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# First Presentation Acute Rheumatic Fever is Preventable in a Community Setting: A School Based Intervention

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BACKGROUND

Robust evidence is lacking for community initiatives to prevent first presentation acute rheumatic fever (ARF) by group A streptococcal (GAS) pharyngitis treatment.

METHODS

We measured the effect of introducing a sore throat clinic program on first presentation ARF into 61 year 1-8 schools with students aged 5-13years (population ~ 25,000) in Auckland, New Zealand. The study period was 2010-2016. A generalized linear mixed model investigated ARF rate changes before and after the staggered introduction of school clinics. Nurses and lay workers treated culture-proven GAS sore throats (including siblings) with 10 days of amoxicillin. ARF cases were identified from a population-based secondary prophylaxis register. Annual pharyngeal GAS prevalence was assessed in a subset.

RESULTS

ARF rates in 5-13 year olds dropped from 88 (95% CI 79, 111)/100,000 pre-clinics to 37 (95% CI 15, 83)/100,000 after 2 years of clinic availability, a 58% reduction.

No change in rate was demonstrated before the introduction of clinics (p=0.88, incidence risk ratio (IRR) for a one year change 0.98 (95% CI 0.63, 1.52)) but there was a significant decrease of first presentation ARF rates with time following the introduction of the sore throat program (p=0.008, IRR 0.61 (95% CI 0.43, 0.88)).

Pharyngeal GAS cross sectional prevalence fell from 22.4% (16.5, 30.5) pre-intervention to 11.9% (8.6, 16.5) and 11.4% (8.2, 15.7) one and two years later (p=0.005)

CONCLUSIONS

ARF declined significantly following school-based GAS pharyngitis management using oral amoxicillin paralleled by a decline in pharyngeal GAS prevalence.

## INTRODUCTION

Acute rheumatic fever (ARF) and its sequel rheumatic heart disease (RHD) are global health challenges, now mostly restricted to developing countries.(1) However in New Zealand (NZ) ARF continues at an unacceptably high rate predominantly in indigenous Māori, and New Zealanders of Pacific Island origin, who together make up one third of New Zealand's young people less than 20 years of age.(2) In these communities the cumulative risk of hospitalization with ARF by the age of 13 years is approximately 1 in 150.(2)

Secondary prophylaxis to control more damaging subsequent attacks of ARF has been highly successful in New Zealand.(3) (4) Children with identified ARF in NZ receive penicillin prophylaxis delivered by nurses, mostly in schools. This is facilitated in Auckland, New Zealand's largest city, by a population-based city-wide register recently audited against hospital discharge and notifiable disease data to confirm completeness.(5)

Robust peer reviewed evidence to control first presentation ARF is lacking to support treatment of streptococcal (GAS) pharyngitis, either with injectable or an oral penicillin, though this is standard practice in many countries.(6) Current practice is derived from randomized trials in military settings which demonstrated with injectable penicillin that first presentation ARF is preventable. (7) However a US pediatric hospital clinic randomized controlled trial of GAS pharyngitis treatment was inconclusive in the control of ARF.(8) Improved access to public clinics in a high risk US inner city population was felt to be the reason for ARF decline over a decade.(9) Ecologic evidence of ARF decline comes from several developing country settings where penicillin and health promotion programs were put in place. (10) School-based and/or community-based before and after interventions (all non-randomized and of variable quality) suggested ARF control was possible. (11) (12) (13).

In New Zealand better quality evidence was called for before an investment would be contemplated to control first presentation ARF. A particular issue for this setting was, and continues to be poor access to general practice primary care for those at high risk of ARF. (14) (www.health.govt.nz-NZ Health Survey 2015).

A cluster randomized school clinic trial (1998-2001) to improve healthcare access for sore throat management (>80 000 person years) found a 21% modelled decline in ARF cases.(15) The control group was usual primary care through general practitioners. The study results were not statistically significant and left uncertainty about the benefit of the intervention. In the study, schools were randomly allocated a clinic. Thus, in a neighborhood siblings and others could be in either an intervention or a control school, which is likely to have resulted in inadequate control of the spread of highly infectious GAS. The study design (cluster randomization by school) did not allow for symptomatic culture-positive siblings or other contacts of an index case of GAS pharyngitis to be treated within the study.

A meta-analysis of school and/or community-based programs including the NZ school trial pointed to the possible effect of primary prevention (an estimated 60% ARF reduction). This led to the NZ Government investing in control of first presentation ARF with the emphasis on school clinics.(www.health.govt.nz) (9, 11) (12) (13) (16) (17) (10) The school clinic model used in the trial was modified to include management of symptomatic siblings and other contacts. In the study area (south Auckland) clinics were introduced incrementally in geographic clusters of schools to the most at risk areas in an attempt to reduce spread of GAS within a community. (18) (19) Sore throat management was embedded in wider school health including skin infection management.

This paper assesses the effectiveness of this school-based (year 1-8) sore throat clinic strategy on first presentation ARF incidence in this geographically demarcated high risk area over the time of school clinic introduction (study A). The outcome of this study was ARF cases on the RF secondary prophylaxis register who had developed ARF while attending one of the study schools.

In addition, we undertook annual cross sectional GAS pharyngeal prevalence (study B) in a subset pre and post the commencement of school clinics to investigate if change in Group A streptococcal pharyngeal burden parallels ARF control. (20) (21, 22) GAS prevalence in a low risk school, based on RHD prevalence, was assessed as a comparator. (23)

## METHODS

### SETTING

This study was conducted in a relatively geographically demarcated population (n~25 000) in south Auckland, NZ where ARF is endemic. Approximately 40% (n~50 cases per year) of NZ cases occur in this region.(2)

### SCHOOL SORE THROAT CLINICS

Schools were assigned a clinic based on an ARF risk score, including school demography, derived from the Auckland population-based rheumatic fever prophylaxis register data (1998-2010). The first clinic commenced in April 2011 in a pilot school, followed by remaining schools (total n=61) incrementally by four geographic clusters from July 2012 to May 2014. (19) ).The order of clinic introduction was not related to ARF risk.

### CLINIC PROCEDURE

The school health team was a registered nurse and a community health worker trained in throat swabbing. A Manual of Operations derived from the earlier school trial was used.(15) (18) (19)

Classrooms were visited daily to ask consented children with a sore throat to go to the clinic for a throat swab. Other health needs including skin infection were also sought. Children were also screened monthly to identify undeclared clinical pharyngitis (ie inflamed throat and/or tonsils with or without exudate) which was then swabbed. No child without symptoms or signs of pharyngitis received a throat swab. Children were not screened for viral symptoms by the community health workers in our program before a throat swab. Standing orders allowed registered nurses to treat culture-positive GAS pharyngitis with 10 days of amoxicillin by delegated authority from a registered medical practitioner. (www.health.govt.nz) Throat swabs were processed at one local laboratory.

Siblings of those students with GAS culture positive pharyngitis were also swabbed and treated if positive for GAS. If swabs were positive for GAS, parents were contacted for a short medical history and free medication provided. Adherence levels were monitored with phone calls at day 5 and 10 and blister packs if required. Once a day amoxicillin for 10 days (>30 kg 750 mg; 30kg or greater 1000mg) was used to improve adherence. (24) (www.heartfoundation.org.nz). In 2015 when all schools were in the program 12 884 courses of amoxicillin were dispensed.

STUDY A: EVALUATING ARF PRIMARY PREVENTION OF FIRST PRESENTATION ARF AS A RESULT OF THE INTRODUCTION OF SCHOOL CLINICS

The study evaluated the change in first presentation ARF from before to after the introduction of a school sore throat clinic program into 61 year 1-8 schools (students aged 5-13 years).

The staggered roll-out meant during the middle years of the study some schools had clinics and others were yet to commence. At any point over the study period (1 January 2010 to 30 June 2016) the participants were all children 5 to 13 years of age (inclusive) attending year 1-8 study schools, regardless of consent or participation. Annual school roll numbers by age, gender and

ethnicity were obtained from the NZ Ministry of Education. Schools report July 1 each year (mid school year). 2015 data were used for the first half of 2016.

OUTCOME MEASURES

ARF cases were assessed from 2010, before the first clinic was introduced to June 2016. Cases were identified from the RF prophylaxis register ((3) (15))

INCLUSIONS: Our study outcome was Auckland-resident first presentation ARF cases from the register attending a study school and categorized as definite or probable using the New Zealand adaptation, with more precise definitions, of the Jones criteria (www.heartfoundation.org.nz). The children were aged 5-13 years. School at diagnosis has been recorded from 1997. (15) (3) Hospitalization is the standard of care for acute cases. Each new referral to the register is scrutinized on a case by case basis by one operator in conjunction with the referring clinician. A diagnostic category (acute rheumatic fever; recurrent rheumatic fever; or a previously diagnosed case of rheumatic heart disease or rheumatic fever) is assigned and acute cases are categorized as definite, probable or possible (www.heartfoundationorg.nz).

EXCLUSIONS: Over the time period of our study (1 January 2010 to 30 June 2016) referrals to the register for prophylaxis were excluded if they were a duplicate, not resident in Auckland at diagnosis, were referred with established rheumatic heart disease without an acute illness, had previously diagnosed ARF, were possible ARF, were a recurrence of ARF, or were not attending a study school or 5-13 years of age.

STATISTICAL METHODS (see Text, Supplemental Digital Content 1, http://links.lww.com/INF/C697 for more detail)

The study had 80% power to detect a 50% reduction (5% significance level) in first case ARF assuming a pre-intervention ARF rate of 60/100,000 per year with 88,800 person years pre-

intervention and 79,200 post intervention.

A generalized linear mixed model investigated ARF rate change before and after initiation of school clinics. All first presentation definite or probable ARF cases in the study period, attending a clinic school at the time ARF presentation, were included. Analysis was performed in SAS 9.3 SAS Institute, Cary, NC, USA.

STUDY B: EVALUATING PHARYNGEAL GROUP A STREPTOCOCCAL PREVALENCE

Study B evaluated cross sectional prevalence of pharyngeal (symptomatic and asymptomatic) GAS before and after the commencement of clinics in a subset of students. For comparison, cross sectional GAS prevalence was also assessed once in a school at low risk of ARF.

STUDY DESIGN, SETTING, PARTICIPANTS AND OUTCOMES:

The study population (n~1500) attended a geographic cluster of 3 schools which were part of the 61 schools who received school clinics.

We assessed pharyngeal GAS prevalence 3 times in these schools, once prior to clinics, and 12 and 24 months later (May/June 2013, 2014 and 2015) to minimize seasonal variation. To assess pharyngeal GAS cross sectional prevalence all consented/assenting children were throat swabbed regardless of symptoms or signs.

A similar cross sectional study of pharyngeal GAS prevalence (July 2014) was conducted in a school at low risk of ARF with students in the same age range (5-13 years) as in the high risk schools. It was considered to be at low risk for ARF as it had similar demographics to a school with no RHD in an echocardiographic study. (23)

Throat swabs were routinely processed at the community laboratory.

STATISTICAL METHODS

To investigate the change in the prevalence of pharyngeal GAS positive swabs in the high risk area a generalized linear mixed model was used with presence or absence of GAS as the binary outcome, including year, age, ethnicity (Māori, Pacific, Other) and gender as explanatory variables and school within year as a random effect.

Analysis was performed in SAS 9.3 SAS Institute, Cary, NC, USA.

Both the ARF school clinic prevention evaluation study (STUDY A) and the GAS pharyngeal prevalence study (STUDY B) were approved by the regional ethics committee. Caregivers of subjects in high risk schools in both studies supplied written informed consent to allow their child to be part of the school program including evaluation. A separate ethics application with written informed consent was obtained for the low risk school in STUDY B.

**RESULTS**

STUDY A

The overall program had a consistently high consent rate (eg 96% in 2015). (19)

Person-years within study schools pre and post the clinic introduction were 79 775 and 76 857 respectively. The population under scrutiny was very similar pre and post the clinic intervention, with most (~90%) being either Māori or Pacific commensurate with the known ARF risk. (2) (Table, Supplemental Digital Content 2, http://links.lww.com/INF/C698). Age groups from these year 1-8 schools (5-13 year olds) were evenly represented before and after the intervention (Table, Supplemental Digital Content 2, http://links.lww.com/INF/C698).

Over the study period there were 124 first presentation ARF cases (108 definite, 16 probable) aged 5-13 years living in Auckland attending a study school. Figure 1 outlines the pattern of referrals to the Auckland regional rheumatic fever register.

Change in rates of ARF cases over time differed from before the introduction of clinics into schools to afterwards (p=0.03). The estimate of the change of slope was -0.47 (SE. 0.22). There was no evidence of a change of ARF rate prior to the introduction of a clinic into a school (p=0.88), with an incidence risk ratio (IRR) of a change of one year of 0.98 (95% CI 0.63, 1.52). However, after the introduction of clinics into schools there was a significant decrease in ARF rate over time (p=.008) with IRR 0.61 (95% CI 0.43, 0.88). The ARF rates in schools with clinic programs within the first, within the second and after 2 or more years were 90/100,000, 52/100,000 and 37/100,000 respectively (Figure 2). We demonstrated a reduction of 58 % of first presentation ARF rates from pre-introduction of clinics into schools to after 2 or more years of operation of clinics.

STUDY B: EVALUATING GROUP A STREPTOCOCCAL PHARYNGEAL CROSS SECTIONAL PREVALENCE (Table 1)

In the high-risk study group, the ethnic breakdown, age bands and gender remained similar in the 3 samplings with mean overall percentages of 40% Māori, 45% Pacific, 15% Other; 50% female; and 25% 5-6 years of age, 24% 7-8 years of age, 24% 9-10 years of age, and 27% 11+ years of age.

There was a significant reduction in GAS prevalence (pre-program compared to one and two years post program combined) (p= 0.005). The modeled prevalence rates of pharyngeal GAS in students were: pre-program commencement (2013): 22.4% (95% CI 16.5, 30.5), one and two years post-program: 11.9% (8.6, 16.5) and 11.4% (8.2, 15.7) respectively. (Table 1)

In the low ARF risk comparison group (consent rate 76 %, 265/350) 265 swabs were taken, with a prevalence of 11.7% (8.3, 16.2).

## DISCUSSION

This study has demonstrated a 58% reduction of first presentation ARF in a geographically defined community setting. This, we suggest, is most likely as a result of quality-controlled school clinics with management of GAS positive pharyngitis using an oral penicillin (amoxicillin). The intervention included control of associated family and community GAS pharyngitis ensuring free care and monitored adherence to treatment.(18) (19) Reduction of pharyngeal GAS prevalence in parallel with the reduction of ARF was demonstrated.

Our study is of a school-based intervention in a geographically distinct area within the New Zealand Rheumatic Fever Primary Prevention program.(25) (26) The national program had a number of elements which could have impacted on our area. These included national health promotion messaging, an attempt to improve access to throat swabbing services through routine general practice primary care and an attempt to improve housing. National health promotion messages may have raised awareness of the importance of a sore throat and perhaps motivated children to declare a sore throat for swabbing in the school setting.

Beyond our study area there are 9 further smaller geographic areas in NZ (approximately 5-15 RF cases per year historically) (2) where a heterogeneous mixture of school clinic and primary care sore throat management with or without skin infection care is being delivered . The NZ Ministry of Health Interim Report (www.health.govt.nz: October 2015) did not show a significant ARF reduction at the time of the evaluation.

We postulate that participants in our study area receive their sore throat treatment almost exclusively through schools. In the District Health Board where this program sits, most (~90%) of 5-13-year-old children at high risk of ARF were in a sore throat program school by the end of the study period. Clinic protocols were strictly observed.(15) (18) . This contention is supported

by the fact that enhanced free sore throat management in routine general practice primary care (so called "drop-in" clinics), funded by the government, were poorly taken up in our study area. In 2015 our school program (population of ~ 25 000) treated 13 408 school-detected GAS positive throat swabs (personal communication PA, DJ). In contrast for the same population (2015) only 613 were treated in "drop-in" clinics (PA, DJ). The funding also enabled at risk secondary schools (population~ 25 000) to offer sore throat management in walk-in clinics (407 treated) (PA, DJ). Routine household contact management (mostly siblings) led to an extra 972 GAS treatments in 2015 (PA, DJ). Data from usual sources of healthcare in general practice for sore throats for this population are unavailable.

The study used the most robust design available. As reduction of first presentation ARF became a government priority a further controlled trial was programmatically and ethically not possible. All areas at high ARF risk were required to commence an intervention. (www.health.govt.nz). An important design feature is the staged roll-out of the program which reduced the confounding of time when assessing changes from before to after the program introduction. Also pre-program ARF data was available from January 2010 and there is a highly scrutinized population-based register from which to identify ARF cases.(3) (15) (5) We cannot attribute causation with certainty due to the limitations of study design in this setting. However, comparison of the rate of change of ARF prior to and after the staggered introduction of a clinic into schools meant that a natural decrease of ARF was unlikely to explain the difference. High consent and participation rates were a strength.(19)

Why were we able to show a significant reduction of ARF compared to the earlier school cluster randomized trial? (15) We hypothesize that reduction in cross contamination of pharyngeal GAS between students in schools and at home was reduced as a result of a change in protocol to allow

this.(19) Symptomatic siblings were swabbed and treated as necessary which was not possible in the original trial due to the design as a sibling may have been in a control school. In addition, the school clinic roll-out by geographic cluster may have reduced cross contamination but this cannot be measured.

Group A streptococcal pharyngitis is highly infectious (nearly a 1 in 2 chance for siblings).(27) We measured cross sectional pharyngeal GAS prevalence (symptomatic and asymptomatic) for guidance of progress towards ARF control. Pharyngeal GAS prevalence in three high risk schools reduced to the level of a low risk school after 1 year of sore throat clinics (Table 2). The control of GAS respiratory disease and ARF through pharyngeal GAS burden reduction has been best studied in the US military. (21) (20) More recently in a small school-based randomized trial in China prevalence and incidence of GAS pharyngitis were reduced with in-school penicillin/erythromycin treatment as compared to mostly symptomatic care by their regular provider, similar to our study findings.(22)

Differentiating viral pharyngitis with associated pharyngeal GAS carriage from true GAS pharyngitis is complex. Certainty requires support of acute and convalescent antibody titers, and *emm* typing, both of which were not practical in our setting. .(www.heartfoundation.org.nz)

When ARF becomes extremely rare as in the New Zealand non Māori / non Pacific population or in most populations in the US, Canada or Europe the risk of failing to prevent a case of ARF by assuming a viral sore throat in association with presumed pharyngeal GAS carriage is almost immaterial as the risk of ARF is so low. The goal in these populations is largely to limit antimicrobial overuse as the chance of failing to prevent a case of ARF is very small. In a high risk population the risk benefit ratio is different. Our population at risk of ARF has ~ a 1 in 150 chance of hospitalization with ARF by aged 13 years.(2)

However, throat culture costs are an important factor in first presentation ARF prevention. A variety of clinical prediction rules using presenting symptoms and signs have emerged with highly variable effectiveness. A systematic review found no definite way of predicting which pharyngitis was caused by GAS in children. (28) From the earlier school program trial (15) , in depth analysis of clinical data over one year from n=12 836 sore throats (n=12 032 GAS negative and n= 804 GAS positive) found the several clinical prediction rules applied to be unsafe in this population at very high risk of ARF. (29) The sensitivity of the best performing test was 54 %, specificity 100 %, and the positive and negative predictive values respectively were 16% and 96%. In New Zealand a peer reviewed algorithm is widely available for primary care management (www.heartfoundation.org.nz) to encourage a differential approach to sore throat management depending on ARF risk (which is based on age, ethnicity and socio-economic circumstances from epidemiologic data). Amoxicillin was trialed once a day to help manage adherence recognizing its wider spectrum. (24) National surveillance has not detected increased pneumococcal resistance to penicillin. (www.esr.cri.nz)

We suggest the demonstrated reduction of 58 % of first presentation ARF over the time of the program evaluation seems most likely to be as a result of school-based GAS pharyngitis management. The authors acknowledge that the study outcome is specific to this population at this time. However, it is consistent with the size (~60%: Relative Risk 0.41, 95% CI: 0.23-0.70) found in the previous meta-analysis. (17) There is a paucity of published quality data in this area. Only 6/677 studies of first presentation ARF with sore throat treatment in community and or school settings were found to have evaluable data (randomized trials or before/after studies)(17) (10) In three school based sore throat studies with evaluable data (other than the NZ trial) a reduction of ARF of ~40-60% was calculated. (11) (12) (13) (17) Two were observational and

one was a before/after study with no blinding or randomization. (17) A 60% reduction of ARF associated with a respiratory illness was demonstrated with improved access to inner city healthcare. (9)

Considering the applicability of this program to diverse settings there are the limitations of school-based healthcare that need consideration. To increase sustainability we embedded the sore throat component in wider school health. In addition in New Zealand secondary prophylaxis is already mostly delivered by nurses in schools.(3) Sore throat management through schools in term time (~ 40 weeks) is a limitation; a minor increase in ARF cases after the main summer holiday was observed.

The burden of ARF/RHD is mostly carried by the developing world where healthcare is often severely limited by costs.(30) School-based healthcare is well established in some developing countries. (31) Adaptation for settings with constrained resources carrying the burden of ARF/RHD might be an intervention integrated into existing healthcare systems (including ARF recurrence prevention) with locally adapted prediction rules for pharyngitis management to avoid laboratory costs(32), awareness raising in the lay and healthcare communities and benzathine penicillin for presumed GAS pharyngitis treatment for simplicity and adherence. Cuba introduced a well described program including secondary prevention.(16) A recent cost-effectiveness study of primary prevention supported this approach.(33)

**CONCLUSIONS:**

This study demonstrates a proof of principle. We have provided robust evidence for the first time, we believe, supporting primary prevention of first presentation ARF using an oral penicillin (amoxicillin) in a community setting, in this case school clinics. This will support modifications for diverse settings where ARF remains endemic.

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Figure Legends:

**Figure 1:** Cases referred to the Auckland Regional Rheumatic Fever Register (1 January 2010-June 30 2016)

Footnote:

Footnote: RHD Rheumatic Heart Disease; ARF acute rheumatic fever (includes chorea); definitions of definite, probable and possible ARF and Recurrences as per www.heartfoundation.org.nz; "register" refers to the Auckland regional rheumatic fever secondary prophylaxis register (see text)

**Figure 2:** The Decline of Acute Rheumatic Fever (students aged 5-13 years) following the Introduction of a School Throat Swabbing Program into designated Study Schools.

Footnotes:

Year 1 refers to the ARF rate in schools which have programs within the first year of implementation. Year 2 refers to the ARF rate in schools within the second year of the implementation of the program and Year 3 refers to the ARF rate in schools after two or more years of the implementation of the program. There were 35 761, 24 809 and 16 287 person years in year 1, 2 and 3 respectively. The y axis ARF rate refers to a case of ARF meeting the study definition from a study school. ARF cases are definite or probable (see Methods).

[+] A significant decrease following the intervention (the introduction of a sore throat school clinic program) was found (p=0.008)

**Table 1**: Cross Sectional Pharyngeal Group A Streptococcal Prevalence (Asymptomatic and Symptomatic) in Year 1-8 School Students

| **PREVALENCE (95% CI)** | | | | |
|---|---|---|---|---|
| Low risk, non-study school<br>(n=265 participants) | Study Schools (n=3) Immediately Pre Program<br>(n=1357) | Study Schools (n=3) 1 year<br>Post Program<br>(n=1597) | Study Schools (n=3) 2 years<br>Post Program<br>(n=1617) | p value* |
| 12%<br>(8%-16%) | 22.4%<br>(16.5%-30%) | 11.9%<br>(8.6%-16.5%) | 11.4%<br>(8.2%-15.7%) | 0.005 |

*comparing pre to post program (excludes low risk school)

**Figure 1**

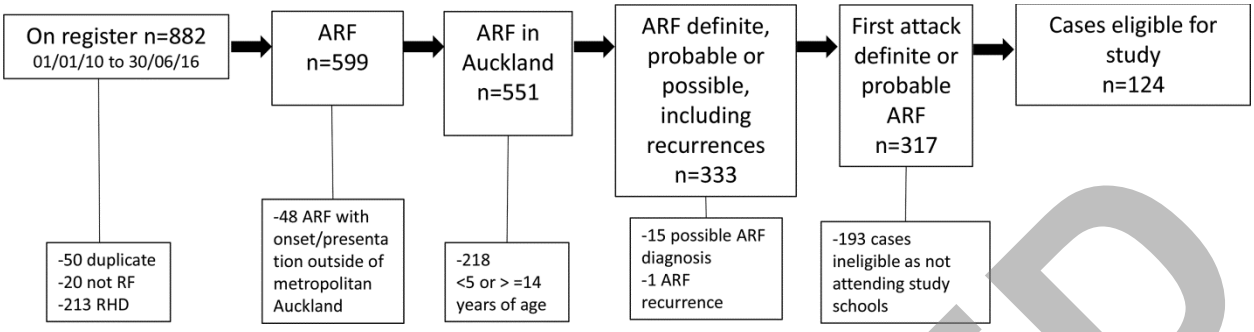

**Figure 2**