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CURRENT OPINION

Application of Transthoracic Echocardiography for Cardiac Safety Evaluation in the Clinical Development Process of Vaccines Against *Streptococcus pyogenes*

Usman Nakakana[1] · Alimamy Serry-Bangura[2] · Bassey Effiom Edem[1,4] · Pietro Tessitore[2] · Leonardo Di Cesare[1] · Danilo Gomes Moriel[1] · Audino Podda[1,3] · Iris Sarah De Ryck[2] · Ashwani Kumar Arora[1]

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Abstract

Superficial infections with *Streptococcus pyogenes* (Strep A), pharyngitis and impetigo can induce acute rheumatic fever, an autoimmune sequela manifesting mostly with arthritis and rheumatic carditis. Valvular heart damage can persist or advance following repeated episodes of acute rheumatic fever, causing rheumatic heart disease. Acute rheumatic fever and rheumatic heart disease disproportionately affect children and young adults in developing countries and disadvantaged communities in developed countries. People living with rheumatic heart disease are at risk of experiencing potentially fatal complications such as heart failure, bacterial endocarditis or stroke. Transthoracic echocardiography plays a central role in diagnosing both rheumatic carditis and rheumatic heart disease. Despite the obvious medical need, no licensed Strep A vaccines are currently available, as their clinical development process faces several challenges, including concerns for cardiac safety. However, the development of Strep A vaccines has been recently relaunched by many vaccine developers. In this context, a reliable and consistent safety evaluation of Strep A vaccine candidates, including the use of transthoracic echocardiography for detecting cardiac adverse events, could greatly contribute to developing a safe and efficacious product in the near future. Here, we propose a framework for the consistent use of transthoracic echocardiography to proactively detect cardiac safety events in clinical trials of Strep A vaccine candidates.

Plain Language Summary

Throat and skin infections caused by certain types of bacteria, named *Streptococcus pyogenes*, are frequent worldwide; however, in many children from less developed countries and disadvantaged communities, infections with *S. pyogenes* lead to a condition called acute rheumatic fever, which usually affects the joints and the heart. Damage to the heart valves may evolve to rheumatic heart disease, a permanent condition with often life-threatening complications. Rheumatic heart disease is an important health problem in places and communities where *S. pyogenes* infections occur frequently. A vaccine against these bacteria would help lower the number of people with valvular heart disease; however, no such vaccine exists yet. Research on vaccines against *S. pyogenes* was on hold for almost 30 years because of initial concerns that vaccinated children might develop acute rheumatic fever more frequently. Recently, researchers started working again on vaccines against *S. pyogenes*, but concerns about the safety of such vaccines persist. Doctors can reliably use echocardiography to diagnose cases of rheumatic carditis (as a sign of acute rheumatic fever) and rheumatic heart disease. Here, we propose a simple approach for the consistent use of echocardiography in clinical research of vaccines against *S. pyogenes* that will allow the detection of any potential heart-related side effects of the vaccine.

✉ Usman Nakakana
usman.n.nakakana@gsk.com

1 Vaccines Institute for Global Health (Global Health Vaccines R&D), GSK, Siena, Italy

2 Vaccines Global Safety, GSK, Siena, Italy

3 Independent consultant, Siena, Italy

4 Present Address: Janssen Biologics BV, Leiden, the Netherlands

1 Introduction

Streptococcus pyogenes, or Group A *Streptococcus*, is a Gram-positive bacterium that colonises the upper respiratory tract or skin, and is responsible for a wide variety of human diseases, including streptococcal pharyngitis, scarlet fever, impetigo, erysipelas and necrotising fasciitis [1]. Children, older adults and immunocompromised individuals are at the

Key Points

The development of Group A *Streptococcus* vaccines has been delayed partly because of safety concerns, including cardiac adverse events.

Echocardiography is an invaluable tool for evaluating cardiac involvement in acute rheumatic fever episodes and rheumatic heart disease.

With the approach proposed here, echocardiography could also be used consistently for a cardiac safety evaluation in Group A *Streptococcus* vaccine clinical trials.

highest risk of *S. pyogenes* infections and their associated complications [2–4]. Diseases caused by *S. pyogenes* are highly prevalent in developing countries, among indigenous populations and in low socioeconomic areas in developed countries [3, 5].

Superficial *S. pyogenes* infections (pharyngitis and impetigo), while relatively benign, are considered a prerequisite for the development of autoimmune nonsuppurative sequelae, including acute rheumatic fever (ARF) and rheumatic heart disease (RHD) [6, 7]; the latter represents the most severe post-streptococcal sequela and is a major driver of mortality [8–10].

Despite the significant global health challenges of *S. pyogenes*, there are currently no licensed vaccines against this pathogen [11, 12]. The quest to obtain a vaccine against scarlet fever began more than two centuries ago, even before the causative agent of the disease had been unequivocally determined [13, 14]. Nevertheless, the development of a Group A *Streptococcus* vaccine (Strep A vaccine) came to a halt after the cross-reactivity of antibodies elicited against some streptococcal components with human tissues was progressively recognised since the 1930s [15–17], and after safety concerns arose that the vaccines might favor the development of ARF and subsequent cardiac damage in the 1960s [18]. Although the link between the ARF cases observed and the immune response to the vaccine antigen was not demonstrated, the US Food and Drug Administration issued a moratorium on Strep A vaccine development in 1979, which was only lifted almost 30 years later [19]. With interest in Strep A vaccine development being reignited in the last 2 decades, the role of safety monitoring, including of cardiac safety events, remains crucial. Transthoracic echocardiography (TTE) is widely accepted as a sensitive method of detecting cardiac involvement in patients with ARF and subclinical RHD [8, 20]; however, the role of TTE in the screening and monitoring of cardiac pathologies/adverse events in Strep A vaccine clinical trials is not adequately defined. Currently, there are no standardised guidelines for the consistent use of TTE in the clinical development of vaccines against *S. pyogenes*.

This review aims to provide an overview of the natural history and burden of ARF and RHD, to discuss the current status of TTE in the clinical development process of Strep A vaccines and to propose a framework for its consistent use in surveillance of cardiac adverse events during vaccine clinical trials. A graphical summary of the review (Fig. 1) is also provided.

2 Natural History of Disease Caused by *S. pyogenes*

Susceptible individuals may develop pharyngitis typically within 5 days after exposure of the upper respiratory tract to *S. pyogenes* or impetigo within 10 days after exposure of the skin (Fig. 2) [21, 22]. Both types of superficial *S. pyogenes* infections usually resolve within 1 week [23, 24]. However, some individuals develop ARF typically within 1–5 weeks following an episode of pharyngitis [25, 26] and possibly impetigo, especially in tropical regions [27, 28]. Evidence suggests that repeated superficial infections with *S. pyogenes*, likely with multiple strains, are required to initiate the autoimmune process leading to ARF [29, 30].

In up to 90% of patients, ARF manifests as an acute febrile illness with joint manifestations; however, in over 50% of adolescents with ARF, carditis also occurs [31]. Rheumatic carditis is a pancarditis characterised by inflammation of the pericardium, myocardium and endocardium, manifesting mostly as valvulitis; its severity can range from subclinical to fulminant carditis that can even result in death [32, 33].

Most ARF episodes, including the clinical and pathological features of rheumatic carditis, observed in the pericardium and myocardium, will fully subside within 6 weeks, and 90% will resolve within 3 months [34]. However, in some individuals, damage to the cardiac valves might persist and lead to scarring [8, 35, 36]. The resulting chronic valvulopathy, named RHD, may develop following the first episode of ARF, or after many years and several recurrent ARF episodes, with each recurrence aggravating the valvular damage [8, 37]. Involvement of the mitral valve is the hallmark of RHD; however, aortic and tricuspid valves are also frequently affected [35, 38]. Clinical manifestations of RHD range from a heart murmur (detected during a routine clinical examination) to atrial fibrillation, infective endocarditis, congestive cardiac failure, embolic stroke and sudden cardiac death [8]. In resource-poor settings, patients may present for the first

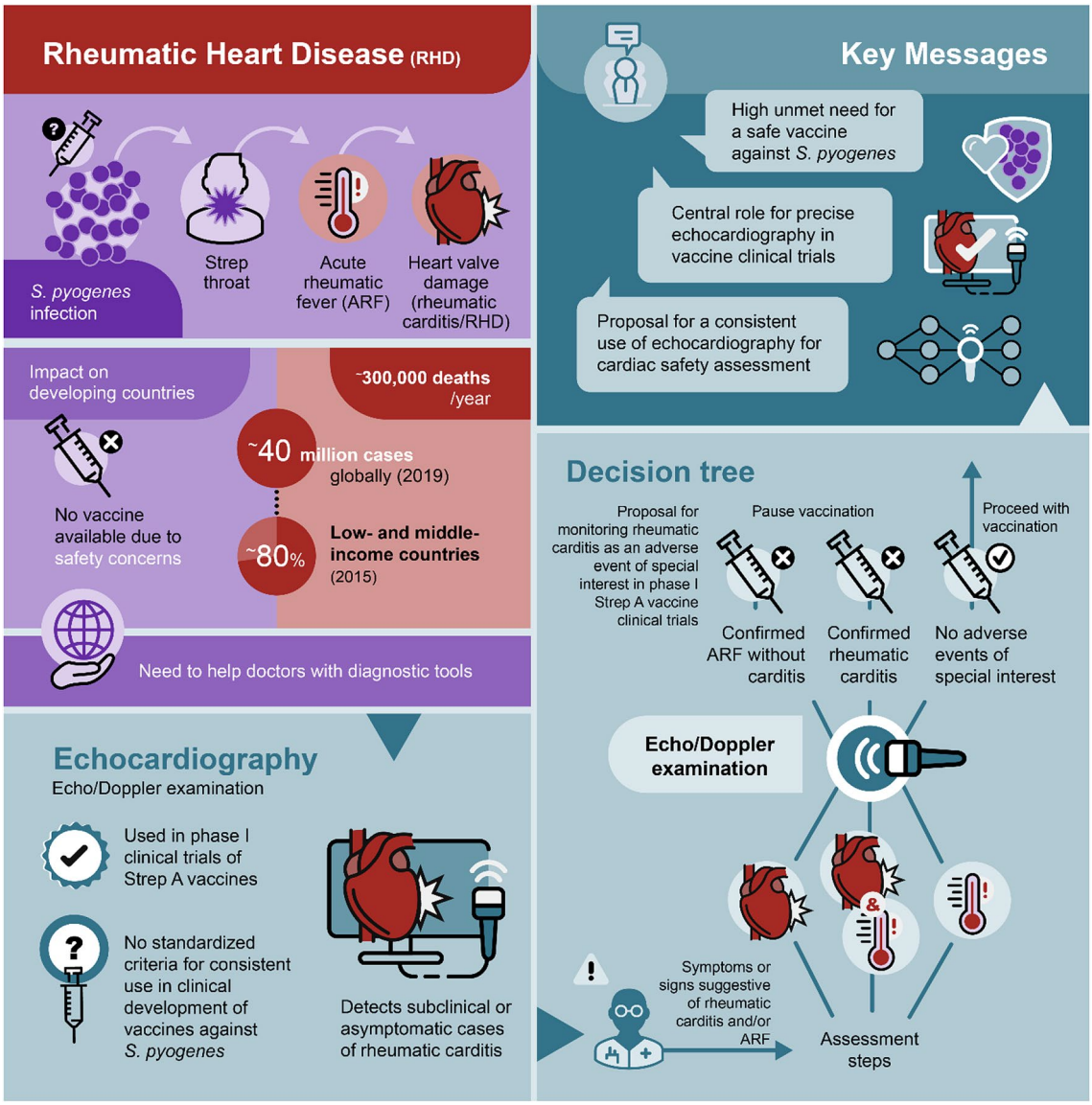

Fig. 1 Graphical summary. *Echo* echocardiography, *Strep A* Group A *Streptococcus*

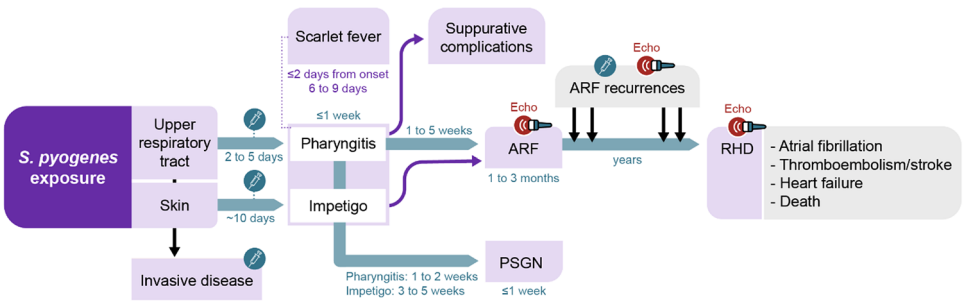

Fig. 2 Natural history of disease caused by *Streptococcus pyogenes*. The syringe icon indicates potential points where vaccines can be used for preventing *S. pyogenes* infections/acute rheumatic fever (ARF) recurrences/rheumatic heart disease (RHD). The *echo icon* indicates points where echocardiography (Echo) can be useful for the diagnosis and follow-up of ARF, ARF recurrences and RHD. *PSGN* post-streptococcal glomerulonephritis

time with a complication of established RHD rather than ARF, owing to a lack of awareness of ARF symptoms, the subclinical nature of some carditis episodes, a similarity of presenting features with common febrile childhood illnesses or the lack of access to medical care [8].

Currently, the most effective intervention for decreasing recurrence of ARF and preventing RHD involves prophylactic administration of antibiotics (mainly benzathine penicillin) [8, 39]. Although penicillin resistance has not been documented for *S. pyogenes*, this strategy has failed to control ARF and RHD because of difficulties with adherence and the extensive public health commitment required, which is beyond the capacity of many health systems in low- and m-income countries (LMICs). Additionally, concerns over the emergence of potential antimicrobial resistance following widespread and/or long-term exposure to antibiotics cannot be dismissed.

3 Burden of ARF and RHD

Worldwide, ARF represents the most common cause of acquired heart disease in children [40]. Over the past decades, ARF rates have decreased in middle-income and high-income settings but remain high in LMICs. Estimating the true burden of ARF is challenging, as clinical signs of ARF are being frequently disregarded and reliable notification programmes are lacking in the most affected areas [41]. In a systematic review that included studies published prior to 2011, reported ARF incidence per year varied between 0.1/100,000 persons in Greece and 826/100,000 persons in Sudan; indigenous people from New Zealand and Australia appeared to be disproportionally affected [42]. Most of the RHD burden originates from LMICs (Fig. 3), with around 80% of all RHD cases in children aged 5–14 years coming from "less developed" countries, according to the definition of the United Nations Population Division [9, 40]. A high burden of disease is also seen in impoverished and socioeconomically disadvantaged communities of high-income countries [43]. Rheumatic heart disease is estimated to account for up to 60% of the annual global deaths related to diseases caused by *S. pyogenes* [40]; in developing countries, mortality rates are likely elevated because of the unavailability of life-saving interventions.

Although ARF incidence in a country should be correlated with that country's RHD prevalence, this is not always the case. For example, a high RHD prevalence in South Africa is associated with a relatively low incidence of ARF (13.4/100,000 persons) [41]; such findings suggest that ARF could be massively underdiagnosed in LMICs [44].

The economic burden of RHD, measured by estimating the resulting economic losses in 107 endemic countries, is huge. The costs of the 222,000 lives lost because of RHD in 2010, mainly originating from South and East Asia, were estimated to range between US$2.2 trillion and US$5.4 trillion. Most of the economic impact of RHD is due to the premature death of children and working-age adults [45].

4 Echocardiography in the Diagnosis of Rheumatic Carditis and RHD

According to the modified Jones diagnostic criteria for ARF, TTE with Doppler should be performed in confirmed or suspected cases of ARF to assess the presence of rheumatic carditis, even in the absence of suggestive auscultatory findings, especially in at-risk populations [46]. The ARF criteria from 1992 only considered symptomatic carditis, which is usually accompanied by a significant pathological murmur, as a major diagnostic criterion [47]. Over time, the

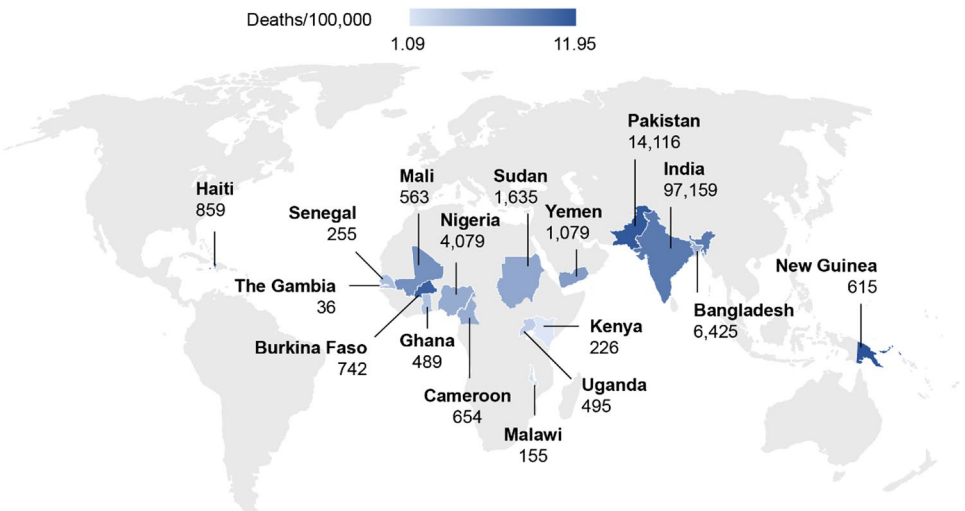

Fig. 3 Burden of rheumatic heart disease in low-income and middle-income countries. Data included in the figure were selectively extracted from the World Life Expectancy website (available from: https://www.worldlifeexpectancy.com/cause-of-death/rheumatic-heart-disease/by-country/; https://www.worldlifeexpectancy.com/world-rankings-total-deaths, accessed 19 May, 2022) and refer to the year 2020. Numbers indicate the total number of deaths caused by rheumatic heart disease in each depicted country

importance of subclinical rheumatic carditis, which can go undetected by auscultation, was also recognised, prompting the development of the modified Jones criteria in 2015 [46].

In addition to representing the current gold standard in diagnosing RHD, TTE is also indispensable for identifying subclinical cases of rheumatic carditis [31, 48] by revealing very mild or silent valvular regurgitation [49–52]. Introduction of TTE screening has revealed a higher prevalence of RHD and more advanced disease in several LMICs than previously identified by clinical examinations [53–55]. This highlights the importance of TTE in diagnosing patients suspected to have rheumatic carditis, especially in vulnerable populations. However, to better characterise lesions caused by RHD, TTE examination sometimes needs to be complemented with transesophageal echocardiography [31, 56] or other assessments [31].

The criteria published by the World Heart Federation (WHF) in 2012 aimed to provide a uniform TTE protocol for diagnosing RHD [57]. The sensitivity and specificity of the 2012 WHF criteria have been demonstrated in many countries [58, 59]; however, they were only moderately reproducible even when used by expert cardiologists [60, 61]. The updated 2023 WHF criteria provide further standardisation of disease definitions, as well as new echocardiographic criteria to diagnose rheumatic carditis and RHD, thus facilitating the application of TTE in large-scale screening programmes [62]. The roll out and implementation of these revised guidelines are expected to improve consistency of the RHD diagnostic process, contributing to the optimisation of treatment programmes. Other national and regional guidelines for the diagnosis of ARF in New Zealand, India and Australia have also included TTE/Doppler in the diagnosis and management of ARF and RHD [34, 63, 64].

5 Echocardiography in Strep A Vaccine Clinical Trials

Currently, several Strep A vaccine candidates are under investigation, targeting either the M protein peptide epitopes or other, non-M protein *S. pyogenes* antigens [11, 65]. Most of these candidates are still in the pre-clinical development phase, with only a few having advanced to phase I and II clinical trials [10].

Because of a risk of Strep A vaccines triggering autoimmune complications, the World Health Organization and the US Food and Drug Administration recommend that researchers seek antigens that have a minimal chance of inducing immunological cross-reactivity, and to prove the safety of candidate vaccines in as many ways as possible. This includes intensive screening of participants for the development of cross-reactive antibodies and TTE to detect subclinical and clinically manifest rheumatic carditis, as a possible adverse event of special interest (AESI) [66]. Despite this call for strict regulations on safety surveillance in Strep A clinical trials, widely applicable strategies for the safety assessment and management of adverse events as well as the harmonisation of trial design and safety protocols are still lacking [12, 67].

Transthoracic echocardiography evaluations have been included in phase I and II clinical trials as part of safety requirements to assess baseline status and to monitor study participants after vaccine administration (i.e. to detect potential subclinical rheumatic carditis) [68–72]. However, the absence of standardised criteria for the consistent use of assessment methods has resulted in variations in the timing and frequency of TTE evaluations performed in trials of Strep A vaccine candidates (Table 1). In addition, only one study [71] provided a detailed description of the TTE examination methodology, which would facilitate the comparison of results across trials and clinical development programmes. While none of the studies reported any relevant TTE findings, in the absence of a clearly described methodology, parameters with varying levels of importance might have been measured, leading to outputs that are confusing or of limited value.

6 Proposal for Harmonisation of TTE Use in the Clinical Development Process of Strep A Vaccines

In the context of developing vaccines against *S. pyogenes*, cardiac safety evaluation will be focused on detecting cases of rheumatic carditis, rather than RHD, as the time required for the latter condition would exceed the typical duration of a vaccine clinical trial. A stepwise application of criteria currently used to diagnose ARF/rheumatic carditis, with a rationale for each step and the definition of relevant outputs, can provide a solid basis for the consistent use of TTE during Strep A vaccine candidate trials and a timely detection of rheumatic carditis events.

We propose here a streamlined approach aimed to standardise the use of TTE in phase I Strep A vaccine clinical trials, planned to be used in upcoming studies of a Strep A vaccine candidate developed by GSK [73]. If consistently applied, this framework would allow investigators to optimise resource use based on findings of both planned and unplanned visits, while minimising the likelihood of missing any cardiac adverse event.

First, all participants should undergo TTE at two timepoints: at the screening visit, to avoid enrolling and vaccinating participants with pre-existing undiagnosed congenital and acquired cardiac lesions (including persistent or

Table 1 Use of TTE in phase I and II trials of Strep A vaccine candidates

Vaccine	Type	Use of TTE	Timepoints	Ref.
Hexavalent prototype (ID Biomedical)	6-valent, M protein-based	Tick	14 days after each of the three vaccine doses At months 6 and 12	[68]
StreptAvax (ID Biomedical)	26-valent, M protein-based	Tick	At baseline 2 months after the third dose of vaccine (month 6)	[69, 70]
StreptAnova (Dalhousie University)	30-valent, M protein-based	Tick	At screening 30 days after the third dose of vaccine (day 211)	[72]
MJ8VAX (Queensland Institute of Medical Research)	Peptide antigen from the conserved carboxyl terminus region of the M protein	Tick	At screening 28 days after vaccination At the final visit (day 350)/on the day of early termination	[71]

Ref. reference, *Strep A* Group A *Streptococcus*, *TTE* transthoracic echocardiography

resolving rheumatic carditis, and subclinical RHD), and at 6 months after receiving the last study vaccine dose, to ensure that participants did not develop cardiac abnormalities during the trial. As ARF episodes occur in the first 3 months following exposure to *S. pyogenes* (Fig. 2), this 6-month timeframe ensures that no cardiac events (including silent subclinical events) potentially caused by the study vaccine are missed.

Second, at each planned vaccination visit (Fig. 4), before administering the study vaccine, investigators should reconfirm that the participant is free from symptoms and signs suggestive of ARF/rheumatic carditis (diagnosed according to the modified Jones criteria [46]) and remains eligible for vaccination. This includes interviewing the participants (using investigator and patient questionnaires similar to those provided in the Electronic Supplementary Material [ESM]) and performing a physical examination (assessing for signs of ARF using the modified Jones criteria [46], Doppler auscultation to identify soft murmurs [74], and electrocardiography). However, even in the absence of findings suggestive of ARF/rheumatic carditis, asymptomatic participants with an incipient *S. pyogenes* infection should not be vaccinated; in their case, establishing whether a potential subsequent episode of ARF/rheumatic carditis was triggered by naturally occurring *S. pyogenes* infection or the study vaccine would not be possible. In all participants pre-vaccination, throat swabs should be collected, and the modified Centor score [75] should be determined; samples from participants with a sore throat and a high likelihood of *S. pyogenes* infection based on modified Centor score >3 should be tested using point-of-care (POC) molecular methods. Point-of-care tests are highly sensitive methods for detecting active *S. pyogenes* infections, while being more specific than the modified Centor score. Using POC diagnostics to confirm *S. pyogenes* infection will limit the number of unnecessary withdrawals from the study. Only patients with no findings suggestive of ARF/rheumatic carditis and with a low likelihood of *S. pyogenes* infection (modified Centor score ≤ 3) or a negative POC test result should be vaccinated.

Third, at any time a participant reports symptoms or signs, and/or has examination findings suggestive of ARF/rheumatic carditis, the steps indicated in the decision tree for monitoring rheumatic carditis as AESI (Fig. 5) should be followed, to ensure the safety of participants and to avoid further vaccination in the case of ARF. The decision tree comprises 3 assessment layers, where positive findings of each layer trigger the progression of the participant to the next one: (1) the participant reports signs or symptoms of ARF/rheumatic carditis as per the investigator/patient questionnaire (ESM); (2) the investigator performs an electrocardiogram to check for a prolonged P-R interval, and Doppler auscultation for heart murmurs of mitral/aortic valves; and (3) TTE, POC test for *S. pyogenes* and assessment of the modified Jones criteria for ARF are performed to identify the cause of the positive cardiac findings. Anti-streptolysin O antibody titres are expected to rise following vaccination with a streptolysin-containing Strep A vaccine, and therefore could not be used to confirm infection; however, ARF can be diagnosed according to the modified Jones criteria based on anti-DNase B titres (or combined serology testing [76, 77]), throat culture and POC tests. Based on the results of the layer 3 assessments, vaccination of individual participants as well as of the entire trial population (in case an AESI is confirmed) can be either continued or placed on hold. In case the trial is put on hold, all efforts should be made to quickly determine the aetiology of ARF and its relationship to vaccination, to allow a quick recommencement of the study or termination if the vaccine is confirmed to cause rheumatic carditis.

The proposed approach has several advantages. It includes an optimised number of TTE examinations that avoids too frequent, resource-consuming evaluations, while

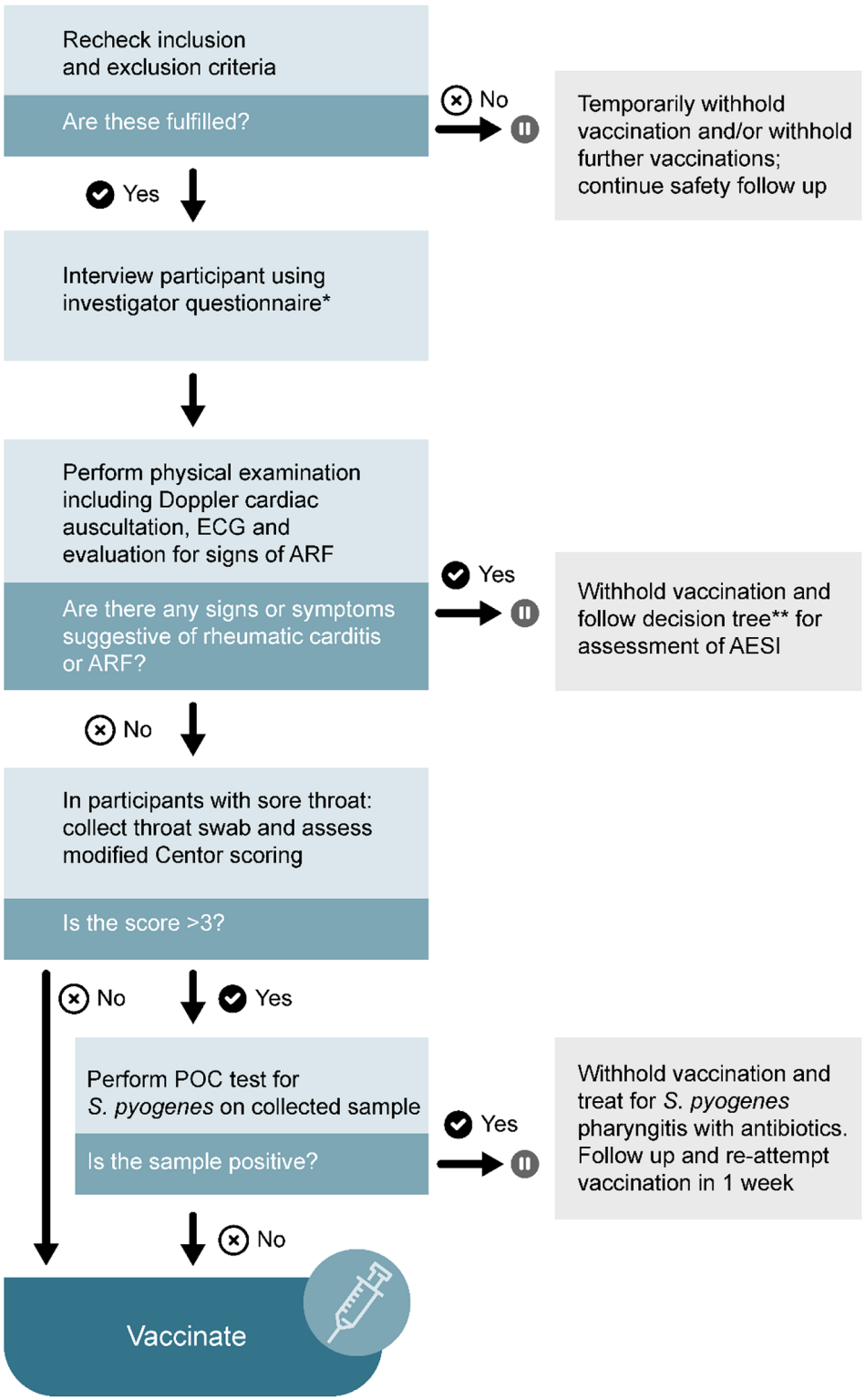

Fig. 4 Proposed process flow for pre-vaccination assessment in Strep A vaccine clinical development programmes. *AESI* adverse event of special interest, *ARF* acute rheumatic fever, *ECG* electrocardiography, *POC* point-of-care, *see ESM, **see Fig. 5

being flexible enough to ensure no cardiac safety signals are missed. Starting with the second dose of vaccine, pre-vaccination assessments allow any potential case of vaccine-induced ARF, including rheumatic carditis, to be identified. The timing of these scheduled visits is optimal for this scope, considering that the visits occur no later than 8 weeks after the previous vaccine dose, while ARF/rheumatic carditis develops typically within 1–5 weeks after the triggering contact with *S. pyogenes* (either through natural infection or potentially through vaccination). The possibility

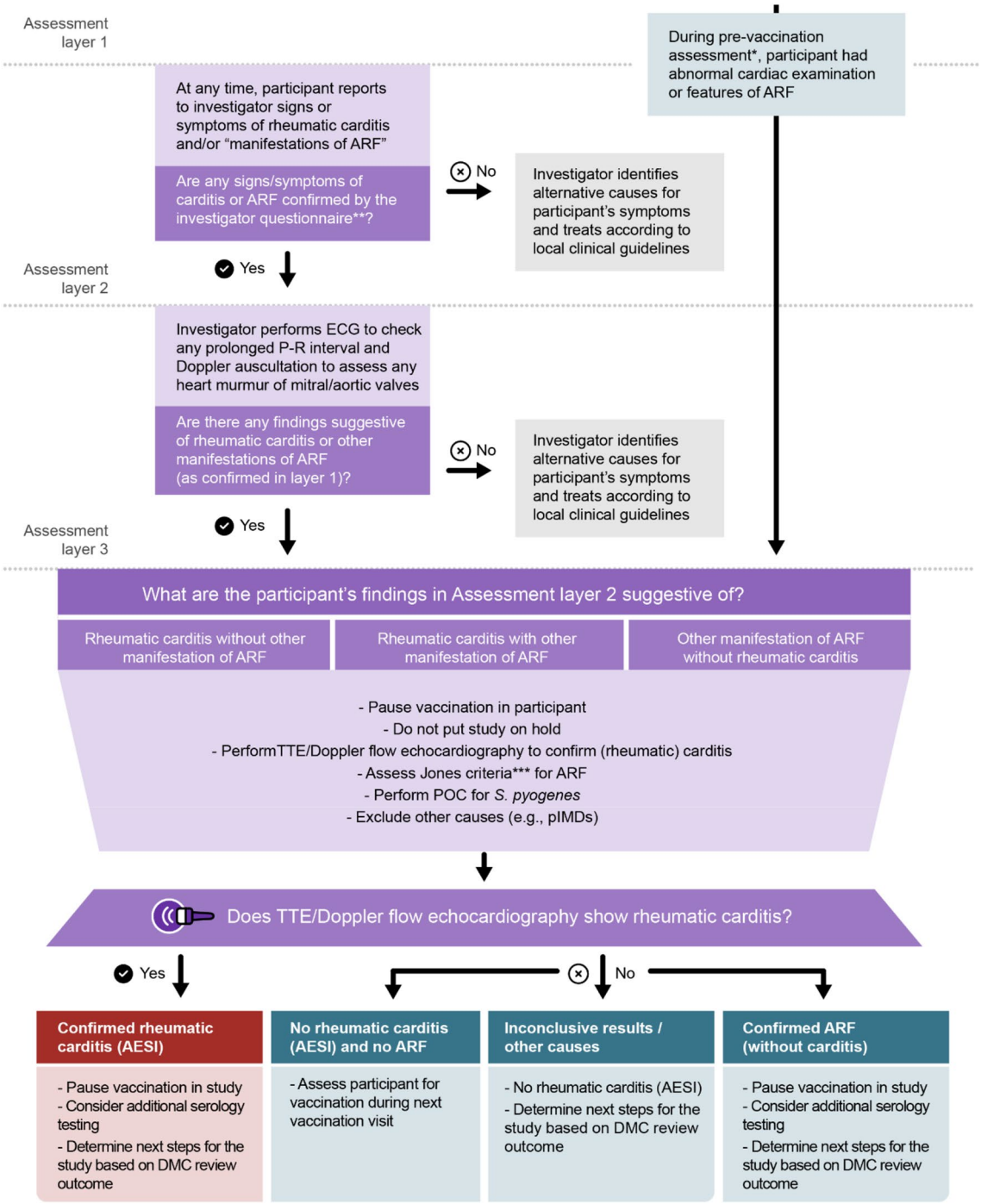

Fig. 5 Proposed decision tree for monitoring rheumatic carditis as an adverse event of special interest (AESI) in Group A *Streptococcus* vaccine clinical development programmes. *ARF* acute rheumatic fever, *DMC* Data Monitoring Committee, *ECG* electrocardiography, *pIMDs* potential immune-mediated diseases, *POC* point of care, *TTE* transthoracic echocardiography, *see Fig. 4, **see ESM, ***determining anti-streptolysin O titres to obtain evidence of *Streptococcus pyogenes* infection would not be useful in clinical trials of Group A *Streptococcus* vaccines that contain streptolysin O; nevertheless, infection can be confirmed according to the modified Jones criteria based on anti-DNase B titres or combined serology testing, throat culture and POC tests

of performing TTE at any time of the study in case there is a suspicion of ARF and rheumatic carditis ensures that symptomatic cases of rheumatic carditis are detected as soon as possible. The key strength of this approach lies in the fact that it is based on existing guidelines and is placed within the context of an existing Strep A vaccine development

programme. To our knowledge, this is the first proposal for a simple easy-to-apply algorithm that can be integrated in Strep A vaccine clinical trials, at least in the initial stages of development, to establish the baseline vaccine safety. In large-scale phase III trials, the algorithm could be further simplified to avoid placing an excessive burden on the study resources. Beyond phase I, Strep A vaccine trials would benefit from the implementation of a TTE diagnostic algorithm (as described in the 2023 WHF criteria [62]), which can be applied by non-cardiologists using handheld echocardiographic units.

The approach proposed in this article has the advantage of creating an overlap between safety and efficacy assessments, as the evaluation of 2 clinical trial efficacy endpoints (pharyngitis and impetigo) is integrated into the pathway for investigating rheumatic carditis as an AESI. However, it must be emphasised that this approach is not the result of an expert consensus and has been created to fulfil the need for a safety assessment tool that can be used across different Strep A vaccine clinical development programmes.

7 Implications of Using TTE in Clinical Trials and Future Directions

Ideally, clinical trials of Strep A vaccines should take place in countries where relevant endpoints (e.g. a significant reduction in ARF/RHD incidence following vaccination) can be measured. In such countries, however, the chance of a study participant contracting *S. pyogenes* disease and subsequently developing ARF and/or rheumatic carditis during the study is also high. A clinical trial design with a well-established safety screening algorithm as the one proposed here can ensure that adverse events following immunisation are correctly detected.

To maximise the utility of TTE and ensure consistency across the different clinical development programmes, a well-defined and easy-to-apply case definition for rheumatic carditis as an AESI/adverse event following immunisation should be formulated and consistently applied. For this, further qualitative research in populations with a high ARF incidence would be needed. In addition, standardising should also be extended to other elements of the TTE surveillance process. The type of equipment used for TTE can influence the diagnostic accuracy of RHD in children [78], so exploring these inter-equipment differences and accounting for them would make the obtained results more reliable. Similarly, some degree of inter-observer variability in how echocardiographic images are interpreted does exist [60, 61, 79]; TTE-specific continuous education and training programmes for sonographers and physicians are needed to improve diagnostic accuracy [79]. In a large clinical trial, using a blinded expert endpoint evaluation committee could ensure consistency in diagnosing key endpoints, including rheumatic carditis and RHD [52].

Integrating TTE in a more complex evaluation frame and combining it with other, less complex tests, as done in the standardised approach proposed here, is key to maximising efficiency while balancing the costs and use of often limited resources. However, as the devices needed to perform TTE become smaller and more autonomous, and interpretation of the findings is performed by artificial intelligence, the challenges of consistently implementing TTE as a cardiac safety assessment tool in Strep A clinical trials, even in LMICs, are removed one by one.

In the future, we can expect to be able to identify individuals at a higher risk of severe cardiac ARF complications [80–82]. For example, biomarkers could potentially be used as predictors and measures of rheumatic carditis, perhaps even leading to the replacement of TTE by simple blood tests [83–85]. Until then, however, we should fully exploit the potential of TTE in detecting cardiac complications of *S. pyogenes* disease.

8 Conclusions

Along with other diagnostic methods and tests, TTE remains an invaluable tool in the clinical development process of vaccines against *S. pyogenes*. Our proposed approach for a simplified, efficient and standardised use of TTE can pave the way for a consensus by experts in the field regarding its consistent application in evaluating the safety of Strep A vaccine candidates.

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Declarations

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Conflict of interest Usman Nakakana, Alimamy Serry-Bangura, Bassey Effiom Edem, Pietro Tessitore, Leonardo Di Cesare, Danilo Gomes Moriel, Audino Podda, Iris Sarah De Ryck and Ashwani Kumar Arora are or were employees of GSK at the time of this study. Usman Nakakana, Alimamy Serry-Bangura, Danilo Gomes Moriel, Audino Podda, Iris Sarah De Ryck and Ashwani Kumar Arora hold shares in GSK.

GSK is currently developing a 4-component vaccine candidate against *S. pyogenes.*

Ethics approval Not applicable.

Consent to participate Not applicable.

Consent for publication Not applicable.

Availability of data and material Data sharing is not applicable to this article as no datasets were generated or analysed during the current study.

Code availability Not applicable.

Authors' contributions All authors contributed to the interpretation of the data and a critical review of the paper for important intellectual content. All authors read and approved the final manuscript.

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