathway[73], and Signal transducer and activator of transcription 3 (STAT3) signaling pathway[74]. Nevertheless, only studies on the RhoA/ROCK, AKT/S6K, and STAT3 signaling pathways have identified intervention targets. These targets should be explored more in future research so that novel drugs that can halt the progression of RHD can be developed[75]. Our literature review identified that there are total of three potential intervention targets that can be used for the treatment of RHD. These targets are: IFN-γ and TNF-α-mediated extracellular matrix remodeling, α-SMA expression in TGF-β1-induced fibroblasts; and phosphorylation of STAT3 to inhibit Th17 cell-related cytokine release. The identification of these pathways along with intervention checkpoints is only the beginning of a new field of pharmacotherapy to prevent and treat RHD.

Conclusion

Echocardiography screening remains the gold-standard for the detection of latent RHD. There is a need for scalability of RHD screening programs in endemic regions to determine the burden of latent RHD with the help of HHE, simplified criteria, and telehealth services. The availability and accessibility of antibiotic prophylaxis should be broadened in underserved RHD-endemic regions, given its proven efficacy in recent studies.

Ethical approval

No ethical approval was obtained for this narrative review.

Consent

Informed consent was not obtained for this review.

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Author contribution

P.L.: conceptualization, validation, resources, and data curation; P.L. and F.P.: methodology and investigation; P.L. and R.A.M.: formal analysis; P.L., F.P., R.A.M., S.Y.M., A.A., G.G., and S.S.: writing – original draft preparation; P.L., F.P., A.A., S.Y.M. G.G., and S.S.: writing – review and editing; P.L., F.P., and R.A.M.: visualization; R.A.M.: supervision; P.L.: project administration. All authors have read and agreed to the published version of the manuscript.

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The authors have no conflict of interest to declare.

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References

[1] Watkins DA, Johnson CO, Colquhoun SM, *et al*. Global, regional, and national burden of rheumatic heart disease, 1990-2015. N Engl J Med 2017;377:713–22.
[2] Lamichhane P, Pokhrel KM, Pokharel P, *et al*. Prevalence of rheumatic heart disease in South Asia: a systematic review and meta-analysis. Int J Cardiol 2022;358:110–9.
[3] Roberts K, Maguire G, Brown A, *et al*. Echocardiographic screening for rheumatic heart disease in high and low risk Australian children. Circulation 2014;129:1953–61.

[4] Karki P, Uranw S, Bastola S, *et al*. Effectiveness of systematic echocardiographic screening for rheumatic heart disease in nepalese schoolchildren: a cluster randomized clinical trial. JAMA Cardiol 2021;6:420–6.
[5] Scheel A, Miller KM, Beaton A, *et al*. Standardization of epidemiological surveillance of rheumatic heart disease. Open Forum Infect Dis, Oxford University Press US 2022;9:S50–S56.
[6] Shrestha NR, Karki P, Mahto R, *et al*. Prevalence of subclinical rheumatic heart disease in eastern Nepal: a school-based cross-sectional study. JAMA Cardiol 2016;1:89–96.
[7] Marijon E, Ou P, Celermajer DS, *et al*. Prevalence of rheumatic heart disease detected by echocardiographic screening. N Engl J Med 2007; 357:470–6.
[8] Rothenbühler M, O'Sullivan CJ, Stortecky S, *et al*. Active surveillance for rheumatic heart disease in endemic regions: a systematic review and meta-analysis of prevalence among children and adolescents. The Lancet Global Health 2014;2:e717–26.
[9] Engelman D, Mataika RL, Kee MA, *et al*. Clinical outcomes for young people with screening-detected and clinically-diagnosed rheumatic heart disease in Fiji. Int J Cardiol 2017;240:422–7.
[10] Zühlke L, Karthikeyan G, Engel ME, *et al*. Clinical Outcomes in 3343 children and adults with rheumatic heart disease from 14 low- and middle-income countries. Circulation 2016;134:1456–66.
[11] Güneş A, Akın A, Türe M, *et al*. Evaluation of children with acute rheumatic fever: a single-center experience. Turk Arch Pediatr 2022;57:26–31.
[12] Tompkins DG, Boxerbaum B, Liebman J. Long-term prognosis of rheumatic fever patients receiving regular intramuscular benzathine penicillin. Circulation 1972;45:543–51.
[13] Beaton A, Engelman D, Mirabel M. Chapter 13 - Echocardiographic Screening for Rheumatic Heart Disease. In: Dougherty S, Carapetis J, Zühlke L, Wilson N, eds. Acute Rheumatic Fever and Rheumatic Heart Disease, Elsevier, San Diego (CA), 2021;261–274. doi: https://doi.org/10.1016/C2017-0-03010-0
[14] Shankar Laudari S. Study of prevalence of rheumatic heart disease among school children in central Nepal. Europ J Prev Cardiol 2017;1 (1 Supplement 1):S13.
[15] Saxena A, Sivasubramanian R, Roy A, *et al*. Echocardiographic screening for rheumatic heart disease among 6,270 asymptomatic school children in India: The rheumatic (rheumatic heart echo utilization and monitoring actuarial trends in Indian children) study. J Am College Cardiol 2011;57: E1349.
[16] Panwar RB, Gupta BK, Choudhary D, *et al*. Evaluation of burden of rheumatic heart disease among school children in north-west india by echocardiography using world heart federation criteria- a preliminary report. Global Heart 2018;13:518–9.
[17] Mirabel M, Fauchier T, Bacquelin R, *et al*. Echocardiography screening to detect rheumatic heart disease: a cohort study of schoolchildren in French Pacific Islands. Int J Cardiol 2015;188:89–95.
[18] Laudari S, Tiwari KK, Pazdernik M, *et al*. Rheumatic heart disease screening among school children in Central Nepal. JACC Case Rep 2019; 1:218–20.
[19] Choudhary D, Panwar SR, Gupta BK, *et al*. Prevalence and follow-up of subclinical rheumatic heart disease among asymptomatic school children in a north-western district of India based on the World Heart Federation echocardiographic criteria. Echocardiography 2021;38:1173–8.
[20] Bhaya M, Panwar S, Beniwal R, *et al*. High prevalence of rheumatic heart disease detected by echocardiography in school children. Echocardiography 2010;27:448–53.
[21] Regmi PR, Adhikaree A, Bhattarai U, *et al*. Rheumatic heart disease in school-attending Nepalese children: a descriptive analysis of the national heart screening database. Indian Heart J 2023;75:363–369.
[22] Paar JA, Berrios NM, Rose JD, *et al*. Prevalence of rheumatic heart disease in children and young adults in Nicaragua. Am J Cardiol 2010;105:1809–14.
[23] Kane A, Mirabel M, Touré K, *et al*. Echocardiographic screening for rheumatic heart disease: age matters. Int J Cardiol 2013;168:888–91.
[24] Carapetis JR, Hardy M, Fakakovikaetau T, *et al*. Evaluation of a screening protocol using auscultation and portable echocardiography to detect asymptomatic rheumatic heart disease in Tongan schoolchildren. Nat Clin Pract Cardiovasc Med 2008;5:411–7.
[25] Roberts KV, Brown AD, Maguire GP, *et al*. Utility of auscultatory screening for detecting rheumatic heart disease in high-risk children in Australia's Northern Territory. Med J Australia 2013;199:196–9.
[26] Reményi B, Wilson N, Steer A, *et al*. World Heart Federation criteria for echocardiographic diagnosis of rheumatic heart disease–an evidence-based guideline. Nat Rev Cardiol 2012;9:297–309.
[27] Karthikeyan G. Measuring and reporting disease progression in subclinical rheumatic heart disease. Br Med J Publ Group 2016:74–5.
[28] Beaton A, Aliku T, Dewyer A, *et al*. Latent rheumatic heart disease: identifying the children at highest risk of unfavorable outcome. Circulation 2017;136:2233–44.
[29] Rémond M, Atkinson D, White A, *et al*. Are minor echocardiographic changes associated with an increased risk of acute rheumatic fever or progression to rheumatic heart disease? Int J Cardiol 2015;198:117–22.
[30] Engelman D, Wheaton GR, Mataika RL, *et al*. Screening-detected rheumatic heart disease can progress to severe disease. Heart Asia 2016;8: 67–73.
[31] Bertaina G, Rouchon B, Huon B, *et al*. Outcomes of borderline rheumatic heart disease: a prospective cohort study. Int J Cardiol 2017;228:661–5.
[32] Bechtlufft BM, Nascimento BR, Sable C, *et al*. Validation of a simplified score for predicting latent rheumatic heart disease progression using a prospective cohort of Brazilian schoolchildren. BMJ Open 2020;10:e036827.
[33] Sanyahumbi A, Beaton A, Guffey D, *et al*. Two-year evolution of latent rheumatic heart disease in Malawi. Congenit Heart Dis 2019;14:614–8.
[34] Shrestha NR, Bruelisauer D, Uranw S, *et al*. Mid-term outcome of children with latent rheumatic heart disease in eastern Nepal. Open Heart 2021;8:e001605.
[35] Kotit S, Said K, ElFaramawy A, *et al*. Prevalence and prognostic value of echocardiographic screening for rheumatic heart disease. Open Heart 2017;4:e000702.
[36] Zühlke L, Engel ME, Lemmer CE, *et al*. The natural history of latent rheumatic heart disease in a 5 year follow-up study: a prospective observational study. BMC Cardiovasc Disord 2016;16:46.
[37] Gutman SJ, Shemesh E, Marwick TH, *et al*. Echocardiographic screening to determine progression of latent rheumatic heart disease in endemic areas: a systematic review and meta-analysis. PLoS One 2020;15:e0234196.
[38] Nunes MCP, Sable C, Nascimento BR, *et al*. Simplified echocardiography screening criteria for diagnosing and predicting progression of latent rheumatic heart disease. Circ Cardiovasc Imaging 2019;12:e007928.
[39] Beaton A, Okello E, Aliku T, *et al*. Latent rheumatic heart disease: outcomes 2 years after echocardiographic detection. Pediatr Cardiol 2014; 35:1259–67.
[40] Beaton A, Aliku T, Okello E, *et al*. The utility of handheld echocardiography for early diagnosis of rheumatic heart disease. J Am Soc Echocardiogr 2014;27:42–9.
[41] Nascimento BR, Sable C, Nunes MCP, *et al*. Comparison between different strategies of rheumatic heart disease echocardiographic screening in Brazil: data from the PROVAR (Rheumatic Valve Disease Screening Program) study. J Am Heart Ass 2018;7:e008039.
[42] Hunter LD, Monaghan M, Lloyd G, *et al*. Interscallop separations of the posterior mitral valve leaflet: a solution to the 'borderline RHD' conundrum? Open Heart 2020;7:e001452.
[43] Hunter LD, Pecoraro AJ, Doubell AF, *et al*. Screening for subclinical rheumatic heart disease: addressing borderline disease in a real-world setting. Eur Heart J Open 2021;1:oeab041.
[44] Ploutz M, Lu JC, Scheel J, *et al*. Handheld echocardiographic screening for rheumatic heart disease by non-experts. Heart 2016;102:35.
[45] Diamantino A, Beaton A, Aliku T, *et al*. A focussed single-view hand-held echocardiography protocol for the detection of rheumatic heart disease. Cardiol Young 2018;28:108–17.
[46] Ali S, Awadallah H, Al Hamim A, *et al*. Handheld echocardiography for screening and control of rheumatic heart disease study in Gezira state. Cardiovasc Diagn Ther 2018;8:p. 500.
[47] Chillo P, Mutagaywa R, Nkya D, *et al*. Sub-clinical rheumatic heart disease (RHD) detected by hand-held echocardiogram in children participating in a school-based RHD prevention program in Tanzania. BMC Cardiovasc Disord 2023;23:1–11.
[48] Telford LH, Abdullahi LH, Ochodo EA, *et al*. Standard echocardiography versus handheld echocardiography for the detection of subclinical rheumatic heart disease: a systematic review and meta-analysis of diagnostic accuracy. BMJ Open 2020;10:e038449.
[49] Saxena A. Rheumatic heart disease screening by "point-of-care" echocardiography: an acceptable alternative in resource limited settings? Transl Ped 2015;4:210.
[50] Ubels J, Sable C, Beaton AZ, *et al*. Cost-effectiveness of rheumatic heart disease echocardiographic screening in Brazil: Data from the PROVAR + study: Cost-effectiveness of RHD screening in Brazil. Global Heart 2020;15:1–11.
[51] Ali F, Hasan B, Ahmad H, *et al*. Detection of subclinical rheumatic heart disease in children using a deep learning algorithm on digital stethoscope: a study protocol. BMJ Open 2021;11:e044070.

[52] Zühlke LJ, Engel ME, Nkepu S, *et al*. Evaluation of a focussed protocol for hand-held echocardiography and computer-assisted auscultation in detecting latent rheumatic heart disease in scholars. Cardiol Young 2016;26:1097–106.
[53] Beaton A, Nascimento BR, Diamantino AC, *et al*. Efficacy of a standardized computer-based training curriculum to teach echocardiographic identification of rheumatic heart disease to nonexpert users. Am J Cardiol 2016;117:1783–9.
[54] Engelman D, Kado JH, Reményi B, *et al*. Focused cardiac ultrasound screening for rheumatic heart disease by briefly trained health workers: a study of diagnostic accuracy. The Lancet Global Health 2016;4:e386–94.
[55] Mirabel M, Bacquelin R, Tafflet M, *et al*. Screening for rheumatic heart disease: evaluation of a focused cardiac ultrasound approach. Circulation: Cardiovasc Imag 2015;8:e002324.
[56] Engelman D, Kado JH, Reményi B, *et al*. Screening for rheumatic heart disease: quality and agreement of focused cardiac ultrasound by briefly trained health workers. BMC Cardiovasc Disord 2016;16:1–9.
[57] Lu JC, Sable C, Ensing GJ, *et al*. Simplified rheumatic heart disease screening criteria for handheld echocardiography. J Am Soc Echocardiogr 2015;28:463–9.
[58] Remenyi B, Davis K, Draper A, *et al*. Single parasternal-long-axis-view-sweep screening echocardiographic protocol to detect rheumatic heart disease: a prospective study of diagnostic accuracy. Heart, Lung and Circulation 2020;29:859–66.
[59] Francis JR, Fairhurst H, Whalley G, *et al*. The RECARDINA Study protocol: diagnostic utility of ultra-abbreviated echocardiographic protocol for handheld machines used by non-experts to detect rheumatic heart disease. BMJ Open 2020;10:e037609.
[60] Johannsen RA, Kaltenborn ZP, Shroff GR. Saving time saves lives! A time focused evaluation of a single-view echocardiographic screening protocol for subclinical rheumatic heart disease. Int J Cardiol 2022;351:111–4.
[61] Lopes EL, Beaton AZ, Nascimento BR, *et al*. Telehealth solutions to enable global collaboration in rheumatic heart disease screening. J Telemed Telecare 2018;24:101–9.
[62] Beaton A, Okello E, Rwebembera J, *et al*. Secondary antibiotic prophylaxis for latent rheumatic heart disease. N Engl J Med 2022;386:230–40.
[63] Engelman D, Mataika RL, Kado JH, *et al*. Adherence to secondary antibiotic prophylaxis for patients with rheumatic heart disease diagnosed through screening in Fiji. Trop Med Int Health 2016;21:1583–91.
[64] Longenecker CT, Morris SR, Aliku TO, *et al*. Rheumatic heart disease treatment cascade in Uganda. Circulation: Cardiovasc Qual Outcomes 2017;10:e004037.
[65] Balbaa A, ElGuindy A, Pericak D, *et al*. An evaluation of secondary prophylaxis for rheumatic heart disease in rural Egypt. Global Cardiol Sci Pract 2015;2015:40.
[66] Chamberlain-Salaun J, Mills J, Kevat PM, *et al*. Sharing success–understanding barriers and enablers to secondary prophylaxis delivery for rheumatic fever and rheumatic heart disease. BMC Cardiovasc Disord 2016;16:1–10.
[67] Russell K, Nicholson R, Naidu R. Reducing the pain of intramuscular benzathine penicillin injections in the rheumatic fever population of C ounties M anukau D istrict H ealth B oard. J Paediatr Child Health 2014; 50:112–7.
[68] Zeisberg M, Hanai J, Sugimoto H, *et al*. BMP-7 counteracts TGF-beta1-induced epithelial-to-mesenchymal transition and reverses chronic renal injury. Nat Med 2003;9:964–8.
[69] Zhao Z, He D, Ling F, *et al*. CD4(+) T cells and TGFβ1/MAPK signal pathway involved in the valvular hyperblastosis and fibrosis in patients with rheumatic heart disease. Exp Mol Pathol 2020;114:104402.
[70] Zhang P, Wang W, Wang X, *et al*. Focal adhesion kinase mediates atrial fibrosis via the AKT/S6K signaling pathway in chronic atrial fibrillation patients with rheumatic mitral valve disease. Int J Cardiol 2013;168: 3200–7.
[71] Narikawa M, Umemura M, Tanaka R, *et al*. Acute hyperthermia inhibits TGF-β1-induced cardiac fibroblast activation via suppression of akt signaling. Sci Rep 2018;8:6277.
[72] Zhang L, Zhang N, Tang X, *et al*. Increased α-Actinin-2 expression in the atrial myocardium of patients with atrial fibrillation related to rheumatic heart disease. Cardiology 2016;135:151–9.
[73] Guo F, Yi X, Li M, *et al*. Snail1 is positively correlated with atrial fibrosis in patients with atrial fibrillation and rheumatic heart disease. Exp Ther Med 2017;14:4231–7.
[74] Chen A, Wen J, Lu C, *et al*. Inhibition of miR-155-5p attenuates the valvular damage induced by rheumatic heart disease. Int J Mol Med 2020;45:429–40.
[75] Xian S, Zeng Z. Signalling pathways implicated in the pathogenesis of rheumatic heart disease (Review). Exp Ther Med 2021;21:76.