RF and RHD Research

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"The future is already here — it's just not very evenly distributed."

—William Gibson

Rheumatic heart disease (RHD) remains a major neglected disease of poverty. It affects an estimated 33 million persons—mostly in low- and middle-income countries (LMICs) and in low-resource settings of vulnerable populations in high-income countries [1-3]. Recent advances and improvements in the early detection, evaluation, and treatment of acute group A streptococcal pharyngitis has made the prevention and control of RHD feasible in many LMICs [4]. Point-of-care antigen diagnostic testing that provides confirmatory results without the need for bacterial culture and relatively uncomplicated clinical practice guidelines for definitive treatment are now available [4]. The combination of primary prevention and long-term secondary prophylaxis strategies also makes the prevention and eradication of RHD possible. However, sustained effective implementation, scale-up, and spread of these strategies have not occurred in many low-resource settings in LMICs, leading to a continuing high burden of RHD [1,2].

Although ideal epidemiological data are sparse, the systematic review from Uganda and Tanzania published in this issue of *Global Heart* shows that along with this high burden, there are frequent nonfatal complications of heart failure, pulmonary hypertension, and atrial fibrillation, with case fatality rates in medical and surgical wards of 17% (95% CI: 13% to 21%) and 27% (95% CI: 18% to 36%), respectively [5]. Their identification of critical barriers and facilitators within the domains of individual knowledge, family support, provider communication and knowledge, and systems design in the effective prevention, treatment, and control of group A streptococcal pharyngitis and RHD provide an appropriate starting point for identifying strategies for addressing the implementation gap [5].

THE IMPLEMENTATION GAP

The continuing challenge of RHD is not one of understanding how to prevent and treat it but rather a failure of widespread implementation of effective prevention and treatment [6]. Imagine a future scenario, a world in which all group A streptococcal pharyngitis is readily identified at the point of care, definitive acute treatment is prescribed, the effective medication is readily available and affordable in all health care settings, and the prescribed long-term secondary prophylaxis is widely acceptable and affordable from the patient's perspective. That future is already here, but as William Gibson so eloquently put it, "it's just not

very evenly distributed." In the continental United States for example, annual incidence of acute rheumatic fever (ARF) declined in the latter part of the 20th century to approximately 0.04 to 0.06 cases per 1,000 children, leading to the discontinuation of ARF as a nationally reportable condition [7]. However, as reported by Beaudoin et al. [8], the incidence of ARF in Samoan persons living in Hawaii and residents of American Samoa, a United States territory in the South Pacific, remains significantly high. In fact, the RHD point prevalence of 3.2 per 1,000 children in August 2013 was nearly 10 times that estimated for high-income industrialized countries [8]. Similar disparities have been noted in indigenous peoples elsewhere in the United States, Canada, Australia, and New Zealand [9-11]. The drivers of these disparities are complex and include social, environmental, genetic, behavioral, and lifestyle factors. Importantly, these disparities also reflect an implementation gap—a gap that could be addressed with rigorous research that advances effective strategies. The good news is that we have evidence of strategies that have worked to reduce the burden of ARF and RHD.

EVIDENCE OF SUCCESSFUL IMPLEMENTATION STRATEGIES

More than 3 decades ago, the World Health Organization, in close collaboration with the International Society and Federation of Cardiology (now the World Heart Federation) initiated a rheumatic fever/RHD program that engaged 16 countries including Mali, Zambia, and Zimbabwe (in Africa); Bolivia, El Salvador, and Jamaica (in the Americas); Egypt, Iraq, Pakistan, and Sudan (in the Eastern Mediterranean); India, Sri Lanka, and Thailand (in South-East Asia); and China, the Philippines, and Tonga (in the Western Pacific) [12]. The program identified and registered 3,135 cases of rheumatic fever/RHD and successfully provided 63.2% coverage in terms of completion of secondary prophylaxis [12]. The occurrence of adverse events (0.3%) and ARF recurrence (0.4%) was low. The program also trained 24,398 health personnel and teachers and used multiple mass media channels (radio, television, posters, pamphlets, and brochures) to advance health promotion and education for the prevention and control of rheumatic fever and RHD.

Among Indigenous communities of Aboriginal Australians, Ralph et al. [13] recently demonstrated that the development and execution of a continuous quality improvement strategy for implementation of national best-practice management guidelines at the primary health care level can successfully improve the management of ARF and RHD. Their systems approach and participatory action

research methodology led to significant improvements in several service delivery indicators, including the proportion of people receiving at least 40% of their scheduled intramuscular benzathine penicillin and the proportion who received influenza vaccination [13].

RESEARCH AGENDA

The time has come for us to translate into action what we know works and to explore strategies for widespread adoption and scale-up in LMICs and low-resource settings in high-income countries. Several research priorities [14] and calls to action [15-20] have been published that can provide important guide posts. In particular, the comprehensive needs assessment tool for planning RHD control programs in low-resource settings published in this issue of *Global Heart* will be an invaluable tool in dissemination and implementation research [21]. This needs assessment tool and other resources now provide clinical and public health research investigators, program developers, RHD advocacy groups, and policy makers invaluable tools for operationalizing the many calls to action for the prevention, treatment, and control of ARF and RHD.

From the perspective of charting the future for global health research to advance the prevention, treatment, and control of ARF and RHD, the recently released National Heart, Lung, and Blood Institute Strategic Vision [22,23] and related perspectives for the post-2015 global health research agenda provide unique opportunities. The 4 strategic vision goals are highly relevant in this endeavor. The first 2 strategic vision goals address fundamental discoveries about normal function and the pathobiology of disease. New investigations from biomedical, social, and behavioral science fields that lead to a greater understanding of strategies that help preserve and promote health, as well as confer resilience against the post-infectious sequelae of group A streptococcal pharyngitis remain important. Innovative strategies that extend insights from fundamental discoveries to improve further understanding of the pathobiology of ARF and RHD will enable strategic clinical investigations that advance clinical and public health management of these diseases.

Very importantly, we need to apply what we know works and ensure a skilled workforce through training, career development, and research capacity building in LMICs. These themes are captured in goals 3 and 4 of the National Heart, Lung, and Blood Institute Strategic Vision. Both early- and late-stage translational research and the related training needs are essential. Research endeavors that lead to the development of affordable diagnostics (including point-of-care devices that enable rapid diagnosis and early detection), and affordable and sustainable clinical and public health interventions will be crucial for maximizing population health impact in the prevention, treatment, and control of ARF and RHD. The World Heart Federation Roadmap, published in this issue of *Global Heart* [24], provides the ideal framework for the wide

variety of strategic stakeholders necessary for sustained success in the prevention and control of RHD at the local, national, regional, and global levels. The time has indeed come for ARF and RHD to move from being neglected diseases of poverty to diseases that can be eliminated worldwide in our lifetime.

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