COMMENTARY

Time to end Rheumatic Heart Disease: Lessons and opportunities from observational registries

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ABSTRACT

The fight against Rheumatic Heart Disease (RHD) is at a critical juncture. Despite the adoption of a global resolution by the World Health Assembly against RHD in May 2018, practitioners working in countries where RHD is endemic continue to be faced with an overwhelming clinical burden, lack of surgical and interventional resources, and insufficient opportunities and funding for research. Recent years have seen the publication of several observational registries, most of which were investigator-initiated, not supported by larger research funders, and coordinated by small teams using paper-based infrastructure. This commentary reflects on the lessons and opportunities that these registries have afforded the field and suggests some areas for further investigation. SAHeart 2019;16:42-46

INTRODUCTION

Rheumatic Heart Disease (RHD), the permanent sequel of Group-A streptococcal disease and the autoimmune phenomenon Acute Rheumatic Fever (ARF), disproportionately affects young people living in low- and middle-income countries. It impacts on fragile health systems, as well as regions of poor health access within more developed countries. The most recent Global Burden of Disease estimates that in 2015 there were 33.4 million RHD cases globally.[1] For a disease that is entirely preventable, this is unacceptable. A concerted global effort is gaining momentum to prevent, manage and eventually eradicate RHD at multiple intersects. In this paper, we focus on key lessons and opportunities, and highlight the role that observational studies will play in achieving control, and the ultimate elimination of RHD.

Registries and the evidence base

A registry may be defined as a database of identifiable persons containing a clearly defined set of health and demographic data collected for a specific public health purpose. It is not merely a paper or electronic database, but is developed to address specific health-related questions and to meet predetermined objectives. Establishing a registry is a simple and effective way of establishing the burden of disease,[2] as well as, in the case of ARF/RHD, a method for monitoring the efficient delivery of prophylaxis and service delivery.[3] Furthermore, through documenting treatment and outcomes in local practice, registries could serve to fill important knowledge gaps in the biology of a disease and its management strategies – both within and between regions.[4] Use of a comprehensive registry was touted as a key strategic target by the World Heart Federation in regions where RHD is endemic.[5]

Criteria have been suggested to evaluate the effectiveness and contribution of registries to the evidence base.[2] The stated purpose and objectives of establishing a registry must be clear, so as to guide its structure and setting. For example, it is important to clarify early on whether the registry will be facility-based or community-based. Clearly defining the function of the registry will also serve to guide the scope, duration, and expected outcomes. Case definitions must be according to acceptable standards, with consideration given to mandating the use of specialised equipment or techniques in resource-challenged environments. Next, it must be borne in mind that the potential for under-reporting may severely compromise the quality of collected information.[6] Thus, it may be worthwhile incorporating into the data collection, existing alternative sources such as laboratory reports or discharge information – so as to reduce reliance on the human interface.

BOX 1: RHD registries: key components to setting up a registry.

Articulate the purpose of the registry and outline the hypotheses underpinning it.
Determine if the registry is the best means to achieve this purpose (if only partially, it may require additional studies or processes alongside the registry).
Identify key stakeholders and determine the extent of the proposed register.
Assess the feasibility – the authors suggest a pilot study – with an evaluation phase.
Build a team that is well versed in registry processes, including ethics approval, standard operating procedures and data integrity.
Establish a governance and oversight plan, including quality control and assurance.
Define the scope of the registry, data needed (data, definitions and derivations document), outcomes measured, and target population. This may be defined by funding, although this should not restrict a registry that is not funded. This can be performed in stages according to funding.
Write a study protocol, including a detailed statistical analysis plan.
Develop an overall project plan, which can include stages, modules and up-scaling with funding.
Finally – apply for funding!

It must be emphasised that good methods are critical. We suggest that careful attention be given to the preparation of a manual of operations, which includes definitions, derivations, analyses, plans and the key hypothesis or hypotheses underpinning the existence of the registry. A peer-reviewed rationale and design publication should preferably precede commencement of the implementation of a registry.[5,12] Box 1 outlines key components of a robust registry.

Any discussion on the implementation of registries cannot ignore consideration of the benefits of using digital technology. Even in resource-challenged environments, extensive network coverage and mobile use is extremely high.[7] The digital platform can serve as the optimal platform to overcome the high cost of maintaining a paper-based registry, and the human resources of managing the day-to-day aspects of a registry. Before implementation, practical feasibility of the registry, especially in terms of likelihood of sufficient "buy-in" by the anticipated consumers, is essential. A situational analysis of issues relating to cultural diversity and the attitudes and workload of healthcare workers may serve to identify potential structural and social barriers to implementation.[7] While the solution of using modern digital era technology to create patient-based registries goes some way to overcoming the problem of underutilisation of registry-based practice, it also introduces problems of its own, related specifically to the quality of data entered. Quality control and quality assurance should be strongly maintained in any database or registry creation. Adding a human interface in the form of dedicated personnel who control and review input and manage databases often differentiates good from poor databases. Good databases are easier to fund and to sustain over time.

Clinical registries also inform Global Burden of Disease data,[1] especially regarding morbidity, non-fatal sequelae and also help in the identification of further data needs. This is a key value of a registry, as it provides an understanding of issues beyond the mere prevalence of the RHD disease burden. Registry data have thus been paramount in defining Disability Adjusted Life Years (DALYs) and Quality Adjusted Life Years (QUALYs). We suggest that future Global burden of disease data needs, expressed in the recent publication,[1] such as stroke burden, surgical outcomes, and age at presentation, be included in future RHD registries.

Significant challenges are inherent in a robust, sustainable registry, and the largest multi-site RHD registry recently published these in detail. A suggestion would be to consider process evaluation and qualitative assessment, alongside a register, to provide information regarding why certain elements worked or did not work and to understand more clearly why outcomes were achieved or not (see Box 2).

Local, global and regional scientific registries in RHD early documentation

In the first part of the previous century, Bland and Duckett Jones published one of the most important longitudinal datasets on RHD, outlining the presenting clinical features, signs of

BOX 2: RHD registries: lessons learned.[33]

A register will not achieve desired outcomes if these are not articulated at the outset with a clear and direct hypothesis.
Involve all stakeholders as early as possible; capacity building is a key outcome of a multi-site register.
Identify research needs in stakeholders as early as possible and address these upfront – e.g. Good Clinical Practice (GCP) experience.
Research excellence, integrity and thorough attention to detail are key.
Registries have positive and negative effects on clinical practice, so be prepared for this and document these.
Funding is very important, but great registries can start without funding. Budget for monitoring, site visits and data checks.
On-site initiation and regular site visits and monitoring are extremely helpful and ensure data integrity.
Include patients as an important stakeholder group and consider the dissemination of the findings of the register in the lay and scientific community.

deterioration, and the mortality related to RHD in thousands of patients from Baltimore.[8,9] This dataset represented the first major study on RHD and resulted in the first version of the Jones criteria. The marked decrease in morbidity and mortality due to ARF and RHD in the United States, and discussed by Massel, et al., told the important story of primary prevention.[10] Despite the fact that these registries are now almost a century ago, they still speak to the need for registries to demonstrate the start and end of this epidemic.

Recent registries: single-centre, country or multi-country

Almost 80 years after the publication of the first longitudinal dataset, Sliwa, et al. published a study of newly diagnosed RHD in the Heart of Soweto study, which demonstrated an alarming incidence of 24.7 per 100 000 and the need for surgery for >20% of patients diagnosed with RHD within 20 months.[11] This was followed by the multi-country prospective Global Rheumatic Heart Disease registry,[12] REMEDY, which confirmed that of 3 343 patients from Africa , Yemen and India, the vast majority were women, young, severely affected, and with significant gaps in evidence-based interventions and a desperate need for cardiac surgery and catheter interventions.[13] These results echoed the findings of a Turkish study, published in 2013, which reviewed the etiologies of valve disease in 1 300 patients across Turkey,[14] with RHD being the major cause of valvular heart disease. Two other countries that have significant burden of RHD have reported data, which have informed the field: India and Uganda. In India, a 3-year prospective paediatric registry showed good adherence to penicillin prophylaxis. Females had greater disease severity and 20% of patients underwent a guideline-recommended intervention. In the Uganda Heart Institute (UHI), 80% of patients are symptomatic on first diagnosis, with 40% already having significant cardiovascular complications.[15] A further registry from sub-Saharan Africa, The VALVAFRIC study, reviewed RHD in Western and Central Africa with a retrospective and prospective design, and reported that patients with RHD hospitalised in sub-Saharan Africa are young, socially disadvantaged, with a high mortality rate, and with extremely low access to surgery.[16]

Long-term outcomes

Okello, et al. reported on the 12-month outcomes of patients enrolled in the UHI registry; there were 59 deaths with a 1-year mortality rate of 17.8%. Most deaths occurred within the first 3 months of presentation.[17] After 24 months, REMEDY reported an overall mortality of 16.9% with a median age of death of 28 years, and with the highest rates in low-income countries – despite age and sex adjustment.[18] Both the Indian paediatric RHD registry and the VALVAFRIC study reported high mortality rates of 3.1% and 16% respectively. In an elegant publication from Australia, Cannon, et al. used Northern Territory data to develop multi-state models to estimate rates of transition between disease states, and to evaluate the cost-effectiveness of potential interventions.[19] Of 591 patients evaluated for progression of disease, surgery or death, 96 (16.2%) patients had severe RHD at diagnosis. Of these patients, 50% had proceeded to valve surgery by 2 years, and 10% were dead within 6 years. Of concern, however, was that although patients with mild RHD at diagnosis were the most stable, with 64% remaining mild after 10 years, 11.4% progressed to severe RHD and half of these required surgery.

Cost-effectiveness analyses

Registry data have also been used for cost-effectiveness analysis. One has investigated the cost of primary and secondary prophylaxis using registry data from Cuba,[20] and suggested from their preliminary findings that primary preventions could be the most efficient and cheapest approach in poor countries. Cannon, et al. used the multi-state models described previously to review a cost-effectiveness model of echocardiographic screening, with a suggested ICER of less than AUD50 000[21] per DALY averted, assuming that RHD can be detected >/=2 years earlier by screening.

Policy and partnerships

Informed by these data providing compelling evidence of collective neglect and a wide gap in any systematic effort to prevent control or manage RHD, key role-players and stakeholders are finally joining forces to take action through policy initiatives and concrete plans.[22] These build on important previous initiatives, such as the Pan-African Society of Cardiology-driven ASAP (Awareness, Surveillance, Advocacy and Prevention) programme[23-25] led by a global initiative of concerned parties such as the World Heart Federation,[26] and spurred on by successful multi-pronged interventions incorporating registers that achieved successes in countries such as Cuba[27] and Tunisia,[28,29] Multiple forces have been united in the fight to eradicate the disease under the umbrella name "RHD Action", resulting in an encouraging momentum of activity, and culminating in the promise of a global commitment on RHD.[30]

In 2015, a practical roadmap outlining 7 major barriers to RHD control in Africa, and strategies to address them, was developed. The plan, called the Addis Ababa Communique, encouraged partnerships between the African Union Commission of health ministries, academia, and other role-players – and provided a comprehensive actionable programme with measurable and achievable outcomes over pre-specified timeframes.[31]

Adding weight to this effort, in 2018 the executive board of WHO recommended a resolution on Rheumatic Fever and RHD, which was spearheaded by New Zealand, and for adoption at the 2018 World Health Assembly. The resolution compels governments and health bodies to recognise RHD as

a global health priority and to commit appropriate resources and funds toward prevention and control.[32] It represents a seismic shift in the RHD landscape. We stand at the precipice of RHD activism; now is the time to act decisively and to diagnose Strep A as early as possible, to institute treatment to prevent ARF, and to manage RHD effectively. The WHO resolution is summarised in Table 1, and the mandate of incorporating patients at the centre of all activities speaks strongly to a patient-based infrastructure – which is the key component of an effective registry. New registers being developed for RHD need to consider key questions in RHD prevention, control and surveillance, in order to meet the high expectations of the resolution (see Box 3).

In summary

Retrospective, and more recently large-scale multi-country prospective registries in RHD, provide a unique opportunity to accurately assess current clinical practice and outcomes. They allow for comparison of data with other institutions and clinical practice guidelines. In particular, they inform the Global burden of disease data,[1] especially regarding morbidity and non-fatal sequelae and help identify further data needs. In RHD, registries have made a critical contribution to our evidence base, clinical management and advocacy efforts. However, they are only useful when used properly, and with careful attention to design, analysis and interpretation.

TABLE I: World Health Assembly Resolution against Rheumatic Heart Disease.

	The resolution urges member states to:	The resolution invites relevant international stakeholders to assist and collaborate and:
	Accelerate multisectoral efforts toward reducing poverty, improving socioeconomic conditions and tackling the known root determinants of rheumatic heart disease.	Put people living with rheumatic heart disease at the centre of the prevention and control agenda, and advocate on behalf of communities affected by rheumatic heart disease.
	Estimate their burden of rheumatic heart disease, implement and resource rheumatic heart disease programmes, and provide improved disease surveillance and good-quality data analysis that facilitate appropriate follow-up and contribute to a broader understanding of the global disease burden.	Raise the profile of rheumatic heart disease and other non-communicable diseases of children and adolescents on the global agenda – with a view to strengthening health systems and alleviating poverty.
	Improve access to primary healthcare, and a primary healthcare workforce trained in prevention, diagnosis and evidence-based management, alongside improving understanding of prevention and control of rheumatic heart disease among at risk populations.	Facilitate timely, affordable and reliable access to existing and new cost-effective medicines and technologies for the prevention and control of rheumatic heart disease and for supporting research and development.
	Ensure timely, affordable and reliable access to cost-effective essential laboratory technologies and medicines, for the diagnosis, prevention and treatment of acute rheumatic fever and rheumatic heart disease.	
	Strengthen national and international cooperation to address rheumatic heart disease, including through setting global and national targets, using and sharing best practice methodologies for prevention and control, and creating national and regional networks.	
The WHO Director-General is requested to:	Reinvigorate engagement, lead and coordinate global efforts on prevention and control of rheumatic disease – with rheumatic heart disease considered broadly across relevant WHO work areas.	
	Support member states in identifying the rheumatic heart disease burden and, where appropriate, developing and implementing rheumatic heart disease programmes and strengthening health systems.	
	Foster international partnerships for resource mobilisation, sharing best practice etiologies, developing and supporting a strategic research and development agenda, and facilitating access to existing and new medicines and technologies.	
	Assess and report on the magnitude and nature of the problem of rheumatic heart disease according to agreed measures, and monitor efforts for the prevention and control of rheumatic heart disease.	

Report on implementation of this resolution to the 74th World Health Assembly.

BOX 3: RHD registries: future needs.

- Monitor the global burden of disease and regional prevalence and incidence trends.
- Provide better understanding of the immunopathogenesis and biology of RHD.
- Monitor adherence to guidelines recommended for prevention and prophylaxis and understand regional variations.
- Monitor adherence to guideline recommended treatment strategies and understand region variations.
- Provide data to improve understanding of regional variation.
- Provide data to inform future trials of therapeutic interventions.

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