Bennett Julie (Orcid ID: 0000-0001-5548-7512)
Oliver Jane (Orcid ID: 0000-0001-5548-7512)
Webb Rachel (Orcid ID: 0000-0002-9855-3919)
Malcolm John (Orcid ID: 0000-0003-4398-6036)

Structured review of primary interventions to reduce group A streptococcal infections, acute rheumatic fever and rheumatic heart disease

Author	Affiliation	Address
Julie Bennett*	Department of Public Health, University of Otago, Wellington, New Zealand	julie.bennett@otago.ac.nz
Nelly Rentta	Department of Public Health, University of Otago, Wellington, New Zealand	neilenuonelly.rentta@otago.ac.nz
William Leung	Department of Public Health, University of Otago, Wellington, New Zealand	william.leung@otago.ac.nz
Anneka Anderson	Te Kupenga Hauora Māori, The University of Auckland, New Zealand The National Hauora Coalition, New Zealand	a.anderson@auckand.ac.nz
Jane Oliver	Peter Doherty Institute for Infection and Immunity, University of Melbourne, Melbourne, Victoria, Australia Murdoch Children's Research Institute, Melbourne, Victoria, Australia	jane.oliver@mcri.edu.au
Rosemary Wyber	Telethon Kids Institute, Perth, Western Australia	Rosemary.Wyber@telethonkids.org.au
Matire Harwod	General Practice and Primary Health Care, University of Auckland, Auckland, New Zealand Papakura Marae Health Clinic, Auckland, New Zealand	m.harwood@auckland.ac.nz
Rachel Webb	Auckland District Health Board Auckland, New Zealand University of Auckland Department of Paediatrics: Child and Youth Health Auckland, New Zealand	RWebb@adhb.govt.nz
John Malcom	Whakatane Hospital General Paediatrics Whakatane, New Zealand	john.malcolm@bopdhb.govt.nz
Michael G Baker	Department of Public Health, University of Otago, Wellington, New Zealand	michael.baker@otago.ac.nz

* Corresponding author: Julie Bennett; Department of Public Health, University of Otago, 23a Mein Street, Newtown, Wellington 6242. Phone 0064 4 918 5248

This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/jpc.15514

Conflict of interest: The authors have no conflicts of interest.

Ethics: The University of Otago Human Research Ethics Committee granted ethical approval for this study (HD19/033). Consultation was also undertaken with the Ngāi Tahu Research Consultation Committee.

Acknowledgments: The authors wish to thank the Health Research Council (HRC) of New Zealand for funding the study (18/079).

Keywords: primary prevention, group A streptococcus, GAS, strep throat, rheumatic fever, rheumatic heart disease, pharyngitis, skin infections

ABSTRACT

Rheumatic heart disease (RHD) is a large, preventable, global public health burden. In New Zealand, acute rheumatic fever (ARF) and RHD rates are highest for Māori and Pacific children. This structured review explores the evidence for primary prevention interventions to diagnose and effectively treat group A *Streptococcus* (GAS) pharyngitis and skin infections to reduce rates of ARF and RHD. Medline, EMBASE and Scopus databases were searched as well as other electronic publications. Included were 50 publications from 1980 onwards. This review has identified that there is little available evidence for effective primary prevention strategies to reduce ARF rates in NZ. However, two primary intervention strategies that should be considered by communities at high-risk of ARF are: the use of school-based clinics to identify and treat GAS pharyngitis and GAS skin infections; and intramuscular benzathine penicillin G (BPG) with lignocaine analgesia in children who present with a GAS positive throat.

Key points

1. NZ Māori and Pacific children continue to have high rates of ARF and RHD.
2. Improving access to diagnosis and treatment of GAS pharyngitis and possibly GAS skin infections for children at high risk of ARF remains central to effective primary prevention of ARF/RHD.
3. Further research is needed to assess the mechanisms of action, optimal use and timing of interventions for the prevention of ARF/RHD through early detection and treatment of GAS pharyngitis and skin infections in NZ.

Key words

Rheumatic fever, rheumatic heart disease, group A streptococcus, primary prevention, GAS

Acute rheumatic fever (ARF), a preventable inflammatory condition, occurs in a small minority (≤3%) of susceptible people in response to untreated Group A *Streptococcus* (GAS) pharyngitis.[1] Rheumatic heart disease (RHD) can occur after an episode or recurrent episodes of acute rheumatic fever (ARF). The process by which GAS pharyngitis leads to ARF is poorly understood, but evidence suggests that GAS infections sometimes initiate the immune mediated processes leading to the development of ARF. More recently, GAS skin infections have been proposed to cause ARF, either directly or in combination with GAS pharyngitis.[2] In some Australian Aboriginal communities with a high burden of ARF and RHD, GAS pharyngitis is rare but GAS skin infections are endemic, supporting the view that GAS skin infections may led to ARF.[3, 4]

While the majority of global RHD burden occurs in low- and middle-income countries,[5] New Zealand (NZ), a high-income country, has amongst the highest reported rates of ARF in the world.[6] In NZ ARF almost exclusively affects indigenous Māori and Pacific children most commonly living in socio-economically deprived areas.[6-8] In response to the inequitable burden of ARF and RHD, in 2011, the NZ Ministry of Health instituted the rheumatic fever prevention programme (RFPP) with the goal of reducing the incidence of first episodes of ARF. This structured review aims to evaluate the evidence for primary prevention interventions that enable early diagnosis and timely treatment of GAS pharyngitis and skin infections in order to effectively reduce the incidence and impact of ARF and RHD in NZ.

METHODS

Search criteria

The search terms were designed around primary prevention objectives and interventions to reduce GAS infections, ARF and RHD. These objectives and interventions were determined by a committee, which included input from Māori, Pacific, Clinical, Public Health, and Economic advisory groups. Objectives included: Diagnosis of GAS infections; managing and treating sore throats; managing and treating skin infections; and health promotion. For a breakdown of interventions, see Supplement 1 (Table S1).

A reference librarian helped refine the search strategy, which involved searching Medline, EMBASE and Scopus databases in October 2019. Other electronic publications were searched using clinicaltrials.gov (US), Analysis and Policy observatory website (APO) and Google search (see Supplement 2 for full details of the search strategy). A preliminary screen of the papers was carried out before exporting to EndNote, before full text screening was done. Publications in all languages were included if the abstract was available in English, and were published from 1980 onwards (reviews and guidelines from 2000). Publications from all countries and all study designs except for individual case-studies were included, with a focus on those relevant to NZ. Broader social, economic and environmental initiatives to prevent and limit GAS infections are not included in this review, including GAS vaccine trials.

Criteria for assessing each intervention

The following criteria were derived for this review by study investigators and were reviewed by advisory groups (Māori, Pacific, Clinical, Public Health, and Economic). Each intervention evaluated in a publication that met inclusion criteria was assessed against eight criteria: 1. Effectiveness at preventing GAS/ARF/RHD; 2. adverse effects; 3, 4, 5 acceptability for participant (co-design, adherence, uptake); 6. feasibility; 7. equity; 8 and costs and cost-effectiveness. The first criterion (effectiveness) was rated using pooled values where possible such as odds ratios, rate ratios, and percentages. To be included in the pooled value, studies first needed to address the same or similar research questions, in similar populations and settings. Costs and cost-effectiveness were described using the local currency (with base-year) and incremental cost per unit of outcome, respectively. The remaining criteria were assessed using a scale of high,

medium, low or no evidence using the framework presented in Supplement 1 (Table S2). Values of 1, 2, 3 were assigned to criteria of low, medium and high evidence respectively. These were averaged to give an overall score for all manuscripts relevant to each intervention. For a summary of the literature and how it was assessed see Supplement 1 (Table S3).

RESULTS

Diagnosis of GAS infections

Clinical decision support aids for assessment of sore throats

Sore throat is a common complaint, and identifying patients with GAS pharyngitis is an important task for clinicians. Clinical decision rules such as the Centor or McIsaac scores were developed to help medical professionals distinguish GAS from vastly more common viral pharyngitis, which does not require antibiotic treatment. In 2008, the National Heart Foundation of NZ developed a local prediction rule based on expert opinion, which utilised the McIsaac revised Centor prediction criteria.[9-11] This prediction rule was reported to perform poorly in an evaluation of 12,000 South Auckland (NZ) school sore throat clinic examinations and culture results.[12] The McIsaac-revised Centor rule was assessed in Auckland general practice patients at high-risk of ARF.[13] In this study, only 12% of children who had a Centor score of three (possible GAS pharyngitis) and 13% of children with a Centor score of four (presumed GAS pharyngitis) had a GAS positive throat swab.

A prospective evaluation of the World Health Organization (WHO) acute respiratory infections treatment programme guidelines concluded that while these guidelines limited unnecessary antibiotic treatment, 88% of children with GAS pharyngitis would not be treated.[14] The McIsaac (modified Centor) score has been shown in some settings to be a valid clinical approach to diagnosing patients presenting with sore throats in primary care settings. However, one study showed that using the McIsaac score did not reduce unnecessary antibiotic prescribing by family physicians.[15] A 2011 meta-analysis reported that as a decision rule for considering antibiotic prescribing (when score ≥ 3), the Centor score has reasonable specificity (0.82: 95% confidence interval (CI); 0.72 to 0.88) and a post-test probability of 12% to 40% based on a prior prevalence of 5% to 20%.[16] Locally applicable clinical decision rules for diagnosis of GAS pharyngitis have been used with some success in other countries [17]. However, those tested in NZ lack the sensitivity and specificity to reliably rule in or out GAS pharyngitis in populations at high risk of developing ARF. It is therefore recommended that as part of a primary prevention strategy to reduce GAS/ARF/RHD the use of any prediction rules need to be validated in the NZ setting, including the assessment of their acceptability and equity.

New diagnosis methods for detection of GAS infection

Timely and accurate diagnosis of GAS infections is important to ensure correct treatment. Throat culture, the most specific means of GAS detection is used in NZ; however, results can take up to 72 hours creating delays in treatment or antibiotics started unnecessarily. A challenge for diagnosing and treating GAS pharyngitis is that some individuals naturally carry GAS in their throats without having evidence of infection or any autoimmune sequelae and it can be difficult to distinguish children with carriage and intercurrent viral pharyngitis from those with acute GAS pharyngitis, particularly in high-incidence ARF populations.[18]

This review identified eight studies investigating new technologies to quickly and accurately diagnose GAS infections. Five of these studies used polymerase chain reaction (PCR) techniques either at the point of care [19] or as a comparison against a reference standard.[20-23] The average sensitivity of these PCR studies ranged from 87% to 100% and the average specificity ranged from 98% to 100%; with positive predictive values (PPV) of 88% to 97% and negative predictive values (NPV) of 97% to 99%. A NZ study that compared routine culture and illumigene GAS assay using loop-mediated isothermal amplification, concluded that the illumigene assay did not perform as well as previously described.[24] The effectiveness and high feasibility of new technologies to quickly and accurately diagnose GAS pharyngitis warrants further investigation.

Managing and treating sore throats

In NZ, current clinical guidelines [25] recommend that high-risk populations who present to primary care or an emergency department with a sore throat, have a throat culture if possible and are treated with a ten day course of oral antibiotics (penicillin, amoxicillin or erythromycin or intramuscular benzathine penicillin G (BPG).[25]

BLIS prophylaxis

Probiotic therapy has been proposed as both a prophylaxis and a potential treatment for GAS pharyngitis. The oral probiotic *Streptococcus salivarius* produces bacteriocin-like inhibitory substances (BLIS), which can counteract the growth of GAS.[26] This review identified five studies which showed a significant reduction in episodes of pharyngotonsillitis caused by GAS in patients who received BLIS K12 in comparison to those who did not (range 60-97%). One NZ randomised control trial reported a reduction in GAS throat infections but the findings were not significant.[27] Both that trial and an Italian one showing prophylaxis benefit in pharyngeal GAS negative pre-schoolers were included in a recent systematic review of evidence to support the use of the probiotic *S. salivarius* K12 (SsK12).[28] The review concluded that SsK12 appears to be safe and well accepted. Further blinded randomised controlled trials to establish the role of probiotics as a prophylactic therapy for the treatment of GAS pharyngitis are recommended.

Sore throat clinics in schools

Following a 2009 structured review, which concluded that treatment of GAS pharyngitis with penicillin in schools and or community-based programmes could reduce ARF cases by 60%, a trial involving 53 schools in Auckland was established.[29] The trial reported a statistically non-significant (p=0.47) reduction in ARF cases in children attending the school clinics.[30] A pilot study concluded that it was acceptable and feasible to deliver targeted primary health care in low socio-economic primary schools. The annual cost of such a programme, in 2011, was estimated to be 510 NZD per child/year.[31] Following these studies, in 2011 NZ implemented the RFPP.

An initial evaluation of the school-based component of the RFPP reported that after two years of operation, ARF rates in 5-13 year olds dropped from 88 (95% CI: 79-111) per 100,000 pre-clinics to 37 (95% CI: 15-83) per 100,000 after two years of clinic availability, a 58% reduction.[32] An evaluation of a school-based programme which carried out daily assessments and treatment of sore throats, reported a 12% reduction in GAS pharyngitis from 2013 to 2014.[33] The 2014 cost of the programme was 280 NZD per child/year. A

subsequent evaluation of the RFPP used national trends of all-age first episode ARF hospitalisation rates before (2009-11) and after (2012-16) implementation of the RFPP. Following RFPP implementation the national ARF incidence rate declined by 28%.[34] The incremental cost per quality-adjusted life-year (QALY) gained was 90,043 NZD for the school-based sore throat service in 2014.[35] A recent retrospective cohort study in the Bay of Plenty reported that school-based programmes with twice rather than thrice weekly sore throat swabbing, in high-deprivation areas with large Māori populations, led to a 60% reduction in ARF incidence for Māori 5-14 year olds. The cost of the programme was 165 NZD per child/year, with an incremental cost per QALY gained of 13,488 NZD.[36] Sore throat clinics in schools have seen an effective reduction in ARF cases in communities at high-risk of developing ARF. These clinics have high uptake levels (80-97%), are highly equitable and acceptable and are cost-effective in areas with a concentrated population of high-risk individuals. Therefore, communities at high risk of ARF should consider utilising school-based clinics to identify and treat GAS pharyngitis.

Increase range of settings for sore throat management

A prospective pilot study investigated a test and treat service in 35 community pharmacies, involving 367 patients, across two United Kingdom regions. Patients who met the Centor scoring criteria were offered a throat swab (42%) and those who had GAS positive swabs, were offered antibiotic treatment (24%). The study reported possible savings to the National Health Service (NHS) from the 41 general practitioner (GP) consultations avoided was among those patients at 2747 GBP in 2015.[37] An evaluation of a NHS sore throat test and treat service in Wales, reported that the service was associated with a reduction in antibiotic prescriptions.[38] A United States study quantified the average amount of pharmacist time (25.3 minutes) required to complete a point-of-care test for a patient presenting with pharyngitis symptoms. These authors concluded that such a service could be implemented in a community pharmacy with limited disruption or change to workflow and staff.[39] The acceptance, uptake, equity, and cost-effectiveness of test and treat pharmacy services for GAS pharyngitis needs further evaluation in the NZ context.

Intramuscular BPG for treatment of GAS pharyngitis

Antibiotic adherence is of concern when treating GAS pharyngitis. One NZ study reported that only 73.8%, of 65 people at risk of ARF, finished the full 10 days of oral antibiotic therapy.[40] An empirical study investigating antibiotic adherence to single dose intramuscular BPG for treatment of GAS pharyngitis reported that BPG injection was an acceptable treatment option to children and whānau (families) in a South Auckland, NZ community.[41] Using a distraction device and local anaesthetic lignocaine (numbing agent) were effective pain management strategies. The study noted that a number of children who received the BPG had repeated sore throats. Some of these children (36%) still had a GAS positive throat swab following BPG administration. A Turkish randomised controlled trial assessing the efficacy of BPG for the treatment of GAS pharyngitis in children reported that there was a 92% reduction in GAS pharyngitis episodes in those who received BPG in comparison to a 21% increase in the control group ($p<0.001$).[42] During the 1970s, compliance to oral antibiotics in Costa Rica for treatment of GAS pharyngitis was poor. As part of a primary health care programme, the standard treatment for suspected GAS pharyngitis changed to intramuscular benzathine penicillin, which saw a significant decline in the incidence of ARF.[43] In the NZ setting treatment of GAS pharyngitis in populations at high risk of developing ARF appears to be acceptable, feasible and equitable. Communities at high-risk of ARF should consider the use of intramuscular BPG with lignocaine analgesia in children who present with a GAS positive throat. The acceptability of repeated treatment of GAS pharyngitis with intramuscular BPG should be explored.

Measures to improve adherence to treatment of sore throats

Empirical research investigated various ways to improve antibiotic adherence.[41] Use of blister packs as a medication delivery option aiming to improve adherence to 10-day courses of oral amoxicillin was not effective. Daily text messages to remind children to take their antibiotics did not significantly reduce the number of post-treatment GAS positive throat swabs. Directly observed therapy, which involved a healthcare professional administering antibiotics daily, significantly improved the number of children who completed their treatment. Here the proportion of post treatment GAS positive throat

swabs was 5% among children who received directly observed therapy, and 21% in controls (p=0.01). The 2014 cost to administer directly observed therapy in a school-based clinic was 87.33 NZD per child, with an additional 127.9 minutes of nursing time per child required.[41] Due to the cost and time involved direct observational therapy is not recommended for primary prevention of ARF in the NZ setting.

Managing and treating skin infections

There are a range of treatment options available for GAS skin infections, from hygiene through topical to systemic therapies, however in NZ there is no standard treatment for GAS skin infections and treatment guidelines are inconsistent.

Screening and treating skin infections as part of sore throat clinics

An evaluation of a school-based primary health care service occurring over 15 weeks in a South Auckland school of 400 children, in a socio-economically deprived area, reported that nurses identified 76 cases of skin infection, 45 of whom they treated.[31] An evaluation of the RFPP involving 61 primary schools (23,762 children) in South Auckland reported treating 17,593 skin infections over 18 months. The vast majority were treated with topical cleaning and covering, if antibiotics were needed (for approximately 4% of the children receiving treatment), topical fusidic acid, or less frequently oral cephalexin or flucloxacillin, were used. The relative risk of skin infection in 2013 (pre-intervention) compared to 2014 (post-intervention) was 1.4 (95% CI: 0.7-2.7).[33] Treating skin infections in a school setting is acceptable, feasible and equitable and is an important measure to prevent serious skin infections that may require hospitalisation. The role of GAS skin infections in the potential development of ARF requires more research.

Treatment of scabies

Scratching associated with scabies infestation can cause damage to the skin, therefore increasing the risk of skin infections. Treating scabies to prevent skin damage is likely to prevent the risk of GAS skin infections. In NZ scabies is predominantly treated through topical medications, such as permethrin. Ivermectin, an oral medication, may be prescribed for severe cases of scabies. This review identified four studies that aimed to

reduce the prevalence of scabies.[44-48] Overall, the studies reported relative reductions in scabies of between 88% and 94% when ivermectin or azithromycin were used as a treatment or relative reductions of 62% to 68% when permethrin was used to treat. In NZ a cohort study utilising health records reported that children admitted to hospital with ARF were significantly more likely to have had a previous scabies diagnosis (adjusted hazards ratio 8.9; 95% CI; 6.3-20.2).[49] An additional study reported that permethrin prescribing as an indicator of scabies was strongly associated with the incidence of ARF.[50] Treating scabies to prevent skin infections is recommended as treatment is acceptable and feasible. However, the potential role that scabies may play in ARF development needs further investigation.

Health promotion

A NZ Rheumatic Fever Awareness Campaign ran during 2014 utilising television, radio and print advertisements to increase knowledge in the link between sore throats, ARF and potential heart damage. The campaign evaluation reported that 60% of parents took health action as a direct result of the campaign.[51] A subsequent 2015 NZ Rheumatic Fever Awareness Campaign was independently evaluated and reported that key messages were understood and effectively reached 95% of the target audience.[52] While the messages were understood, the families' experience of public health messaging in the context of their daily lives may guide a more critical and culturally safe health promotion that looks beyond awareness and behaviour and towards equity.[53]

In the 1990s the French Caribbean Islands of Martinique and Guadeloupe conducted an ARF/RHD eradication programme.[54] The programme was associated with a progressive decline in the number of cases of ARF in both islands (78% reduction in Martinique and 74% reduction in Guadeloupe). In addition, recurrent cases declined with no open-heart surgery required among under 18 years of age since 1989. A comprehensive Cuban ARF awareness and prevention programme that ran from 1986-1996 and included both primary and secondary prevention and health promotion saw a progressive decline in the occurrence and severity of ARF and RHD, with a marked decrease in the prevalence of RHD in school children from 2.27 patients per 1 000

children in 1986 to 0.24 per 1 000 in 1996.[55] Any primary prevention strategy for ARF should include health promotion initiatives.

DISCUSSION

NZ Māori and Pacific children continue to have unacceptably high rates of ARF and RHD. This review has identified that there is little available evidence for effective primary prevention strategies to reduce ARF rates in NZ. Further research to assess the mechanisms of action, optimal use, timing and economic costs of primary prevention interventions is needed. In addition, there remains a need for research involving and led by populations affected by ARF/RHD to determine accessibility, acceptability and social costs of primary prevention interventions.

The first primary prevention strategy recommended is the use of school-based clinics to identify and treat GAS pharyngitis and GAS skin infections in areas that have a concentrated population of individuals at high-risk of developing ARF. These clinics have high uptake levels (80-97%), which may identify cases that would otherwise be missed. The second primary intervention strategy that should be considered by communities at high-risk of ARF, is the use of intramuscular BPG as the first treatment option for GAS pharyngitis in populations at high risk of ARF, with the use of lignocaine analgesia. This treatment option has been shown to be an acceptable, effective, affordable treatment option that has few reported adverse effects.[41] However, the acceptability of repeated treatment of GAS pharyngitis with intramuscular BPG needs further investigation.

Primordial prevention is also an important consideration for ARF/RHD prevention but is outside the scope of this review. The eradication of ARF and RHD from almost all high-income countries indicates that these diseases can be controlled and eliminated. It is unacceptable that children continue to suffer and die from a preventable heart condition in what is considered a high-income nation.

REFERENCES

[1] Rammelkamp CH, Jr. Epidemiology of streptococcal infections. *Harvey Lect*. 1955; **51**: 113-142.

[2] McDonald M, Currie BJ, Carapetis JR. Acute rheumatic fever: a chink in the chain that links the heart to the throat? *Lancet Infect Dis*. 2004; **4**: 240-245.

[3] O'Sullivan L, Moreland NJ, Webb RH, Upton A, Wilson NJ. Acute Rheumatic Fever After Group A Streptococcus Pyoderma and Group G Streptococcus Pharyngitis. *Pediatr Infect Dis J*. 2017; **36**: 692-694.

[4] Thomas S, Bennett J, Jack S, Oliver J, Purdie G, Upton A, Baker MG. Descriptive analysis of group A Streptococcus in skin swabs and acute rheumatic fever, Auckland, New Zealand, 2010–2016. *The Lancet Regional Health - Western Pacific* 2021; **8**.

[5] Carapetis JR. Rheumatic heart disease in developing countries. *N Engl J Med*. 2007; **357**: 439-441.

[6] Bennett J, Zhang J, Leung W, et al. Rising Ethnic Inequalities in Acute Rheumatic Fever and Rheumatic Heart Disease, New Zealand, 2000-2018. *Emerg Infect Dis*. 2021; **27**: 36-46.

[7] Milne RJ, Lennon DR, Stewart JM, Vander Hoorn S, Scuffham PA. Incidence of acute rheumatic fever in New Zealand children and youth. *J Paediatr Child Health*. 2012; **48**: 685-691.

[8] Webb R, Wilson N. Rheumatic fever in New Zealand. *J Paediatr Child Health*. 2013; **49**: 179-184.

[9] Centor RM, Witherspoon JM, Dalton HP, Brody CE, Link K. The diagnosis of strep throat in adults in the emergency room. *Med Decis Making*. 1981; **1**: 239-246.

[10] McIsaac WJ, White D, Tannenbaum D, Low DE. A clinical score to reduce unnecessary antibiotic use in patients with sore throat. *CMAJ Canadian Medical Association Journal*. 1998; **158**: 75-83.

[11] New Zealand Rheumatic Fever Guidelines Group. Evidence-based, best practice New Zealand Guidelines for Rheumatic Fever: 3. Proposed Rheumatic Fever Primary Prevention Programme. National Heart Foundation of New Zealand, The Cardiac Society of Australia and New Zealand. 2009.

[12] Kerdemelidis M. Are clinical criteria enough to predict Group A Streptococcal (GAS) pharyngitis in a New Zealand school clinic setting? . *Public health*. University of Otago, University of Otago, 2012.

[13] Jamiel Y. The validity of scorecard as a predictive of streptococcal pharyngitis by throat swab. *Medical Science (General Practice)*. Auckland University, Auckland, 2005.

[14] Steinhoff MC, Khalek MKAEI, Khallaf N, et al. Effectiveness of clinical guidelines for the presumptive treatment of streptococcal pharyngitis in Egyptian children. *The Lancet*. 1997; **350**: 918-921.

[15] McIsaac WJ, Goel V, To T, Permaul JA, Low DE. Effect on antibiotic prescribing of repeated clinical prompts to use a sore throat score: lessons from a failed community intervention study. *J Fam Pract*. 2002; **51**: 339-344.

[16] Aalbers J, O'Brien KK, Chan W-S, et al. Predicting streptococcal pharyngitis in adults in primary care: a systematic review of the diagnostic accuracy of symptoms and signs and validation of the Centor score. *BMC Medicine* 2011; **9**.

[17] Engel ME, Cohen K, Gounden R, et al. The Cape Town Clinical Decision Rule for Streptococcal Pharyngitis in Children. *The Pediatric infectious disease journal*. 2017; **36**: 250-255.

[18] DeMuri GP, Wald ER. The Group A Streptococcal Carrier State Reviewed: Still an Enigma. *Journal of the Pediatric Infectious Diseases Society*. 2014: piu030.

[19] Rao A, Berg B, Quezada T, et al. Diagnosis and antibiotic treatment of group a streptococcal pharyngitis in children in a primary care setting: impact of point-of-care polymerase chain reaction. *BMC Pediatr*. 2019; **19**: 24.

[20] Uhl JR, Adamson SC, Vetter EA, et al. Comparison of LightCycler PCR, rapid antigen immunoassay, and culture for detection of group A streptococci from throat swabs. *J Clin Microbiol*. 2003; **41**: 242-249.

[21] Dunne EM, Marshall JL, Baker CA, et al. Detection of group a streptococcal pharyngitis by quantitative PCR. *BMC Infectious Diseases*. 2013; **13**.
[22] Slinger R, Goldfarb D, Rajakumar D, et al. Rapid PCR detection of group A streptococcus from flocked throat swabs- a retrospective clinical study. *Annals of Clinical Microbiology and Antimicrobials*. 2011; **10**.
[23] Agarwal N, Kapoor S, Mangla A, et al. Utility of Detecting sof Gene as Evidence of Streptococcus pyogenes Infection in Acute Rheumatic Fever. *Indian Pediatrics*. 2019; **56**: 311-313.
[24] Upton A, Bissessor L, Farrell E, Shulman ST, Zheng X, Lennon D. Comparison of illumigene Group A Streptococcus Assay with Culture of Throat Swabs from Children with Sore Throats in the New Zealand School-Based Rheumatic Fever Prevention Program. *Journal of Clinical Microbiology*. 2016; **54**: 153-156.
[25] Heart Foundation of New Zealand. New Zealand Guidelines for Rheumatic Fever: Diagnosis, Management and Secondary Prevention of Acute Rheumatic Fever and Rheumatic Heart Disease. 2014.
[26] Jack RW, Tagg JR, Ray B. Bacteriocins of gram-positive bacteria. *Microbiol Rev*. 1995; **59**: 171-200.
[27] Doyle H, Pierse N, Tiatia R, Williamson D, Baker M, Crane J. Effect of Oral Probiotic Streptococcus salivarius K12 on Group A Streptococcus Pharyngitis: A Pragmatic Trial in Schools. *Pediatric Infectious Disease Journal*. 2018; **37**: 619-623.
[28] Wilcox CR, Stuart B, Leaver H, et al. Effectiveness of the probiotic Streptococcus salivarius K12 for the treatment and/or prevention of sore throat: a systematic review. *Clinical microbiology and infection: the official publication of the European Society of Clinical Microbiology and Infectious Diseases*. 2019; **25**: 673-680.
[29] Lennon D, Kerdemelidis M, Arroll B. Meta-analysis of trials of streptococcal throat treatment programs to prevent rheumatic fever. *Pediatric Infectious Disease Journal*. 2009; **28**: e259-264.
[30] Lennon D, Stewart J, Farrell E, Palmer A, Mason H. School-based prevention of acute rheumatic fever: a group randomized trial in New Zealand. *Pediatr Infect Dis J*. 2009; **28**: 787-794.
[31] Gray S, Lennon D, Anderson P, Stewart J, Farrell E. Nurse-led school-based clinics for skin infections and rheumatic fever prevention: results from a pilot study in South Auckland. *New Zealand Medical Journal*. 2013; **126**: 53-61.
[32] Lennon D, Anderson P, Kerdemilidis M, et al. First Presentation Acute Rheumatic Fever is Preventable in a Community Setting: A School-based Intervention. *Pediatric Infectious Disease Journal*. 2017; **36**: 1113-1118.
[33] Anderson P, King J, Moss M, et al. Nurse-led school-based clinics for rheumatic fever prevention and skin infection management: evaluation of Mana Kidz programme in Counties Manukau. *New Zealand Medical Journal*. 2016; **129**: 37-46.
[34] Jack SJ, Williamson DA, Galloway Y, et al. Primary prevention of rheumatic fever in the 21st century: evaluation of a national programme. *International Journal of Epidemiology*. 2018; **47**: 1585-1593.
[35] Jack S WD, Galloway Y, Pierse N, Milne R, Mackereth G, Zhang J, Oliver J, Baker MG. Interim Evaluation of the Sore Throat Component of the Rheumatic Fever Prevention Programme – Quantitative Findings. The Institute of Environmental Science and Research Ltd. , Porirua, New Zealand, 2015.
[36] Walsh L, Innes-Smith S, Wright J, et al. School-Based Streptococcal A Sore-Throat Treatment Programs and Acute Rheumatic Fever Amongst Indigenous Māori: A Retrospective Cohort Study. *Pediatr Infect Dis J*. 2020.
[37] Thornley T, Marshall G, Howard P, Wilson AP. A feasibility service evaluation of screening and treatment of group A streptococcal pharyngitis in community pharmacies. *J Antimicrob Chemother*. 2016; **71**: 3293-3299.

[38] Mantzourani E, Evans A, Cannings-John R, et al. Impact of a pilot NHS-funded sore throat test and treat service in community pharmacies on provision and quality of patient care. *BMJ Open Qual*. 2020; **9**.
[39] Corn CE, Klepser DG, Dering-Anderson AM, Brown TG, Klepser ME, Smith JK. Observation of a Pharmacist-Conducted Group A Streptococcal Pharyngitis Point-of-Care Test: A Time and Motion Study. *J Pharm Pract*. 2018; **31**: 284-291.
[40] Mathan JJ, Ekart J, Houlding A, Payinda G, Mills C. Clinical management and patient persistence with antibiotic course in suspected group A streptococcal pharyngitis for primary prevention of rheumatic fever: the perspective from a New Zealand emergency department. *N Z Med J*. 2017; **130**: 58-68.
[41] National Hauroa Coalition. Rheumatic Fever Prevention Programme: Antibiotic adherance trial. Auckland, 2019.
[42] Akşit S CS, Dokucu G. Seasonal benzathine penicillin G prophylaxis for recurrent streptococcal pharyngitis in children. *Acta Paediatr Jpn*. 1998; **40**: 256-258.
[43] Arguedas A, Mohs E. Prevention of rheumatic fever in Costa Rica. *The Journal of pediatrics*. 1992; **121**: 569-572.
[44] Romani L, Marks M, Sokana O, et al. Efficacy of mass drug administration with ivermectin for control of scabies and impetigo, with coadministration of azithromycin: a single-arm community intervention trial. *The Lancet*. 2019; **Infectious diseases. 19**: 510-518.
[45] Romani L, Steer AC, Whitfeld MJ, Kaldor JM. Prevalence of scabies and impetigo worldwide: a systematic review. *Lancet Infect Dis*. 2015; **15**: 960-967.
[46] Romani L, Whitfeld MJ, Koroivueta J, et al. Mass Drug Administration for Scabies Control in a Population with Endemic Disease. *N Engl J Med*. 2015; **373**: 2305-2313.
[47] Kearns TM, Speare R, Cheng AC, et al. Impact of an Ivermectin Mass Drug Administration on Scabies Prevalence in a Remote Australian Aboriginal Community. *PLoS Negl Trop Dis*. 2015; **9**: e0004151.
[48] Andrews RM, McCarthy J, Carapetis JR, Currie BJ. Skin disorders, including pyoderma, scabies, and tinea infections. *Pediatr Clin North Am*. 2009; **56**: 1421-1440.
[49] Thornley S, Marshall R, Jarrett P, Sundborn G, Reynolds E, Schofield G. Scabies is strongly associated with acute rheumatic fever in a cohort study of Auckland children. *J Paediatr Child Health*. 2018; **54**: 625-632.
[50] Thornley S, King R, Marshall R, et al. How strong is the relationship between scabies and acute rheumatic fever? An analysis of neighbourhood factors. *J Paediatr Child Health*. 2020; **56**: 600-606.
[51] Arthur S, TNS New Zealand Limited. 2014 Rheumatic fever campaign evaluation. Health Promotion Agency, Wellington, 2015.
[52] Vermillion P, Akroyd S, Tafuna P, et al. Evaluation of the 2015 rheumatic fever awareness campaign. Allen + Clarke, Wellington, New Zealand, 2015.
[53] Anderson A, Spray J. Beyond awareness: Towards a critically conscious health promotion for rheumatic fever in Aotearoa, New Zealand. *Social science & medicine*. 2020; **247**: 112798.
[54] Bach JF, Chalons S, Forier E, et al. 10-year educational programme aimed at rheumatic fever in two French Caribbean islands. . *Lancet*. 1996; **347**: 644-648.
[55] Nordet P, Lopez R, Dueñas A, Sarmiento L. Prevention and control of rheumatic fever and rheumatic heart disease: the Cuban experience (1986-1996-2002). *Cardiovasc J Afr*. 2008; **19**: 135-140.