Roadmap to incorporating group A *Streptococcus* molecular point-of-care testing for remote Australia: a key activity to eliminate rheumatic heart disease

Strep A POCT is a critical element in preventing acute rheumatic fever and will contribute to the elimination of rheumatic heart disease in Australia

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Group A β-haemolytic *Streptococcus pyogenes* (Strep A) most commonly causes superficial infections of the throat (pharyngitis) and skin (impetigo). In Australia, one-third of primary school aged children have an episode of pharyngitis each year,[1] with Strep A identified in about 20% of children with symptomatic pharyngitis and 10% of asymptomatic children.[2-4] Superficial Strep A infections are the sole precursor of acute rheumatic fever (ARF) and rheumatic heart disease (RHD),[5] with risk likely to be driven by both pharyngitis and impetigo.[6] These autoimmune sequelae are a major cause of morbidity and mortality in developing countries and among Indigenous people living in high income countries.[7] The burden of ARF and RHD in remote Australian communities is high and disproportionately affects Aboriginal and Torres Strait Islander people.[8] The reported mortality rates of RHD in Aboriginal populations are among the highest worldwide (28.4 per 100 000 population; 95% CI, 24.1–32.7).[9] This is despite ARF and RHD being preventable through the early treatment of Strep A pharyngitis and impetigo.[10] In this article, we focus on the use of molecular point-of-care testing (POCT) in the diagnosis of pharyngitis, which is the dominant superficial infection leading to ARF.

Diagnosing and treating Strep A pharyngitis

Australian guidelines recommend people at high risk of ARF be treated with antibiotics for Strep A pharyngitis based on clinical diagnosis.[11] However, international clinical scoring guidelines[12] used to predict Strep A pharyngitis are considered ineffective in Australia.[6] Confirmatory microbiological testing is thus recommended to support antibiotic prescription. Throat swabs sent for laboratory culture from remote clinics may take up to 5 days to return a result and are of little use to guide treatment decisions at the time of clinical presentation.

Recently, molecular POCT for COVID-19 has been implemented in rural and remote Australia[13,14] using the GeneXpert platform (Cepheid). This POCT operates within a quality framework which includes training and competency assessment, quality control, external quality assurance, risk management and clinical governance, consistent with the National Pathology Accreditation Advisory Council guidelines for POCT.[15] Molecular POCT integrates sample preparation, nucleic acid extraction, amplification, and detection of the target sequences in samples using real-time polymerase chain reaction[16] and can be conducted during the initial patient consultation with results in 6 minutes for Strep A. Following specific program and competency assessment, POCT with throat swabs can be performed by non-laboratory staff including doctors, nurses and Aboriginal health practitioners[14,17,18] and utilises disposable closed cartridges for each sample, minimising risk of contamination.[14,17,19]

Accurate diagnosis of Strep A pharyngitis could be a game changer in ARF and RHD prevention strategies, and reduce inappropriate antibiotic prescribing. In the absence of POCT, clinicians decide whether to prescribe treatment for Strep A pharyngitis: a single injection of intramuscular benzathine benzylpenicillin G,[20] or a 10-day course of oral phenoxymethylpenicillin.[6] Improving diagnostic accuracy for Strep A pharyngitis could therefore reduce over-prescription of antibiotics contributing to antibiotic resistance (eg, methicillin-resistant *Staphylococcus aureus*) and avoid missed opportunities to treat Strep A pharyngitis to prevent ARF[21-23] appropriately.

Benefits and challenges of molecular POCT for Strep A

Molecular POCT is accurate and can deliver results which are more sensitive than gold standard culture methods and rapid antigen detection tests.[24] A prospective evaluation of the GeneXpert POCT for Strep A reported a sensitivity of 100% and specificity of 83.5%.[19] The usefulness of Strep A molecular POCT in remote living populations in Australia at high risk of ARF has been shown in laboratory-based studies, clinical practice and a surveillance study.[17,25] A prospective observational study in Queensland found that access to Strep A molecular POCT allowed practitioners to better direct antibiotic prescribing to Strep A positive patients.[26] Although the reduction in antibiotic prescribing in this study was minimal, the shift towards targeted antibiotic prescribing for patients with Strep A improved from 60% before implementation to 98.8% after implementation.[26] The potential benefits and challenges associated with the implementation of Strep A molecular POCT in remote primary care services in Australia are summarised in the Box. It is estimated that between 2016 and 2031,

Potential benefits and challenges associated with Strep A point-of-care testing (POCT) in rural and remote Australia

Benefits	Challenges
• Rapid diagnosis and treatment of Strep A pharyngitis during initial patient consultation • Reduction in the rates of ARF and RHD in remote Australia • Reduction in onward transmission (infections averted) • Reduction in health care costs associated with acute and chronic sequelae (ARF and RHD) • Reduction in inappropriate antibiotic prescription and decreased risk of antimicrobial resistance • Reduced costs of transporting swabs from remote communities • Empowered upskilled health service staff • Improved patient and provider satisfaction • Reduced laboratory costs to process swabs for culture • Improved health literacy and opportunity for health promotion and education	Costs associated with: • Equipment including POCT devices* • Annual device maintenance and quality test costs • Staff time conducting the test • Consumables (cartridges, swabs) • Training resource development • Maintaining workforce skilled in POCT (ie, where turnover of staff is high, and staff are fully utilised) • Sustainable funding (eg, Medicare Benefits Schedule rebate) • Staff training and competency assessment time • Implementing quality management and connectivity systems • POCT scale up and implementation of a new POCT • Clinical governance and accreditation

ARF = acute rheumatic fever; RHD = rheumatic heart disease; Strep A = group A β-haemolytic streptococci. * GeneXpert (Cepheid) devices and connectivity systems already exist in remote primary care services and may not need to be costed unless a different device was utilised. ◆

without additional actions, over 10 000 Aboriginal or Torres Islander people would be affected by ARF or RHD, with associated diagnosis and long term management costs totalling $317 million (or more than $31 000 per case).[27]

Lessons learned from POCT for sexually transmitted infections and COVID-19

The existing network of POCT for COVID-19 and sexually transmitted infections (STIs) in remote and rural Aboriginal health services is relevant to the implementation of Strep A POCT.[28] The COVID-19 pandemic created an urgent need for rapid diagnostic tests to detect infections and enable swift public health responses.[28] The Aboriginal and Torres Strait Islander COVID-19 POCT program was established in April 2020 using the GeneXpert platform and rapidly scaled up. As of June 2020, the national COVID-19 POCT program transitioned from the single SARS-CoV-2 GeneXpert assay to the multiplex respiratory GeneXpert assay, which simultaneously tests for SARS-CoV-2, influenza A and B, and respiratory syncytial virus.[14] To date, almost 100 services are now performing POCT for COVID-19, and more than 73 000 tests have been conducted in primary care, with 50% of the enrolled sites more than 10 hours' drive from laboratory facilities. POCT for STIs is also being scaled up using services established through the COVID-19 program.[14]

The utilisation of existing GeneXpert platforms and the experienced infrastructure supporting their use were significant enablers to implementation and rapid scale up.[14] Other enablers included Aboriginal clinical governance to ensure community ownership, the staggered rollout of equipment, virtual training and competency assessments, quality and risk management processes, support and partnerships with public health departments, Aboriginal Community Controlled Health Organisations and laboratories, capacity building for remote health care workers, and national guidelines and policies[14] to ensure the highest standards are met. As for COVID-19 POCT, a cartridge is also available for Strep A POCT on the GeneXpert platform.[29] Rapid establishment and governance of this infrastructure could be adapted and diversified for implementation of Strep A POCT. Developing tools to support health workers to diagnose and treat Strep A infections through a comprehensive sore throat and skin program in high risk communities is a key priority of the RHD Endgame Strategy[30] to eliminate ARF. Strep A molecular POCT is a game changer imminently poised for implementation.

Barriers to the COVID-19 POCT program (likely similar for any POCT program) included high staff turnover, frequent training of busy staff, and a limited global supply of cartridges. Other concerns included the quality of testing performed at each site and the accuracy of the test conducted by health care workers who often have conflicting clinical priorities. Regular refresher training sessions, helpdesk phone support, and error rate monitoring and reporting assisted program staff facing such challenges.

Implementing molecular POCT for Strep A

For Strep A POCT to be routinely used in primary care, the physical infrastructure, training and quality framework, sustainable funding mechanisms and clinical guidelines must be attainable. A rebate for a Strep A POCT is currently not listed on the Medicare Benefits Schedule (MBS).[26] To be considered for MBS listing in the Australian public health system, regulatory approval from the Therapeutic Goods Administration (TGA) is required together with an application to the Medical Services Advisory Committee (MSAC).[31] The performance of Strep A POCT by trained operators must have high concordance with gold standard conventional laboratory techniques. Additional costs associated with providing Strep A POCT need to be considered against its potential clinical and public benefit.

The uptake and utilisation of Strep A POCT in remote regions will need to be evaluated to confirm the potential benefits described in this article, similar to the evidence accumulated for molecular POCT for STIs.[13,18,24,32] Co-designed, culturally appropriate educational and promotional resources informed by

people living with ARF will need to be developed to ensure that changes to practice incorporate their needs and perspectives. Further research is needed to understand the impact and benefits of multi-pathogen POCT for populations and health services, particularly regarding workload and workforce requirements to sustain POCT in rural and remote regions.

Next steps

The Medical Research Future Fund recently awarded a $10 million grant to a team of researchers, clinicians and government partners to develop a national framework to evaluate and scale up POCT for infectious diseases including those caused by Strep A. This provides a unique opportunity to develop the evidence base for the use of Strep A POCT to enhance primary prevention strategies for ARF and RHD through accurate diagnosis and timely treatment.

This is also an opportunity to ensure that current knowledge gaps are addressed, to facilitate a high quality MSAC submission. Following TGA approval of the *in vitro* diagnostic device for Strep A, it is essential that comparative evidence is generated to demonstrate the clinical benefits and cost-effectiveness of Strep A POCT compared with the current standard of care in Australia.[33] Additionally, an Indigenous-led governance model should be established to ensure cultural safety and community ownership of the processes and outcomes of the research program.

Given the increasing pipeline of POCT and momentum to expand decentralised testing across Australia, evaluations are urgently needed to determine the population benefits, health service impacts and costs associated with integrated multi-pathogen POCT. These will ensure that adequate frameworks including workforce planning and funding models are in place to support further scale up. The infrastructure, rationale and need for Strep A molecular POCT in remote Australia, where prevention of ARF has the highest economic and societal benefit, is crucial. Work to progress this concept and seek approval for an appropriate funding mechanism has commenced. Implementation of Strep A molecular POCT is a critical element in preventing ARF and will contribute to the elimination of RHD in Australia.[30]

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