Primary prevention of rheumatic fever in children: Key factors to consider

To the Editor: We applaud the efforts by Irlam *et al.*[1,2] to conduct a cost-effectiveness analysis of primary prevention of rheumatic fever (RF) in children. The authors used a Markov decision analysis cohort model to assess seven different treatment strategies for children presenting with sore throat. A particular strength of the study was the inclusion of costs relating to secondary prevention and development of chronic rheumatic heart disease (RHD). The authors concluded that using clinical criteria for the diagnosis of pharyngitis without culturing for group A streptococci is the most cost-effective intervention for the prevention of RF and RHD in settings where these diseases are endemic.[1] However, we believe that they have not fully considered several important issues.

The authors chose to use a clinical decision rule to diagnose group A streptococcal pharyngitis in children presenting with sore throat that requires only two of three features to be present for treatment to be initiated: enlarged cervical nodes; absence of rash; and absence of rhinitis.[3] This clinical decision rule is highly sensitive (92%), but is poorly specific (38%), which means that while only 8/100 children would be missed, 62/100 children with sore throat would receive antibiotic treatment unnecessarily. While this strategy may be better than treating all, we believe that the authors have underappreciated the importance of the unintended consequences resulting from overuse of antibiotics, particularly antibiotic resistance. The authors correctly point out that resistance to penicillin in group A streptococci has never been reported; however, they did not consider the impact of widespread use of penicillin on drug resistance developing in other bacteria. A key example is the promotion of penicillin-resistant *Streptococcus pneumoniae,* a worldwide health problem that was originally described in South Africa (SA), where it is has been strongly associated with injudicious use of antibiotics in patients with viral infections.[4-6]

Some of the probability assumptions used in the model may not be applicable to most settings. A key issue in this study was the incidence of sore throat used (8.7/1 000 child years, 0.87%). This figure, derived from an RF registry in the Vanguard community, is extremely low compared with published data, which suggest that sore throat occurs in at least 33% of children/year.[7-9] The study used a figure of 15% for the prevalence of group A streptococci in the pharynx; this means that only 1 - 2 of every 1 000 children/year experience a group A streptococcal sore throat (1.3/1 000 child years). Data from other RF-endemic countries suggest a far higher incidence of group A streptococcal sore throat by a factor of over 100 times: 147/1 000 child years in Fiji and up to 950/1 000 child years in India.[9,10] The very low incidence of both sore throat and group A streptococcal-positive sore throat reported by Irlam *et al.* suggests that many SA children do not present for care, which is a concern for a public healthcare programme that relies on treatment of sore throat. In addition, the use of such a low incidence of group A streptococcal sore throat may have underestimated the expected costs from associated complications.

The study did not include rapid group A streptococcal antigen tests in the Markov model on the basis that these tests have 'low sensitivity'. While the sensitivity of a few of these tests is low, the majority of modern tests have sensitivity >85% and nearly all have high specificity (>95%).[11] A number of immunoassay rapid tests and the majority of the newer molecular rapid tests have sensitivity >90%. These figures compare very favourably with the clinical decision rule outlined in the study, particularly because the higher specificity of rapid tests would substantially reduce overdiagnosis. Rapid tests have decreased in cost over time, with many being cheaper than culture, and potentially applicable to low-income settings. Rapid tests have clear advantages for the diagnosis of group A streptococcal pharyngitis because an on-the-spot clinical decision can be made. This is important because a considerable portion of the cost attributed to culture in the study by Irlam *et al.* was the cost of a return visit, which would be obviated by a rapid test. We believe that a low-cost rapid test that has high sensitivity and a fast turnaround time should be a research priority for the RF research community, particularly in low-income settings.

Diagnosis and treatment of group A streptococcal pharyngitis is important in the control of RF and RHD. We agree with the authors that in resource-poor populations, the very ones that are most affected by rheumatic disease, a pragmatic approach to the diagnosis of group A streptococcal pharyngitis that minimises cost is necessary. However, factors other than cost, such as antibiotic resistance and the likelihood of the target population presenting with sore throat, should also be considered when developing clinical guidelines and public health interventions.

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Irlam *et al*. respond: We appreciate the interest of Steer and Danchin in our article,[1] and wish to respond to the key issues they raise.

Their concern about the overuse of penicillin on the resistance of bacteria other than group A streptococci is certainly a valid one that requires close attention. SA has had one of the highest reported rates of pneumococcal penicillin resistance in the world,[2] but the full impact of resistance in *S. pneumoniae* in our setting needs to be properly assessed.[3] While overuse of penicillin for the treatment of suspected group A streptococcal pharyngitis may affect pneumococcal resistance rates, this needs to be weighed against the risk of a missed streptococcal throat progressing to acute rheumatic fever (ARF).

The very low incidence of sore throat (8.7/1 000 child years) and prevalence of group A streptococcal-positive sore throat (15% in children presenting with sore throat, 0.13% overall) in the Vanguard Study Area population between June 2008 and June 2010 may largely be a result of under-presentation at urban primary healthcare clinics in this setting. Incidence data for this study were derived from all the clinics covering a defined local geographical area of Cape Town. While patients attending private medical facilities would have been missed, it is expected that this will be a very small number, because most people in the area use public sector healthcare facilities. As we showed in our original paper, however, the higher the incidence, the more cost-effective either the clinical decision rule or 'Treat All' strategies become, which makes our results even more applicable to regions with higher incidence.[4] When we used rates similar to those suggested by Steer and Danchin, the strategy of 'Treat All' becomes preferable. Nevertheless, in our paper we call for wider efforts to complement this opportunistic, cost-effective, passive strategy of RF and RHD prevention at primary healthcare clinics. For example, active screening for RHD using portable echocardiography and computer-assisted auscultation followed by secondary prophylaxis is currently being undertaken and evaluated in schools in the same community.[5]

Our primary reason for the exclusion of rapid group A streptococcal antigen tests in the Markov model was that these tests are not currently used in public sector primary healthcare settings in SA. We agree that a low-cost rapid test with high sensitivity and a fast turnaround time should be a research priority that may, in the light of cost-effectiveness modelling and large-scale evaluation studies, prove to be a very useful addition to updated clinical guidelines for the management of RF and RHD in the public sector in SA. Funding is currently being sought to conduct a study on the utility of rapid streptococcal tests.

We thank Steer and Danchin for their critique. We share their concern for safety and effectiveness as well as cost in developing clinical guidelines and public healthcare interventions for early prevention of ARF and RHD.

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