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Editorial

Out-of-pocket costs in rheumatic heart disease care: A major barrier to equity in cardiovascular health

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Rheumatic heart disease (RHD) results from untreated and often repetitive episodes of Rheumatic Fever (RF), which in turn is caused by uncontrolled group A beta-hemolytic streptococcal (GAS) infection in a susceptible host. In endemic areas for RHD the disease starts during childhood or adolescence, thus requiring continuous linkage to the health system for its management and prevention of complications across the lifespan. Antibiotics are essential to prevent recurrences of RF (secondary prophylaxis) and for treatment of symptomatic GAS infections (primary prevention). Since the 1950s, prophylaxis has been achieved via intramuscular (IM) administration of benzathine penicillin G (BPG), a crystalline powder formed through the fusion of 2 penicillin G molecules and characterized by very low solubility and in vivo hydrolysis. These features together with the absence of known GAS resistance to BPG in vitro and with slow absorption from IM injection – producing prolonged therapeutic serum concentrations – result in long half-life, providing prolonged bactericidal protection and making it particularly effective for primary and secondary prevention of GAS infections. However, the mechanism for the apparent persistent susceptibility of GAS to BPG is relatively poorly understood.

Once diagnosed with RF or RHD people (even if asymptomatic) should undertake long-term or lifelong secondary prophylaxis. Because RHD is a preventable non-communicable diseases condition that disproportionately affects the world's poorest and most vulnerable, cost is of importance for its control. Reliable data on the purchase price of BPG is difficult to secure, but the drug is part of the essential medicines list of the World Health Organization (WHO). However, for people with indication for secondary prophylaxis for RHD, even where the drug itself is free or relatively affordable, patients may still need to incur the costs related to the health care provider who administers the injection, and transportation costs to and from the health care facility. Additionally, in patients with significant chronic valve heart disease the costs of long-term management of heart failure, control of arrhythmia, anticoagulation, prophylaxis of bacterial endocarditis, diagnostic procedures and interventions (interventional catheterization and surgery) need to be added.

There are major concerns about access to BPG worldwide, and several opportunities for intervention, improvement and research.¹ Since its entry in the market in the 1950's conditions requiring treatment with this drug have also become less common in high-resource settings. On the other hand, the development of new antibiotics has narrowed the clinical indications for BPG. The WHO recommends continuous administration of secondary prophylaxis with BPG to prevent colonization or infection of the upper respiratory tract with GAS and the development of recurrent attacks of RF; however, there is some uncertainty over the optimum frequency of administration. Most guidelines recommend 4-weekly administration as a pragmatic choice, with an option to escalate to 3-weekly or 2-weekly administration if there are unexplained recurrences or very high risk. Furthermore, the optimal duration of secondary prophylaxis is controversial, with the minimum duration being 10 years in most guidelines, with the possibility of lifelong regular administration in severe rheumatic heart valve disease (RHVD).

The World Heart Federation Roadmap for reducing cardiovascular morbidity and mortality through prevention and control of RHD identifies barriers that limit access to and uptake of proven interventions for the prevention and control of RHD²; the cost of secondary prevention is one of those barriers because the disease usually affects the poorest segments of the society.

In this issue Arvind et al [pageXX] report on out-of-pocket expenditure for administration of monthly BPG injections for secondary prophylaxis in patients with RHVD, using data from a registry-based initiated in a tertiary care center in Northern India. Like in many other countries, the majority of patients received secondary prophylaxis at peripheral health care facilities, either government run or private clinics near their place of residence, but needed periodical follow up at the tertiary health facilities. The authors took advantage of these visits, to prospectively collected data on self-reported costs incurred for administration of secondary prophylaxis by families of young RHD patients presenting to the tertiary care centre. Their results from 420 patients registered over five years – predominantly from low socioeconomic strata (73.3%) living in rural areas (87.1%) – describe the out-of-pocket expenditure for getting access BPG prophylaxis at [median (IQR)] USD 3.45 (2.35–6.46). The cost of the drug represented 30% of the total out-of-pocket costs, with cost for drug administration and transportation costs comprising 22% and 48.0% of the total costs respectively; the cumulative costs incurred for reaching the health care facility and administering the drug exceeded the cost of the drug in 166 (39.5%) patients. Interestingly, there was no correlation between the patient compliance and its socioeconomic class, and no difference in compliance by origin (rural or urban areas) or distance travelled.

The fact that less than one fifth of the patients in the study were assisted in government clinics, while over 80% were people from rural and/or low socio-economic status, raises concerns regarding accessibility and affordability, particularly considering that - like in other endemic areas in Asia, Africa and Latin America - access to health care is low, social protection systems are weak, and health insurance systems do not reach the most disadvantaged. As suggested by the authors, out-of-pocket costs are a key barrier to adherence to BPG, mainly for patients from lower economic strata, for whom they represent a considerable proportion of the monthly average household income. Moreover, they entail further risk of out-of-pocket catastrophic spending due to failure of prophylaxis, that causes recurrent episodes of RF and multiple admissions to hospital; this further impoverishes the families in the long term, perpetuating the cycle of poverty and poor disease outcomes. Therefore, policy interventions to boost adherence to secondary prophylaxis must also be directed at investments in lowering the *total* costs of its administration at primary health centers throughout the country. This is crucial to achieve reduction of morbidity and mortality by RF/RHD.

In aiming to achieve the Sustainable Development Goals, and particularly trying to provide Universal Health Coverage, there is need to bridge the gap in policy and care models for poverty-related diseases such as RHD, which affect predominantly the poorest billion people in the world. Arvind et al. shown that despite being a disease related to poverty, in most endemic areas several aspects of RHD management can only be provided with quality at tertiary care centers, thus increasing the costs of care for the health system and the patients. Several factors contribute to this namely patient's lack of awareness, shortage of health professionals with skills for diagnosis and management of RF/RHD, scarcity of resources to address the complexity of the diagnosis and management of complications - such as heart failure, stroke, arrhythmia and endocarditis - within the public health systems. The recently published *Lancet* Commission report on non-communicable diseases and injuries of the poorest billion³ shows for the first time that among the poorest billion, people with a diverse set of severe NCDs - amongst which is rheumatic heart disease - live 20 fewer healthy years than in high-income countries. The report provides the clearest-ever picture of how quality care and other cost-effective, proven solutions can save millions of lives each year if

scaled to reach everyone in need. Decentralization of care and translation of existing knowledge into policy and practice are key to achieve this goal.

In 2018, the WHO prioritized control of RF/RHD, but key barriers to the control of RF must be recognized. Despite being a WHO essential drug, BPG is still not available to all; furthermore, its current formulations require frequent injections and follow-up, imposing a heavy burden on fragile primary health care systems in developing countries. Moreover, there is a clear case for research into alternative molecules for easier administration to support secondary prophylaxis of RHD worldwide, and for an actionable framework for vaccine development to regulatory and policy decision making, availability, and use. Fortunately, in response to the 2018 World Health Assembly resolution calling for better control and prevention of RF/RHD, the WHO has started efforts to influence prioritization of investments by governments, and a research and development technology roadmap. This may be key to improve equity in access to RHD prevention and control, and cardiovascular health in general.

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