Is Primary Prevention of Rheumatic Fever the Missing Link in the Control of Rheumatic Heart Disease in Africa?

Ganesan Karthikeyan, MBBS, MD, DM; Bongani M. Mayosi, MBChB, DPhil

Abstract—Rheumatic fever and rheumatic heart disease continue to be major public health problems in the developing world, particularly in the countries of sub-Saharan Africa. Because of its cost effectiveness, secondary prophylaxis is advocated as the principal means of disease prevention and control. However, in developing countries, valvular damage, due to earlier, unrecognized episodes of rheumatic fever, has already occurred by the time secondary prophylaxis is instituted. Secondary prophylaxis cannot reduce the incidence of new cases of rheumatic fever and has not been shown to alter the natural history of rheumatic valvular disease. Experience from several regions of the world suggests that incorporation of a strategy of primary antibiotic prophylaxis into a comprehensive program for disease control can reduce the incidence of rheumatic fever and rheumatic heart disease. In this article, we argue that a strategy of primary antibiotic prophylaxis, with appropriate modifications, can be successfully implemented in resource-poor settings across the world and should be a key component of any rheumatic heart disease control program. This, we believe, is essential for reducing the global burden of rheumatic heart disease. (Circulation. 2009;120:709-713.)

Key Words: rheumatic heart disease ■ prevention ■ epidemiology

Worldwide, nearly 16 million people suffer from rheumatic heart disease (RHD), and more than 200,000 deaths occur due to the disease and its sequelae. The vast majority of this burden is borne by less developed countries, particularly those in the African continent. The highest prevalence of RHD in the world is found in sub-Saharan Africa (5.7 per 1000 school children), and it is estimated that more than 1 million children between the ages of 5 and 14 years are affected by the disease. This might well be an underestimate, given that recent cross-sectional studies using echocardiographic screening have found a much higher prevalence. Although the developed world is for the large part free of RHD, there has been an unexplained resurgence and persistence in some areas.

Despite the existence of proven preventive strategies for more than 50 years, prevalence rates in sub-Saharan Africa have not shown any significant decline. An important reason for this is the lack of improvement in living conditions in most countries and the slow pace of improvement in others. This may also be because current approaches to control of RHD rely almost entirely on secondary prophylaxis, as recommended by the World Health Organization (WHO) and several national bodies. In this article, we present arguments as to why a strategy that relies exclusively on secondary prevention is unlikely to reduce the burden of RHD in the developing world and highlight the importance of incorporating primary prevention strategies, suitably modified to local conditions, for the success of any RHD control program.

Prevention of Rheumatic Fever and RHD: Rationale and Strategies

Rheumatic fever (RF) occurs in 0.3% to 3% of patients who have pharyngitis due to group A streptococcal (GAS) infection, as an autoimmune response to the infecting agent. Involvement of heart valves during an acute episode of RF (carditis) leads to valve damage and chronic RHD. In studies from developing countries in the postpenicillin era, 50% to 80% of patients who have carditis develop chronic RHD at long-term follow-up. Patients who have had carditis in the past are more likely to develop carditis during recurrences. There are no proven treatments that alter the natural history of RF. Therefore, prevention is the key to reducing the burden of disease in the community. Given our understanding of the pathogenesis of RHD, 2 broad strategies for prevention are applicable. Primary prevention involves the detection of asymptomatic GAS sore throats in susceptible individuals in the community (mainly children) and treatment with a course of oral or parenteral penicillin. Secondary prophylaxis is achieved by periodic administration of penicillin to individuals who have had previous episodes of RF or have RHD, with the aim of preventing recurrent GAS sore throat. Secondary prevention reduces the risk of recurrences of rheumatic fever, but it has not been shown to reduce the development of chronic RHD or mortality due to RHD.

Several arguments have been made against adopting primary antibiotic prophylaxis for the prevention of RF and
RHD as a public health intervention in the community.\textsuperscript{9,15} The principal objection to such an approach is the expense and logistic difficulty of providing accurate bacteriologic diagnosis before instituting antibiotic therapy. The cost of a strategy of performing a throat swab culture for confirming GAS infection, followed by treatment with penicillin, was recently estimated to be about $50 per person.\textsuperscript{16} This translated to a total cost of $252.1 million for a population of 5 million children.\textsuperscript{16} In another analysis, the cost per disability-adjusted life year (DALY) gained using a strategy of primary prevention was $1049, and the cost per life saved was $40,920.\textsuperscript{17} Similarly, using a decision analysis model, other investigators have calculated the incremental cost of treating based on culture (compared with no treatment) to be $88,246 per additional life saved.\textsuperscript{18} In contrast, secondary prophylaxis using 3- or 4-weekly injections of benzathine penicillin has been found to be cost-effective at $142 per DALY gained and $5520 per death averted.\textsuperscript{17} It must, however, be noted that these findings are based on cost estimates from developed countries and may not be applicable to the situation in Africa. Other reasons for not favoring such primary prophylaxis relate to the poor health-seeking behavior in people with sore throats in resource-poor countries and the suggestion that a large proportion of patients who develop RF do not report having had a recent sore throat.\textsuperscript{4}

**Why Is Secondary Prevention Not Sufficient for Preventing RHD?**

Unlike in developed countries, where access to health care is good and the health-seeking behavior of people favors early presentation, in poor countries, the first inciting episode of streptococcal pharyngitis goes largely undiagnosed and untreated. As a result, susceptible patients have already suffered substantial valve damage from unrecognized episodes of RF by the time they come to clinical attention. Often patients present for the first time with symptoms due to the hemodynamic consequences of the resulting valve disease. The subsequent clinical course of these patients is largely determined by the natural history of the valve lesions. Although secondary prophylaxis reduces recurrent RF episodes,\textsuperscript{14} there is no evidence to suggest that such treatment alters natural history once significant valve damage has occurred.\textsuperscript{5} Moreover, the early episodes of acute RF in children in Africa often follow a fulminant course, which may require surgery in the acute phase of illness.\textsuperscript{19–21} Therefore, it is crucially important to prevent the first episode of rheumatic carditis if any headway is to be made in reducing the number of people with rheumatic valve disease.

**Is Primary Prevention an Effective Strategy?**

The proof of principle for the effectiveness of primary antibiotic prophylaxis as a strategy (ie, treatment of symptomatic patients in high-risk groups) comes from the successful use of intramuscular penicillin in US army personnel more than half a century ago.\textsuperscript{22} Subsequently, in the 1960s, reductions in the incidence of RF were documented by several investigators, with the introduction of facilities for the prompt diagnosis and treatment of streptococcal sore throat. In an inner city area of Baltimore, the establishment of a health center charged with identifying and treating episodes of sore throat reduced the incidence of RF from 27 per 100,000 inhabitants to 11 per 100,000 inhabitants. The incidence remained unchanged in areas of the city without a neighborhood health center.\textsuperscript{23} A systematic review of hospital-based studies of primary prophylaxis found that antibiotic treatment of GAS sore throat reduced the attack rate of RF by 70%, with intramuscular penicillin reducing it by as much as 80%.\textsuperscript{6} This translated into 1 case of RF prevented for every 50 to 60 patients treated. Although the number needed to treat is likely to be much higher when primary prophylaxis is applied to the community, these studies provide convincing biological rationale for such a strategy. Further, a recent controlled trial among school children in China showed that a strategy of systematic identification and treatment of GAS infections may also reduce GAS carriage rates and the incidence of subsequent GAS infections.\textsuperscript{24} Primary prophylaxis may therefore contribute to cumulative reductions in RF incidence over time. However, several authorities have suggested that a substantial proportion of streptococcal sore throats that lead to RF may be asymptomatic.\textsuperscript{9,15} But this supposition is based entirely on evidence from retrospective data, with a high likelihood of recall bias. Further, there are issues related to interpretation of the data as well. For instance, the study by Veasy et al\textsuperscript{4} (which is often cited to support the occurrence of asymptomatic episodes) reported only the proportion of patients who had “a sore throat severe enough that the parents considered seeking medical care” and not all patients who had any sore throat. Education of patients (and the parents of susceptible children) from high-risk communities on the potential seriousness of a sore throat can be expected to improve reporting rates. Finally, incontrovertible evidence that primary prevention really works comes from the remarkable success of Costa Rica and Cuba in almost completely eradicating rheumatic fever with comprehensive programs incorporating a component of primary prevention.\textsuperscript{25,26} Although these were not controlled studies, they were applied to whole communities, thereby eliminating any selection bias. Further, the declines in RF incidence were not observed in otherwise similar populations in adjoining countries or provinces that did not have such programs. This suggests that the decline in RF was over and above any favorable temporal trends that may have occurred as a result of improvement in living conditions. The success of these programs therefore provides strong evidence that a strategy of primary antibiotic prophylaxis is effective in reducing the incidence of RF. The issue that remains is that of feasibility.

This line of reasoning assumes that the principal streptococcal infection preceding RF is that of the throat and not the skin. Although streptococcal pyoderma is believed to be an important cause of RF in aboriginal communities in Australia, there is little evidence for such a relationship among Africans.\textsuperscript{27}

**Is Primary Prevention a Feasible Strategy in Africa?**

Analyses performed in developed country settings suggest that the cost and logistics of a primary prevention program...
involving bacteriologic diagnosis of GAS infection may be prohibitive. However, costs may be lower in developing countries because of lower wages. And because a strategy of primary prevention is more labor intensive (manpower for plating, processing, and interpreting culture results) than secondary prevention, the differences in cost between the 2 strategies may be much less in developing than in developed countries. Some preliminary data from India suggest that primary prevention may in fact be affordable relative to secondary prevention. In a population served by a tertiary care public hospital, Soudarssanane et al found that the output to input ratios were greater for primary than for secondary prevention (1.56 versus 1.07). This was partly because throat swab culture was inexpensive (approximately $2) and physician consultation fees are very low (approximately $0.5) in public hospitals in India. Lower personnel costs may similarly make primary prevention an affordable and efficient strategy in Africa; this needs to be tested in formal cost-effectiveness analyses.

Even under the assumption that the costs of delivery of primary prevention are higher in Africa, substitution of bacteriologic diagnosis (which is the most expensive aspect of such a strategy) with sensitive, alternative methods of diagnosis of bacterial sore throat can substantially reduce costs and improve feasibility. One such alternative is the application of clinical decision rules to diagnose GAS pharyngitis.

Clinical Diagnosis of Streptococcal Sore Throat

Clinical algorithms for diagnosing bacterial pharyngitis, although far less accurate than throat swab culture, can conceivably substantially reduce the number of patients receiving unnecessary antibiotic therapy. Several clinical decision rules are available for the diagnosis of streptococcal sore throat. In order to be an effective replacement for bacteriologic diagnosis, the decision rule must be easy to apply and must correctly diagnose most cases of streptococcal sore throat while keeping overtreatment of viral sore throats to a minimum. Walker et al studied the diagnostic performance of several clinical decision rules as applied to data obtained from Egyptian children with symptoms of sore throat. Some clinical decision rules proved to be highly sensitive (>90%) and at the same time reduced overtreatment of culture-negative cases by as much as 40%. Two of the rules tested, those proposed by McIsaac et al and Steinhoff et al, were found to detect 92% of culture-positive cases and avoided treating 31% to 38% of culture-negative cases. Other investigators have suggested an alternative strategy of identifying non-GAS sore throat using decision rules in order to improve diagnostic accuracy. In a study conducted among children in Brazil, Smeesters et al showed that the use of a 3-question rule to identify non-GAS throat infection would have reduced unnecessary antibiotic treatment by up to 55%.

Clinical decision rules reduce unnecessary antibiotic use in some children, but they also fail to detect varying proportions of children with positive cultures, with the implication that they would not receive antibiotic therapy. The decision rule with the worst performance in this regard is the one advocated by the WHO. When applied to children in Brazil, Croatia, and Egypt, this rule missed up to 96% of children with positive cultures. The McIsaac et al and Steinhoff et al rules performed much better. In the study by Walker et al, they missed 9% and 16% of the children with a throat culture positive for GAS, respectively. The algorithm developed by Smeesters et al missed 16% of children with positive cultures. Some investigators have suggested that a 16% false-negative rate is acceptable because this figure is much lower than the general pediatric GAS carriage rates of 20% to 50%. They argue that because serologic evidence of infection was not sought in most of the studies, the positive throat cultures among patients not detected using clinical rules might not represent true infections. Nevertheless, despite the false-negative results, the systematic implementation of a primary prevention program incorporating any of these algorithms would represent a major improvement over the existing situation in Africa.

However, even the validated decision rules are likely to have different performance characteristics depending on the populations in which they are used. Tailoring decision rules to a specific population allows for improvement in performance characteristics. A version of the WHO’s Integrated Management of Childhood Illness program adapted to Turkey introduced and tested guidelines for empirical antibiotic therapy for sore throat. A simple clinical decision rule incorporating common symptoms and signs had high sensitivity for detecting culture-positive GAS pharyngitis. Optimizing the pretest probability of GAS infection using risk stratification schemes may also improve the performance of clinical decision rules. As an example, the New Zealand guidelines for management of sore throat recommend risk stratification of patients using demographic (eg, Maori or Pacific peoples) characteristics before application of clinical decision rules to guide decisions about empirical antibiotic use.

Delivery of Primary Prevention

The most crucial elements of any program are the logistics of implementation. The successful campaigns in Costa Rica and Cuba are models worth emulating in this regard (Figure). In Costa Rica, a comprehensive program was launched beginning in the 1970s. Three important aspects of this program are worth emphasizing: (1) The need for throat swab culture to confirm streptococcal sore throats was eliminated and diagnosis was made entirely on clinical grounds, (2) sore throats were treated with a single intramuscular injection of benzathine penicillin, and (3) an educational campaign was launched to inform physicians, nurses, health technicians, and medical students about the need to treat streptococcal sore throats. Over the next 2 decades, there was a dramatic decline in the incidence of RF to 1 per 100,000 inhabitants in 1991. The campaign in the Pinar del Rio province of Cuba was similar in that it involved the detection and treatment of sore throats combined with increasing community awareness, in addition to secondary prevention, and was associated with an identical decline in the incidence of RF. Another important feature of the programs in these countries was that both were integrated into the existing healthcare systems and used existing infrastructure, thus incurring little incremental cost.
In the Cuban province, the additional cost incurred was just $2000 per year, which was mainly spent on the educational campaign.25 Moreover, with the reduction in RF incidence, the direct spending on RF/RHD care decreased progressively from a high of $145,000 per year at the beginning of the program to $22,000 per year after 10 years.25

Safety of Primary Prevention

The 2 principal concerns of a primary antibiotic prophylaxis program, particularly one where a substantial proportion of individuals without streptococcal sore throats may receive benzathine penicillin, are (1) the problem of anaphylaxis and (2) the emergence of bacterial resistance. Contrary to popular belief, serious allergic reactions and anaphylaxis with benzathine penicillin prophylaxis for RHD are rare. The International Rheumatic Fever Study Group reported that after more than 32,000 injections and 2736 patient-years of follow up, the incidence of anaphylaxis was 1.2/10,000 injections, and the incidence of death was 0.31/10,000 injections (1 death in all).26 During the Costa Rican campaign, no deaths due to penicillin were reported, and anaphylaxis was reported only sporadically.26 In the same vein, strains of GAS, Streptococcus pneumoniae, and Hemophilus influenzae isolated at the National Children’s Hospital in Costa Rica continued to be 100% sensitive to penicillin 2 decades after the RHD control program was implemented.26 Indeed, despite the widespread use of penicillin worldwide, GAS infections have continued to remain susceptible to the antibiotic.

Primary Prevention in Africa

Treatment of sore throat is already part of the Integrated Management of Childhood Illness program in Africa, and penicillin is on the essential drug list of the WHO. Therefore, our call is for the implementation of existing policy within existing health systems, which we believe is within the reach of most African countries. The Awareness Surveillance Advocacy Prevention (ASAP) Program is an ongoing prevention program being implemented under the auspices of the Pan African Society of Cardiology (www.pascar.co.za)44 with the support of the national Departments of Health of South Africa, Ghana, and Egypt and the World Heart Federation. In addition to the objectives of raising awareness about the disease in the community and among physicians, ASAP aims to implement primary prevention strategies in tandem with secondary prevention within the existing primary healthcare system. Pilot programs will be developed at selected sentinel/demonstration sites in the participating countries, which will ultimately serve as the basis for the establishment of national programs for the control of RF/RHD in these countries.45

Conclusions

We believe that a preventive program that relies almost exclusively on secondary prevention, such as the one advocated by the WHO, is unlikely to reduce the burden of RF and RHD in Africa. A strategy consisting of educating health personnel to recognize bacterial sore throat using simple clinical algorithms (instead of relying on a bacteriologic diagnosis), followed by a single injection of benzathine penicillin for the treatment of suspected cases, has been shown to be effective. The implementation of such a strategy through the existing healthcare infrastructure may be efficient and cost-effective and has the potential to reduce the burden of RF/RHD. The recently devised ASAP program is the first step toward implementing such a comprehensive preventive strategy in Africa.44 The initial effort and expense in integrating primary prevention into national RHD programs can be expected to be more than offset by the reduction in the number of patients with severe valvular disease who will subsequently require expensive tertiary care. Finally, it cannot be overemphasized that RF/RHD is a disease of poverty. Therefore, over and above the preventive strategies, living conditions and access to healthcare must improve substantially in order to reduce disease burden in sub-Saharan Africa.

Sources of Funding

Dr Karthikeyan was a Heart Outcomes Prevention Evaluation (HOPE) Scholar at the Population Health Research Institute at McMaster University, Hamilton, Ontario, Canada in 2008–2009. Dr Mayosi is funded in part by the Medical Research Council of South
Africa, National Research Foundation, Medtronic Foundation, and the Lily and Ernst Hauserm Trust.

Disclosures
None.

References
Is Primary Prevention of Rheumatic Fever the Missing Link in the Control of Rheumatic Heart Disease in Africa?
Ganesan Karthikeyan and Bongani M. Mayosi

Circulation. 2009;120:709-713; originally published online August 10, 2009; doi: 10.1161/CIRCULATIONAHA.108.836510

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/120/8/709

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org//subscriptions/