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Unravelling the within-host dynamics of Group A Streptococcus infection from population-level observations of strain diversity and infection prevalence

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Group A *Streptococcus* (GAS) is a ubiquitous human pathogen composed of over 230 different molecular sequence types. GAS is responsible for a broad spectrum of diseases - from superficial infections of the skin and throat to life-threatening invasive infections and post-infection sequelae. Even though most GAS infections are mild and easily treated, GAS-related disease remains a major cause of death and disability globally. This burden is greatest in settings of poverty, including developing countries and in Indigenous populations of many developed countries. Safe and effective vaccines against GAS are urgently needed to reduce this overall burden, and reduce health inequalities.

Development of vaccines and other disease reducing strategies is currently hampered by our incomplete understanding of the within and between-host dynamics of GAS infection, immunity and transmission. Studies provide limited information on the progression of GAS disease without treatment (the natural history of disease), on the relative competitiveness of GAS strains within and between hosts, and on the immune response to GAS skin infection (the predominant infection type in many host settings where GAS disease is hyper-endemic). Assessments of these key variables are all confounded by the considerable diversity of GAS. Epidemiological studies provide relevant data on the total population prevalence of GAS infections and associated disease, in relation to the diversity of GAS strains circulating in different host populations. Meta-analyses of these studies demonstrate that the level of GAS transmission and GAS-related disease in a particular host population is positively associated with the total number of strains circulating at any one time. Specifically, studies conducted in settings where GAS disease is hyper-endemic report dozens of different circulating strains, while those conducted in low prevalence settings report circulation of only a handful of distinct strain types.

In this work, we use an individual-based model of GAS transmission to explore hypotheses about the within-host dynamics of GAS infection and immunity. Specifically, we examine the conditions that must hold with respect to within-host dynamics to generate observed population-level associations between infection prevalence and strain diversity. Our results reveal how a positive association between these two population-level measures can emerge for multi-strain pathogens that elicit strong strain-specific immunity following infection with low to intermediate levels of cross-strain immunity protecting against re-infection. The same association between prevalence and diversity can also emerge for pathogens that elicit weak strain-specific immunity following infection, but only if they can co-infect hosts with multiple strains. Given that a strong strain-specific immune response following GAS skin infection is unlikely, we propose that co-infection is a key enabler of high levels of strain diversity in host settings where GAS disease is hyper-endemic. Our findings also suggest that development of vaccines capable of eliciting strong cross-immunity over multiple strain types will be needed to impact on the burden of GAS disease.

Primary author: CHISHOLM, Rebecca (University of Melbourne)

Co-authors: Dr CAMPBELL, Patricia (University of Melbourne); Dr LACEY, Jake (The Peter Doherty Institute for Infection and Immunity; The University of Melbourne); Dr DAVIES, Mark R. (Peter Doherty Institute for Infection and Immunity; University of Melbourne); Dr TONG, Steven Y. C. (The Royal Melbourne Hospital; University of Melbourne; The Peter Doherty Institute for Infection and Immunity; Menzies School of Health Research, Charles

Darwin University); Prof. MCVERNON, Jodie (Murdoch Childrens Research Institute; Peter Doherty Institute for Infection and Immunity; University of Melbourne); Dr GEARD, Nicholas (University of Melbourne)

Presenter: CHISHOLM, Rebecca (University of Melbourne)

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