COMMENTARY

Adherence to Secondary Prophylaxis Among Patients with Acute Rheumatic Fever and Rheumatic Heart Disease

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COMMENT

Acute Rheumatic Fever (ARF) and its chronic sequela Rheumatic Heart Disease (RHD) contribute substantially to cardiovascular disease burden and mortality worldwide. It is estimated that RHD is present in over 30 million people and causes more than 300,000 deaths per year [1]. ARF and RHD are highly preventable in principle. Indeed, there have been marked declines in the global incidence of ARF and the prevalence of RHD over the last century, with near eradication in many industrialized countries, albeit with persistence in marginalized populations and across low-middle income countries [2]. The 71st World Health Assembly recently adopted a resolution identifying prevention and control of RHD as a global priority [3]. However, multifaceted strategies are required to reduce the occurrence of RHD and its associated burden. Socioeconomic disadvantage thwarts control of the disease at each stage of its natural history. Firstly, the concomitants of poverty (particularly household overcrowding and poor sanitation) strongly influence the likelihood of Group A Streptococcus (GAS) infection [4]. Secondly, reduction of ARF cases through timely antibiotic treatment of GAS infections is predicated on access to high-quality primary health care [5].

Given the barriers to implementation of upstream disease control measures, prevention of re-infection with GAS among persons with a history of ARF/RHD is critical to the reduction of disease burden. Secondary Prophylaxis (SP) entails regular and lengthy administration of penicillin, with the rationale of maintaining circulating penicillin at levels that are bactericidal for GAS, thereby reducing the likelihood of reinfection [6]. Intramuscular injections at 3-4 weekly intervals are recommended in preference to daily oral administration [3]. The duration of SP is determined according to guidelines based on stratification of recurrence risk [7], although these recommendations may require context-specific modification [8]. In the absence of an effective

vaccine against GAS infection (despite considerable international efforts to this end) [9], SP will remain a cornerstone of ARF/RHD control for the foreseeable future.

Consequently, a systematic review of SP adherence and its determinants is timely, especially as the WHA's resolution begins to be globally actioned. The recent review in this journal by Kevat *et al*. [10] encompasses peer-reviewed English-language studies published during the two decades up to mid-2014 that provide data on the degree of adherence achieved and/or factors associated with adherence. Twenty studies were identified, from culturally and geographically diverse settings. The review has the merits of assessing study quality and explicitly reflecting on gaps in knowledge. There is an inevitable potential for systematic reviews to become outdated rapidly with the publication of new studies. Since the publication of the review by Kevat *et al.*, more than ten additional pertinent studies have been published, from Australia [11-13], Egypt [14], Fiji [15, 16], India [17], Jamaica [18], New Zealand [19, 20], Uganda [21] and Zambia [22].

A principal limitation lies not in the review process *per se* but in the interpretability of the findings among the included studies. This is constrained firstly by the heterogeneity of the metrics used to define adherence (*e.g.*, proportion of injections administered, either to an individual patient or across the study group) and the SP regimens used (intervals ranging from two-weekly to monthly). Additionally, the published studies manifest generally small sample sizes and limited replication of suspected determinants investigated. The reported adherence levels vary markedly.

Nevertheless, two key messages emerge from the data identified in the review or published subsequently. Firstly, the findings underscore that the determinants of effective SP implementation arise at the interface of health systems and the patient milieu. Examples of factors repeatedly identified as influencing adherence include geographic remoteness and physical distance to health facilities vis-à-vis transport options [15, 18, 23, 24], inconvenience to patients exacerbated by competing priorities (such as schooling or employment) and clinic wait times [14, 18], the quality of provider-patient relationships and communications [23, 25-27], fear of painful injections [18, 19, 28], the degree of education and dis-

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ease awareness among patients (or, in the case of children, their parents) [14, 19, 27, 28], and levels of support from family and friends [24, 25].

Secondly—and unsurprisingly—these challenges are manifested in the suboptimal achievement of adherence across diverse settings, with reported adherence ranging from as low as 6% [15]. Unsatisfactory adherence is documented among marginalized populations in developed countries (with advanced and highly resourced health systems) [29, 30] as well as in less affluent jurisdictions. It has proven difficult to establish satisfactory adherence even with a well-resourced rigorously designed, multicomponent intervention intended to promote community engagement and support patient self-management along with honing health systems for the delivery of SP [12, 13].

Clearly, effective SP strategies are dependent on the identification of eligible patients through surveillance, which in turn requires sophisticated diagnostic technologies and information systems. This will require sustainable, adequately resourced health systems that integrate diagnosis and screening with patient follow-up for SP and medical therapies. Data systems such as registries that incorporate routine evaluation of SP have the potential to enhance patient surveillance and follow-up [31, 32]. Optimisation of health systems for adherence with SP requires a holistic notion of access, encompassing the flexibility to adapt services to individual patient requirements and cultural contexts, in addition to the physical proximity of health service provision [33]. Prolonged follow-up of patients across the transition from childhood through adolescence to early adulthood presents special challenges [34].

Finally, new technologies may facilitate SP adherence. Novel formulations of long-acting penicillin in development have the potential to reduce injection frequency [35]. 'Smart' technologies utilizing mobile devices that provide patients with reminders are currently being trialed [36].

As the WHA resolution [3] is actioned, SP continues to be a fundamental and potentially cost-effective [37] element of global ARF/RHD control. Further research on evidence-based programs that address the multiplicity of recognized barriers to adherence must be prioritized and operationalized into service delivery so that SP can be transformed into a realistic strategy for health systems.

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