Preceding group A streptococcus skin and throat infections are individually associated with acute rheumatic fever: evidence from New Zealand

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ABSTRACT

Introduction Acute rheumatic fever (ARF) is usually considered a consequence of group A streptococcus (GAS) pharyngitis, with GAS skin infections not considered a major trigger. The aim was to quantify the risk of ARF following a GAS-positive skin or throat swab.

Methods This retrospective analysis used pre-existing administrative data. Throat and skin swab data (186 981 swabs) from the Auckland region, New Zealand and antibiotic dispensing data were used (2010–2017). Incident ARF cases were identified using hospitalisation data (2010–2018). The risk ratio (RR) of ARF following swab collection was estimated across selected features and timeframes. Antibiotic dispensing data were linked to investigate whether this altered ARF risk following GAS detection.

Results ARF risk increased following GAS detection in a throat or skin swab. Māori and Pacific Peoples had the highest ARF risk 8–90 days following a GAS-positive throat or skin swab, compared with a GAS-negative swab. During this period, the RR for Māori and Pacific Peoples following a GAS-positive throat swab was 4.8 (95% CI 3.6 to 6.4) and following a GAS-positive skin swab, the RR was 5.1 (95% CI 1.8 to 15.0). Antibiotic dispensing was not associated with a reduction in ARF risk following GAS detection in a throat swab (antibiotics not dispensed (RR: 4.1, 95% CI 2.7 to 6.2), antibiotics dispensed (RR: 4.3, 95% CI 2.5 to 7.4) or in a skin swab (antibiotics not dispensed (RR: 3.5, 95% CI 0.9 to 13.9), antibiotics dispensed (RR: 2.0, 95% CI 0.3 to 12.1)).

Conclusions A GAS-positive throat or skin swab is strongly associated with subsequent ARF, particularly for Māori and Pacific Peoples. This study provides the first population-level evidence that GAS skin infection can trigger ARF.

INTRODUCTION

Infection with group A streptococcus (GAS) can trigger an immune-mediated response in a small minority of people, resulting in acute rheumatic fever (ARF).1 The immunological processes by which GAS infections trigger ARF are poorly understood.2 For around 60% of ARF cases, permanent cardiac damage, termed rheumatic heart disease (RHD), persists. ARF recurrences can worsen existing cardiac damage and produce new damage.3 Estimates indicate that in 2015, there were 34 million people living with RHD worldwide with 320 000 associated deaths that year.4 ARF
produces an inequitable burden of disease, with the highest rates in low and middle-income countries and among some, often Indigenous-minority, populations living in high-income countries. In New Zealand, the rate of initial ARF hospitalisations for Indigenous Māori children aged 5–14 years was 36 per 100000 (2000–2018 inclusive), while the rate for Pacific children in this age group was 80 per 100000 population, representing some of the highest rates of ARF in the world.8

GAS pharyngitis is most common among 5–14-year-old children and causes around 37% of all pharyngitis episodes in this age group.5,9 Historically, ARF has been considered a consequence of untreated GAS pharyngitis. GAS pharyngitis is usually described in the literature as preceding ARF by around 2–3 weeks6 although ARF may take longer to present. One study of ARF (n=251 cases) observed that 8% of cases occurred more than 45 days after GAS pharyngitis was diagnosed.7 GAS carriage is not thought to be associated with ARF.8

More recently, GAS skin infections have been proposed as triggering ARF, either directly or in combination with GAS pharyngitis.9 10 New Zealand has a high and increasing incidence of skin infections, with the burden borne predominately by Māori and Pacific children.11–13

In New Zealand, rapid testing for GAS is not recommended, with GAS detected using laboratory swab culturing, which usually requires around 48 hours. Consequently, an empiric antibiotic prescription is recommended for people at high risk of ARF, where GAS pharyngitis is clinically suspected, with the patient instructed to cease taking antibiotics if the throat swab culture result turns out to be GAS negative.14 When diagnosing ARF, hospitalisation is standard-of-care for all suspected cases. A throat swab is routinely collected as part of the diagnostic workup.15 Around half of all national ARF cases reside in the Auckland region.8 An intensive ARF prevention programme has been operating there since 2012, which focuses on sore throat management. Here, throat swab culturing is used to detect GAS pharyngitis, with prompt antibiotic dispensing to treat the infection before ARF occurs, free of charge to eligible individuals.16

The high incidence of ARF in the Auckland region of New Zealand and the active sore throat management programme operating in that region, combined with highly integrated, routinely collected administrative health data, provides a unique opportunity to investigate the risk of ARF following a GAS-positive throat or skin swab. The aim of this study was to quantify the risk of ARF following a GAS-positive throat or skin swab by linking routinely collected administrative data.

**METHODS**

**Data sources and linkages**

In New Zealand, all publicly and privately funded hospital admissions are recorded in the national minimum data set (New Zealand Ministry of Health National Minimum Dataset; NMDS), which includes diagnostic information with international classification of diseases (ICD) coding. Labtests Ltd, the sole community pathology laboratory provider has serviced the whole Auckland region since late-2009, routinely collecting data on swabs it receives for processing, including the culture result.17 The National Pharmaceutical Collection contains claim and payment information from pharmacists for subsidised pharmaceutical dispensing, including antibiotic dispensing, with data on more than one billion scripts.18 The universal National Health Index (NHI) number enables the identification of individuals in health data and linkage of their information across data sets.

All ARF diagnoses corresponding to hospitalisations from 1988 to 2018 inclusive were obtained from the NMDS (ICD-10: I00-I02 and ICD-9: 390–392), as were all RHD diagnoses (ICD-10: I05-I09 and ICD-9: 393–398). The first admission with ARF/RHD as principal diagnosis for each patient was identified and all later entries excluded. All individuals with an admission for RHD preceding their first ARF hospitalisation were excluded. Admissions for non-New Zealand citizens were removed. Hospital transfers were excluded, so only the first record was included for each ARF hospitalisation. This first ARF hospitalisation was then taken to represent an initial episode of ARF. The data set was restricted to initial ARF hospitalisations from 2010 to 2018 inclusive. Data on patients’ 2013 New Zealand Deprivation Index score (NZDep), prioritised ethnicity, age and sex were added to all data set entries using information contained in the NHI. The NZDep score is an ecological measure of socioeconomic deprivation based on national census data.19

Auckland is the largest city in New Zealand, with a population of approximately 1.4 million people at the 2013 census. At that time, the city had a prioritised ethnic population mix of 10% Māori, 12% Pacific Peoples, 21% Asian and 57% European/Other.20 Prioritised ethnicity grouping allocates individuals to a single ethnic group based on a prioritised order of Māori, Pacific Peoples, Asian and European/Other. For example, if an individual identifies as being both Māori and European, that person will be classified as Māori for the purposes of data analysis.

We identified 25 antibiotic formulations likely to treat GAS infections using published literature relating to antimicrobial treatment of GAS (online supplemen
Swabs were cultured onto tryptic soy sheep blood agar through a laboratory information system search for all panel codes related to throat, wound and skin swabs. Data analysis was performed using SAS V.9.4, GraphPad Statistical analyses matching the encrypted NHI across data sets. Associated antibiotic dispensing event were also identified by hospitalised with initial ARF during the study period. Individual who had had a throat or skin swab and were associated the encrypted NHI, with laboratory swab data to identify on all data sets. ARF hospitalisations were matched, using linkage by 8–90 days for children in the highest risk age group. Restricting analyses to this time period and age group maximised the sensitivity for detecting potentially causative infections.

RESULTS
Prevalence of GAS positive throat and skin swabs
We included all throat (1 430 183) and skin (436 798) swab culture results for the Auckland population over an 8-year period (2010–2017). GAS was detected in 14.3% of throat swabs and 12.7% of skin swabs. Māori and Pacific Peoples had a slightly higher proportion of GAS detection in throat swabs compared with European/Others (Māori RR: 1.05 Pacific RR: 1.01, p<0.01, figure 1A). Māori and Pacific children had a markedly higher prevalence of GAS detection in skin swabs compared with European/Others (Māori RR: 4.93, Pacific RR: 5.37p<0.0001; figure 1B).

ARF following concurrent GAS-positive skin and throat swabs
Seven people had concurrent (±14 days) GAS-positive skin and throat swabs 8–90 days prior to hospitalisation for ARF (3.4 per 100 000 GAS-positive swabs). The risk of initial ARF hospitalisation was increased following concurrent GAS-positive throat and skin swabs compared with when throat and skin swabs were GAS negative (RR: 17.1, 95% CI 4.5 to 104.0). These seven cases were excluded from subsequent analyses.

Risk of ARF following GAS-positive swabs
The ARF risk was highest for Māori and Pacific children aged 10–19 years and was concentrated during the 8–90 days following swab collection (figure 2A,B). For every 100 000 GAS-positive throat swabs, 315 Māori/Pacific children aged 10–19 years were hospitalised with initial ARF within 365 days of throat swab collection (figure 2A). For every 100 000 GAS-positive skin swabs, 151 Māori/Pacific children aged 10–19 years were hospitalised with a diagnosis of initial ARF within 365 days of skin swab collection (figure 2B).

ARF following a GAS-positive throat swab
The risk of initial ARF hospitalisation was markedly increased in the 8–90 days following collection of a GAS-positive throat swab, RR: 5.1, 95% CI 3.8 to 6.9 (table 1). Children aged 10–14 years had a particularly high risk of initial ARF hospitalisations 8–90 days following a GAS-positive throat swab (105.6 per 100 000 throat swabs). The risk appeared to increase with age group; however, there were small ARF case numbers among those aged older than 19 years.

Females had a higher risk of ARF in the 8–90 days following a GAS-positive throat swab than males (RR: 1.93, 95% CI 1.73 to 2.17) (table 1). In boys, ARF risk was highest for those aged 10–14 years and was concentrated during the 8–90 days following swab collection (figure 2B).
5.6, 95% CI 3.8 to 8.6). Māori and Pacific Peoples had an increased risk of ARF during this period (Māori RR: 5.8, 95% CI 3.3 to 10.3, Pacific RR: 4.5, 95% CI 3.7 to 6.3). Low case numbers meant that risk could not be assessed for other ethnicities (table 1).

When antibiotics were dispensed within 7 days of a GAS-positive throat swab collection, there was no statistically significant reduction in the risk of initial ARF hospitalisation 8–90 days following swab collection: Antibiotics were not dispensed (RR: 4.1, 95% CI 2.7 to 6.2), antibiotics dispensed (RR: 4.3, 95% CI 2.5 to 7.4; table 1).

**ARF following GAS-positive skin swab**
The risk of initial ARF hospitalisation was highest, 8–90 days following a GAS-positive skin swab (RR: 15.5, 95% CI 5.4 to 44.5) (table 2). Children aged 10–14 years had a particularly high risk of initial ARF hospitalisation 8–90 days following a GAS-positive swab (94.7 per 100 000 GAS-positive skin swabs). Males had a higher risk of initial ARF during this period (RR: 21.3, 95% CI 4.4 to 102.6), as did people living in areas of high socioeconomic deprivation (Quintiles 4/5). Māori and Pacific Peoples had an increased risk of initial ARF 8–90 days following GAS-positive swab collection, with findings for Pacific People most apparent in the 10–19 year age group (RR: 6.1, 95% CI 1.2 to 30.4). Low case numbers meant that risk could not be assessed for other ethnicities (table 2).

When antibiotics were dispensed within 7 days of GAS-positive skin swab collection, no statistically significant reduction in the risk of initial ARF hospitalisation was noted over the subsequent 8–90-day period: antibiotics not dispensed (RR: 3.5, 95% CI 0.9 to 13.9), antibiotics dispensed (RR: 2.0, 95% CI 0.3 to 12.1).

**DISCUSSION**
This study provides a clear link from GAS detection in throat and skin swabs to the subsequent development of ARF in a large population, observed over an extended period of time (2010–2018). Results indicate that both GAS pharyngitis and GAS skin infections are strongly associated with the development of ARF. There was a
Table 1  Risk of initial acute rheumatic fever hospitalisation (2010–2018) following a GAS positive throat swab (2010–2017), Auckland, New Zealand

| Risk of initial ARF hospitalisation during specific time window (total population) | ARF risk following GAS positive throat swab* | ARF risk following GAS negative throat swab† | RR |
|---|---|---|---|
| Total ARF following GAS positive swab | Total GAS positive swabs | ARF per 100,000 GAS positive swabs | Total ARF following GAS negative swab | Total GAS negative swabs | ARF per 100,000 GAS negative swabs | Risk of ARF following GAS-positive swab versus GAS-negative swab RR (95% CI) |
| ARF 1–7 days of swab | 34 | 204,085 | 16.7 | 35 | 1,223,456 | 2.9 | 5.82 (3.63 to 9.34) |
| ARF 8–90 days of swab | 84 | 204,085 | 41.2 | 99 | 1,223,456 | 8.0 | 5.14 (3.84 to 6.88) |
| ARF 1–365 days of swab | 236 | 204,084 | 115.6 | 599 | 1,223,456 | 49.0 | 2.36 (2.03 to 2.75) |

Risk of initial ARF hospitalisation, restricted to 8–90 days

| Age group (years) (8–90 days following swab) | ARF risk following GAS positive swab | ARF risk following GAS negative swab | RR |
|---|---|---|---|
| Total ARF following GAS positive swab | Total GAS positive swabs | ARF per 100,000 GAS positive swabs | Total ARF following GAS negative swab | Total GAS negative swabs | ARF per 100,000 GAS negative swabs | Risk of ARF following GAS-positive swab versus GAS-negative swab RR (95% CI) |
| <5 | 0 | 14,954 | – | 0 | 108,358 | – | – |
| 5–9 | 24 | 95,942 | 25.0 | 40 | 502,493 | 8.0 | 3.14 (1.89 to 5.21) |
| 10–14 | 49 | 46,380 | 105.6 | 51 | 281,904 | 18.1 | 5.64 (3.93 to 8.67) |
| 15–19 | 7 | 115,39 | 60.7 | 5 | 86,256 | 5.8 | 10.47 (3.32 to 32.97) |
| 20–29 | 4 | 13,133 | 30.5 | 2 | 83,588 | 2.4 | 12.73 (2.33 to 69.49) |
| >29 | 0 | 22,137 | – | 0 | 160,857 | – | – |

| Gender (8–90 days following swab) | ARF risk following GAS positive swab | ARF risk following GAS negative swab | RR |
|---|---|---|---|
| Total ARF following GAS positive swab | Total GAS positive swabs | ARF per 100,000 GAS positive swabs | Total ARF following GAS negative swab | Total GAS negative swabs | ARF per 100,000 GAS negative swabs | Risk of ARF following GAS-positive swab versus GAS-negative swab RR (95% CI) |
| Male | 40 | 98,433 | 40.6 | 48 | 546,398 | 8.8 | 4.63 (3.04 to 7.04) |
| Female | 44 | 105,652 | 41.6 | 50 | 677,058 | 7.4 | 5.64 (3.76 to 8.64) |

| Prioritised ethnicity (8–90 days following swab) | ARF risk following GAS positive swab | ARF risk following GAS negative swab | RR |
|---|---|---|---|
| Total ARF following GAS positive swab | Total GAS positive swabs | ARF per 100,000 GAS positive swabs | Total ARF following GAS negative swab | Total GAS negative swabs | ARF per 100,000 GAS negative swabs | Risk of ARF following GAS-positive swab versus GAS-negative swab RR (95% CI) |
| Māori | 23 | 44,990 | 50.0 | 23 | 266,521 | 8.6 | 5.79 (3.25 to 10.33) |
| Pacific | 57 | 80,854 | 70.5 | 73 | 476,335 | 15.7 | 4.48 (3.70 to 6.32) |
| Māori and Pacific | 80 | 126,844 | 63.1 | 98 | 742,856 | 13.2 | 4.78 (3.56 to 6.42) |
| Asian | 0 | 14,221 | – | 0 | 132,879 | – | – |
| NZ European/Other | 4 | 63,020 | 6.3 | 0 | 347,271 | – | – |

| Socio-economic deprivation (NZ Dep quintile) (8–90 days following a swab) | ARF risk following GAS positive swab | ARF risk following GAS negative swab | RR |
|---|---|---|---|
| Total ARF following GAS positive swab | Total GAS positive swabs | ARF per 100,000 GAS positive swabs | Total ARF following GAS negative swab | Total GAS negative swabs | ARF per 100,000 GAS negative swabs | Risk of ARF following GAS-positive swab versus GAS-negative swab RR (95% CI) |
| 1 (low deprivation) | 1 | 23,842 | 4.2 | 0 | 132,310 | – | – |
| 2 | 3 | 23,693 | 12.7 | 5 | 134,763 | 3.7 | 3.41 (0.82 to 14.28) |
| 3 | 6 | 19,834 | 30.3 | 3 | 108,675 | 2.8 | 10.96 (2.74 to 43.83) |
| 4 | 12 | 22,591 | 53.1 | 15 | 131,431 | 11.4 | 4.65 (2.18 to 9.94) |
| 5 (high deprivation) | 62 | 114,125 | 54.3 | 75 | 616,277 | 12.2 | 5.19 (3.71 to 7.26) |

**Boldfaced values relate to the Total data. Significance is P > 0.05.**

*GAS-positive skin swabs were excluded ± 14 days of all throat swabs.
†GAS-negative swabs were also culture negative for group C/G streptococci.
ARF, acute rheumatic fever; GAS, group A streptococcus; RR, risk ratio.
Table 2  Risk of initial ARF hospitalisation (2010–2018) following a GAS positive skin swab (2010–2017), Auckland, New Zealand

| ARF risk following GAS positive skin swab* | ARF risk following GAS negative skin swab†* | RR |
|------------------------------------------|------------------------------------------|----|
| Total ARF following GAS positive swab    | Total GAS positive swabs                 | ARF per 100 000 GAS positive swabs |
| Total ARF following GAS negative swab    | Total GAS negative swabs                 | ARF per 100 000 GAS negative swabs |

**Risk of initial ARF hospitalisation during specific time window (total population)**

| ARF 1–7 days of swab | 2 | 54217 | 3.7 | 0 | 380755 | – | – |
| ARF 8–90 days of swab | 11 | 54217 | 20.3 | 5 | 380755 | 1.3 | 15.45 (5.37 to 44.48) |
| ARF 1–365 days of swab | 24 | 54217 | 44.3 | 27 | 380755 | 7.5 | 6.24 (3.60 to 10.82) |

**Risk of initial ARF hospitalisation, restricted to 8–90 days**

| Age group (years) | Total ARF following GAS positive swab | Total GAS positive swabs | ARF per 100 000 GAS positive swabs | Total ARF following GAS negative swab | Total GAS negative swabs | ARF per 100 000 GAS negative swabs | RR (95% CI) |
|-------------------|--------------------------------------|--------------------------|-------------------------------------|--------------------------------------|--------------------------|-------------------------------------|-------------|
| <5                | 0 | 11894 | – | 0 | 41158 | – | – |
| 5–9               | 1 | 10815 | 9.2 | 2 | 21721 | 9.2 | 1.00 (0.09 to 11.08) |
| 10–14             | 6 | 6334 | 94.7 | 2 | 19736 | 10.1 | 9.36 (1.89 to 46.36) |
| 15–19             | 3 | 4755 | 63.1 | 1 | 21262 | 4.7 | 13.42 (1.40 to 129.06) |
| 20–29             | 1 | 6290 | 15.9 | 0 | 37139 | – | – |
| >29               | 0 | 14129 | – | 0 | 239735 | – | – |

**Gender (8–90 days following a swab)**

| Gender | Total ARF following GAS positive swab | Total GAS positive swabs | ARF per 100 000 GAS positive swabs | Total ARF following GAS negative swab | Total GAS negative swabs | ARF per 100 000 GAS negative swabs | RR (95% CI) |
|--------|--------------------------------------|--------------------------|-------------------------------------|--------------------------------------|--------------------------|-------------------------------------|-------------|
| Male   | 7 | 29448 | 23.8 | 2 | 179199 | 1.1 | 21.30 (4.42 to 102.55) |
| Female | 4 | 24763 | 16.2 | 3 | 201505 | 1.5 | 10.85 (2.43 to 48.47) |

**Prioritised ethnicity (8–90 days following a swab)**

| Prioritised ethnicity | Total ARF following GAS positive swab | Total GAS positive swabs | ARF per 100 000 GAS positive swabs | Total ARF following GAS negative swab | Total GAS negative swabs | ARF per 100 000 GAS negative swabs | RR (95% CI) |
|-----------------------|--------------------------------------|--------------------------|-------------------------------------|--------------------------------------|--------------------------|-------------------------------------|-------------|
| Māori                | 3 | 13335 | 22.5 | 1 | 37023 | 2.7 | 8.33 (0.87 to 80.10) |
| Pacific              | 7 | 25148 | 27.8 | 4 | 62401 | 6.5 | 4.27 (1.25 to 14.60) |
| Māori and Pacific    | 10 | 38483 | 26.0 | 5 | 98424 | 5.1 | 5.11 (1.75 to 14.97) |
| Asian                | 1 | 2375 | 42.1 | 0 | 38533 | – | – |
| NZ European/Other    | 0 | 13359 | – | 0 | 243794 | – | – |

**Socio-economic deprivation (NZ Dep quintile) (8–90 days following a swab)**

| Socio-economic deprivation (NZ Dep quintile) | Total ARF following GAS positive swab | Total GAS positive swabs | ARF per 100 000 GAS positive swabs | Total ARF following GAS negative swab | Total GAS negative swabs | ARF per 100 000 GAS negative swabs | RR (95% CI) |
|---------------------------------------------|--------------------------------------|--------------------------|-------------------------------------|--------------------------------------|--------------------------|-------------------------------------|-------------|
| 1 (low deprivation)                        | 0 | 4510 | – | 0 | 82065 | – | – |
| 2                                           | 1 | 5753 | 17.4 | 0 | 81027 | – | – |
| 3                                           | 2 | 6183 | 32.3 | 0 | 70165 | – | – |
| 4                                           | 2 | 8543 | 23.4 | 1 | 51142 | 2.0 | 11.97 (1.09 to 132.02) |
| 5 (high deprivation)                       | 6 | 29228 | 23.6 | 5 | 95456 | 5.2 | 4.90 (1.38 to 17.36) |

**Risk of initial ARF hospitalisation, during 8–90 day window restricted to Māori and Pacific aged 10–19 years**

| Gender | Total ARF following GAS positive swab | Total GAS positive swabs | ARF per 100 000 GAS positive swabs | Total ARF following GAS negative swab | Total GAS negative swabs | ARF per 100 000 GAS negative swabs | RR (95% CI) |
|--------|--------------------------------------|--------------------------|-------------------------------------|--------------------------------------|--------------------------|-------------------------------------|-------------|
| Male   | 6 | 4426 | 135.6 | 2 | 8983 | 22.3 | 6.10 (1.23 to 30.15) |
| Female | 2 | 4004 | 49.9 | 1 | 8037 | 12.4 | 4.01 (0.36 to 44.24) |

**Prioritised ethnicity (8–90 days following a swab)**

| Prioritised ethnicity | Total ARF following GAS positive swab | Total GAS positive swabs | ARF per 100 000 GAS positive swabs | Total ARF following GAS negative swab | Total GAS negative swabs | ARF per 100 000 GAS negative swabs | RR (95% CI) |
|-----------------------|--------------------------------------|--------------------------|-------------------------------------|--------------------------------------|--------------------------|-------------------------------------|-------------|
| Māori                | 2 | 2886 | 69.3 | 1 | 5698 | 17.6 | 3.95 (0.36 to 43.60) |
| Pacific              | 6 | 5546 | 108.2 | 2 | 11324 | 17.7 | 6.12 (1.24 to 30.39) |

**Socio-economic deprivation (NZ Dep quintile) (8–90 days following a swab)**

| Socio-economic deprivation (NZ Dep quintile) | Total ARF following GAS positive swab | Total GAS positive swabs | ARF per 100 000 GAS positive swabs | Total ARF following GAS negative swab | Total GAS negative swabs | ARF per 100 000 GAS negative swabs | RR (95% CI) |
|---------------------------------------------|--------------------------------------|--------------------------|-------------------------------------|--------------------------------------|--------------------------|-------------------------------------|-------------|
| 1 (low deprivation)                        | 0 | 202 | – | 0 | 781 | – | – |
| 2                                           | 0 | 515 | 13.4 | 0 | 1335 | – | – |
| 3                                           | 1 | 742 | 134.8 | 0 | 1702 | – | – |
| 4                                           | 2 | 1351 | 148.0 | 1 | 2924 | 34.2 | 4.34 (0.39 to 47.70) |
| 5 (high deprivation)                       | 5 | 5622 | 88.9 | 2 | 10283 | 19.4 | 4.58 (0.89 to 23.59) |
| Total                                       | 8 | 8432 | 94.9 | 3 | 17025 | 17.6 | 5.39 (1.43 to 20.32) |

**Antibiotics dispensed (within 7 days of swab among Māori and Pacific People aged 5–19 years)**

| Antibiotics dispensed | Total ARF following GAS positive swab | Total GAS positive swabs | ARF per 100 000 GAS positive swabs | Total ARF following GAS negative swab | Total GAS negative swabs | ARF per 100 000 GAS negative swabs | RR (95% CI) |
|-----------------------|--------------------------------------|--------------------------|-------------------------------------|--------------------------------------|--------------------------|-------------------------------------|-------------|
| Antibiotics           | 3 | 6906 | 43.4 | 2 | 9278 | 21.6 | 2.01 (0.34 to 12.05) |
| No antibiotics        | 6 | 9477 | 63.4 | 3 | 16529 | 18.1 | 3.49 (0.87 to 13.94) |

*GAS-positive throat swabs were excluded 14 days of all skin swabs.
1GAS-negative swabs were also culture negative for group C/G streptococci.
ARF, acute rheumatic fever; GAS, group A streptococcus; RR, risk ratio.
significant increase in the ARF risk for Māori and Pacific Peoples during the 8–90-day latency period following GAS detection from a throat or skin swab. This risk was markedly higher than the baseline risk for Māori and Pacific Peoples who had a skin or throat swab collected, but GAS was not detected. These findings support the well-established clinical view that GAS pharyngitis is an important initiating agent of ARF. They also add new evidence that GAS skin infection has a similar propensity to cause ARF, both alone and in combination with concurrent pharyngitis. Dispensing antibiotics was not associated with a reduction in ARF risk following detection of GAS in a throat or skin swab. This finding is extremely concerning and implies that ARF primary prevention interventions may be failing to protect high-risk groups.

While a causal association between the presence of an organism and the occurrence of disease cannot be confirmed using observational data alone, this analysis comprehensively evaluates the risk of an initial ARF hospitalisation by swab culture result in a large population. The ARF risk is likely underestimated by these analyses as cases of GAS pharyngitis may not come to clinical attention and GAS skin infection may be treated empirically within primary care without a swab. The absence of a protective effect following antibiotic dispensing may be due to poor compliance with treatment or may indicate the importance of immune priming following repeated GAS infections. A major strength of this study is that the exposed population (ie, GAS culture positive individuals) are being compared with a demographically very similar but unexposed population (ie, GAS culture negative individuals), thus controlling for major confounders. Furthermore, the data sources are likely fairly complete, given that hospitalisation is recommended as standard of care for all suspected ARF cases in New Zealand, and rapid testing for GAS is not recommended. However, it is possible that there are systematic differences between GAS-positive and negative groups. For example, GAS detection could be a consequence of household crowding, which in turn may increase the risk of ARF through repeated environmental exposures to GAS. As case numbers were low, we were not able to assess whether the risk of ARF increased with repeated GAS detection.

Māori and Pacific children have among the highest rates of ARF in the world and experience health disparities across many chronic and acute conditions, and inadequate socioeconomic deprivation. While the pathogenesis of ARF is not fully elucidated, a clearly increased risk was observed for Māori and Pacific children following GAS detection in a throat or skin swab. ARF is triggered following a complex interplay of susceptibility, immunological and environmental factors. Immune priming from repeated GAS exposures likely plays a major pathogenic role, especially given that no genetic risk factors have been consistently identified. A further indication of immune priming in early childhood is demonstrated in our study by the higher GAS detection in throat swabs for European/other children aged 5–9 years, but no corresponding ARF risk. ARF is still a rare disease in New Zealand. Although ARF is usually thought to follow GAS infection by around 3 weeks, low case numbers necessitated the use of the 8–90-day period to maximise sensitivity for detecting causative infections.

As pre-existing administrative data were used for these analyses, the data may be affected by errors, including misdiagnosis and miscoding. The sensitivity of ICD coding for ARF would have changed during the study period as the diagnostic criteria were refined and awareness of ARF increased with the recent national prevention programme. Despite this, the NMDS was estimated to be 79% sensitive for detecting true cases of ARF during 2011–2015. Swab data are likely highly complete as these are provided by the sole community service provider for the Auckland region. These data are also likely to reflect cases where throat or skin infection was clinically suspected. It is not normal practice to use swab culturing to screen for GAS carriage, nor is treatment of carriage recommended. While antibiotic dispensing would be captured in the National Pharmaceutical Collection, topical antiseptics purchased without prescription are not, so dispensing data may correspond to more severe skin infections. Regardless, no protective effect from antibiotic dispensing was observed on the risk of developing ARF 8–90 days after GAS detection in either a throat or a skin swab.

CONCLUSION

Prompt antibiotic treatment of GAS infections in groups with a known high risk of ARF is required to terminate the infective process, reducing the risk of poor outcomes, and to limit GAS transmission. Targeted sore throat management interventions should remain a key strategy in the prevention of ARF. A new focus should also be placed on addressing the burden of skin infections to reduce the risk of ARF in New Zealand. Such an approach would mirror strategies that led to dramatic reduction in ARF in Cuba and Costa Rica. Multifactorial interventions should aim to reduce socioeconomic deprivation, improve housing conditions, lower household crowding, improve access to healthcare and raise health literacy. These measures can supplement primary prevention interventions targeting GAS infections, aiming for a meaningful and sustained reduction in ARF in New Zealand.

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