

New evidence supports a greater focus on streptococcal skin infections to prevent rheumatic fever

We noted with interest the recent report finding a relationship between establishment of a skin health program and a sustained reduction in impetigo for children living in remote communities in Western Australia.¹ Although the results suggest it was the impact of heightened awareness which caused this reduction, rather than the intervention itself, this study is an important reminder of the multiple benefits from reducing skin infections. These benefits include the potential to protect against post-streptococcal diseases such as acute rheumatic fever (ARF) and acute post-streptococcal glomerulonephritis (APSGN).^{2,3}

ARF can progress to rheumatic heart disease (RHD), resulting in considerable global morbidity and mortality, mainly in low and middle-income countries,⁴ but also for Indigenous and Pacific Peoples in Australia and Aotearoa New Zealand.^{5,6} Group A *Streptococcus* (GAS) infection is the established trigger for the immune dysregulation that causes ARF.²

Evidence suggests that group A *Streptococcus* skin infection has a role in priming and triggering acute rheumatic fever

For many decades prevention of ARF has focused on the treatment of GAS pharyngitis; however, there is growing evidence that GAS skin infections can also trigger ARF.^{7,8} Two recent case-control studies add weight to this conclusion and support the need to explore skin infection prevention and treatment as a key intervention to prevent ARF and RHD.^{9,10}

The first of these paediatric case-control studies investigated risk factors for ARF in Auckland, Aotearoa New Zealand.⁹ It found that while most cases of ARF were preceded by a reported throat infection, some cases were preceded by only a skin infection. Other major modifiable factors were exposure to household crowding and barriers to accessing primary health care.⁹

The second study investigated risk factors for GAS skin and throat infections.¹⁰ These GAS infections were also associated with barriers to accessing primary health care. There were no other specific risk factors for GAS throat infection. By contrast, GAS skin infection had a very similar pattern of risk factors to ARF, including household crowding, suggesting these infections may be a pathway by which poor housing conditions drive an increased ARF risk.

Further evidence supporting a role for skin infections in initiating ARF comes from a large-scale record linkage study of 1.9 million throat and skin swabs in Aotearoa New Zealand.¹¹ These swabs, collected from the Auckland population over an eight-year period (2010–2017), were individually linked to cases

of ARF that occurred in the same population over the subsequent year. The risk of ARF following a GAS infection was highest in the eight to 90 days after swabbing, calculated by comparing rates observed in children with GAS-positive versus GAS-negative swabs. Importantly, the risk was similarly elevated for both GAS skin infections (risk ratio [RR], 5.1; 95% confidence interval [CI], 1.8–15.0) and throat infections (RR, 4.8; 95% CI, 3.6–6.4) in Māori and Pacific Peoples.¹¹

One unresolved question with the distribution of ARF and RHD in Aotearoa New Zealand is to identify the factors that drive the extreme ethnic gradient, with ARF rates 20 times higher for Māori and 44 times higher for Pacific children and young people than for non-Māori/non-Pacific children and young people.⁶ While there is an ethnic disparity for cases of GAS pharyngitis swabbed in primary care settings,¹² this gradient is far more marked for GAS skin infections.¹³ Rates of GAS skin infections are four times higher for Māori and almost seven times higher for Pacific children and adolescents compared with non-Māori/non-Pacific children and adolescents.¹³ For those who are repeatedly positive for GAS skin infections, the rate ratios are even higher at tenfold and 15-fold respectively.¹⁴

Further evidence for a greater emphasis on GAS skin infections comes from evaluation of past ARF control efforts in Aotearoa New Zealand. These efforts have focused on timely detection and treatment of GAS throat infections with oral antibiotics, although identified skin infections are also managed, mainly with topical treatments. Despite a highly organised school-based sore throat management program operating since 2012, covering higher risk communities across the country, there has not been a consistent decline in ARF incidence.^{15,16}

Related serological research suggests that multiple prior GAS infections contribute to the immune dysregulation that causes ARF. This process is described as “immune priming”, where repeated GAS infections trigger immune dysregulation and a loss of tolerance. It results in antibodies and immune cells that react with human tissue and inflammatory-driven tissue damage, particularly in the heart, joints and central nervous system, which are characteristic of ARF.¹⁷ In addition, serum samples collected as part of the ARF risk factors study⁹ showed significantly more type-specific GAS antibodies in cases than controls.¹⁸ Furthermore, GAS skin infections induced an increased breadth of antibody responses compared with GAS throat infections, corroborating the possible role of GAS skin infections as priming events for ARF.¹⁹

These findings add support for prevention and treatment of skin infection in children to reduce GAS

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exposures that may contribute to ARF. Detected GAS skin infection rates are highest in children under ten years of age, so that group should be a major focus.¹³ Our recent studies also suggest that prevention could extend to better treatment of eczema¹⁰ and scabies infections,⁹ both of which may facilitate GAS skin infections.

Need for research to investigate group A *Streptococcus* skin infection interventions to prevent acute rheumatic fever

An international consensus group convened by the National Heart, Lung, and Blood Institute of the US National Institutes of Health identified a series of knowledge gaps and proposed research priorities to reduce the large global burden of RHD.²⁰ These priorities included investigating interventions to ensure sustained reduction in GAS skin infections and their effect on suitable ARF endpoints (eg, GAS transmission, immune priming).

There are opportunities to use available observational data to further investigate the role of exposure to GAS skin infections in early childhood by extending existing data linkage studies retrospectively to cover infections in the first five years of life and the relationship to subsequent risk of ARF.¹¹ This research could also include the other important immune-mediated disease of APSGN, which in Aotearoa New Zealand has similarly elevated rates for Māori and Pacific children.²¹

There are important questions about the mode of action of antibiotics for preventing the immune dysregulation that follows GAS infections. This concern was highlighted by the Aotearoa New Zealand record linkage study that found no protective effect from oral antibiotic use identified by linked dispensing data.¹¹ One approach for investigating the serological response to GAS skin infections, and potentially how this could be modified with antibiotic treatment, are challenge studies which have already been used for studying the response to GAS throat infections and could be extended to skin infections.²²

There are also large knowledge gaps around the most effective ways to treat bacterial skin infections in general, including those caused by GAS.^{23,24} This area is complicated by the fact that many of these infections are polymicrobial, and treatment is often presumptive without microbiological confirmation.²³ There are questions about the potential benefits of topical versus oral and injectable antibiotics, and the choice of agents to use. Other questions include the added benefits of treating scabies and eczema along with hygiene measures to prevent bacterial skin infection.^{24,25}

It will ultimately be important to consider trials to assess the impact of potential interventions for prevention and management of GAS skin infections in children. Such trials are challenging to conduct and may produce inconclusive results, as was seen recently in Australia.¹ ARF rates have been used as endpoints in controlled trials, but required very large study populations and have not shown a significant

protective effect in some of these intervention studies (eg, school-based sore throat treatment in Auckland, Aotearoa New Zealand,²⁶ and mass treatment of scabies in Fiji²⁵). Alternative endpoints will be needed. They would almost certainly include the incidence of clinical and laboratory-confirmed GAS skin infection as a primary endpoint. Another endpoint to consider is serological evidence of immune priming, which is known to be associated with a higher risk of ARF.¹⁸ Such secondary endpoints could require only a modest study size to test various interventions but need further evaluation to assess their validity.

Conclusion and future directions

Australia and Aotearoa New Zealand are world leaders in researching rheumatic fever, its causes, and potential interventions. This research has contributed evidence supporting the case for vaccine development and highlighted the long-established need to invest in improving social determinants such as adequate housing and primary health care access to prevent ARF.⁹ Both countries have also built up expertise in evaluating interventions which is critically needed before rolling out mass treatment programs.^{1,15}

Effective prevention and treatment of skin infections has been neglected particularly for underserved and Indigenous populations in both Aotearoa New Zealand and Australia. This situation must change. As the research summarised here has shown, there is growing evidence that effective management of GAS skin infection may prevent both ARF initiation and priming, and potentially APSGN also. An added benefit is that success in this area is inherently worthwhile, as skin infections themselves are a major cause of childhood illness, hospitalisation and avoidable economic cost.²⁷

Generating strong, convincing evidence about effective prevention and treatment of skin infections and its benefits in reducing immune-mediated diseases will almost certainly require a large, sustained, international research effort. Perhaps it is time for a shared research agenda for Aotearoa New Zealand and Australia to tackle GAS skin infection. Such action would further develop the successful trans-Tasman collaboration that has already evolved to combat ARF.

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