NRHS'18

NATIONAL RHEUMATIC HEART SUMMIT 2018

In association with CSI, ICC, API, IAP & IAE Kerala Chapters

Index

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Chief Editor

Dr. Jabir A
Executive Editor

From the Editors' desk

Yes, we are speaking about Rheumatic Fever and Rheumatic Heart Disease.

In an era where cardiology conferences speak about statins and drug-eluting stents, a few people felt that this social disease, with the poorest amongst its victims, should not be forgotten. The Rheumatic Heart Club of Kerala and the Departments of Cardiology and Cardiothoracic surgery of Govt. Medical College, Kottayam led the way and the idea received support from all professional bodies. Hence NRHS-2018 and this publication.

Kerala holds a unique position in health care related indices in India. Among the various achievements of this state, the dramatic decline in the incidence of rheumatic fever -0.1/1000 in 2016- over the last few decades is especially noteworthy. ICMR data indicates a progressive decline in the prevalence of Rheumatic heart disease from 1970-2010- from 5.3 to 2.9 to < 1 per 1000 schoolchildren. However, even as there are regions like Kerala with dramatic decline, these studies also point out areas with current prevalence figures of 1.5/1000 .In some regions, the figures are shockingly higher. Such data underline the importance of a constant vigil in areas with low prevalence and all-out effort in areas with high prevalence. Therefore, cardiologists and other healthcare professionals need to be constantly updated on the strategies in the management of this problem. NRHS-2018 is an attempt in this direction.

We received an overwhelming response from the professional community and the leaders of the society to the idea of holding a national conference on Rheumatic fever and Rheumatic heart disease in Kottayam. This publication captures the best wishes of a number of them and presents a few articles in the 'Must Read 'category for the student and the professional who wish to have a quick update in this field. Regrettably, we could not include the content of the talks in the conference, which would have further enhanced the value of this publication.

The editors record their profound gratitude to all those who helped us in bringing out this souvenir on time.

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No.1541/Press/CMO/17 December 29, 2017

MESSAGE

I have great pleasure to note that the Rheumatic Heart Club of Kerala is organizing a National Rheumatic Heart Summit-NRHS-2018, in association with the departments of Cardiology and Cardio-Thoracic Surgery of Kottayam Medical College and supported by a number of professional bodies.

Rheumatic Fever and Rheumatic Heart Disease are essentially diseases of the poor and hence seldom talked about. Kerala has made great strides in controlling this problem, but the situation in many other states is very different. I hope that this seminar will discuss ways and means to consolidate the gains of Kerala in this regard and put forward concrete recommendations to eliminate the disease from India.

I wish NRHS-2018 all success

Pinarayi Vijayan

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MESSAGE

I am happy to know that Rheumatic Heart Club Kerala in association with the departments of Cardiology and Cardio Thoracic Surgery of Govt. Medical College Kottayam, CSI, ICC, API, lAP, IAE is bringing out a Souvenir in connection with the National Rheumatic Heart Summit 2018. The theme of the conference is to 'Eliminate Rheumatic Fever and Reduce the burden of Rheumatic Heart Decease in India by 2025'. Rheumatic Fever and Rheumatic Heart Decease are essentially deceases of the poor and hence seldom talked about. Kerala has made great strides in controlling this problem, but the situation in many other states is very different. I appreciate your initiative and wish you all success in this endeavor.

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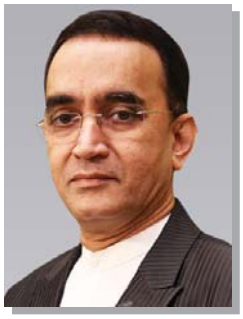

MESSAGE

At a time when every cardiologist's focus is on interventional cardiology,taking interest on rheumatic heart disease is highly appreciable. As usual the cardiologists of Kerala have set themselves apart by taking this initiative and they should be congratulated for this laudable effort.

There is no doubt that this disease continues to trouble the population of our country and I hope this conference will give us some right directions in tackling this disease.

With best wishes

Dr. K. Sarat Chandra, MD.DM.FACC.FESC.FCSI
President - CSI

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From the desk of Chairman Organizing Committee

It has been my pleasure to be associated with the National Rheumatic Heart summit-18, being held in Kottayam on 11 February, 2018.

The epidemiology of Rheumatic Fever (RF) and Rheumatic Heart Disease (RHD) in Kerala has undergone a dramatic change over the last few decades. In the 1960-1990 period, the wards were full of patients with RF and RHD.We could demonstrate clinical signs of any lesion, whenever we wanted, to medical students, due to the abundance of patients with RHD at any time in the hospital. We saw a new case of RF every week. Patients reported regularly for injections of Benzathein Penicillin. Today, on the other hand, medical students, hardly see any case of RF or RHD. I am told that DM students have to struggle to find a case of RHD for discussion. This dramatic decline may be related to overall improvement in economic conditions in the state. The incidence of RF/RHD still continues to be significantly high in many other states. The reasons for the change in epidemiology need to be investigated and discussed. NRHS-18, I hope, will provide a platform for such discussion.

I congratulate the Scientific Committee for putting together a programme which will update the student and practitioner alike on RF/RHD.The highlight of the conference is the First Rheumatic Heart Club oration, by Prof.GeorgeCherian, whose contribution to the understanding and teaching of this disease has been immense.

Let me welcome all of you to this wonderful meeting.

Dr. George Jacob FRCP, FACC
Former Professor of Cardiology,Govt Medical College,Kottayam.
Former Chief of Cardiology,Caritas Hospital,Kottayam.

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From the desk of Organising Secretary

National Rheumatic Heart Summit (NRHS' 18) has been organized with the intention to popularise and garner support for the "Global Resolution" for prevention and control RF and RHD going to be presented at the World Health Assembly of WHO in May 2018 under the initiative of World Heart Federation and RHD Action as part of their "#Time to Tackle RHD" movement.

Moreover 'Rheumatic Heart Club Kerala', a registered social initiative started in 1997 by the cardiology and Cardithoracic departments of Government Medical College Kottayam, with the major objective of prevention and control RF and RHD in Kerala, had launched an ambitious project "Zero RF Kerala by 2020", in December 2017.

In this scenario the managing committee of 'Rheumatic Heart Club Kerala' thought it is appropriate to convene a 'National Rheumatic Heart Summit' to discuss the newer development in the pathogenesis, diagnosis and management of RF and RHD and also to identity the ways and means to over come the hurdles in the primary and secondary prevention and also in the control of RF and RHD in India. Therefore the NRHS'18 has included a detailed panel discussion in the program in which leading experts in the country who have vast experience in the subject would be participating.

Apart from the various topics to be presented by the eminent speakers with in-depth knowledge in the subjects, the first "Rheumatic Heart Club Oration" will be delivered by Dr.George Cherian the former professor and HOD Cardiology CMC Vellore and the past president of Cardiological Society of India, who is considered as the father figure of cardiology in India.

Before I conclude let me express my great privilege and pleasure to invite and welcome all the senior faculty members and dear delegates who have come across the country for the NRHS'18 at Government Medical College, Kottayam having the credit of doing the first heart transplantation in Government sector in Kerala.

Kottayam is considered as the elite district in Kerala bordered by the famous tourist destinations like Kumarakom, Thekady, Vagamon and Munnar. On behalf of the organising committee I would like to welcome you once again to Kottayam "the land of lakes, latex and literacy "

Dr. S. Abdul Khadar
Prof. & HOD Amala Institute of Medical Science, Thrissur.
Former Prof. of Cardiology,
Govt. Medical College Kozhikode & Kottayam.

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From the desk of Chairman Scientific Committee

Dear Colleagues

Greetings to one and all.

Rheumatic fever (RF) and its sequel Rheumatic Heart Diseases (RHD) together is the commonest cardiovascular disease of the young adults all over the world. Over the past 50 years, there has been a significant fall in the prevalence of RHD in the developed western world so much so that it ceases to be a major health problem. However RHD remains a major health problem in developing countries of the world including India. In India, in state like Kerala, where the health standards and literacy are high, during the past 25 years there has been a striking decline in RF and RHD. The story is different in states like UP and Bihar where RHD is still a major health problem.

Rheumatic Fever, being a sequel of streptococcal throat infection, is preventable, if we can eradicate or promptly treat the streptococcal sore throat. The relevance and aim of **"National Rheumatic Heart Summit 2018" (NRHS' 18)** is mainly based on the concept that RF and RHD can be prevented and eradicated. The scientific programme of NRHS'18 mainly focuses on educating the doctors involved in the care of these patients to bring down / eradicate the menace of RHD from India by 2025.

As Scientific committee chairman, with the help and inputs from scientific committee vice chairpersons, Prof. R. Suresh Kumar and Prof. N.Sudhayakumar and organizing secretary Prof. S.Abdul Khadar and other organizing committee members, I have planned a scientific programme which caters to the needs of each and everyone involved in the management of RF and RHD patients. Starting from primordial prevention of RF, the scientific programme includes complex management problems like oral anticoagulation in prosthetic valve patients, balloon mitral valvuloplasty and mitral valve repair in RHD.

I am quite sure, the initiative being taken by **Rheumatic Heart Club of Kerala** will go a long way in meeting the aim of **"Rheumatic Heart Disease free India by 2025".**

I hope NRHS' 18 will be a grand success.

Prof. Rajan Joseph Manjuran

Sr. Cardiologist, Pushpagiri Medical College, Thiruvalla
Former Prof. of Cardiology, Govt Medical College, Kottayam.
Former Prof. of Cardiology, Pushpagiri Medical College, Thiruvalla.

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The portrait of a living legend Prof. George Cherian

The First Rheumatic Heart Club Oration is being delivered by a great doyen of modern Cardiology in India. His contribution is being recalled by his long-term friend.

Professor George Cherian has been in the practice, teaching and clinical research in Cardiology since 1959. He is best known for his contributions for setting up the post graduate training programs in this country along with pioneers like the late Professors Sujoy Roy, Kamala Vytilingam and Professor S Padmavati.

Professor Cherian took over as Head of the Department of Cardiology at Vellore founded by Professor Vytilingam .The Department over the years grew to be one of the leading centers in India and has been the training ground for many of today's senior cardiologists including many of the senior figures in this city. Professor IP Sukumar was largely responsible for the growth of Pediatric Cardiology

Dr George Cherian graduated from the Christian Medical College, Vellore with the University First Rank. His early training was at Vellore .He was later Fellow at the Massachusetts General Hospital. He took a technical early retirement after about 25 years from Vellore and was later Visiting Professor at the University of California at Los Angeles and later Professor and Head of the Cardiac Centre at the Faculty of Medicine, Kuwait University.

Professor Cherian is Past President of Cardiac Society of India and was Chairman of the National Board in Cardiology. He has been an Examiner for DM and DipNB and for the Royal College, Edinburgh and an Advisor to several organizations like the ICMR, WHO, Armed Services of India, IMC ,API, UPSC and Royal College of Physicians.

He is Emeritus Fellow of the American College of Cardiology and has been an extra mural Faculty Member for American College of Cardiology & the International Society and Federation of Cardiology (ISFC).For many years he represented India and Asia Pacific on the Clinical Cardiology Council of the ISFC. Professor George Cherian has over 220 publications and contributions to national and international text books and monographs in cardiology. His paper on juvenile mitral stenosis published in the British Heart Journal is among the first on that subject. Was involved in studies on the epidemiology of rheumatic heart disease in school going children with Professors Grace Koshy and V.Benjamin.The estimation of Penicillin levels following benzathine penicillin injections established the need for 3 weekly injections instead of monthly injections. While at Hammersmith he published the first study on the use of beta blockers in hypertrophic cardiomyopathy in the BMJ.His wide interests are apparent from publications in diverse fields like congenital heart disease, valvular heart disease, pericardial diseases, cardiomyopathy and coronary artery disease in young patients. One of his recent contributions has been on the value of the detection of mediastinal lymph nodes in the diagnosis of tuberculous etiology of pericardial effusions which has been lauded by the American Journal of Medicine as the only significant contribution in this field in recent years.

He is currently associated with Narayana Institute of Cardiac Sciences, Bangalore as Professor of Cardiology and Senior Consultant and Academic Head pursuing his interests in patient care, teaching and clinical research. He is Chair of the group on chronic thromboembolic pulmonary hypertension at NH which is one of the leading institutions worldwide in pulmonary thromboendarterectomy.

Dr. George Jacob FRCP, FACC
Former Professor of Cardiology, Govt Medical College, Kottayam.
Former Chief of Cardiology, Caritas Hospital, Kottayam.

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Rheumatic Heart Club Kerala

The story of Twenty Years of Continuing Fight against Rheumatic Fever and Rheumatic Heart Disease

Dr. V L Jayaprakash
State co-ordinator
Professor of Cardiology,
GMCH, Kottayam.

> "Eliminate Rheumatic Fever and Reduce the Burden of Rheumatic Heart Disease in India by 2025".

Introduction

Two decades ago, before the beginning of Rheumatic Heart Club Kerala (RHCK), the story of patients with rheumatic fever and rheumatic heart disease was miserable. Hundreds of patients were seen waiting in front of the injection room of the medical college for their turn of Penicillin test dose or Benzathein Penicillin injection. The wards were crowded with large number of patients with rheumatic fever or rheumatic reactivation, multivalvular heart disease with cardiac failure, atrial fibrillation with fast ventricular response, valvular heart disease with infective endocarditis, severe mitral stenosis with embolic stroke, and pulmonary infarction with haemoptysis and so on. As treatment, the only surgery routinely done was closed mitral valvotomies. Those who required valve replacement for calcific mitral stenosis, severe aortic or mitral regurgitation or combination lesions either had to wait indefinitely in the long surgical waiting list of SCTIMST or had to run here and there for funds. There was nobody to hear their grievances or address their problems there was no national or regional prevention or control program for rheumatic heart disease .This was the back ground when the departments of Cardiology and Cardiothoracic surgery at GMCH, Kottayam, thought of starting an NGO to address the problems of rheumatic heart patients.

RECOLLECTIONS OF A PIONEER

During my tenure in TDMC Alappuzha from 1965-1981, ICMR and WHO supported my study of rheumatic fever and rheumatic heart disease in school children in 5 to 15 years of age. I covered about 50,000 children in 15 schools during 1967-70, with an ICMR unit in Alappuzha .The incidence of RF &RHD was 2.2/1000. Those with RF/RHD were given penicillin prophylaxis under my guidance for three years and it was continued until students left school. The high incidence of RF and RHD was seen among children with poor living conditions. The incidence came down with improvement in social setup and increased awareness among the public. I was supported in my studies by Dr. S.Thankam, Dr.R.K Shenoy and Dr. Ahmed Kabeer.

I am happy to know that the National Rheumatic Heart Summit being organized in connection with the movement for "Zero Rheumatic Fever Kerala - 2020". I wish the conference all success.

Story of Prabhakaran and Yehia

Prabhakaran, a case of rheumatic heart disease- severe AR, moderate AS was admitted in SCTIMST for aortic valve replacement. But he could not undergo the surgery for want of funds .He got discharged and was admitted in the cardiology ward of GMCH Kottayam with severe depression and LV failure .He remained in the hospital for 2 weeks crying loudly in great agony and dyspnea. He eventually died due to cardiac deterioration.

Similarly Yehia, a 23 year old man from Fort Kochi, was referred to our department with rheumatic multivalvular heart disease, infective endocarditis and cardiac failure .He also died after one month's stay in the hospital. Yahiya was very poor, with nobody to support, except his old grand-mother, who had no formal education even to understand the problems of his grandson .These two deaths were a big emotional trauma for the entire staff of the ward and faculty members of the department. This was a great impetus for the idea of RHCK.

Silver Jubilee Year of the department of Cardiology, Kottayam

1996 was the 25th anniversary year of the department and we planned to do 25 heart surgeries to mark the silver jubilee. We approached the leading newspaper of Kerala ' Malayala Manorama' to help us mobilise funds for valve surgery, collecting contributions from the public. At that time Manorama was busy with 'Lathur earthquake project' and could not take up our cause. We decided to invite the health minister, late Sri A.C Shanmughadas, for the inauguration of Rheumatic Heart Club on May 1st 1997 and present the problem to him. At that time, the only government support was 20,000 rupees from the Prime Minister's relief fund. Chithra valve was not available and the Medtronics valve was very costly. The minister patiently listened to the briefing by Dr P Chandra Mohan and Dr Rajan Manjuran, Professors of Cardithoracic surgery and Cardiology and patrons of RHCK. He lauded the efforts of the departments and agreed to start a scheme to fund valve surgery for rheumatic heart patients. The result is the "Society for financial aid to poor patients" through which patients were given Rest. 50,000/- for valve surgery and Rs 10,000 /-for balloon valvuloplasty .This was a great encouragement for the goal of prevention and control of rheumatic fever and rheumatic heart disease, the major objective of RHCK. We have been continuing our fight against rheumatic fever and rheumatic heart disease for the last 2 decades. We got support from our colleagues, media, government, politicians, bureaucrats, social forums and philanthropists. Yet, we do not feel that we have done enough and we fear that we have not been able to convince the society of importance of our mission its true perspective.

Prof George Jacob inaugurated the website of National Rheumatic Heart Summit 2018 Seen are Dr RJ Manjuran, Dr Raju George Dr Suresh Kumar Dr S AbdulKhadar Dr Jabir A Dr VL Jayaprakash Dr K Jayaprakash Dr Rayihanathul Misiriya

Highlights of activities of RHCK

As a result of the continuous effort of **RHCK** the prevalence of rheumatic fever has come down to low level over this period and it was 0.1/1000 in Kerala during 2016. In 2017 there were only 19 cases rheumatic fever diagnosed in Kerala.

Inauguration by late Sri.A.C Shanmugadas the Health and Family Welfare Minister on May 1st 1997.

a. In an effort to prevent and control rheumatic heart disease RHCK identified rheumatic fever and rheumatic heart disease prevalent areas and

conducted public awareness classes and rheumatic heart disease detection camps in these areas.

b. RHCK started a registry containing all the details of patients with rheumatic fever and rheumatic heart disease for further follow up and treatment.

c. Annual Conferences and family get-together of patients with rheumatic fever and rheumatic heart disease have been one of the major activities of RHCK. Cardiac evaluation camp was conducted during the Annual Conference with the help of senior cardiologists. ECG and Echo cardiograms were done as part of the clinical evaluation. Ministers, MP's, MLA's, office bearers of local self - government bodies and social activists were regular guests for the annual conferences, thus providing them an opportunity to understand the various problems faced by the patients.

d. Continuing Medical Education (CME) programmes were organized for young cardiologists, pediatricians, physicians and general practitioners at Kottayam, Perinthalmanna, Thrissur and Thiruvalla.

e. Identified 'RHD Base Hospitals' in the government and private sector for the evaluation and treatment of rheumatic fever and rheumatic heart disease patients at concessional rate.

f. Booklet about rheumatic fever and rheumatic heart disease in local language (Malayalam) was prepared and distributed in schools and libraries. The school students who were on preventive treatment for rheumatic fever and rheumatic heart disease helped in distributing the booklets in schools. A summary about rheumatic fever and rheumatic heart disease was read in the school assembly to educate the students and teachers.

g. Bulletins, notices, bill boards, and stickers made to educate the public and exhibited in public places... Articles on rheumatic fever and rheumatic heart disease were published in the local newspapers and weeklies. Electronic (TV) and social media (like WhatsApp and Facebook) were also liberally used to spread the messages and news of RHCK.

h. "Hridayapuraskaram" award was started by RHCK and presented to individuals selected for their outstanding contribution in the prevention and control of rheumatic fever and rheumatic heart disease since 2004. The first award was given in 2004 to late. Sri.A.C Shanmugadas, Health and Family Welfare Minister who started a government society in 1998 to give financial aid to poor rheumatic heart disease patients undergoing valve surgery or balloon procedure. The second award was given in 2008 to Sri. K.M Mathew, Chief Editor of "Malayala Manorama" news paper which started "Hridaya Poorvam Project" and helped hundreds of rheumatic heart disease patients to undergo valve surgery. Third award was given in 2011 to Dr.P.Chandramohan, who did the maximum number of heart surgeries for rheumatic heart disease patients in Kerala. The fourth award was given in 2014 to Prof.Dr. D.V Nair, who as HOD, Medicine, MCH, Alappuzha piloted the first prevalence study of RF/RHD in Kerala in 1972.

It must be noted that the developments in the educational field, the economic progress, high literacy level and universal health delivery system in Kerala all favorably influenced the drop in the prevalence of RF/RHD.

j. "Hridayasparsham programme" was started to identify and encourage Rheumatic heart disease patients requiring valve surgery by conducting camps in district head quarters.

NRHS'18 1st organising committee meeting

"Eliminate Rheumatic Fever and Reduce the Burden of Rheumatic Heart Disease in India by 2025".

Measures to be implemented to achieve the goal

Registry of Rheumatic Fever and Rheumatic Heart Disease

A registry of rheumatic fever and rheumatic heart disease is essential for the follow-up and treatment of patients with rheumatic fever and rheumatic heart disease. A complete registry of rheumatic fever and rheumatic heart disease of every state in India is to be made by conducting camps in all the district head quarters hospitals of India with the support of cardiologists, physicians, pediatricians and general practitioners and government machinery after giving wide publicity through print and visual medias.

Primary and Secondary Prevention

Steps should be taken to ensure uninterrupted free supply of oral Penicillin V and Benzathein Penicillin injection in India so that streptococcal throat infection can be treated promptly , thus preventing rheumatic fever For continuous secondary prophylaxis of RF, the availability of Penicillin is very essential. Now there is a shortage of Penicillin V and Benzathein Penicillin injection in India. Public sector manufacturers - Hindustan Antibiotics and Kerala State Drugs and Pharmaceuticals (KSDP) should be given support to manufacture Penicillin V and Benzathein Penicillin.

Safe Injection Rooms

The scare of penicillin reaction is creating a big hurdle in giving the best and cheap treatment for Streptococcal throat infection and thus preventing rheumatic fever and rheumatic heart disease. Hence at least 2 centers, preferably Government Medical College Hospitals or District hospitals having "Safe Injection Room" with all facilities to handle emergency, should be identified in each district to give Benzathein Penicillin injection for patients with streptococcal throat infection and secondary prophylaxis for rheumatic fever and rheumatic heart disease.

Booklet of Rheumatic Ferver and Rheumatic Heart Disease

. In our school curriculum and school textbooks there is no mention about rheumatic fever and rheumatic heart disease even though it is the commonest heart disease affecting children and young adults .RHCK has published a booklet of rheumatic fever and rheumatic heart disease and given to schools through patients and relatives and also to Anganvadi teachers. Notices containing essential information of rheumatic fever and rheumatic heart disease are given to schools to be read in the assembly. This booklet must be given to the all schools, educational institutions and libraries in India.

Rheumatic Heart Champion

World Heart Federation and WHO requested the developing and the under developed countries ,where rheumatic fever and rheumatic heart disease are prevalent in large number, to identify a public figure of importance as "rheumatic heart champion". RHCK has declared Dr.B.Ekbal, Neuro Surgeon, Former Vice Chancellor of Kerala University and Planning Board Member who has been associating with the activities of rheumatic heart club in the prevention and control of rheumatic fever and rheumatic heart disease as the rheumatic heart champion of Kerala. Thus the credit of declaring rheumatic heart champion for the first time India goes to Kerala.

Rheumatic Heart Day

In order to attract the attention of public students and teachers about the importance of prevention and control rheumatic fever and rheumatic heart disease, Govt of

റുമാറ്റിക് ഹാർട്ട് ക്ലബ്ബ് കേരള 19-ാം വാർഷികസമ്മേളനം പ്രൊഫ. ജോർജ്ജ് ജെയ്ക്കബ് ഉദ്ഘാടനം ചെയ്യുന്നു.

ഡോ. രാജു ജോർജ്ജ്, ഡോ. ശോഭാ എ.,
ഡോ. ജോസ് ജോസഫ് (പ്രിൻസിപ്പൽ), ഡോ. റംലാബീവി എ. (ഡി.എം.ഇ)
ഡോ. വി.എൽ. ജയപ്രകാശ്, ഡോ. എസ്. അബ്ദുൾ ഖാദർ
എന്നിവർ സമീപം

India must be requested to declare a national day for rheumatic heart disease.

Apex Body

To implement the program and for the periodic evaluation of the progress of the project, a core committee should be constituted in each state. State Minister of Health and Social Welfare, Secretary of Health and Social Welfare, State Mission Director (NRHM), Planning Board Member who is looking after health related matters, Director of Health Services, Director of Medical Education, DMO's, Medical College Principals, Nursing College Principals, Office bearers of IMA, Cardiological Society of India, Indian

Academy of Pediatrics, Associations of Physicians of India, Association of ENT Surgeons, Qualified Private Medical Practitioners, Health Workers, Anganwadi Teachers and other interested persons must be included in the committee.

Regional Centre for Treatment and Prevention of RF/RHD

Cardiology department of one government medical college in each state should be given the responsibility to function as "Regional Centre for Treatment and Prevention of Rheumatic Fever and rheumatic heart disease".

Global Initiative

We must join the global initiative against Rheumatic Fever and Rheumatic Heart Disease, which is the most common cardiovascular disease in children and young adults in all developing countries. Rheumatic heart disease is a preventable disease that currently affects over 33 million people world wide. Rheumatic heart disease kills 275,000 people every year and a few rich countries (USA and UK) have managed to reduce their burden, but other countries continue to struggle with the disease. Rheumatic heart disease is a life long condition which needs continuous follow up and treatment. However even now there is no national programme for the prevention and control of Rheumatic Fever and rheumatic heart disease in India.

Under the **"# Time to Tackle RHD"** programme, the World Heart Federation and WHO together plan to pass a global resolution to tackle rheumatic fever and Rheumatic heart disease in World Health Assembly in May 2018. The support of Asian and African countries is very important and crucial for the resolution to get passed in the World Health Assembly. RHCK has requested Govt of India to support this cause.

NRHS'18 Organising Committee

Towards Rheumatic Fever Free Kerala

Zero Rheumatic Fever Kerala By 2020

സ്ട്രോപ്റ്റോകോക്കസ് എന്ന രോഗാണുവാണ്
റുമാറ്റിക് ഫീവറിന്റെ കാരണം
5 മുതൽ 15 വയസ്സുവരെയുള്ള കുട്ടികളിൽ
സ്ട്രോപ്റ്റോകോക്കസ് അണുബാധ
മൂലമുണ്ടാകുന്ന തൊണ്ടകാറിച്ചയുടെ
അനന്തര ഫലമായിട്ടാണ്
റുമാറ്റിക് ഫീവറിന്റെ ലക്ഷണങ്ങളും
അതേ തുടർന്ന് റുമാറ്റിക് ഹൃദ്രോഗവും ഉണ്ടാകുന്നത്.
ഡോക്ടറുടെ നിർദ്ദേശപ്രകാരം
പത്ത് ദിവസം തുടർച്ചയായി പെൻസിലിൻ–വി ഗുളിക
കഴിക്കുകയോ ഒരു ബൻസാത്തിൻ പെൻസിലിൻ
കുത്തിവെപ്പ് നൽകുകയോ ചെയ്താൽ
റുമാറ്റിക് ഫീവർ പൂർണ്ണമായും തടയാൻ കഴിയും.

"റുമാറ്റിക് ഹൃദ്രോഗം മൂലമാണ് എന്റെ
ഇളയ സഹോദരൻ
ചെറുപ്പത്തിൽ മരണമടഞ്ഞത്.
റുമാറ്റിക് ഹാർട്ട് ക്ലബ്ബിന്റെ
നേതൃത്വത്തിൽ 2020–തോടെ
കേരളം റുമാറ്റിക് ഫീവർനിയന്ത്രണം
കൈവരിക്കാൻ ഒരുങ്ങുകയാണ്.
ഞാനും അതിൽ പങ്കാളിയാണ്.
നിങ്ങളും ആ ശ്രമത്തെ പിന്തുണയ്ക്കണം."

കേരളത്തിന്റെ റുമാറ്റിക് ഹാർട്ട് ചാമ്പ്യൻ
ഡോ. ബി. ഇക്ബാൽ.

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Rheumatic fever & Rheumatic Heart Disease: The last 50 years

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Rheumatic fever (RF) and rheumatic heart disease (RHD) continue to be a major health hazard in most developing countries as well as sporadically in developed economies. Despite reservations about the utility, echocardiographic and Doppler (E&D) studies have identified a massive burden of RHD suggesting the inadequacy of the Jones' criteria updated by the American Heart Association in 1992. Subclinical carditis has been recognized by E&D in patients with acute RF without clinical carditis as well as by follow up of RHD patients presenting as isolated chorea or those without clinical evidence of carditis. Over the years, the medical management of RF has not changed. Paediatric and juvenile mitral stenosis (MS), upto the age of 12 and 20 yr respectively, severe enough to require operative treatement was documented. These negate the belief that patients of RHD become symptomatic ≥20 years after RF as well as the fact that congestive cardiac failure in childhood indicates active carditis and RF. Non-surgical balloon mitral valvotomy for MS has been initiated. Mitral and/or aortic valve replacement during active RF in patients not responding to medical treatment has been found to be life saving as well as confirming that congestive heart failure in acute RF is due to an acute haemodynamic overload. Pathogenesis as well as susceptibility to RF continue to be elusive. Prevention of RF morbidity depends on secondary prophylaxis which cannot reduce the burden of diseases. Primary prophylaxis is not feasible in the absence of a suitable vaccine. Attempts to design an antistreptococcal vaccine utilizing the M-protein has not succeeded in the last 40 years. Besides pathogenesis many other questions remain unanswered.

Key words Antistreptococcal vaccine - heart disease - myocarditis - rheumatic fever - rheumatic heart disease - streptococcal infections - subclinical carditis

Rheumatic heart disease (RHD) follows rheumatic fever (RF), as a non-suppurative manifestation of group A beta haemolytic streptococcal (GAS) pharyngitis. RF is widely accepted as an immunological disorder following GAS infection. Although the burden has come down in developed countries, RHD continues to be a prominent cause of morbidity and mortality in developing countries of the world. This review highlights the changes that have occurred in the area of RF and RHD in the last 50 years.

Historical perspective

About 100 years back RF/RHD was believed to be a disease of "temperate climate". In 1835, Malcomson observed that rheumatism was prevalent among sepoys[1] and in 1870 Moore[2] reported numerous cases

of rheumatism in Rajasthan. Rogers[3] indicated absence of RF in India as except one possible case he did not find RHD in 4800 postmortem records in 37 years in Calcutta (Kolkata) inspite of 25 cases of mitral stenosis which he labelled as non rheumatic. Megaw[4] reported RHD from plains of India but felt that it was less common than seen in colder climates. Clark[5] reported absence of haemolytic streptococcal infections and low prevalence of RF/RHD in tropics. Keats[6] did not find a single case of RHD in 600 autopsies in Amritsar. Drury[7] found mitral valve disease in 62 per cent and mitral stenosis in 10 per cent in an analysis of 319 clinically diagnosed cases of heart disease admitted to the Medical College Hospital in Calcutta (Kolkata). Basu[8] found 8.3 per cent cases of rheumatic carditis and pericarditis in 446 patients of acquired heart disease. Hughes and Yusuf[9] referred to mitral stenosis in an article on heart disease in Punjab[9]. Hodge reported on rheumatism and indicated that it was not rare in India.

The first clinical evidence of RF came from Punjab by Wig in 1935[11] and on rheumatism in childhood and adolescence by Kutumbiah in 1940[12]. This was followed by a large number of hospital-based surveys for the relatively "new" disease accounting for 20 to 50 per cent admissions in hospitals in various parts of the country (Table I). With the results, rheumatic fever was labelled as severe or malignant in India with multivalve involvement and congestive cardiac failure even in the initial attack of RF[21]. Roy delineated the features of RF and compared with features seen in Boston (USA)[22]. The presence of RF/RHD was not only established but also considered to be the commonest heart disease in the country by mid 1950s.

Table I. Percentage of RHD patients in hospital admission

Author	Place	Year	(%)
Kutumbiah[13]	Madras (Chennai)	1941	39.5
Bannerjea[14]	Calcutta (Kolkata)	1965	44.6
Sanjeevi[15]	Madras (Chennai)	1946	46.8
Vakil[16]	Bombay (Mumbai)	1954	24.7
Padmawati[17]	Delhi	1958	39.1
Devichand[18]	Shimla	1959	50.6
Mathur[19]	Agra	1960	35.1
Malhotra[20]	Punjab	1963	27.6

Burden of the disease in India

The information regarding the burden of disease comes from hospital data, population based studies and school surveys. Hospital based data between 1945 and 1963 indicated that anywhere from 20 to 50 per cent hospital admissions for cardiac patients were for RHD (Table I). Since the hospital-based data do not represent the population of the region, there is a bias towards the worst affected and those seeking admission for procedures. Additional bias may be introduced through changes in the population served by the hospital over many years. With increasing marginalization of the poorer sections of the society some hospitals may no longer be serving those who are worst affected with RHD. Perhaps the most important source of bias is in the preference of the admitting units. With emergence of the epidemic of coronary artery disease (CAD), hospital admissions are largely represented by CAD patients in most hospitals.

Population based surveys for prevalence are very few and scattered. (Table II). In a study in rural Haryana prevalence of RHD was found to be 2.2/1000 in 5 to 30 year old subjects[23]. Mathur in a study of the urban population of Agra found RHD in 1.8/1000 in the same age group[24]. Berry[25] studied the urban population of Chandigarh and found RHD in 1.23/1000 male and 2.07/1000 in the female population of all age groups. A recent Indian Council of Medical Research (ICMR) study (between 2000 and 2010) in 10 different, mostly urban, locations of the country found the prevalence to range from 0.2 to 1.1/1000 for RHD and 0.0007 to 0.2 /1000 for RF[26]. The data were based on registration of all cases in one million population by approaching hospitals, private practitioners and extensive advertising for establishing a registry of all known cases. The recent registry data suggests decline but registries are able to collect about 50 to 70 per cent cases. Hence, overall decline is debatable.

ICMR has conducted three school-based surveys in children 5 to 14 yr in age over a 40-year period between 1970 and 2010. The first survey from 1972 to 1975 was in schools at Agra, Alleppy, Bombay (Mumbai), Delhi and Hyderabad. The second from 1984 to 1987 included schools at Delhi, Varanasi and Vellore.

Table II. Prevalence of RHD in population surveys

	Age group (yr)	N	Prevalence/1000
Roy[23]	5-30	4847	2.2
Mathur *et al*[24]	5-30	7953	1.8
Berry[25]	5-30	19768	1.87
	All ages	33361	1.55

The third study included children from 10 centres in the country located at Shimla, Jammu, Chandigarh, Jodhpur, Indore, Kochi, Wayanad, Mumbai, Vellore and Dibrugarh. It has a wider coverage but not of the whole country. In the first study (1972-1975), 1,33,000 children were evaluated and the prevalence of RHD varied from 0.8 to 11/1000, overall 5.3/1000. The second study (1984-1987) included 53,786 children and the prevalence ranged from 1.0 to 5.6/1000 overall 2.9/1000. The third and the largest study included 1,76,904 school children with a prevalence varying from 0.13 to 1.5/1000 (overall 0.9/1000) in the 5 to 14 yr age range[26]. The data suggest a progressive decline in RHD from 5.3 to 2.9 to below 1.0/1000 between 1970 to 2010. In the last study echocardiographic evaluation was performed in all children clinically diagnosed to have a heart murmur and children with congenital heart disease could be excluded. In a study on 1,18,212 school children 4-18 yr in age a heart murmur was found in 389 normal children. Echo evaluation identified 61 children with RHD giving a prevalence of 0.5/1000 children in Uttar Pradesh[27]. Studies from Punjab, Gujarat, Rajasthan, Uttar Pradesh and Tamil Nadu have found the prevalence to range from 0.67 to 4.54/1000 children (Table III). The figures are variable but suggest a decline in the prevalence of RHD over time, however, whether they identify a real decline in prevalence is a difficult question to answer. At the same time, addition of echocardiographic RHD surveys of normal children have introduced a new dimension to the assessment of disease burden. Most available echocardiographic evaluation studies for the presence of RHD in school children suggest more than 10 to 20 times higher prevalence of clinically "silent" RHD (Table IV). The reliability or acceptability of the prevalence data based on clinical evaluation alone is not known with certainty. Further, echocardiographic diagnosis has fallacies and follow up studies of the clinically silent or subclinical (SC) RHD are required to establish the significance of disease identified through echocardiography alone. Is this "subclinical" valve disease really silent RHD? A long-term follow up of the patients is required to establish the natural history of disease identified through echocardiography alone.

An analysis of the shortcomings associated with the estimation of the prevalence of RF/RHD in our country has been discussed earlier[38]. The overall prevalence estimated to be about 1.5-2/1000 in all age groups, in India (total population about 1.3 billion) suggests that there are about 2.0 to 2.5 million patients of RHD in the country.

Table III. Prevalence of rheumatic heart disease (RHD) in school surveys

Place	Year	Age (yr)	Prevalence/1000
Punjab[28]	1988-91	5-15	2.1
Gujarat[29]	1986	8-18	2.03
Punjab[30]	1987	6-16	1.3
Uttar Pradesh[31]	2000	7-15	4.54
Tamil Nadu[32]	2001-2	5-18	0.68
Rajasthan[33]	2006	5-14	0.67

Global and Asian burden of RF/RHD

The burden of RF/ RHD has been described in detail by Carapetis and colleagues[39,40]. Excluding developed economies, the global burden of RHD in the 5 to 14 yr old children was estimated to be 0.8 - 5.7/1000 with a median of 1.3/1000. The estimated number of children would be about 2.4 million (Table V). Subsequent data from studies in Asia suggested that the number of children with RHD in Asia could be between 1.96 to 2.21 million. The findings were extrapolated to include all ages and estimated that globally there were 15.6 - 19.6 million patients. In the study of Asian countries the burden of RHD was estimated to be 10.8 - 15.9 million patients. The estimates of RHD in Asian countries

Table IV. Prevalence of subclinical carditis in echo studies of school children

Place	n	Clinical	Echo	Subclinical
Nicaragua[34]	3150	13 (4)	150 (48)	137 (44)
Tonga[35]	5053	78 (15.4)	169 (33.4)	91 (18)
Cambodia[36]	3677	8 (2.2)	79 (21.5)	71 (19.3)
Mozambique[36]	2170	5 (2.3)	66 (30.4)	61 (28.1)
India[37]	6270	5 (0.8)	128 (20.4)	123 (19.6)

Tonga auscultation positive 46% silent 54 % (figures calculated)
Figures in parenthesis are per 1000

Table V. Global and Asian magnitude of RF/RHD (Excluding developed economies)

RHD	Age (yr)	No. of patients (Million)
Global	5-14	2.4
Asia	5-14	01.96 - 2.2
Global	all ages	15.6 - 19.6
Asia	all ages	10.8 - 15.9
Acute RF		n / year
Global	5-14	336000
	All ages	471000
If 282 60% have RHD 188.4 40% potential RHD	282000 new cases 189000	
Estimated deaths	Rate/year (%)	n / year
Global	1.5	233000 - 294000
Asia	3.3	356000 - 524000

Source: Refs 39, 40

indicate that the global burden is significantly higher than the earlier estimates for children as well as all age groups.

On the basis of 1.5 per cent mortality per year, global deaths from RHD were estimated to be 233,000 - 294,000/year. The mortality in Asian countries was calculated on the basis of a study showing 3.3 per cent per year mortality[41]. As such the mortality in Asia accounts for 356,000 to 524,000 deaths/year suggesting that the global mortality must be higher.

For acute RF a global estimate in the 5-14 yr age group suggested 336000 new cases per year. Extrapolating to all ages it indicated that about 471,000/ year get RF. Calculating on the basis of 60 per cent patients of RF getting carditis, about 282,000 new cases of RF are added each year with the remaining 40 per cent or 189,000/year having a potential for subclinical RHD (Table V). A review of the incidence of acute RF, in population based studies in the world has estimated that the overall incidence varies from 5 to 51/100,000 population with a mean of 19/100, 000[42].

These estimates do not take into account subclinical carditis identified on the basis of echocardiography and Doppler studies in surveys of school children (Table IV). Although the exact significance of the subclinical carditis in terms of morbidity has not been established, it cannot be disregarded. Studies suggest that subclinical RHD can progress to clinical RHD. At the same time it is well known that recurrences of RHD have mimetic features and the subclinical disease may become a clinically obvious disease in recurrences in the absence of secondary prophylaxis[43]. The magnitude of subclinical carditis, 10 to 20 times higher than manifest RHD, indicates the difficulties regarding secondary prophylaxis. Secondary prophylaxis is ethically mandatory in this age group. Can we identify children with subclinical carditis and not put them on secondary prophylaxis ?

Diagnosis of RF

The criteria for the diagnosis enunciated by Dr T. Duckett Jones' have been modified, revised and updated by the American Heart Association (AHA)[44]. The diagnostic criteria consist of major manifestations carditis, arthritis, subcutaneous nodules, erythema marginatum and chorea. Rheumatic carditis resulting in a more or less permanent damage to the heart is the main virulent manifestation of RF.

The minor manifestations consist of fever, arthralgia, elevated sedimentation rate, C-reactive protein (CRP) and prolonged PR interval in the electrocardiogram. Presence of two major or one major and two minor manifestations with an evidence for recent GAS infection (essential criterion) indicate acute RF. Evidence for recent GAS infection can be in the form of a positive throat culture, elevated anti-streptococcal, antibodies or presence of features for recent scarlet fever, rare in our country.

The components of major, minor and essential criteria for the diagnosis remain more or less as before in AHA guidelines[44]. The updated criteria emphasize the value of indolent carditis and chorea to be accepted as evidence of RF and have removed previous RF or presence of RHD as a minor manifestation to simplify the diagnosis of first attack of RF. In the presence of previous history of RF/RHD one major or more than one minor criterion is acceptable for the diagnosis of recurrent RF. Additionally echocardiogram based diagnosis of carditis has been questioned in the absence of clinical findings to indicate cardiac involvement. The clinical manifestations of RF, except for minor differences in frequency, is the same all over the world. In our country erythema marginatum is not recognized possibly because of the darker skin complexion (Table VI)[22,45-48].

It needs to be emphasized that the diagnostic criteria are guidelines that help in the identification of RF. However, physicians have a right to make a

Table VI. Major manifestations of acute RF

	Roy[22]		Padmawati & Arora[45]	Sanyal *et al*[46]	Agarwal & Agarwal[47]	Vaishnava *et al*[48]
	Delhi	Boston	Delhi	Delhi	Allahabad	Vellore
N	113	490	-	102	100	166
Carditis	46	53	14	33	51	97
Arthritis	32	58	36	67	68	2.4
Chorea	5	19	4	21	16	5.4
SC nod	3	12	1	2	5	1.2
E. marg	0	11	0	2	0	0

Figures indicate percentage of patients
SC nod, subcutaneous nodules; E. marg, erythema marginatum

diagnosis of RF on the basis of clinical judgment even if the updated criteria are not satisfied. This may be due to *(i)* absence of history suggestive of RF in almost 50 per cent patients of RHD, and *(ii)* identification of subclinical carditis by echocardiographic studies, indicating inadequacy of clinical diagnosis.

Identification of RF

RHD can occur only after a patient has had RF. Evaluation of data indicates that about 65 per cent patients get clinically recognizable RHD following RF. In the global estimate a conservative figure of 60 per cent carditis has been used for calculating the burden of RHD[39]. This suggests that at least 40 per cent patients who have had RF could be potentially patients of subclinical carditis. On the basis of Utah study, 27 per cent patients had subclinical carditis[49]. Hence, the actual estimated burden could be much more than the actual burden. Secondly, most prevalence figures indicate that the prevalence of RF in surveys is about one tenth or even less than that of RHD (0.1/1000 vs 1/1000)[26]. The inference could be that the diagnosis of RF is being missed more often than desirable or acceptable. Less than half of all RHD patients give history of past RF. Unfortunately, diagnosis of past RF is not possible unless patients give history of arthritis, arthralgia, chorea or have established RHD. Hence, retrospective diagnosis or identification of past RF is missed or not available in almost 50 per cent patients with RHD.

Follow up of patients with pure chorea without RHD or of patients who have had RF but no clinical evidence of carditis indicates that RHD can develop over a period of time. Bland[50] in a 20 year follow up of patients with isolated chorea found 23 per cent patients without clinical carditis to develop RHD predominantly mitral valve obstruction (MS). Similarly, Aron *et al*[51] in a 30-year follow up of 50 patients of pure chorea ended up with RHD, predominantly MS, in 34 per cent patients. Roy *et al*[52] drew attention towards the onset of symptomatic severe MS below the age of 20 yr and designated it as juvenile MS in India. In our evaluation of children below 12 yr of age who have been operated for MS 57 per cent gave history consistent with RF, haemodynamic studies in 29 and operation in 35 of the 42 patients indicated moderately severe to severe MS requiring operative treatment below the age of 12 yr[53]. The assessment of the exact time of RF and the interval between RF and onset of symptoms of MS could be fallacious since it was dependent entirely on the past history of arthritis and arthralgia. Nine patients became symptomatic, within a year and five within two years, all below 12 yr in age. The youngest patient was six years old at the time of operation without a history suggestive of RF[53]. In a subsequent evaluation of 125 children below of the age of 12 yr with isolated mitral stenosis, past history of rheumatic fever was available in 54 (51%)[54].

These studies indicate that MS can occur very quickly following RF. Secondly 43-50 per cent developed significant mitral obstruction without a history to suggest RF indicating that acute RF is not being recognized, possibly because RF is occurring with subclinical carditis but without arthritis, arthralgia, subcutaneous nodules, and chorea. Missing a clinical diagnosis of acute RF in children less than 12 yr of age is most disturbing since the time available to forget the manifestation of acute RF is very short if we accept that RF must have occurred beyond the age of 2 to 3 yr in most.

Presence of subclinical carditis diagnosed using echocardiography in surveys of 5-14 yr old children

when combined with the findings of the children with MS suggests that RF is being missed more often than desirable. Some patients have only one clinical manifestation - fever with valvulitis during the episode of RF and the diagnosis of RF is being missed since the carditis is asymptomatic, mild and not associated with any murmurs (subclinical). The findings suggest that the diagnosis of RF based on the 1992 guidelines of AHA are necessary but insufficient in identifying RF in a fairly large number of patients[44].

Diagnostic tests in RF/RHD

The diagnostic tests can be considered as those meant for *(i)* diagnosis of RF, *(ii)* presence of active vs. inactive RF in recurrences, and *(iii)* identification of carditis and valve damage in RHD.

***Diagnosis of RF*:**

(1) The diagnosis of RF is dependent on some laboratory tests included as minor criteria and consist of the following:

(i) Acute phase reactants (leukocytosis, elevated sedimentation rate and presence of C reactive protein CRP).

(ii) Prolonged PR interval in the electrocardiogram.

(2) The diagnosis requires presence of essential criteria in the form of evidence for recent GAS infection and consists of:

(i) elevated antistreptococcal antibodies,

(ii) positive throat culture for GAS, and

(iii) evidence for recent scarlet fever- rare in India.

Elevated erythrocyte sedimentation rate (ESR) is a nonspecific evidence for an active disease. It is elevated in acute RF but can be normal if the patient has congestive failure and can be high in the presence of anaemia. Normal CRP is against the diagnosis of active RF. Prolonged PR interval can be seen in the electrocardiograms in patients with active RF. Prolonged PR interval is a non specific finding and does not indicate the presence of myocarditis. Elevated antistreptococcal antibodies identify recent streptococcal infection. A fair amount of confusion exists about the exact level of antibodies to be considered as high. Generally antistreptolysin O (ASLO) is the commonest antibody measured. It appears in about 7 to 10 days and peaks in 2 to 3 wk[55]. It is considered high if the figure is more than the baseline value present in the community. In endemic areas the baseline ASLO could be 250 Todd units or more whereas in non-endemic areas it could be as low as 50 Todd units. Increasing titres indicate recent GAS infection. Using two antibody titres, that is, ASLO combined with deoxyribonuclease B titres increases the specificity of diagnosis to 90 per cent[56].

Presence of GAS in throat culture with low values of ASLO suggests a carrier state. As such a positive throat culture for GAS cannot be taken as recent infection unless the antibody titres are elevated.

Presence of active vs. inactive RF in recurrences: Two investigations have been tried to assess the presence or absence of active RF in patients with recurrences besides ESR, CRP and evidence for recent GAS infection.

(i) Induced subcutaneous nodules (SCN): Massell *et al*[57] tried inducing SCN by injecting five dl autologous blood drawn from a vein and injecting over the olecranon process of one elbow and saline in the other elbow. Frictional pressure was applied to the injected sites. Appearance of a SCN in 5 to 10 days was accepted as indicating active RF. Vasan modified this test and used concentrated leukocyte injection instead of whole blood with 86 per cent sensitivity and 94 per cent specifically to identify active RF. The test offers the advantage of being cheap and easily available everywhere. The potential utility of the test lies in identifying active RF. However, additional validation studies are perhaps needed.

(ii) Myocardial biopsy: A study of myocardial histology to identify active vs. inactive RF was utilized in patients of RF[59]. Myocardial biopsies were performed in 89 patients of active RF and chronic RHD to identify active carditis Myocardial biopsies failed to improve on clinically assessed presence of active RF. Myocardial biopsy was felt to be insensitive for identifying presence of active carditis[58].

Rheumatic carditis and valve damage

The virulence of RF is related to its capacity to cause cardiac damage. Clinically carditis has been reported by several investigators in the initial attack in India (Table VI)[22,45-48]. Rheumatic carditis has been considered to be a pancarditis causing pericardial, myocardial and endocardial disease.

Pericarditis occurs in about 15 per cent cases. It is identified by the presence of a pericardial friction rub and may be associated with precordial chest pain. It can be evanescent and may appear for a brief period. An echocardiogram can identify the effusion, which

never results in tamponade and subsides without any sequelae.

Studies strongly suggest that RF does not cause myocarditis. Absence of myocarditis has been documented by *(i)* absence of increase in markers of myocardial damage - MB fraction of creatinine kinase (CK-MB), troponin I & T and myoglobin[60-62], *(ii)* normal left ventricular systolic function and myocardial contractility by echocardiographic studies[62,63], *(iii)* radionuclide studies using technetium pyrophosphate scanning and indium^{III} labelled anticardiac myocin Fab (FAB) do not indicate presence of myocardial damage[64,65], *(iv)* myocardial biopsy studies have not been able to identify the presence of myocarditis[59], *(v)* normalization of heart size and disappearance of congestive failure following surgical mitral and/or aortic valve replacement in patients deteriorating in spite of aggressive medical management[66], *(vi)* histopathology of the left ventricular myocardium showing absence of myocardial or inter-myocardial connective tissue damage[67] and *(vii)* immunopathology of Ashoff nodule (AN), the diagnostic marker of rheumatic pathology, being derived from mesenchymal cells, complete absence of cells of myocardial origin in AN and absence of actin, myosin and desmin (of myocardial origin) in the AN indicating that AN is not of myocardial origin[68]. Hence, congestive cardiac failure in acute RF is due to an acute volume overload from mitral and/or aortic regurgitation but not due to myocarditis *per se*.

Rheumatic endocarditis represented by cardiac valve involvement results in the only permanent damage from RF. Pathological evaluation of the valves of patients dying from acute RF indicates microscopic disease in each of the four cardiac valves[69]. However, clinically mitral valve involvement occurs in 90 to 95 per cent of whom in 20 to 25 per cent, it is associated with aortic valve disease as well. Clinically isolated aortic valve involvement has been reported in less than five to eight per cent cases[70,71]. Tricuspid valve involvement in acute RF is uncommon and the pulmonary valve involvement very rare. Tricuspid valve disease has been found to occur in up to 30 to 50 per cent in necropsy studies[72]. Since pericarditis subsides without sequelae and myocarditis does not occur, the morbidity and mortality of RF is determined by valvulitis the cause of permanent cardiac damage in RF.

In an evaluation of patients with RF the final diagnosis regarding the presence or absence of carditis is determined by clinical findings related to the mitral and aortic valve disease. Clinically carditis has been found in anywhere between 14 to 97 per cent patients (Table VI). The commonest clinical finding is the presence of mitral regurgitation with or without aortic regurgitation.

Table VII. Frequency of subclinical (SC) carditis in acute RF

Studies	N	RHD	SC (%)	Carditis (%)
Lanna *et al*[72]	40	28	02 (5)	30 (75)
Hilario *et al*[73]	22	08	05 (22.7)	13 (59)
Figuero *et al*[74]	35	15	10 (28.6)	25 (71)
Araujo *et al*[75]	462	258	72 (15.6)	330 (71)

SC, subclinical carditis

More recent studies on patients with acute RF utilizing echocardiography have brought out the shortcomings of auscultation in identifying valve disease which does not result in haemodynamic abnormalities consisting of regurgitant systolic (mitral) or diastolic (aortic) murmurs. This has resulted in the identification of sub-clinical carditis (SC). Data for SC are now available from a number of studies. However, follow up data are insufficient. Subclinical carditis has been assessed by echocardiographic and Doppler (E&D) studies in *(i)* patients with acute RF, *(ii)* follow up of patients with past RF who were clinically judged not to have carditis (NHD), and *(iii)* evaluation of normal children. SC has been found in 5 to 29 per cent patients of acute RF (Table VII)[73-76] by E&D studies. In the Utah epidemic of acute RF clinically identifiable carditis was present in 64 per cent whereas SC diagnosed by E&D was found in 27 per cent resulting in an overall prevalence of 91 per cent[49]. Although the American Heart Association (AHA) has not accepted E&D studies for the identification of carditis, many clinicians feel that E&D studies are necessary for the care of patients with acute RF since SC cannot be disregarded. Follow up data on patients of acute RF with SC are unsatisfactory. Available follow up E&D studies indicate that the SC can worsen to become clinically obvious RHD, improve or remain unchanged. Lanna *et al*[73] reported an 8-year follow up on 40 patients of RF. Initially they found two patients with SC but after eight years six lost clinical evidence of mitral regurgitation resulting in eight patients (20%) having SC. Araujo *et al*[76] followed 462 patients for 2 to 23 yr (mean 13.6 yr). Initial evaluation indicated that 258 (56%) had carditis and 204 without clinical evidence for heart disease. E&D studies identified 72 (16%) with SC. At the end of follow up (13.6 yr) the number with clinical carditis

went up to 298 (65 from 56%)[76]. The E&D studies thus indicate that patients identified as SC could improve and lose features of SC or become worse and develop clinical carditis (RHD).

A review of SC involving more than 1700 patients found overall prevalence to be 16.8 per cent[77]. WHO criteria for the identification of SC by E&D were satisfied by 10 studies which gave a prevalence of 18.1 per cent. Of the 99 patients whose follow up of up to 2 years was available, 48 per cent showed improvement and 52 per cent either no change or became worse indicating variable course of SC[77].

In one of the largest study of 1000 patients of acute RF with a 100 per cent 20 year follow up, 154 (15%) patients developed RHD out of 347 (35%) patients initially diagnosed as NHD (labeled as potential RHD), indicating the presence of SC in retrospect[78]. In the same study 32 (20%) of the 157 children with pure chorea (NHD) developed RHD, predominantly mitral stenosis in 20 years identifying the presence of SC. Bland and Jones[78] in their study made two crucial statements while detailing the delayed appearance of RHD. Both statements are sharp clinical judgments (in 1951) in the absence of investigative facilities for identification of carditis.

"It may be that minimally scarred valves (initially silent as far as physical signs are concerned) provide a locus **for ---------- deformed and** stenotic orifice"[78].

"In an occasional instance a blowing diastolic murmur (slight aortic regurgitation) of grade 1to 2 intensity has been observed to disappear. We suspect that minimal scarring persists in spite of the absence of murmurs or enlargement. Postmortem examination in one instance following accidental death supports this suspicion, as well as the insidious appearance of mitral stenosis in a few patients 10 to 20 years later[78]".

A large amount of data is now accumulating and identifying SC by E&D studies of normal children (Table IV). The exact significance of SC identified in apparently normal school children needs to be established. The criteria for identifying SC by E&D studies need careful definition. Presently WHO and World Heart Federation (WHF) guidelines are available[79,80]. WHO has used only Doppler based guidelines identifying the presence and severity of valve regurgitation. WHF has used changes in valve morphology as well as Doppler estimation of valve regurgitation. At least one study has already indicated that WHO guidelines are insufficient[81]. Logically diagnosis of SC should be based on changes of valve damage as well as the haemodynamic consequences of valve damage. We believe that morphological changes indicating valve damage should be considered more important and essential rather than the presence of valve regurgitation alone, since it is the rheumatic valve damage which is responsible for the haemodynamic changes in RHD.

At present we need to *(i)* establish E&D guidelines for identification of SC, *(ii)* identify the magnitude of SC in apparently "healthy" children, and *(iii)* follow up studies of SC in apparently healthy children to decide the line of management. If follow up studies indicate that SC can deteriorate to RHD in the absence of secondary prophylaxis those identified as having SC will have to be put on secondary prophylaxis. In the absence of long term follow up it is desirable to evaluate adults 20 to 35 yr in age to find out the prevalence of SC. This should help in defining the course of SC to some extent. The study from Nicaragua of 376 adults identifying 23/1000 with SC is useful but too small for any conclusion[34].

Pathogenesis of RF

It is well established that RF causes permanent damage only to the cardiac valves. Clinically the mitral aortic, tricuspid and pulmonary valves are involved in order of frequency. Mitral valve involvement is the commonest and the pulmonary valve involvement is rare. However, pathological evaluation of valves from patients dying of acute RF indicates that microscopic involvement of tricuspid and pulmonary valves occurs in almost 100 per cent cases[69]. The cardiac valve damage is the basic reason why RF needs to be controlled to reduce the morbidity and mortality related to RF.

Cardiac valves are derived from the ventricular myocardium by a process of undermining. The valves are composed of a central core of connective tissue covered on both sides by endothelium. The central core of connective tissue is derived from the ventricular myocardium - muscle and inter-myocardial connective tissue. Histopathology indicates absence of myocardial and connective tissue damage in carditis due to acute RF. Immuno-histopathology excludes myocardial damage in RF. Hence, the site of damage in the valves derived from the ventricular myocardium has to be the valve endothelium[82]. Endothelium *per se* consists of two components – the endothelial cells and the basement membrane to which the cells are attached. By

exclusion the findings suggest that the valve damage is related to the valve endothelium- the endothelial cells, the basement membrane and the substance binding these together[82].

It is well established that RF follows GAS infection of the tonsillopharynx and does not follow skin infection. Mesothelium and endothelium are derived from mesenchymal cells. Mesothelial cells cover tonsillopharyngeal region whereas ectodermal cells, which are completely different in composition from mesothelial cells, cover skin. Why should RF follow pharyngeal infection but not dermal infection? Is it because the GAS infection affecting the pharyngeal mesothelial cells sensitizes the cells in a way which later manifests as endothelial cell damage of the valve tissue and mesothelial cell damage elsewhere (arthritis, *etc*.) later on ?

Pathogenesis of RF is not known. Research to elucidate the pathogenesis has been directed almost exclusively toward myocarditis and myosin for the last more than 60 years without any breakthrough[83,84]. An alternative approach with endothelium as the target of rheumatic damage as well as guidelines for further research have been suggested in the hope that these may help in identifying the GAS antigen (s) responsible for RF[82].

Acute RF: duration of disease

A combination of some clinical manifestations and laboratory tests put together by Jones, revised and modified from time to time by the AHA, identify the syndrome of RF. Elevated ESR and CRP are nonspecific and identify the presence of an active inflammatory disease. Elevated anti-streptococcal antibodies indicate streptococcal infection. Thus there is no specific investigation, which is diagnostic for RF. Of the clinical manifestations arthritis, erythema marginatum and carditis suggest acute and active RF. Subcutaneous nodules and chorea are late manifestations and indicate past RF not active RF.

The inference that RF lasts 10 to 12 wk in about 80 per cent patients was dependent on the elevated ESR and CRP. As of today we do not know the duration of active rheumatic "process" *per se*. Arthritis suggests active RF, however, if the rheumatic process is active why should arthritis subside without treatment? The central nervous system (CNS) damage occurs with acute RF. At the time patients present with chorea the ESR and CRP may be normal indicating absence of an active disease process. Is the rheumatic inflammation active or inactive at the time a patient presents as chorea? Hence high or normal ESR and CRP do not identify active or inactive rheumatic process. Why should chorea occur three to six months after the CNS damage that occurs during acute RF? What is the duration of active rheumatic inflammation in RF? The damage resulting from active rheumatic process has to be separated from the residual effect of the damage caused by the rheumatic disease. The duration of the disease in acute glomerulonephritis, the other non-suppurative manifestation of GAS infection, is less than seven to ten days[85]. Majority of patients recover within that time. Urinalysis continues to show microscopic haematuria for several months in spite of clinical recovery. Unfortunately there are no investigations, which can identify active rheumatic disease process itself.

Management

There has been no significant change in the management of acute RF in the last 50 years. Patients need penicillin to eradicate GAS present in throat. Anti inflammatory agents - aspirin or steroids - are used to control rheumatic activity. Aspirin or steroids do not cure RF. These suppress the inflammatory response which lasts for about 12 wk in more than 80 per cent patients. Hence, the standard dose of aspirin (90-120 mg/kg/day) is given for ten weeks and tapered in the next two weeks. The dose of prednisone 60 mg/day above 20 kg and 40 mg /day below 20 kg in weight is given for three weeks and tapered in the next nine weeks. The standard 12 week course can be reduced to four to eight weeks depending on the patient's response. Patients without carditis can have weekly follow up of ESR and CRP. If they normalize, the course can be reduced to a shorter period. Aspirin is preferred over steroids as long as the carditis is mild and the patient is not in congestive failure. However, with severe carditis and congestive failure steroid is the drug of choice because of the more potent suppressive effect.

Non-steroidal anti-inflammatory drugs (NSAIDs) have not been systematically utilized to establish their usefulness. Immunosuppressive agents like azathioprine and cyclosporine A have also been considered for acute rheumatic fever. Despite of the concerns of side effects, toxicity and late onset of lymphomas with the use of these immunosuppressive it is possible to argue that a short course of 6 to 8 wk may result in a greater benefit than harm. However, most ethics committees will hesitate to permit systematic testing of these agents.

It is now well accepted that rheumatic endocarditis involving heart valves is the main cause of morbidity and mortality in RF. Surgical management consisting of mitral and /or aortic valve replacement in patients whose congestive failure cannot be controlled by aggressive medical treatment during acute RF, is life saving. It the congestive failure cannot be controlled with maximal medical therapy and the patient is deteriorating due to mitral regurgitation, mitral valve replacement during active RF is indicated. In spite of clinical evidence for active RF, the heart size returns to normal and congestive failure disappears, confirming that rheumatic myocarditis plays little or no role in the mortality of RF[66].

Management of chorea: It has a self limiting course, hence parents need reassurance. The children could be treated with sedatives like phenobarbitone 30 mg thrice daily. chlorpromazine, valium, diphendydramine or promethazine can be used as sedatives. Haloperidol 5 to 10 mg twice daily has been used effectively. Although aspirin and steroids are not supposed to have a place in the treatment of chorea, some patients have shown dramatic response to steroids, if they do not show adequate response to sedatives[86,87]. Since, long term follow up of chorea patients have identified subclinical carditis in 20 to 30 per cent patients, penicillin prophylaxis is essential and should be continued on a long term basis[50,51].

Rheumatic heart disease: Surgical management of valve disease was the standard approach till balloon mitral valvotomy was introduced in 1985. Mitral stenosis could be corrected surgically either by closed valvotomy, open commissurotomy or by valve replacement if the valve was calcified. Balloon valvotomy provides results as good as surgical valvotomy and has become the treatment of choice in spite of being more expensive. For mitral regurgitation the choice of treatment would be valve repair especially in younger patients to avoid long-term anti-coagulant therapy. Most patients with mitral or aortic valve regurgitation end up with valve replacement. Hence, although surgical help is very useful it is expensive and requires prolonged care with anticoagulant therapy with the associated complications of valve thrombosis and systemic embolic disasters especially in the low-income population of the country. Over a long follow up period relatively few patients remain free of events.

Balloon mitral valvotomy has been utilized in the paediatric patients below 12 yr in age with acceptable results. It has been extended to patients of mitral stenosis with acute RF, without additional risk and acceptable results. In the presence of acute RF restenosis rate was, however, 40 per cent compared to 10 per cent in those without active RF[88,89].

Prevention of RF and RHD

A disease which follows a bacterial infection should, theoretically, be preventable if the organism does not become resistant to antibiotics. GAS have remained sensitive to penicillin and should have been eradicated. Unfortunately despite a decline in prevalence, RF continues to occur in socioeconomically disadvantaged populations and even developed countries have witnessed resurgences in localized areas[49,90]. Steps in the development of RF consist of GAS pharyngitis, which should be symptomatic enough to require medical attention, throat culture to confirm the diagnosis and ensuring that the course of penicillin treatment has been completed. The last epidemic of RF in Utah area in USA occurred in well to do middle class families, absence of overcrowding and with access to good medical care. The findings of the epidemic indicated that the preceding pharyngitis was asymptomatic in 78 per cent, 18 per cent obtained medical help and the 10 day course of oral penicillin was not completed by patients[49,90].

Prevalence of RF/RHD has been attributed to overcrowding and unhygienic living related to low socio-economic status. Unhygienic living results in persistent GAS in the environment. Since GAS spreads by droplet dissemination, overcrowding causes cross infection from person to person. Low socio-economic status may undermine nutrition and seriously limit access to medical treatment. Poor nutritional status is believed to contribute to a decreased immune response. The result is not only endemic RF but also a more severe or virulent disease (Fig. 1).

It is possible at the same time that the initial attack of RF is mild and results in mild carditis, which remains subclinical, undiagnosed, and as such the patient does not get prophylaxis to prevent recurrences. In low socio-economic settings, recurrences causing further cardiac damage result in symptomatic RHD with multivalve involvement and congestive failure identified as the first attack of severe (malignant) RF (Fig. 2). The high prevalence of subclinical carditis found by echocardiographic studies suggests that the initial attack of RF is probably relatively mild and in the absence of secondary prophylaxis it is the recurrences,

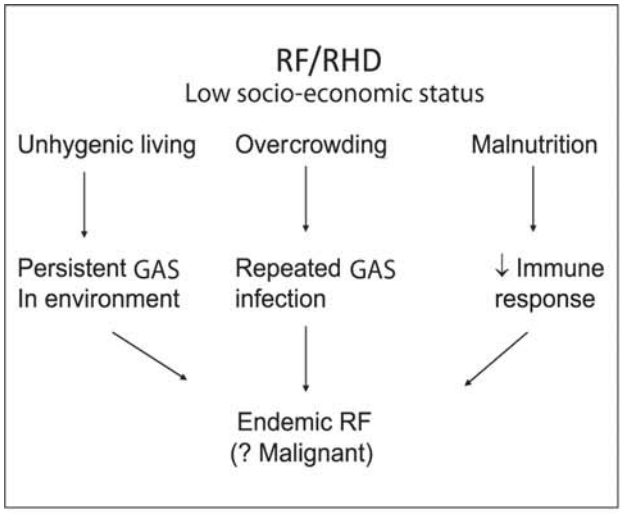


Fig. 1. Relationship of low socio-economic status to rheumatic fever (RF).

which are responsible for patients presenting with severe disease being labelled as the first attack of RF.

The strategies for prevention consist of primordial prevention, primary prevention and secondary prevention.

Primordial prevention: It requires, preventing the development of 'risk factors' in the community to prevent the disease in the population and thus protect individuals. Requirements for primordial prevention in relation with RF and RHD consist of *(i)* improvement in socio-economic status, *(ii)* prevention of overcrowding, *(iii)* improving nutritional status, *(iv)* availability of prompt medical care, and *(v)* public education regarding

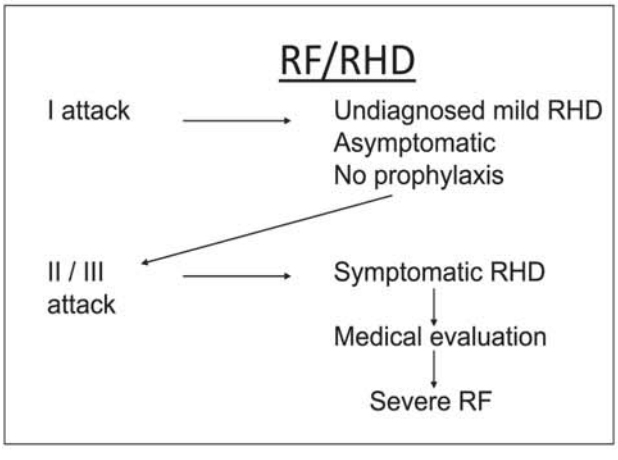


Fig. 2. Possible mechanism to explain why RF appears to be severe in the initial attack.

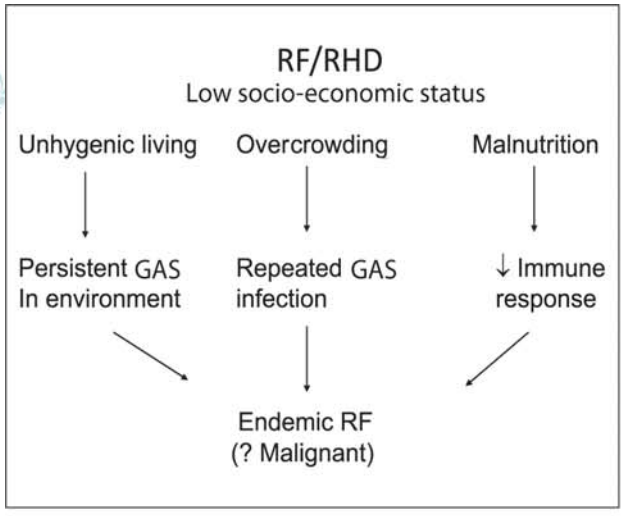
the risk of RF from sore throat specially below the age of 15 yr.

Improvement in nutrition improves immune response and the capacity of individuals to resist and fight infection. Public education is the most important component for primordial prevention. Unless parents know that a sore throat can cause RF and RHD, it is most unlikely to be seen by a physician and treated. Improvement in socio-economic status and preventing overcrowding cannot be relied upon to reduce the burden of RHD.

Primary prevention: Primary prevention is theoretically feasible but practically extremely difficult to achieve. Primary prevention requires identification of (GAS) sore throat and use of penicillin to eradicate the streptococci. The requirement for primary prevention consist of *(i)* public awareness regarding danger of RF from sore throat *(ii)* identification of sore throat as being due to GAS infection, and *(iii)* use of injectable penicillin to cure the infection.

It is important to know that oral penicillin may not be effective in preventing RF. RF occurred in 15 to 48 per cent children given oral penicillin for 10 days in an earlier epidemic in USA[90]. Compliance of a 10 day oral treatment even in educated families is not certain. It is, therefore, essential that injectable penicillin is used to prevent RF. The recommended dose of penicillin is 400,000 units of procaine penicillin twice daily for ten days. Although recommended, one injection of 1.2 mega units of benzathine penicillin may not be enough to eradicate GAS infection especially in endemic areas[91]. Since GAS infection spreads through droplets from person to person, eradication of GAS even in one individual will reduce the total burden of the organism in the community. The inability to utilize primary prevention at the community level is due to the large number of sore throats requiring treatment to prevent a single episode of RF.

Community level management requires a sledgehammer approach, that is, each sore throat must be treated. At present, bacteriological facilities required to identify GAS sore throat at the community level for the whole country, would be expensive, do not exist and are not likely in the near future. Hence, each sore throat will need to be treated to reduce the cost. Treating each sore throat is logistically not feasible. Anywhere from 3 to 20 per cent of sore throats can be due to GAS infection, the rest being viral infections, which do not require treatment. About 0.3 per cent of streptococcal



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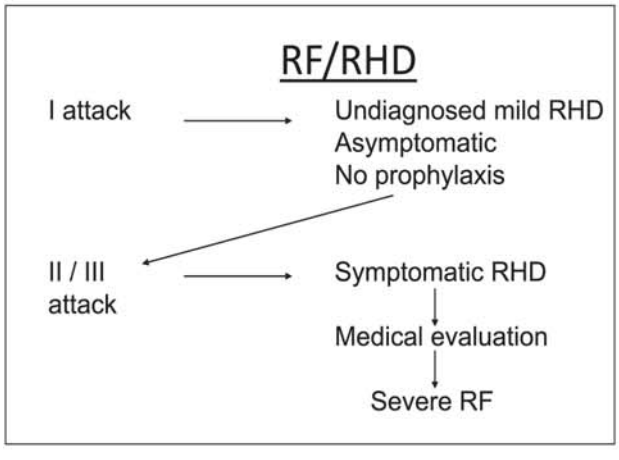

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The vaccine may not be effective against infection by a strain that has mutated after being incorporated in the vaccine even in a very short time[95].

GAS infection has resulted in lethal toxic shock syndrome without expressing M-protein, electron microscopy failing to identify M-protein fibrils on the surface of the organism and the isolate failing to resist phagocytosis, suggesting the absence of "functional M-protein"[96].

M-protein has been excluded as the antigen responsible for acute GN the other non suppurative manifestation of GAS infection[85].

The surface M-protein of GAS was designated as the virulence factor of GAS. The similarity in the structure of M-protein and the human tropomyosin has resulted in accepting, without proof, that it is responsible for RF. There is no evidence to indicate that M-protein is the antigen responsible for RF.There is no information regarding the role M-protein plays in the suppurative diseases due to GAS infection.

Toxic shock syndrome occurred in the absence of functional M-protein and the paediatric nephrologists have excluded M-protein as being responsible for acute GN. Therefore, there is evidence that at least two, one suppurative and one non-suppurative of the various GAS related manifestations are unlikely to be prevented by a vaccine based on M-protein The vaccine if and when available is expected to prevent GAS infection. This will prevent GAS infection related diseases - necrotizing fasciitis, toxic shock syndrome, acute glomerulonephritis, rheumatic fever, pyoderma and septic arthritis, *etc*.

Unfortunately in spite of extensive evaluation and efforts it has not been possible to formulate a M-protein based vaccine in the last 40 years. We need to consider as to why it is necessary to start from RF and its relation with GAS M-protein to make a vaccine. Why are we not looking for the virulent epitope of GAS from infections causing septic shock, pyoderma or septic arthritis for its suitability for anti GAS vaccine, since the interest is in preventing GAS infection? It is well known that GAS infection precedes rheumatic fever but which epitope of GAS results in rheumatic fever is not known. The interest is in preventing GAS infection by a suitable vaccine, which should prevent all GAS infection related manifestations. Prevention of rheumatic fever, pyoderma or glomerulonephritis will be specific benefits of such a vaccine.

The answer to the question "Is it possible to prevent rheumatic fever"? has to be "No", for primary prevention at the community level. Primary prevention will have to wait till a safe and effective GAS vaccine becomes available.

In our country the health of the child generally remains a priority responsibility of the parents even when the child becomes an adult. Hence, prevention of RF and RHD is possible to a large extent if we can provide the message, in local languages, to the population (parents) that sore throats should not be neglected; that sore throats should be shown to a doctor for treatment to prevent RF and RHD. Radio and television are available for reaching each corner of the country and should be utilized for this purpose. If education can be made compulsory till the age of 15 yr, school health education and school health care facilities can be utilized to control RF.

RF and RHD continue to be an undesirable burden. RF occurring at a young age results in morbidity as well as mortality in adolescents and young adults, and also becomes one of the major causes of loss of the most productive years of life in our country. With the identification of subclinical carditis in normal children, the total burden of RHD is much higher than that estimated in various studies. Although the disease (RF) follows a bacterial (GAS) infection, the pathogenesis has not been worked out in more than 60 years. Duration of the disease, specific medical treatment to control or prevent cardiac damage and primary prevention of RF continue to be elusive. Primary prevention has to depend on designing a vaccine to prevent GAS infection related suppurative as well as non-suppurative disease manifestations.

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The WHF Roadmap for Reducing CV Morbidity and Mortality Through Prevention and Control of Rheumatic Heart Disease

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ABSTRACT

Rheumatic heart disease (RHD) is a preventable non-communicable condition that disproportionately affects the world's poorest and most vulnerable. The World Heart Federation Roadmap for improved RHD control is a resource designed to help a variety of stakeholders raise the profile of RHD nationally and globally, and provide a framework to guide and support the strengthening of national, regional and global RHD control efforts. The Roadmap identifies the barriers that limit access to and uptake of proven interventions for the prevention and control of RHD. It also highlights a variety of established and promising solutions that may be used to overcome these barriers. As a general guide, the Roadmap is meant to serve as the foundation for the development of tailored plans of action to improve RHD control in specific contexts.

1. INTRODUCTION

Rheumatic heart disease (RHD) is a preventable non-communicable condition that disproportionately affects the world's poorest and most vulnerable. Globally, 32 million people suffer from the condition, which kills 275,000 people annually [1]. Driven by poverty, poor access to health services and other health system weaknesses, the majority of people with RHD live in low- and middle-income countries, with the remainder in vulnerable communities of wealthy countries [2].

In recent years, the need for concerted global action to control non-communicable diseases, including RHD and other cardiovascular diseases (CVD), has become a high priority on the global health agenda. This prioritisation is evident in the UN political declarations on the Prevention and Control of Non-Communicable Diseases ('25 by 25' target), the WHO Global NCD Action Plan, and the UN Sustainable Development Goals [3,4].

With CVD as the leading cause of premature mortality worldwide, and more than 80% of deaths occurring in low- and middle-income countries, the World Heart Federation (WHF), as the world's leading global CVD organization, launched its Roadmap Initiative in 2014 to guide and support those seeking to improve CVD control.

The WHF Roadmaps are global implementation strategies designed to help governments, employers, non-governmental organizations (NGOs), health activists, academic and research institutions, health care providers and people who have been affected by CVD, take action to better prevent and control CVD [5,6]. The Roadmaps synthesise existing evidence on the efficacy, feasibility and cost-effectiveness of various strategies. They also identify potential barriers (roadblocks) to their implementation, and propose potential solutions to bypass them.

The WHF Roadmap for reducing morbidity and mortality through improved prevention and control of RHD complements existing roadmaps on tobacco control [7], raised blood pressure [8], and the use of secondary prevention for CVD [9], and follows the 2013 WHF position statement on the prevention and control of RHD [10].

As part of its 2013 statement on RHD, the WHF endorsed the ambitious goal of achieving a 25% reduction in premature deaths from rheumatic fever (RF) and RHD among individuals aged <25 years by 2025 [10]. To achieve this, the WHF also defined five targets:

- Foster at least one prominent public figure as an 'RHD champion' in every country where RHD is endemic,
- Ensure that 90% of countries with endemic RHD have integrated and comprehensive control programmes by 2025,
- Ensure the availability of high-quality benzathine penicillin G for 90% of patients with RHD in 90% of countries with a high burden of this disease,
- Establish at least one hub of training, research, and advocacy for RF and RHD in each WHO-defined geographic region by 2025,
- Test a group A β-haemolytic streptococcal vaccine in phase III clinical trials in RHD-endemic countries within 10 years [10].

The WHF RHD Roadmap will contribute to reaching these targets by acting as a resource to raise the profile of RHD nationally and globally, and by providing a framework to guide and support the strengthening of national, regional and global RHD control efforts.

The Roadmap's content is derived from searches for relevant systematic and narrative reviews of existing evidence found in Medline and the Cochrane Library; a synthesis of relevant peer-reviewed and grey literature published since 2012; and an iterative process of expert consultation involving 11 Writing Committee and 12 Reviewing Committee members drawn from the global WHF membership network and key stakeholders in RHD control.

Given the diverse settings in which RHD is endemic and the array of opportunities for intervention (even within individual countries), this Roadmap is best considered a generic framework for local adaptation and is intended to serve as a basis for developing region- or country-specific roadmaps.

Developing and effectively implementing country-specific roadmaps will require a coalition of the following stakeholders: health professionals; government departments and agencies; in-country and regional health organizations; NGOs; and industry, patient and community groups to advocate for the inclusion of RHD in national NCD action plans and various other national planning instruments.

The process also requires a range of local expertise that includes knowledge of medicine, cardiology, cultural and social contexts, prevention, health promotion, health systems, economics, and government priorities. Section 10 discusses this process further.

2. WHAT ARE RF AND RHD?

Rheumatic fever is an inflammatory disease involving the joints, skin, heart and brain, which develops following an untreated or partially treated group A β-haemolytic streptococcal (GAS) infection of the throat (streptococcal pharyngitis). Up to 30% of sore throats in children and young people are caused by GAS, and 0.3% to 3% of young people with an untreated GAS sore throat will develop RF [11,12].

Personal susceptibility, the type of GAS strain and poor socio-economic conditions that facilitate bacterial transmission and exposure, particularly overcrowded housing, are key risk factors for RF (see Fig. 1). In some regions, streptococcal skin infection has also been implicated in the disease process [13].

After recovery from the initial episode of RF, up to 60% to 65% of patients develop valvular heart disease [11,14] and the risk of RF recurrence following GAS infection rises to 50% [15,16]. Repeated GAS infections without appropriate treatment with benzathine penicillin G lead to RF recurrences and progressive valve damage—the defining characteristic of RHD—which can, in turn, cause atrial fibrillation, heart failure, stroke and endocarditis.

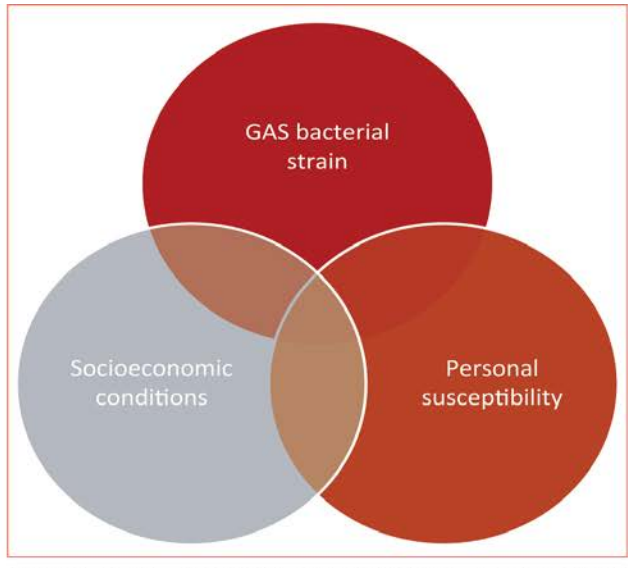

FIGURE 1. The interplay of risk factors for rheumatic fever.

A key determinant of disease progression is the number of times RF recurs in an individual [17]. As cardiac impairment worsens, disability increases and quality of life decreases. Surgery or cardiac catheterisation often become necessary, and patients who do not have access to such treatment ultimately die prematurely from RHD and its complications. In a large study conducted in 14 low- and middle-income countries, the median age of death was 28.7 years [18].

3. CHANGING BURDEN OF A PREVENTABLE DISEASE

By the 1980s, RF and RHD had virtually disappeared from high-income regions of North America and Europe [19,20]. However, the disease burden persists in low- and middle-income countries, home to 79% of people living with RHD [2], and in some indigenous populations of higher-income countries [21,22].

According to the WHO Global Health Estimates, the overall burden of RHD has declined over the past decade, though progress has been uneven [23]. Figures 2 and 3 illustrate the total deaths and disability-adjusted life-years (DALYs) estimated for each WHO region during 2000 and 2012. DALYs are a summary measure of health that capture both premature mortality and morbidity among prevalent cases in a single statistic. Reflecting morbidity in measures of burden is important as many people living with RHD are disabled by its long-term complications, which include heart failure, atrial fibrillation, stroke, infective endocarditis, and pregnancy-related complications.

At the global level, the number of deaths and DALYs attributed to RHD have decreased by 0.75% and 1.33%, respectively, since 2000. Progress was most notable in high-income countries and in middle-income countries in Europe and Southeast Asia. However, the total number of

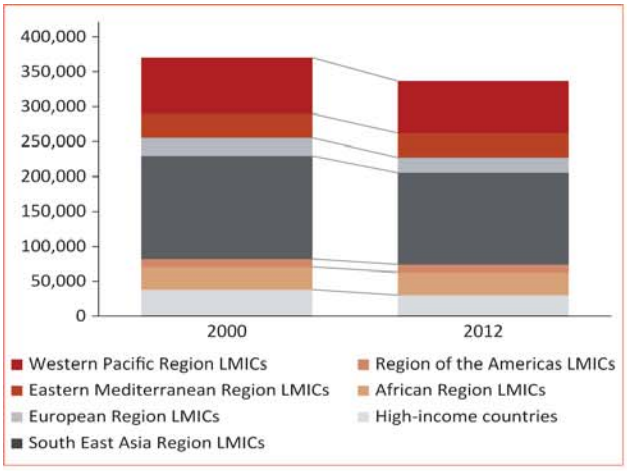

FIGURE 2. Global deaths from RHD by WHO region, 2000-2012. Adapted from WHO Global Health Estimates (GHE) database. LMIC, low- and middle-income country.

deaths in Africa and the Eastern Mediterranean increased over this period.

Burden of disease estimates have also been produced by the Global Burden of Disease (GBD) studies from the Institute for Health Metrics and Evaluation. The GBD 2013 study estimated 275,000 deaths globally (95% uncertainty interval [UI]: 222,600-353,900) for 2013 in comparison to the WHO estimate of 337,335 deaths [24]. The GBD 2013 study also estimated 32.9 million (31.6 to 34.0 million) prevalent cases and 9.5 million (7.9 million to 12.0 million) DALYs from RHD in 2013 [1,24]. Together, these findings suggest that the reductions in mortality may be resulting in an increased prevalence.

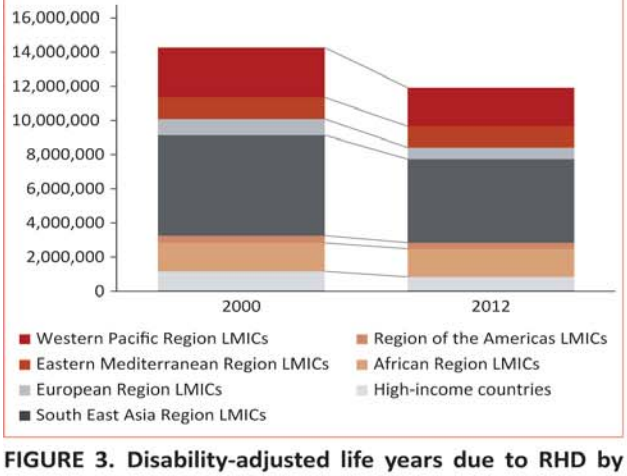

FIGURE 3. Disability-adjusted life years due to RHD by WHO region, 2000-2012. Adapted from WHO Global Health Estimates (GHE) database. LMIC, low- and middle-income country.

4. WHY CONTROL RF AND RHD?

There are a number of compelling reasons to act on RHD, in addition to the total global burden of disease [25]. As noted above, progress on RHD has been uneven, with some low-income areas experiencing increases in mortality as compared to high-income areas where mortality has decreased. Therefore, RHD contributes to rising health inequality at the global level.

Unlike many other CVDs, RHD is a preventable condition acquired in childhood that is amenable to early and effective intervention. This presents a rare opportunity to avert the immense personal burden and social costs associated with premature cardiovascular morbidity and mortality [26]. The potential economic gains from a societal perspective are even greater, as the burden of RHD is disproportionately borne by young, economically active people in low-income countries [26,27]. Therefore, controlling RHD supports overall economic and social development, both directly and indirectly.

RHD acts as a tracer condition that reveals issues in the performance of health systems. Comprehensive RHD control spans the whole health system, requiring robust primary care systems all the way up to specialised tertiary and quaternary care. RHD control programmes also present an opportunity to model good practice in the delivery of services to those with chronic conditions that require ongoing management. If done well, the learning and experience can be transferred to benefit other public health programmes.

Given the elevated risk associated with poverty and the impoverishing effects of the disease, addressing RHD is also an issue of equity in all affected countries, regardless of income level. It is also a matter of equity for women's health, as pregnancy and labour are particularly dangerous for women with RHD [28].

5. THE HEALTH CARE JOURNEY IN RHD

Although local differences in health services can be profound, people with streptococcal pharyngitis ('strep throat'), RF and RHD share a number of common health care needs. These common pathways are illustrated in Figure 4, which draws on the Continuum of Care (CoC) Framework for Health Systems developed by Medtronic Foundation. The framework acknowledges the interrelated nature of strep throat, acute RF and RHD, and traces a stylised version of the patient journey through the types (and level) of intervention required at each stage. These are numbered CoC1 to CoC10 in the Figure.

For instance, an unwell individual or their caregiver must initially decide to seek care for the illness (CoC2), and then engage with the health system (CoC3) where they should be appropriately diagnosed (CoC4) either with strep throat (path 1), rheumatic fever (path 2) or rheumatic heart disease (path 3). Those with strep throat should receive appropriate treatment with intramuscular benzathine penicillin G (BPG), ideally at the primary care level (CoC6). Those diagnosed with rheumatic fever should begin secondary prophylaxis

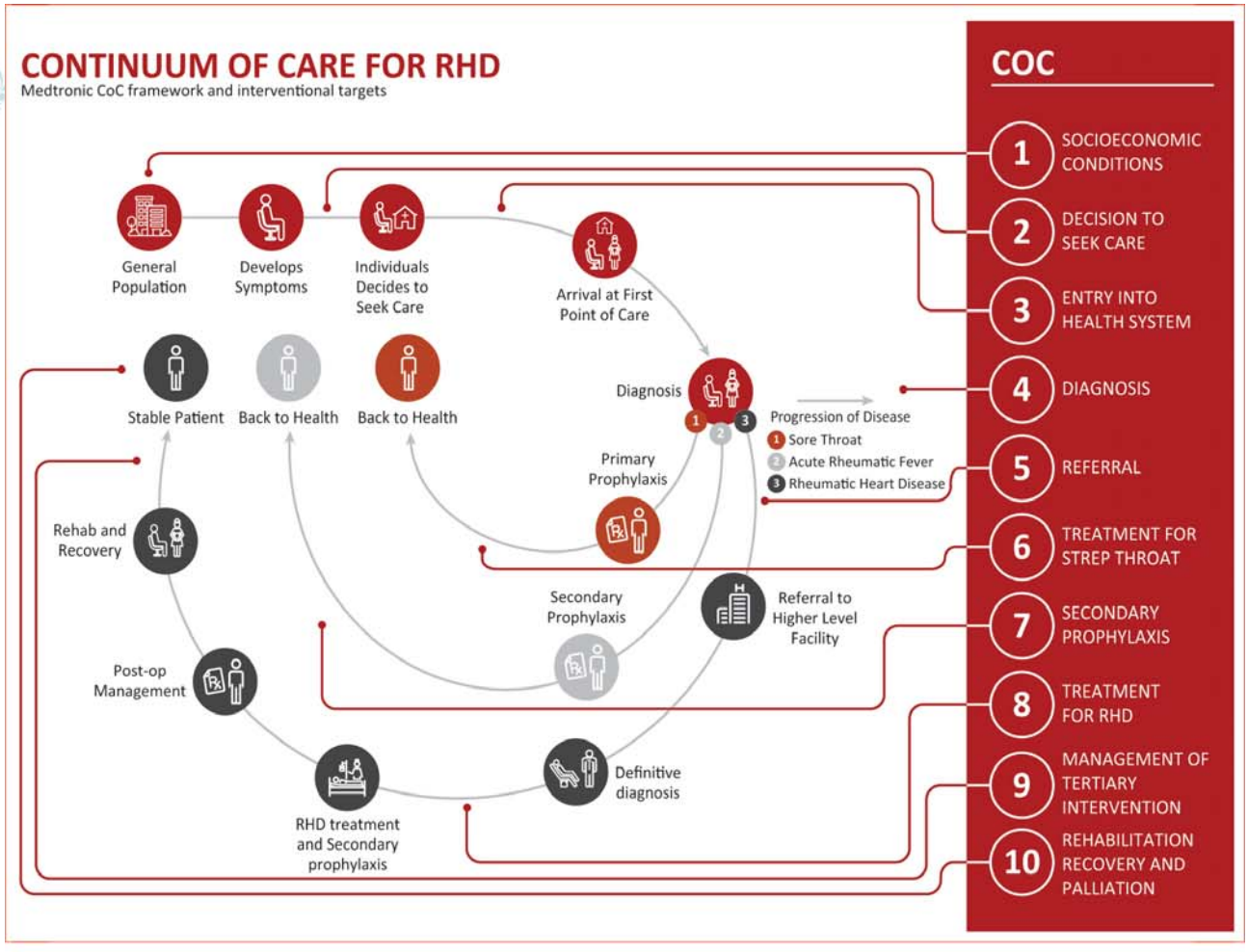

FIGURE 4. RF and RHD Continuum of Care. RF, rheumatic fever; RHD, rheumatic heart disease.

using BPG (CoC7) also at the primary care level, and be referred for appropriate investigation at higher levels. And those with RHD should be referred (CoC5) for appropriate treatment at higher levels of care (CoC8), after which they should receive the appropriate follow-up care (CoC9 and CoC10). The framework also underscores the roles that poverty and the social determinants of health play as crucial risk factors for RHD (CoC1).

As a patient-centred framework, the CoC facilitates an understanding of the care seeking process from the individual's—or their caregiver's—perspective, while permitting the systematic identification and categorisation of the various needs and opportunities of patients, providers, communities and the wider health system to manage cases of GAS sore throat, RF and RHD appropriately, and prevent the progression of disease.

6. KEY INTERVENTIONS FOR TREATMENT AND PREVENTION

Underpinning the CoC are a number of evidence-based interventions to alter the outcome of disease. The WHF and RhEACH have developed a matrix (Figure 5) to summarise these treatments and a wide range of supporting interventions into a resource called the TIPS (Tools for Implementing RHD Control Programmes) Handbook [29]. These are typically considered in four domains:

- Primordial (address the underlying social determinants of health that exacerbate GAS exposure and RHD risk)
- Primary (treatment of strep throat to prevent the development of RF following GAS infection)
- Secondary (prevent development of new GAS infections following the first episode of acute RF to prevent subsequent RF recurrences and delay or prevent development of severe RHD)
- Tertiary (control RHD symptoms and extend the life of those living with RHD)

6.1. Primordial prevention

As a disease with aetiology and risk factors strongly associated with poverty, structural interventions designed to address the social determinants of health are believed to be

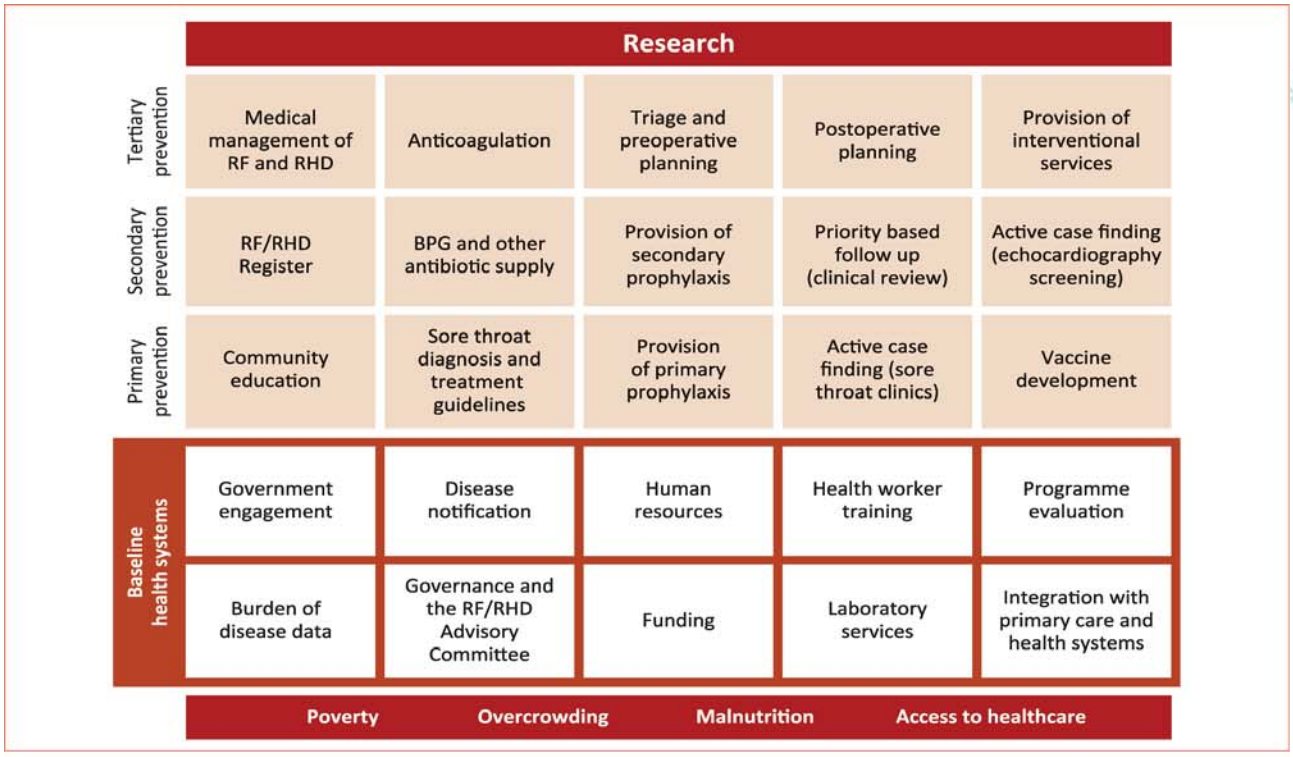

FIGURE 5. TIPS matrix of RHD control supporting interventions. RHD, rheumatic heart disease; TIPS, Tools for Implementing RHD Control Programmes.

critical for RF and RHD control [30,31]. These interventions aim to reduce exposure to GAS infection by addressing household overcrowding and other social determinants of health.

While such interventions traditionally lie beyond the scope of health system strengthening, there may be scope for primordial activity, such as education on overcrowding, to be combined with other RHD control efforts [29]. In addition, a wide range of government policies outside the health sector may also influence the primordial determinants of RHD. Therefore, advocacy on the association between RHD and poverty will help to ensure that governments, development partners, non-governmental organizations and other important actors view RHD control as a priority.

6.2. Primary prevention

Primary prevention involves prompt diagnosis and treatment of GAS throat infections in young people, with effective use of antibiotics to prevent the development of RF. This requires patients or their caregivers to seek care, receive appropriate diagnosis and adhere to prescribed treatment. A systematic review evaluating the effectiveness of antibiotics in preventing RF found a substantial protective effect: in patients with a sore throat and symptoms suggestive of a GAS infection, antibiotic treatment using intramuscular BPG could reduce the risk of RF by up to 80% [32]. A more recent review has endorsed penicillin as the antibiotic of choice for GAS pharyngitis [33].

However, many roadblocks exist to the provision of effective primary prevention. From the patient's perspective:

- Since most sore throats are viral in nature and tend to be self-limiting, sore throat may not be considered an illness that warrants medical care, or its link with RF/RHD may be poorly understood, consequently affecting the uptake of effective care,
- Access to preventive services and medication may be hindered by distance or costs, particularly if paid for out-of-pocket (e.g. transport, fees for diagnosis and medications) [30],
- Poor adherence to antibiotic treatments may result from a lack of understanding of the purpose of treatment, and fear of injections, among other things.

From the health systems perspective, the delivery of effective primary prevention may be hindered by:

- Shortages and stock outs of essential antibiotics, including quality BPG, which may result from inefficient procurement and supply chain management practices, or supply issues at the production/manufacturer level [34],
- Poor understanding among health professionals about the purpose of treating sore throat and the link with RHD,

- Insufficient knowledge or systems at primary care level for the effective management of sore throat,
- Absence of standardised clinical guidelines,
- Inadequate training, resources or capacity to act on clinical guidelines which may be due to a lack of practical local clinical guidelines or, where they do exist, ineffective dissemination and uptake of guidelines among health professionals,
- Limited geographic coverage of existing primary healthcare services,
- Reluctance to administer penicillin out of concern for anaphylaxis [35], resulting in onerous skin testing before administration in some settings and, in others, blanket bans on penicillin administration.

While primary prevention is ideally delivered through the existing primary care system, alternative approaches, such as school-based sore throat clinics, have been suggested as a means of identifying GAS infections within the community and overcoming some of the aforementioned barriers to seeking care. While available evidence on the effectiveness of such programmes in preventing RF is limited [36], the recent experience of the sore throat management component of New Zealand's RF primary prevention programme suggests that school-based approaches may be beneficial when focused on areas of high RF incidence [37]. However, the high costs, workloads and logistical challenges associated with its delivery will likely limit its application in resource-constrained settings.

Currently there is no effective vaccine for GAS (discussed further in Section 8).

6.3. Secondary prevention

The mainstay of secondary prevention involves the use of antibiotic prophylaxis in those with a history of RF to prevent subsequent recurrences, with the aim of limiting progression to severe RHD.

The preferred antibiotic is intramuscular BPG, which must be administered every 28 days (shorter dose intervals may be used in some settings based on evidence about the duration of the protective effect of BPG, logistics of delivery and acceptability to patients), consistently for a minimum of 10 years after the first acute RF episode. Oral regimens provide inferior protection from RF recurrence, but may be required for people with a penicillin allergy [38-40].

Effective delivery of secondary prevention requires identification of all individuals at risk of RF recurrence, prompt initiation of antibiotic prophylaxis using BPG and on-going antibiotic delivery until the period of risk has passed. Consequently, adherence to secondary prophylaxis may be low. One study in Uganda noted that 46% of patients received less than 80% of the required injections over a 6-month period [41].

Because secondary prophylaxis is similar to primary prevention in that it is ideally delivered through the primary care system and relies on BPG as the antibiotic of choice, many of the potential roadblocks are also similar. From the patient perspective:

- RF may go undiagnosed because symptoms are mild or absent, or because families cannot afford to seek care,
- The costs associated with the long duration of prophylaxis may be prohibitive, particularly if families must pay for BPG out-of-pocket [42]. The indirect costs of travel for injections may also be high, further increasing the risk for non-adherence, especially among patients or caregivers who do not value or understand the purpose of on-going follow up and treatment, or the benefits of monitoring one's disease status,
- Poor adherence may also arise due to pain from regular injections,
- Poor acceptability due to lack of trust or confidence in the care provided or a perceived lack of patient/carer support may also affect adherence [42].

From the health systems perspective:

- Clinicians may not have the training or resources to diagnose RF accurately [43],
- Lack of local guidelines, or their ineffective implementation can lead to inconsistent diagnosis, treatment and management of patients,
- Unreliable supply of quality antibiotics, especially BPG, and injection equipment is an important determinant of non-adherence [34,44],
- Concerns about anaphylaxis, particularly among asymptomatic children, may make some health professionals reluctant to administer BPG [35], and in some settings this has led to bans on penicillin administration,
- Lack of primary care infrastructure to support delivery of secondary prevention.

The core supporting intervention for the delivery of secondary prophylaxis is the national RF and RHD register, which has remained a critical part of RHD control since the 1970s. Registers benefit those living with RF/RHD in various ways. They improve the delivery of consistent and standardised secondary prophylaxis, help to ensure that care is prioritised by need, and help to identify and support people with poor adherence. As a national information system, registers also contain important information about mortality, surgeries received and medical histories of individual patients, in addition to incidence and prevalence data and other important indicators over time [29,45].

RHD may be asymptomatic for years or decades, particularly if the first episode of RF was mild or undiagnosed. Identifying subclinical RHD cases through echocardiography screening has been advocated as a tool to support secondary prevention. In order to standardise the criteria used to diagnose subclinical RHD using echocardiography, a group of international experts under the auspices of the WHF has published evidence-based criteria for echocardiographic diagnosis of subclinical RHD in screening programmes [46].

However, the priority of RHD control programmes should be to deliver effective secondary prophylaxis services before implementing echocardiographic screening programmes. The utility and cost-effectiveness of screening and treating subclinical cases should also be further investigated in more diverse settings [47].

6.4. Tertiary intervention

Tertiary RHD interventions aim to treat symptoms, reduce disability and ultimately delay death from RHD. Depending on the type and severity of a patient's condition, tertiary interventions may include surgical valve repair, valve replacement, balloon mitral valvuloplasty or medical management of the complications of RHD.

In the context of a developing country, it may be reasonable to include tertiary medical and surgical services within the remit of RHD control programmes where capacity and resources permit [45]. Valve repair has been shown to be preferable to replacement as patient survival is better and anticoagulation is not needed; however, repeat operations are often required [48,49].

Patients with valve replacements require lifelong anticoagulation using warfarin. This gives rise to a number of additional roadblocks in resource-limited settings as effective anticoagulation involves regular monitoring, regular dose adjustments and requires a reliable medicine supply.

Making anticoagulation management available at primary care level has been suggested to improve access for these postoperative patients and for others requiring anticoagulation for arrhythmias and heart failure. Providing surgeries in these contexts may be prohibitively expensive for governments and patients alike [50].

In many developing countries, cardiac surgery facilities do not exist; the small minority of patients who do receive tertiary care either travel overseas, or benefit from international teams who visit on short-term bases [51]. Several countries such as South Africa, India, and Brazil have increased capacity to deliver tertiary interventions [52]. Others in Africa have initiated surgical training programmes to address this gap, but this has not yet started to address the scale of the problem given that the vast majority of RHD cases in the region present with established disease and severe complications [53].

While the ability to deliver tertiary interventions is important, where such capacity does not already exist, efforts should be made to invest in improving primary and secondary prevention, which are much more affordable and likely to reduce the future burden of disease, even if they cannot address the need for treatment [54].

7. KEY HEALTH SYSTEM REQUIREMENTS FOR RHD CONTROL

Examining the roadblocks at each level of intervention reveals several core health system features that are required for the effective implementation of RHD control programmes.

7.1. Human resources

A complementary range of clinical, allied health, public health and administrative skills that reflects the local burden of disease is required to implement RHD control programmes. However, experience from successfully implemented programmes has revealed the importance of a single key contact dedicated to developing and delivering the programme [29].

Engaging existing networks of community health workers and nurses, who operate in rural and remote areas, presents an opportunity to greatly expand programme coverage and explore new delivery models for RHD control. In low- and middle-income countries, community health workers have been shown to be effective at delivering a variety of primary care interventions, including malaria case management [55], family planning services, and antenatal counselling and referral [56]. Their skill set and position within communities make them an ideal channel to administer RHD awareness campaigns and provide support to patients and carers.

7.2. Healthcare delivery

Many core components of RHD control programmes are well suited for a primary care approach, including delivery of primary and secondary prophylaxis, diagnosis of suspected RF and patient/community education. The renewed drive toward universal access to primary care provided by the Sustainable Development Goals presents a unique window of opportunity to achieve this integration [57].

In addition to increasing service access for patients, the efficiencies gained from the sharing of infrastructure and resources also contributes to the sustainability of RHD control programmes. In Nepal, a national programme focused on promoting community awareness, the delivery of secondary prophylaxis, RHD register development, health worker training, and guideline development has been integrated into primary care since 2007; and in 2013 a pilot primary prevention project was initiated at 42 primary health centres [35].

The devastating consequences of RHD during pregnancy and labour also require RHD control to be integrated with maternal care. Ensuring adequate counselling for women of childbearing age living with RHD, adequate antenatal case detection services and appropriate care during the perinatal period are essential components of a comprehensive RHD program. There are also recent initiatives that seek to integrate RHD care into other existing chronic disease management programmes. One innovative approach being trialled in Uganda aims to integrate RHD surveillance and treatment within the existing HIV/AIDS infrastructure that has been successfully scaled-up after many years of domestic and foreign investment [58].

7.3. Physical resources

A continuous supply of affordable, quality intramuscular BPG for use as primary and secondary prophylaxis is a critical input for successful RHD control programmes. Invented in 1928, this antibiotic has been included on the WHO Essential Medicines List since the first edition was published in 1977. However, several important concerns remain about BPG shortages at production level, efficacy and quality, and persistent stock outs which continue to limit access [34].

To improve availability of BPG and other essential medicines required for control programmes, they must be registered with the national pharmaceutical regulator and included on national formularies/essential medicines lists. RHD control programmes must also have sufficient capacity to forecast, quantify, procure and distribute medicine supplies.

Because BPG is also used to prevent transmission of syphilis in pregnant women to the foetus, and as prophylaxis in children with sickle cell disease, information flow is critical to inform each of these processes and to minimise the risk of stock outs.

For example, in Fiji, BPG usage data collected through the Rheumatic Fever Information System are used by the Fiji Pharmaceutical Biomedical Services to help ensure a more consistent supply of BPG to health facilities across the country. Where there is insufficient capacity in procurement and supply chain management, support is available from alternative procurement agents including UN agencies, and a range of international and non-governmental organizations [59].

Clear, practical, evidence-based clinical guidelines must be developed for each intervention provided and adapted to the particular context. To ensure they are used to inform the care provided, guidelines must be widely available at primary care level, translated into local languages as needed, and health care providers must be aware and trained on how to use them.

To embed them further into clinical practice, guidelines may be integrated into medical education and the process of professional audit. Guidelines for RHD control should also include advice on how to educate patients about the risks of sore throat, RF and RHD; how to support patient adherence to secondary prophylaxis; and how to administer BPG injections safely, comfortably and confidently.

Embedding RHD control programmes within the Ministry of Health and other public health infrastructure is crucial for ensuring continued leadership, finance and, consequently, a sustainable and coordinated national response. However, successful experiences from Nepal and Sudan have shown that collaborations between government and NGOs, such as national heart foundations and professional societies, also provide effective models for programme governance [35,60].

Where government support and recognition of the need for RF/RHD control is lacking, advocacy must be used to mobilise political will and raise RHD control as a priority. A key advocacy figure at country level is the national or even regional 'RHD Champion' to whom the WHF targets refer in Section 1. RHD Advisory Committees, comprised of a broad and inclusive range of stakeholders, are another important channel for conducting such advocacy, and can also play a role in the design, implementation and oversight of control programmes.

Programmes require sustained long-term funding to realise population-level impact, and therefore rely on strong advocacy and a good understanding of programme costs. In resource-constrained settings, public sources should finance primary and secondary prevention, as they are cost-effective and represent good value for money [12,61-64]. Public financing for prevention should aim to deliver care that is free at the point of service or that poses minimal cost to patients.

Financing tertiary care and making it affordable to patients in these settings, if included, presents a great challenge given the socio-economic position of those most affected and the high costs of building and maintaining the required capacity and infrastructure. Where these resources do not exist, tertiary care could initially be financed and delivered through alternative models [51]; and where there are shortfalls in public financing, additional funds may be available from various external sources such as international donor agencies, professional organizations and charities [29]. However, ensuring equitable and affordable access to tertiary care requires effective financial protection, such as that provided by comprehensive insurance and universal health coverage.

Ultimately, the goal of RHD control is to reduce the incidence of acute RF and the prevalence of RHD, which, over time, will decrease the need for costly tertiary interventions.

As discussed in Section 6, national RF and RHD registers are essential to support the delivery of secondary prophylaxis, and are important information systems that provide data to assess disease burden, target interventions according to need, and evaluate programme impact over time. Recently, an open-source, low-cost software application, called eRegister, has been developed by the Pan-African Society of Cardiology for RHD treatment and prevention programmes [65]. Based on the WHF framework for RHD patient registers, the software ensures the capture of standardised data, facilitating the production of indicators for programme monitoring and evaluation. It is

also designed as a readily adaptable, cloud-based, mobile platform that allows for simultaneous data collection by field workers using mobile devices, and by providers using computer terminals in clinics and hospitals.

7.8. Patients and caregivers

Ensuring patients, parents, schoolteachers, carers and communities are aware of the risks posed by untreated sore throat, RF and RHD through campaigns has been a core element of many successful RHD control programmes [35,66,67]. Raising awareness aims to increase the likelihood of seeking prompt care for sore throat, or when one shows signs and symptoms consistent with acute RF.

Successful community-level campaigns have taken a multichannel approach, targeting several areas, as well as mass media, to reach as many people as possible. School and educational institutions should also be targeted, as the most vulnerable population for GAS infections are school-aged children [68]. In Kenya, the use of an interactive digital module to train school-going children on RHD was shown to increase knowledge and awareness [69].

While the efficacy of the clinical interventions and elements required for successful implementation of RHD control programmes are relatively well understood, the continuing global burden of this preventable disease highlights the ongoing knowledge-practice gap in RHD control. There are a number of important unanswered questions (Table 1), which will require robust research in order to produce the high-quality evidence needed to influence public health policy and programmes.

Innovative approaches that address roadblocks to effective care will also be required to close the knowledge-practice gap in RHD control. The remainder of this section explores a selection of these potential solutions, some of which address RHD and others which draw inspiration from innovative solutions used to address other conditions. Note that many of the innovative approaches described below require further research, development and evidence from trials before they can be adopted and scaled-up for RHD control. Such points could inform the long-term RHD research agenda. Other ideas, however, could be pursued immediately.

8.1. Diagnosis of sore throat

Although throat cultures remain the gold standard for the diagnosis of GAS pharyngitis, the availability of rapid point-of-care antigen detection tests and clinical decision rules have created opportunities for new diagnostic approaches [70]. However, evaluations of available rapid tests have found considerable variation in their specificity and sensitivity [70-73], and the tests have not been validated in all endemic regions, so product selection must be carefully considered. The current cost of rapid tests is also likely to limit their use in resource-constrained settings [70]. Alternatively, a meta-analysis evaluating seven clinical decision rules suggested that the Joachim protocol could potentially be used either alone or in combination with a rapid test to guide treatment decisions in some settings [74].

8.2. RHD diagnosis and screening

As described in Section 6, the application of echocardiography for identifying subclinical RHD cases is currently under investigation. However, the introduction of new devices and the decreasing cost of equipment have increased the potential to apply this approach more widely in developing countries for RHD diagnosis and screening. For example, one recent study in Uganda, which evaluated the use of a relatively affordable handheld ultrasound device against standard portable echocardiography for diagnosis, found it to be highly sensitive (90.2%) and specific

TABLE 1. Unanswered questions related to the knowledge practice gap in RHD control

• What factors determine effective integration of RHD control activities into primary care or other existing programmes (e.g. chronic disease, perinatal or sexual health services)?
• What programme characteristics contribute to improved delivery, uptake and adherence to secondary prophylaxis?
• How can the supply and demand for BPG be better linked, or a more acceptable product be developed to control RHD?
• How can successful experiences of implementing and scaling up comprehensive RHD control programmes be replicated? And what are the key factors that contributed to their success?
• What is the relative cost-effectiveness of different approaches to RHD control, including different models for delivering primary prophylaxis and comprehensive RHD control programmes?
• What is the clinical impact and cost-effectiveness of echocardiographic screening and other early case detection strategies, and how can it be made more practical and affordable?
• What are the best approaches for increasing the availability and quality of epidemiological data on RHD disease burden, particularly in low- and middle-income countries?
• How can people living with RHD be best empowered to improve self-management and outcomes?

Adapted from Carapetis and Zühlke [53].

(92.9%) in distinguishing between normal patients and those with RHD, when images were blindly reviewed according to the 2012 WHF guidelines [75].

The use of portable echocardiograms by trained nurses for screening has also recently been studied in Fiji [76,77]. Following brief focused training, participating nurses in one study were able to obtain adequate-quality images and make reliable assessments on the presence and extent of valvular regurgitation in more than 2000 children [77]. While further research is required, these early studies do show some promise for models that include task shifting as a means of introducing population-level screening in high-prevalence, resource-poor settings.

8.3. Acceptability of BPG

The success of primary and secondary prophylaxis would benefit from improved acceptability of BPG. In practice, this requires a regular supply of a high-quality product that can be readily administered with minimal pain. The development of longer-acting BPG formulations would support adherence by reducing the frequency of injections and the financial burden of administering prophylaxis for both patients and programmes [52]. In the interim, an innovative low-cost device that uses vibration to reduce discomfort from BPG injections has been trialled in New Zealand. When used with a local anaesthetic, the device reduced the pain and fear reported by children [78].

Incentive-based interventions have been used to improve medication adherence for conditions such as drug or alcohol dependence, HIV and tuberculosis. A review found that such incentives increased adherence by a mean of 20 percentage points, but that effects varied widely [79]. Incentive-based interventions have been frequently used to influence health-seeking behaviour in low- and middle-income countries (e.g., to encourage antenatal care and immunisations), and there is potential for secondary prophylaxis to benefit from such schemes.

8.4. mHealth solutions

The use of mobile devices to support the delivery of medical care or public health services is collectively termed mHealth. Despite being a relatively new area of intervention, there have been many pilot studies of a wide range of applications. While there continues to be some debate about the evidence base supporting the scale-up of mHealth [80], there are a few applications that have the potential to benefit RHD control. Applications have been developed to support adherence to antiretroviral and tuberculosis treatment, many of which have been designed for use and trialled in developing country settings [81,82].

The SMS for Life application is a text message-based platform for reporting stock levels of artemether-lumefantrine (AL), the first line treatment for uncomplicated malaria, and also of rapid diagnostic tests (RDTs) for malaria at peripheral facilities. In one pilot study conducted among selected public facilities in Kenya, weekly stock counts of AL packs and RDTs were sent via a structured incentivised SMS communication process from health workers' personal mobile phones to a web-based system accessed by district managers. At the end of the pilot period, stock-outs of AL were eliminated and RDT stock-outs declined by 24 percentage-points. The platform has since been scaled up in Tanzania to include over 5,000 public health facilities across the country [83,84].

8.5. Patient and community empowerment

Strategies that seek to engage and empower people living with RHD and their carers have the potential to greatly enhance the RHD response. A diverse array of approaches has been developed, largely as part of the response to HIV/AIDS [85] and increasingly for non-communicable diseases, which target different levels of individual involvement. At one end of the spectrum, interventions such as healthy living training for patients, one-to-one counselling and patient support groups aim to increase knowledge about the disease, influence treatment-seeking behaviour and improve overall quality of life. For example, some programmes have adopted the use of patient-held records and RHD calendars that act as treatment reminders, while providing health information messages [52].

Approaches at the other end of the spectrum aim to empower affected individuals to be more active advocates and champions of a wider response. In Kenya, patients are being enabled to provide each other with health education and peer support [86]. In Fiji, a young RHD patient-advocate currently sits as a permanent member on the national RHD technical advisory committee, which provides high-level technical advice to the Ministry of Health. RHD patients and their carers in Fiji are also represented on a national working group formed specifically to better understand and address poor patient adherence rates [87].

8.6. Access to tertiary interventions

With growing capacity for cardiac surgery in a number of low- and middle-income countries, there is scope to implement bilateral or regional programmes that allow RHD patients living in countries with insufficient capacity to access tertiary interventions abroad [52]. Such a reciprocal agreement has existed between Malta and the United Kingdom since 1975 [88]. Under the agreement, nearly 300 Maltese nationals are referred annually for specialist care in ophthalmology, cardiac surgery, oncology and neurology, with one third of these patients being children.

8.7. GAS vaccine

The search for a GAS vaccine began in the 1950s yet, despite early human trials, no effective product for clinical use is available. Vaccine development faces several challenges, including limited commercial viability, the regional

TABLE 2. Potential solutions to address barriers to improved RHD control

Level of intervention	Roadblock	Potential solutions
Primary	Prompt medical care is not sought for sore throat in children and young people	• Targeted school- and community-level education and awareness campaigns
	Poor adherence to antibiotics	• Targeted school- and community-level education and awareness campaigns • Ensure affordable and easy access to effective treatment • Provide single dose of injectable BPG rather than longer course of oral antibiotics • Support and enable health care professionals to deliver BPG injections confidently and safely • Reformulate BPG to make injections more acceptable to patients and providers
	Inappropriate management of sore throat in primary or community care services	• Ensure practical, evidence-based local guidelines are available and accessible • Provide professional training on use of guidelines • Integrate guidelines into clinical education and professional audit • Consider use of point-of-care diagnostics and clinical decision rules to improve diagnosis
	Reluctance to administer BPG due to concerns for anaphylaxis	• Ensure guidelines include safe administration techniques • Deliver training to providers on the risk of anaphylaxis and safe administration techniques • Ensure emergency kits and epinephrine (adrenaline) syringes are available
Secondary	RF cases are not identified	• Ensure primary care staff are sufficiently trained to identify suspected RF cases • Ensure robust protocols exist for referring suspected cases for definitive diagnosis • Support access to essential technologies including simple blood tests and echocardiography
	No register-based programme	• Advocate for public investment in register infrastructure, including the implementation of electronic register platforms (eRegister) • Seek external sources of funding and technical support
	Cases do not enrol or are not promptly enrolled into a register-based programme	• Targeted school- and community-level education and awareness campaigns about the value of secondary prevention • Increase health workers' awareness and appreciation of register-based system
	Enrolled cases are poorly managed	• Ensure practical, evidence-based, local treatment guidelines are available to support delivery of standardised care

(continued)

TABLE 2–*continued*. Potential solutions to address barriers to improved RHD control

Level of intervention	Roadblock	Potential solutions
		• Provide professional training on use of guidelines • Integrate guidelines into clinical education and professional audit • Implement electronic register platform (eRegister) to support follow-up and patient review
	Reluctance to administer BPG due to concerns for anaphylaxis	• Ensure guidelines include safe administration techniques • Provide training for providers on safe administration techniques • Ensure emergency kits and epinephrine (adrenaline) syringes are available
	Poor adherence to long term prophylaxis	• Train staff to administer secondary prophylaxis confidently and safely with minimal pain • Ensure guidelines include advice on how to support patient adherence • Include reminder and recall systems in register-based programmes • Introduce outreach services to follow up non-adherent patients • Consider decentralised dispensing and mobile injection delivery where feasible • Consider mHealth reminder and incentive-based solutions • Implement empowerment strategies, including patient/carer support groups and awareness sessions • Reformulate BPG to make injections more acceptable to patients and providers
Tertiary	Poor access to surgical interventions	• Develop bilateral or regional programmes to provide cross-border care • Develop regional centres of excellence for cardiac surgery in appropriate countries
Health systems	RHD control is not prioritised	• Conduct advocacy for RHD control • Gather data on local burden of disease, its economic impact and the benefits of investing in RHD control • Identify national RHD champions • Mobilise RHD Advisory Committee • Ensure RHD control is embedded within government ministry/department of health
	Insufficient funds	• Conduct RHD control advocacy to mobilise funding from government and other sources • Generate cost savings by integrating RHD control into existing primary care and other programmes • Generate cost savings by employing efficient medicines procurement strategies

(continued)

TABLE 2–*continued*. Potential solutions to address barriers to improved RHD control

Level of intervention	Roadblock	Potential solutions
	Poor availability of BPG and other essential medicines for RHD control	• Ensure all required medications are registered with national regulator and included on national formulary/essential medicines list • Train programme staff on effective forecasting, quantification, procurement and distribution • Strengthen information systems used to manage procurement and distribution of medicines • Consider mHealth solutions to reduce risk of stock outs • Advocate for BPG production solutions at a global level
	Limited coverage of current RHD control programmes	• Integrate RHD control into existing primary care and other programmes • Provide training on RHD prevention and control to primary health care workers
	Preventive services are unaffordable	• Targeted campaigns to increase awareness of where to obtain affordable/public preventive care
	Poor access to diagnostics in peripheral settings	• Ensure availability of essential laboratory services and echocardiography in selected sites • Consider implementing anticoagulation management in primary care, where feasible • Document the utility of rapid point-of-care diagnostics for GAS infection to help build the market case for these devices

variability of GAS strains and a theoretical risk of stimulating an autoimmune response [70,89].

However, research has progressed and several vaccine candidates against GAS infection are currently in various stages of pre-clinical and clinical development. These include M protein-based vaccines (N-terminal vaccine candidates and M protein conserved region vaccines), and non-M protein vaccine candidates representing conserved GAS antigens [90,91].

In addition to preventing sore throat and RF, a GAS vaccine could potentially provide protection against skin infection/impetigo and severe invasive GAS disease including pneumonia, bacteraemia, necrotising fasciitis and streptococcal toxic shock syndrome. Unlike RF/RHD, these invasive diseases cause significant morbidity and mortality in high-income settings; a GAS vaccine relevant to both high- and low-resource settings may provide a compelling economic opportunity [89].

This market segmentation approach and the feasibility of developing a viable product has recently garnered the attention of the WHO Product Development for Vaccines Advisory Committee [92]. Once available, a product development partnership model may help to accelerate progress towards the registration of an effective GAS vaccine. Since the 1990s, a number of these international public-private collaborations have introduced a plethora of new medications, vaccines and diagnostics to benefit populations in low- and middle-income settings [93-95].

9. ROADMAP TO ADDRESS EXISTING ROADBLOCKS

Overcoming the barriers—whether individual, community or system-related—that prevent individuals from receiving care for sore throat, RF and RHD are crucial to achieving optimal population-level RHD control. While the roadblocks obstructing this journey will vary by setting, Table 2 charts a map of potential solutions that may be used to overcome them.

10. ADAPTING TO DEVELOP REGIONAL AND NATIONAL RHD ROADMAPS

The examples of successful, cost-effective and comprehensive RF/RHD control programmes implemented in resource-constrained settings demonstrate the great

potential for impact in other settings with high RHD burdens [35,63,66,67].

As discussed above, the RHD and other WHF Roadmaps describe only general principles that must be adapted to produce region- or country-specific roadmaps. The WHF has described this process in a companion article [96], but it generally involves:

- Developing and convening a multi-sectoral coalition to undertake the adaptation,
- Conducting a situation analysis to characterise the epidemiologic profile, the healthcare system and policy environment,
- Conducting policy dialogues to identify and discuss specific barriers and potential strategies that are appropriate to the given context,
- Developing a plan of action and a process to evaluate the implementation of the selected strategies.

The process requires a broad range of stakeholders (e.g., public health specialists, health care professionals, government organizations, regional health organizations, industry, advocacy and patient groups) and a broad range of expertise (e.g., knowledge of medicine, cardiology, prevention, health promotion, health systems, economics, governmental priorities, and cultural and social contexts).

To support this general process, a set of tools has been developed to adapt the WHF RHD Roadmap to specific national contexts. RhEACH has prepared a detailed Needs Assessment Tool to conduct the situation analysis and to develop, implement, monitor and evaluate adapted roadmaps.

In parallel, the WHF is developing additional guidance for convening multi-sectoral coalitions and conducting policy dialogues at national level. RHD country and global scorecards will also be developed to facilitate progress monitoring, international comparisons and evaluation of attaining targets.

Over time, country and regional experiences will be reported back and integrated with other emerging evidence to inform the updating and revision of the WHF Roadmaps.

11. CONCLUSION

Effective interventions to prevent the devastating consequences of RHD have existed for many decades. Yet, many people die prematurely each year due to RHD related complications, most of whom are from low- and middle-income countries or from poor and vulnerable groups in countries where the disease has, otherwise, disappeared.

The WHF Roadmap for improved RHD control identifies the various barriers that limit access to and uptake of these proven interventions. It also highlights a variety of proven and promising solutions that could be used to overcome these 'roadblocks'. As a general guide, this Roadmap is meant to serve as the foundation for the development of tailored plans of action to improve RHD control in specific contexts.

The Continuum of Care is registered to the Medtronic Foundation. Medtronic Foundation and RhEACH are founding partners of RHD Action (www.rhdaction.org). Medtronic Foundation focuses on expanding access to quality chronic disease care among underserved populations worldwide. RhEACH (www.rheach.org) is a technical support and policy translation initiative that aims to amplify rheumatic heart disease control efforts worldwide, and provides clinical, technical, and research support to the global RHD Action movement. The authors would like to acknowledge and thank Prasanga Hiniduma-Lokuge for her critical input, scientific contribution and commitment to this document and to RHD. We would also like to thank the following Reviewing Committee members for lending their expertise, and for providing useful comments and suggestions during the development of this document: Jonathan Carapetis, Liesl Zühlke, Chris Longenecker, Steve Justus, Anita Saxena, Bongani Mayosi, Lamia El Tigani Mahmoud, Dejuma Yadeta Goshu, Chrissie Pickin, and Pablo Perel.

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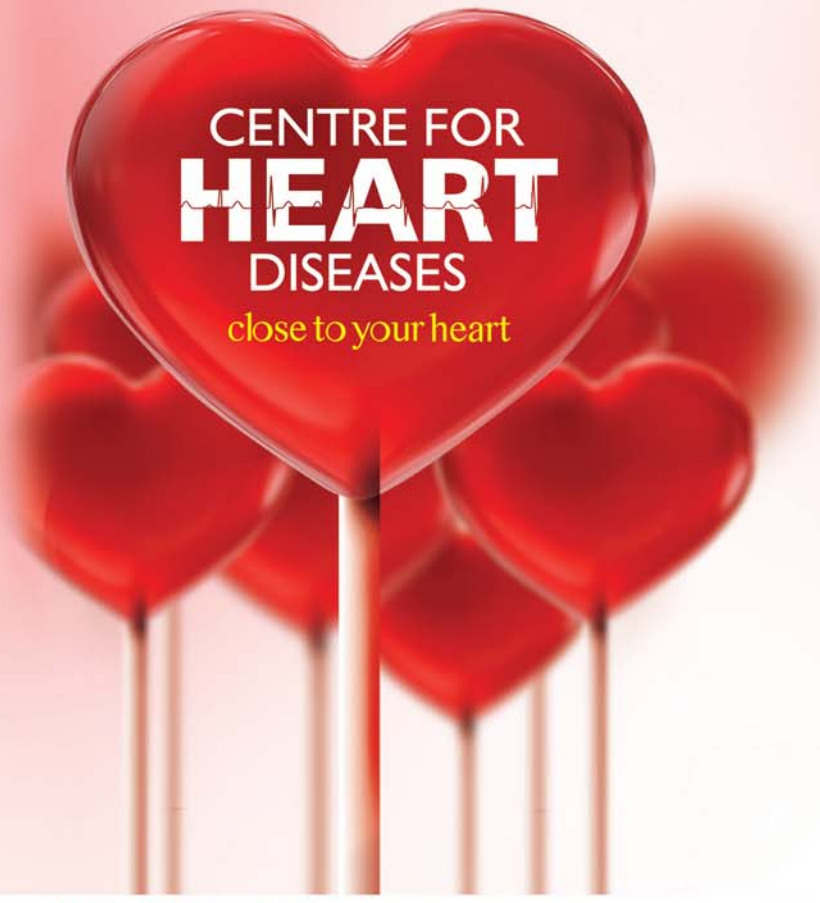

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