Cover sheet

# Short title: Can one month of BLIS K12 lessen Group A Streptococcal carriage and infection?

# Full title: Can one month of BLIS K12 Probiotic with Streptococcus Salivarius taken by Whakatane Primary School children prevent colonization with Group A Streptococcus pathogens, decrease GAS Sore throats in this study, and in larger studies Acute Rheumatic Fever ARF?

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**Clinical Laboratories** Pathlab BOP

**Prescribers** of antibiotics for GAS EBPHA Medical Practices, Dr J Malcolm and Rapid response clinics

# Introduction

# Can one month of BLIS K12 Probiotic with Streptococcus Salivarius taken by Whakatane Primary School children prevent colonization with Group A Streptococcus pathogens, decrease GAS Sore throats in this study, and in larger studies Acute Rheumatic Fever ARF?

# Précis

We propose to offer a probiotic BLIS K12 to about 500 Whakatane primary school children. In small trials in Italy and Kawerau, NZ it has decreased acute Group A Streptococcal GAS sore throats and recurrent GAS sore throats respectively, both while taken and for many months to follow. Using an open stepped wedge design we will compare GAS colonization and point prevalence of GAS sore throats as our primary outcome measures; The yet to start school rates will be controls for the first month then participants.

Summary

Group A Streptococcal GAS sore throats lead in some cases (3%), to acute rheumatic fever (ARF).[[1](#_ENREF_1)] Following ARF, the majority of those affected will have Rheumatic Heart Disease, (RHD) the severity of which can range from subclinical valve changes, which may resolve or not, to recurrences and complications which can and often do cause earlier adult death.[[2-4](#_ENREF_2)] .

Approximately 150 New Zealanders each year die from RHD. Increasingly and disproportionately many are Maori and Pacific. NZ European, Pakeha New Zealanders had similar ARF rates in the 1930s and 1940s to the rates that Maori and Pacific suffer currently. Many older folk with RHD are Pakeha with mean RHD death rates in their 80s. These adults have significant empathy for the current generation, with new ARF and RHD. However the impact on life expectancy of RHD is currently greatest for Pacific and Maori. For example Maori men with RHD currently die 14 years before Maori men without.[[3](#_ENREF_3)]

Highly effective secondary ARF prevention, in the Bay delivered by the Bay of Plenty District Health Board BOPDHB District Nursing Service DNS, provides four weekly intramuscular Benzathine Penicillin to those who already have had ARF at least till at least age 21 years[[5](#_ENREF_5), [6](#_ENREF_6)]. This is the main strategy to prevent **recurrent** ARF attacks with worsening severity of Rheumatic Heart Disease.

New First episode ARF in New Zealand increasingly affects mainly Maori and Pacific people and fewer Pakeha. While mainly a disease with onset in those in Education Decile 1 and NZ Deprivation index 9 and 10 [[7](#_ENREF_7)], it is not confined to those situations.

The District Health Boards adjacent to the Bay of Plenty,[[8](#_ENREF_8)] Tairawhiti to the East, Lakes to the South and Waikato to the West have similar mainly Maori, and higher deprivation areas of ARF and RHD morbidity. [[9-11](#_ENREF_9)]

In the Bay of Plenty (BOP), NZ, **first attacks of Acute Rheumatic Fever** affect on average 9 school aged pupils yearly, with a trend of more presenting in their teens. The majority of these are Maori, residing in the Eastern Bay of Plenty EBOP [[12](#_ENREF_12), [13](#_ENREF_13)]. Ethnic miscoding is common [[14](#_ENREF_14)] and re-examination of MOH notified “2013 BOP ARF” patient declared ethnicities confirmed that 100% were Maori rather than 80% initially reported to the Ministry of Health ([[15](#_ENREF_15)]. A subsequent audit of BOP ARF 2000-14 confirmed this direction and extent of ethnic miscoding and that 95% of BOP affects ARF Maori or Pacific youth.( Walsh Scarfe Malcolm 2015). These findings support EBOP “public health” **ARF Primary prevention projects** targeting Education Decile 1 and 2 schools with mainly Maori school pupils from higher deprivation homes.

School based primary prevention ARF programmes successfully prevent and treat GAS sore throats caused by rheumatogenic strains of GAS. They have been shown to lessen the incidence of ARF [[16-19](#_ENREF_16)] and thus new developing RHD. Current NZ school based ARF prevention programmes are focussed on GAS detection through throat swabbing and patient’s GP standing orders of antibiotic treatment of GAS sore throats for 10 days often with once daily amoxicillin.[[20](#_ENREF_20)]

This trial differs from solely antibiotic based approaches, as it proposes to utilise a probiotic for one month, BLIS K12 which was developed from University of Otago research in Dunedin New Zealand.[[21-24](#_ENREF_21)] It has been successfully used in Italy for three months,[[25](#_ENREF_25)] in a small trial, to prevent GAS sore throats in children in day care centres, from developing by reducing the GAS colonization and is undergoing a twelve month trial in Porirua, NZ [[26](#_ENREF_26)].

GAS **colonization rates** measure the proportion of all children with GAS in their throats whether or not they have symptoms. **GAS sore throats rates** are a smaller group, those GAS colonized children with sore throat symptoms that is GAS sore throats expressed as a proportion of the total population (or in an age band eg 5-15 years) of children. Sometimes GAS sore throats are expressed as GAS positive sore throats as a proportion of children with sore throats . The distinctions are important. The context and methodology of this study lends itself particularly well to measure the impact of BLIS K12 on the former GAS colonization.

To gauge the effect of trialling BLIS K12 on school aged children, the trial will examine the **GAS colonization rates** before, immediately after, at one, three and four months intervals after commencement of a one month course of BLIS K12. GAS colonization is the main primary outcome measure of the success of the trial. These measures will give an indicative picture of the degree and duration of protection afforded and school acceptability.

Whakatane children will also access their GP’s for sore throats, swabs, risk evaluation and treatment following Ministry of Health National Heart foundation algorithm and guideline [[27](#_ENREF_27)], or new Whakatane Rapid Response ARF clinics. If GAS is recurrent NZ Primary Care Handbook 2012 [[28](#_ENREF_28)]) and NHF ARF guideline 2014 details alternative antibiotic regimens for treatment of these children co-amoxyclavulonic acid being the most commonly used local regimen. BLIS K12 has also been used effectively as an adjunct to the treatment of recurrent GAS [[29](#_ENREF_29)] so will be offered to those that acquire GAS more than three times in the course of this 3 month study

This Whakatane study has significant differences in intervention duration, and associated school interventions from the concurrent Porirua BLIS K12 study. Firstly In Porirua BLIS K12 is to be given continuously for 12 months to their school children. Secondly in Porirua the school children are also part of a sore throat in schools public health nurse programme, where children with sore throats are identified at school, and thirdly their sore throats are swabbed in their schools, treatment arranged and facilitated when positive on GP standing orders and PHN follow- up. The Porirua programme and those in four other EBOP school programmes are based on the successful Whangaroa[[16](#_ENREF_16)] and South Auckland studies [[17](#_ENREF_17)]

**Further outcome measures** will include the measurement of the point prevalence of acute **GAS sore throats** before and after a month of the probiotic, BLIS K12, at the time of two follow up swabs immediately and two months later. Study “GAS sore throats” will be by pupil report of soreness, when throat swabs are taken noted by the swabbing trained Kaiawhina, community health worker, CHW. Family Doctor name of General Practitioner GP and named practice will be recorded on consenting.

With a staggered start (stepped wedge) study design, changes in the first school’s GAS carriage rate, in response to BLIS K12 will be compared to the carriage in the yet to be started third school. These controls address the previously described changes in GAS carriage within and over seasons[[21](#_ENREF_21), [30](#_ENREF_30)].

Other secondary outcome measures will include measuring consenting children and their whanau awareness of sore throats and ARFin the proposed schools.

Between the four swabs within schools, upon children reporting throat they will be , advised to go to their family medical practice for a swab and possibly antibiotics or to the soon to be started 2015 ARF Rapid response clinic.

General Practice and Pathlab throat swabs for these children before and after this intervention will monitor whanau utilization of GP and General Practice servicing of GAS sore throats. General Practice use of best practice guidelines for GAS sore throats management [[31](#_ENREF_31), [32](#_ENREF_32)] will also be promoted and noted as well as the number of pupils presenting to Practices with swabbed sore throats and GAS sore throat from schools from the school catchment areas. Parental consent will have been obtained to inform GP of study swab results and to enquire about previous and subsequent 6 months throat swabs. Consultation with local General Practices will inform the practice staff of the study, its potential benefits, and solicit support with antibiotic prescribing, cognisant of antibiotic allergies and intolerances where they are known.

This research is a joint venture between Te Tohu o Te Ora o Ngati Awa (NASH) Pareake O’Brien R/N and colleagues and Eastern Bay Primary Health Alliance (EBPHA) Sandra Ball R/N and colleagues with Whakatane Paediatrics, BOPDHB Dr John Malcolm’s support.

 While the initiative and innovation of a one month BLIS K12 has been local Whakatane based, there has been valued consultation with University of Otago Professors Julian Crane and Michael Baker regarding the study hypothesis, design and outcome measures. Professor Chris Frampton suggested the stepped wedge design introduction of the probiotic to local schools . Dr Jo Scott Jones GP Opotiki has commented on this proposal in an earlier draft in December 2014. While these contributions have been invaluable the innovation and any ommisions are of the proposal partners.

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## Aim

**To assess if one Month of BLIS K12 Probiotic, with Streptococcus Salivarius, taken by Whakatane Primary School children prevents or limits colonization with Group A Streptococcus pathogens, and decreases GAS Sore throats, and if so duration of benefit.**

## Short description;

This research aims to decrease Group A streptococcal GAS colonization, to prevent Group A streptococcal (GAS) sore throats for pupils in three education Decile one Whakatane schools with high numbers of Maori pupils. They will **take probiotic BLIS K12 lozenges , containing Streptococcus Salivarius ,sucking them daily for one month near the peak Group A Streptococcus season April /May/June.** Pre BLIS GAS colonization and GAS sore throats will be treated with appropriate 10 day antibiotics courses, usually once day amoxicillin. Post BLIS GAS colonization will be treated similarly and with a further month of BLIS K12.

BLIS K12 lozenges contain Streptococcus salivarius a naturally occurring throat commensal with 2 bacteriocins with activity against Group A Streptococcus GAS[[22](#_ENREF_22), [33](#_ENREF_33)]. BLIS K12 has been shown in both an Italian pilot paediatric study to be 90% protective against GAS sore throats while taken for three months, with 60% protection in the 6 months to follow [[25](#_ENREF_25)] and to have similar significant benefits 86% protection for recurrent GAS sore throats to follow when taken for one month in Kawerau New Zealand [[29](#_ENREF_29)]

## Introduction; full study description

## Group A Streptococcal GAS colonization;

New Zealand school studies over time, almost 30 years apart, in both the North and South islands, in areas ranging from high incidence ARF areas Wairoa, East Coast North Island, [[34](#_ENREF_34)] to low ARF areas at the time in Dunedin, Otago South Island [[21](#_ENREF_21)], have shown that it is not uncommon for one in five children to be GAS colonised. These and recent studies at the onset of Bay of Plenty ARF primary prevention studies show similar findings Kawerau 2010, [[35](#_ENREF_35)] and Ngai Tuhoe 2014.[[36](#_ENREF_36)]

Similar GAS colonization rates can also be expected in Whakatane EBOP, at the onset of this study. We anticipate 20% GAS positive throats swab rate for Maori primary school pupils in EBOP education Decile one schools. Our interest in school GAS burden or carriage has been based on the premise that interventions decreasing total GAS load for children may also limit transmission child to child, and also GAS sore throats, and ARF. Impact on GAS colonization is proposed as one of the mechanisms for the success of the Whangaroa ARF primary prevention programme.[[16](#_ENREF_16), [17](#_ENREF_17)]. Hence GAS colonization rate is the primary outcome measure of this study.

Annual and Seasonal variation in GAS colonization rates has been noted predating intervention studies. Tagg noted over more than 2 years, Dunedin seasonal variation of children’s apparent asymptomatic GAS colonization was noted with the first February summer testing session 9% (later years 22%) and four months later winter June 29% and a November spring 27% the GAS colonization rate remaining on the other 6 samples close to 22%. [[21](#_ENREF_21)] Tagg pointed out that while Stanhope in Wairoa East Coast, had found a decade earlier a very high ARF rate, the GAS positivity rate over 12 months varied from 7 to 16%. [[34](#_ENREF_34)]. While GAS colonization is a potential contributing factor, these studies challenge the possible theory that the relatively low occurrence of rheumatic fever in the South Island in that era was due to purely a lower total carriage rate of Group A streptococci.

Not all GAS are equally rheumatogenic. Lancefield Types also matter. Rheumatogenic Streptococcal types have been identified for some decades. Barry reported a Hawkes Bay primary school outbreak due to Serotype M type 5 NZ.[[37](#_ENREF_37)] Lancefield M types and T patterns were documented.[[38](#_ENREF_38)] More recently genotype studies are underway [[26](#_ENREF_26)] as the possibility of vaccine development attracts research money and a streptococcal vaccine may cease being the mirage of an effective cure on the horizon. This study is able to report heavy or light growth but unable the BOP Pathlab advise on routine testing to assess Lancefield typing, gene studies or Salivarius colonization[[39](#_ENREF_39)]whereas the Porirua study is exploring these aspects. While swabbing technique is as standardized as possible there is local EBOP caution utilizing reports of heavy or light growth from the laboratory lest they reflect swabbing technique rather that degrees of colonization [[40](#_ENREF_40)] .

Some streptococci are beneficial, persistent oral and throat flora. The non-random distribution of streptococci in the childhood Dunedin population was pointed out by Tagg 1990 While 7% had GAS sore throats over 2 years, 53% had a positive GAS swab over 2 years that is asymptomatic colonization.. Tagg pointed out the difficultly differentiating colonization and subclinical infection. Of interest 13% of the children had 44% of the positive streptococcal cultures. Subsequent studies detailed the characteristics and safety of alpha haemolytic Streptococcus salivarius a protective safe bacterium which makes bacteriocins limiting Group A Streptococcus; These findings of the ability of Salivarius to colonize throats over time, limiting GAS led to this studies intervention development. Thus studies to de-colonize or alter the colonization are being undertaken.

Many factors, some organism factors, Streptococcal affinity, adherence and persistence, as well as rheumatogenicity, and some host factors in those colonized and infected appear important as well as protective patterns such as pre-existing or subsequent Streptococcal Salivarius colonization in those not GAS colonized appear important in GAS infections.

Kawerau is a neighbouring town to Whakatane, with 1400 school pupils. Kawerau is inland from Whakatane with similar socioeconomic, education deciles, ethnicities and ARF cases incidence and risk factors to the Whakatane area. GAS colonization findings from Kawerau 2010 and Ngai Tuhoe area 2014 both on school sweeps of about 20% are relevant to the proposed Whakatane study as benchmarks prior to interventions such as BLIS K12. This leads us to estimate that the **baseline Whakatane schools GAS colonization rate** will be close to 20%.

While Kawerau schools have sore throat swabbing for GAS at their schools, with antibiotics prescribed for GAS positive sore throats on GP standing orders, Whakatane proposed study schools have throat swab access through their GP surgeries and treatment there or soon to be established Rapid Response ARF clinics. Some GP surgeries are up to 7km from these schools and children’s homes with opening hours and access difficulty for simultaneously working parents .

The impact of interventions on Kawerau School children’s GAS throat colonization rates are known, having been assessed pre commencement and during the current ARF school prevention programme, where community health workers swab sore throats in schools. Pre commencement whole school population GAS colonization was 20% in 2010, declining to about 10% after three years of the school sore throat programme, declining further to about 6% in 2014 with the addition of skin sepsis interventions. These Kawerau findings 2010 preceded and contribute to the HRC GAS prevalence study 2013-4 led by Prof D Lennon. and serve as benchmarks (presented ASID 2015) The similar GAS colonization found in adjacent Ngai Tuhoe area (Te Kaokao o Takapau 2014) after a year of a similar programme and Kawerau of 20% baseline are likely to be found in Whakatane. These communities GAS carriage assessments aimed to benchmark, then check the impact of these ARF primary prevention programmes on the school age GAS throat streptococcal burden, as one of the considered mechanisms for their efficacy on ARF in such school programmes. e.g. the absence of ARF for some years from Whangaroa. Comparing the rate of GAS carriage decline within the study and, following different interventions in EBOP will form part of secondary outcomes.

## Group A Streptococcal GAS sore throats are not all classic pharyngitis.

**GAS rates in those with sore throats; This section explains the rationale for accepting GAS sore throats as infected whether or not classic pharyngitis is present in this study.**

DHB and Ministry of Health funded ARF Primary prevention in schools programmes including four in the Eastern Bay of Plenty EBOP have operated since 2009. The National Heart Foundation, NHF had suggested the threshold for initiating such programmes where ARF rates have been greater than 50/100,000 per year. They are modelled on the South Auckland studies and subsequent meta-analysis showing their efficacy Lennon and, Whangaroa Ngati Hine success [[16](#_ENREF_16), [17](#_ENREF_17)]. These initiatives and subsequent programmes 2008-2014, were supported by Associate Minister Tariana Turia and Minister of Health Tony Ryall. Other factors of less geographic mobility, community cohesion of the Ngati Hine team working with Helen Herbert may have also contributed to the spectacular 8-10 year Whangaroa small town eradication of ARF[[16](#_ENREF_16)] in contrast to the more modest but large scale statistically significant success in big city Auckland schools. [[17](#_ENREF_17), [18](#_ENREF_18)]

Children in these classrooms, who put up their hands when asked if they have sore throat, have a swab for GAS. **Those with GAS positive “sore throat swabs” are treated with 10 days oral antibiotics, the main intervention of these programmes**. The Porirua study of one year of BLIS K12 is embedded within such a school programme[[26](#_ENREF_26)]

While part of the schools swabbing and treatment rationale is that the programme has a community protocol not needing clinical assessment, normal **appearances may not exclude clinically GAS important infec**tion as explained later in this section. The NHF Sore throat Algorithm 2006 for family practices and all doctors, while having a clinical scoring system had a low threshold for swabbing school age children in ARF endemic areas and treating GAS positive children. With more recent Pharmac support (and implicit acknowledgment that earlier focus in Ministry of Health advisory documents of 1995 on viral prevalence, and judicious antibiotics had not adequately supported GP role in ARF prevention)[[41](#_ENREF_41)] the Primary care handbook 2012, and MOH sore throat algorithm 2014 [[27](#_ENREF_27)] support swabbing and treating on a risk factor algorithm.

Based on the four EBOP ARF prevention school programme findings where 1400 pupils, 74% of highest risk ARF pupils are enrolled ,**we expect 20% of children with sore throats when asked will have GAS positive throat swabs, pre Blis K12 in this Whakatane study**.[[42](#_ENREF_42)] Their throat appearances are less predictable At times the tonsils, tonsillar pillars and or posterior pharynx appears red, or from the description of dysphagia and the child’s finger pointing to the site of discomfort a more posterior pharynx is the site of infection. The reasons that many are GAS positive but have limited signs includes possible posterior pharyngeal infection, coincidental viral infection and carriage, and some difficulty separating GAS colonization and sub clinical infection. [[21](#_ENREF_21)] [[27](#_ENREF_27)].

While severe persistent and recurrent tonsillar infection is often streptococcal infection, a high proportion of streptococcal infection may not be associated with **classic pharyngitis** signs. Over 27 months in the Dunedin 1987-89 observational study 7/103 children with 858 total samples that is 7**% had all three of clinical symptoms, signs and Group A Streptococcus[**[**21**](#_ENREF_21)**]** The children’s family doctor was advised about these.

Actively soliciting sore throat symptoms regardless of presence or absence of classic signs gets a higher yield of GAS sore throats. Clinical scoring systems for sore throats identify the most purulent tonsillitis needing antibiotics and when persistent or closely recurrent at times need ENT referral for tonsillectomy. An Opotiki GP who also worked with Aboriginal Australians found normal appearances in children with sore throats do not exclude the presence of GAS [[43](#_ENREF_43)] **GAS sore throats rates thus vary significantly on how solicited.**

**Subclinical GAS infection does appear to have an impact**. We know from echocardiography screening 2010, in nearby Kawerau and Ngai Tuhoe rohe areas that of 550 children at least four had undetected RHD.[[35](#_ENREF_35), [44](#_ENREF_44), [45](#_ENREF_45)]. Of EBOP children about 1; 138 have been infected with GAS ( either sub clinically or not recollected) developed subclinical ARF then RHD on strictly defined echocardiography criteria[[46](#_ENREF_46)]. Baltimore studies quoted by Shulman point out that 1/3 of those with ARF have not had or recognised a preceding sore throat.[[47](#_ENREF_47)] A few EBOP children presenting with severe RHD, some in congestive heart failure, requiring cardiac surgery on presentation or shortly thereafter have no recall of preceeding sore throats [[48](#_ENREF_48)]. While historically clinicians have at times implied limited patient recall of preceding sore throats, subclinical throat infections with pathological impact are also plausible. ARF primary programmes relying on symptomatic sore throats are the cornerstone of NHF prevention strategy in high ARF areas and might be anticipated to decrease ARF by 60-70% though the impact in Whangaroa for many years appeared greater.

Carapetis Steer and others in Australia link GAS skin infections also to ARF. Recent NZ programmes including neighbouring Kawerau’s EBPHA ARF team have added skin sepsis interventions to their ongoing school based ARF primary prevention programme, with impact on both skin sepsis and GAS sore throat colonization. [[49](#_ENREF_49)] with early indications of parallel decline in ARF ( ASID 2015).

EBPHA evaluation has documented two trends within four ARF primary prevention sore throat swabbing programmes. In the background is the knowledge that most children’s sore throats are viral, with multiple viral and bacterial annual exposures. Increasingly we accept that viral and bacterial infections can occur simultaneously. [[50](#_ENREF_50)]. Firstly a **decline of GAS positive sore throat swabs as a percentage of swabs taken trends from close to 20% at onset of each programme to 10% average in subsequent years. Secondly each year there is a decline in GAS positive rates from as high as 14% to as low as 4-8% from term one to term four, summer to spring** There are smaller about 3% annual and intraregional variations within EBOP.[[42](#_ENREF_42)]

## Innovation and rationale of Blis K12

### Background of BLIS K12; Biological plausibility

BLIS K12 has been developed from the research of Professor John Tagg, Emeritus Professor Microbiology University of Otago, Dunedin and through colleagues in the BLIS Technologies Centre for Innovation Otago University.[[21](#_ENREF_21), [22](#_ENREF_22), [33](#_ENREF_33)]

BLIS K12 is an oral probiotic containing Streptococcus Salivarius, a naturally occurring alpha haemolytic streptococcus strain which is able to colonize and persist in the mouth. It helps maintain healthy oral bacteria to improve dental hygiene and limits the colonization of mouth by harmful bacteria such as Group A Streptococci otherwise known as GAS [[51](#_ENREF_51)] It is a lozenge which ideally is taken at night, is safe to suck at night as it dissolves as the person sleeps. In this study it is proposed to take in the afternoon at school.

GAS infection is known to cause bacterial sore throats which can lead to complications developing such as tonsillitis and acute rheumatic fever. Group C and G Streptococci cause problematic recurrent pharyngitis but they have not been implicated as causing ARF. They also appear BLIS K12 responsive. [[52](#_ENREF_52)]

BLIS K12 is optimally commenced at the end of 10 day antibiotic course for GAS sore throats. The rationale is that pharyngitis will be treated, rheumatogenic beta haemolytic Group A Streptococcal strains will be killed and then replaced with alpha haemolytic Salivarius which has been shown to persist, [[21](#_ENREF_21), [22](#_ENREF_22)] [[45](#_ENREF_45)]and to secrete bacteriocins combating GAS.

In an Italian paediatric trial 2012 with day care centre pupils, the use of BLIS K12 limited GAS sore throat symptomatic infection for 90% of pupils while on the 90 day course and to a helpful but lesser extent in about 65% of pupils in the 6 months follow up. [[25](#_ENREF_25)]

**Introducing Streptococcus Salivarius**

( This section contains extracts in italics copied with permission from Professor Crane’s HRC Rheumatic Fever Research Partnership application to offer 12 months BLIS K12 in Porirua;[[26](#_ENREF_26)] The Whakatane investigators are aware of and have read many of Prof Tagg’s ( Dunedin N.Z) and Piedro’s (Italy) papers)

*<<****This organism is a naturally occurring human oral commensal that produces a variety of Bacteriocin-like Inhibitory Substances, (BLIS) that have in vitro bactericidal activity against S. pyogenes (with no resistance yet detected in tested strains)*** *This led to further studies by Tagg et al [*[*53*](#_ENREF_53)*] in New Zealand showing the K12 strain produces a variety of BLIS, including two anti-S****. pyogenes lantibiotics (a class of peptide antibiotics), salivaricin A (SalA) and salivaricin B (SalB*** *) More recent studies have identified more of the bacteria and the bacteriocin’s properties [*[*54*](#_ENREF_54)*,* [*55*](#_ENREF_55)*]*

***Clinical studies show that school children with high oral cavity concentrations of this specific strain of S. salivarius in the oral cavity were significantly less likely to develop GAS pharyngitis or to carry the S. pyogenes in the oral cavit****y.*

***The inhibitory effect on these oral pathogens and the lack of any pathogenic effect of S. salivarius itself, suggested that S. Salivarius might be a useful probiotic to improve oral health, and reduce S. pyogenes pharyngitis.[***[***56***](#_ENREF_56)***]***

***This led to the development and commercialisation of the specific strain of S. Salivarius, designated, K12 in New Zealand. The preparation is widely available OTC (Over the Counter) in New Zealand and internationally and has GRAS (Generally Regarded as Safe) status in the USA. (FDA) [***[***57***](#_ENREF_57)***,*** [***58***](#_ENREF_58)***]***

***The efficacy of this probiotic organism to reduce GAS throat infections and thus reduce ARF urgently needs to be formally investigated****. >>*

### Recent Relevant and ongoing New Zealand BLIS K12 community GAS research;

**Porirua context (of BLIS K12 trial) within one of the national ARF primary prevention programmes in schools, contrasted with proposed Whakatane schools’ programme.**

### Porirua; The first BLIS K12 trial where it is to be taken for 12 months for whole school populations for GAS sore throat prevention was announced in 2013 and awarded to a team led by Professors Dr Julian Crane and Dr Michael Baker, team members having previous probiotic research and epidemiology of ARF experience respectively .

The schools in Porirua, like our proposed schools in Whakatane have pupils 5-12yrs age, the schools are Education Decile one and two , high New Zealand Deprivation index and those most currently vulnerable Pacific and Maori in Porirua, and Maori in Whakatane.

The parallel Ministry of Health, Porirua ARF primary prevention sore throat in schools programme involving 2000 pupils has been running for 12 months prior to BLIS K12 commencing. Teachers in Porirua have been asking pupils about sore throats several times a week for a year preceding BLIS K12 introduction and the Public Health Nurses swabbing those with sore throats in school time will be constant. In the Porirua study both **whole school GAS asymptomatic carriage rates** and **GAS sore throats rates** will be compared between control and BLIS K12 classrooms. **The rate of GAS detection before and after BLIS K12 will be mainly influenced by the introduction of BLIS K12, the only major new variable.** It is a **blinded Randomized controlled trial, the Porirua trial pupils randomized by classroom to receive active BLIS K12 and placebo lozenges.**

**Our planned Whakatane study in contrast** is an open non randomised intervention study, our probiotic intervention one month in duration, with three months follow-up, with the main outcome measure GAS colonization. Over two months prior to baseline GAS rate and commencing BLIS K12 and during and following the trial children will be encouraged and parents will be informed that if they have a sore throat to see their General Practitioners or, Rapid Response ARF clinics. We will offer three core throat swabs, one prior to one month probiotic BLIS K12, another a month later on completion and a third three months after commencing. We will treat after checking allergies with GP those GAS positive throat swabs identified on the core study swabs. Our CHW swab team will ask whether the child’s throat is sore at the time .We will derive at three points both GAS carriage and GAS sore throat point prevalence.

 Using a stepped wedge design, staggered start, the first schools’ pupils will be offered the core swabs above, GAS positive treated 3-4 days later when swabs results become available for 10 days and then offered BLIS K12 for 4 weeks. During this 6 week period the third school will have their first, swab, and positives treated when the first school starts BLIS, and a further swab a second one five week later before they commence their month of BLIS. The third schools first swab will provide pre-treatment controls for the first schools, the second at the time of post BLIS K12 in the first schools will controlling for seasonal variation in GAS. Any drop in GAS colonization in the first school will be compared with any change in the third schools. The first school will be offered a further swab at 4 months to check if the BLIS K12 effect is more prolonged than 3 possibly 4 months as suggested in our Kawerau . small study (See detail Page 26)

# Context; Eastern Bay of Plenty GAS sore throat and ARF interventions

ARF primary school prevention, using ten day treatment of GAS sore throats identified, often with once daily amoxicilin prescribed,[[20](#_ENREF_20)] has been rolled out to 74% high risk EBOP pupils. Most of these schools are Education Decile one, with high Maori ethnicity rolls with homes in high residential NZ deprivation index, from census areas and TLA where most ARF cases have presented in recent years.[[12](#_ENREF_12)]

**However it has been difficult to design and resource targeted interventions for Whakatane higher risk pupils**, mainly **Maori in higher NZ Deprivation areas of Whakatane town and immediately surrounding areas, a heterogeneous community.** Community, GP and a Ngati Awa ARF awareness programme have been the main Public Health strategies for Whakatane. While identifying successful trends within the current regional school programmes indicative of possibly declining ARF needing full and longer evaluation[[30](#_ENREF_30), [59](#_ENREF_59)], and apparently rising case numbers from Whakatane, we have identifed some of the challenges planning sore throat initiatives for Whakatane schools. This proposal supports a trial for some Whakatane schools addressing Group A Streptococcal carriage. With BLIS K12 used as a universal school primary prevention tool, if effective students do not need to speak up that they have a sore throat, to be supported combating Group A Streptococcus.ie a targeted whole school “universal” preventative tool.

# ARF Primary Prevention School Programmes in Eastern Bay of Plenty with some contrasts between Opotiki, Kawerau and Whakatane TLA.

**ARF primary prevention school programmes in the EBOP** have been running in primary schools since 2009 with local Community Health Workers CHW the backbone of this work with EBPHA Rheumatic Fever Registered Nurse Clinical Lead and Evaluation personnel. These programmes began initially in 2009 from Opotiki by Te Wheke Atawhai, in Whakatohea iwi rohe, since 2010 from Kawerau EBPHA in Tuwharetoa ki Kawerau rohe, since 2011 from Murupara by Te Ika Whenua in Ngati Manawa rohe. Since 2012 Te Kaokao o Takapau, Taneatua has delivered though the northern schools of Ngai Tuhoe rohe and later through subcontracting southern rural communities including Ruatahuna Ngai Tuhoe and Minginui Ngati Whare with a subcontract to Hinepukohurangi Trust. It is important within the large Whakatane TLA to note that the Ngai Tuhoe and Ngati Manawa two projects address inland school children’s GAS sore throats but don’t address more coastal schools within Ngati Awa rohe.

From results collected, in the four programmes increased sore throat swabbing and treatment has led to declines in GAS of the order from 20% to 10% GAS in those with sore throats checked. School age Community GAS colonization rates have fallen similarly in the two areas checked Kawerau and Te Kaokao o Takapau, Ngai Tuhoe.

The CHW are local, committed, industrious, and innovative, part of a dynamic wider ARF sector group with a range of interventions and sites from Te Manu Toroa, Tauranga, Te Korowai Aroha, Rotorua, Te Tohu o te Ora o Ngati Awa NASH and those previously mentioned, who meet quarterly in school holidays and engage well with pupils, whanau, Teachers, GP practices, ARF Clinical Lead with Public Health Service Toi te Ora nursing.

Opotiki and Kawerau primary pupils often live and go to school in these same areas. Their ARF School programmes have targeted **all** schools (especially primary and early high school) in the Opotiki and with specific high school education curriculum in Kawerau TLA.

Whakatane ARF case reviews, identify children and young people who live in one area and school in an adjacent area. Sometimes their schooling is at Whakatane Primary Schools, Whakatane Intermediate, Whakatane High and Trident High and for some residence some distance, more rurally eg in Ngai Tuhoe rohe, with both home and school being a potential source of GAS. Kawerau whanau with pupils with recurrent GAS sore throats had few GAS carriers[[29](#_ENREF_29)]

In contrast this study’s Whakatane primary schools are outside ARF primary prevention school sore throat swabbing programme areas. They are within the area where Te Tohu o Te Ora o Ngati Awa, Ngati Awa Health and Social Services, NASH, holds a Rheumatic Fever promotion contract.

At Whakatane Hospital, the only and sentinel Eastern Bay hospital, referral centre for ARF, ARF admissions from the GAS school swabbing ARF areas school attendees have declined. [[48](#_ENREF_48)]. Ingram Seal while with TTO demonstrated rolling five year average ARF incidence by TLA declined in Opotiki and Kawerau TLA with high coverage schools programmes for most pupils. Such indicative trends for Opotiki and Kawerau are reassuring from a quality assurance point of view and less so for Whakatane TLA. The Ngai Tuhoe rohe ARF school based primary prevention programme from Taneatua (also covering much of Urewera and Waimana census area) lies within Whakatane TLA as does Te Ika Whenua’s school prevention programme in the southern reaches of the Whakatane TLA with local impact expected but understandably do not cover urban Whakatane or surrounds in Ngati Awa rohe. Thus improving ARF trends have been less apparent for the whole Whakatane TLA; [[30](#_ENREF_30)]. Whakatane TLA has more heterogeneous populations, GAS awareness and GP treatment interventions not reaching some at ARF risk Whakatane town and immediate surrounds school pupils as assessed by ARF presentations to Whakatane Hospital.

A trend towards slightly older diagnosed cases some early high school and later was noted and confirmed by Twitchin 2014. Caution that with small total ARF numbers, year to year fluctuations and wide confidence limits and statistical reservations Twitchin 2014, has led to further programme assessment, aggregating the results of all the BOP ARF primary prevention projects over their 3-5 years duration with comparative historical controls from the same areas and contemporaneous controls from adjacent non programme area, with the support of the Medical Officer of Health TTO Public Health service and Paediatric supervision[[59](#_ENREF_59)] (showing incidentally also early indications of ARF decline in the school programme areas compared to the Western Bay of Plenty usual treatment “control areas”.)

# ARF Primary Prevention School Programmes Nationally in New Zealand

The evidence for ARF primary prevention schools programmes South Auckland larger study,[[17](#_ENREF_17), [18](#_ENREF_18)] with tens of thousands of pupils, and meta-analysis of similar studies [[19](#_ENREF_19)] and the Ngati Hine, Helen Herbert, Whangaroa 3000 total residents [[16](#_ENREF_16)] and successful experience, supported that model. Helen Herbert from Ngati Hine visited the EBOP, assisting, raising awareness and supporting the Hauora and PHA based ARF school programmes. School programme use of intermittent whole school throat swab sweeps for GAS carriage and treatment is undergoing assessment in Auckland Lennon. School sweeps are hoped to address the limitation of asymptomatic GAS infection and children who may under-report symptoms of GAS throat infections.

These limitations of school sore throat programmes, needing self-declared sore throats was illustrated Dr Stan Schulman of American Academy of Paediatrics[[47](#_ENREF_47)] presenting to NZ National Heart Foundation at Te Awatea, Middlemore Hospital 2013. He noted that 2/3 of children with Acute rheumatic fever recollected a preceding sore throat in Baltimore USA. Thus a decline of ARF of 66% might be the best expected outcome of sore throat programmes. These concerns are well founded. In the EBOP primary prevention projects, audits confirmed several of the few children who have had ARF from these primary schools, have included children who have been less articulate; a shy girl, a special needs boy with intellectual disability and another boy with behavioural and learning problems[[60](#_ENREF_60)]. Also the finding that the small area of some three thousand population Whangaroa had no ARF cases for 8 years after a decade of 1-3 ARF cases yearly suggests other mechanisms apart from sore throat awareness may contribute to such apparent increased total programme effectiveness for some years.[[16](#_ENREF_16)] Firstly awareness may have increased as demonstrated in EBOP,[[61](#_ENREF_61)], secondly familiar local community health workers may encourage a greater proportion of those with GAS sore throats to report and thirdly possibly an effect of decreased community carriage as in EBOP may have contributed.

# ARF Primary Prevention School Programmes; BLIS K12 strategy benefit

Thus interventions which address GAS carriage if well targeted, effective and especially if also as in this study, the intervention actively colonizes throats with protective bacteria, the intervention may protect from GAS sore throats and thereby ARF; The probiotic BLIS K12 may protect both articulate self-aware pupils and the voiceless children at risk who don’t put up their hand to a sore throat question in class, from friendly well known community health workers**.**

Interventions currently impacting on Whakatane GAS and ARF

Whakatane township, itself and immediately surrounding areas are not covered by the four ARF primary prevention school programmes. Swabbing and treatment of Group A streptococcal sore throats has been the mainstay of management by General Practice and to a lesser extent Whakatane Hospital ED. . Of the Whakatane ARF cases, some have not recognised or identified preceding sore throats, **others** have retrospective recollection of sore throats but not presented with them. Te Tohu o te Ora o Ngati Awa NASH has had a local awareness programme, Toi te Ora Public Health a regional newspaper and local iwi and generic radio one and most recently the Ministry of Health a Television awareness campaign in prime time.

 Whakatane has census areas for example “West Whakatane”, “Oriini Census Area” identified as having high ARF incidence.[[12](#_ENREF_12)]. Some ARF presentations to Whakatane Hospital have been of Whakatane primary school pupils, some new residents. Others new ARF cases attend Whakatane intermediate and high schools reside in adjacent higher risk areas where their younger siblings are treated, under currently funded ARF primary prevention projects. .The Whakatane TLA includes several more affluent low risk areas too.

As previously discussed the larger Whakatane Territorial Land authority[[62](#_ENREF_62)] extends inland to Te Kaokao o Takapau run programmes from Taneatua in Ngai Tuhoe rohe. as far south as Ngati Whare rohe near Minginui and Ruatahuna within southern parts of Urewera CAU Whakatane TLA served by a subcontract from Te Kaokao o Takapau to Hinepukohurangi Trust. Te Ika Whenua Hauora based in Murupara serves Ngati Manawa rohe.

However significant awareness raising by Toi te Ora Public Health Service, EBPHA NASH, Paediatrics and other health organisations has been associated with increased **GP Practice throat swabbing six fold in the Eastern Bay**, with GP swabbing possibly well targeted with approximate a 20% GAS positivity [[61](#_ENREF_61)] [[42](#_ENREF_42)]. Whakatane thus has had GP and ED awareness raised to some extent, with increased clinical and practice management and case review feedback.

**Whanau awareness**.

For parents and GP’s there has been a practice shift towards “sore throats matter” “sore throats can damage your heart”. While acknowledging that four out of five, or nine out of ten sore throats will be viral, programmes encourage pupils and whanau to check out sore throats for the sake of both frequent GAS and serious sequelae. Nationally funded programmes on prime time TV eg the Katoa twins, also support this awareness.

In this trial, we propose to offer BLIS K 12 in three Whakatane based primary schools, which are at high ARF risk, but without such school programmes. The section “Other Whakatane schools” in Research Methods addresses the coverage limitations of this study being a trial rather than a programme which if effective might be extended

In summary Whakatane school children currently access their GP practices, and to lesser extent Whakatane Emergency Department ED for sore throats presentations. A rapid response ARF clinic is to be established in 2015 in Whakatane.

# Factors impacting on ARF as a potential outcome measure; Improved diagnostics and case ascertainment

**Echocardiography since 2006 has become standard practice in NZ ARF diagnosis;** RHD is now quantified with mild moderate and severe cardiac involvement with echo and clinical measures. Detection is expected now of the former two categories often inaudible to stethoscope assessment; Mild and moderate valve cardiac changes in structure and function in ARF and RHD are increasingly well defined NHF and international diagnostic criteria. Clinical examination alone with its higher threshold has become inadequate to exclude ARF and RHD. In 2006 NZ and Australian Echocardiographic ARF diagnostic criteria were published, have been applied in BOP, and increasingly have became embedded, [[63](#_ENREF_63)]

**Increased BOP case ascertainment and ascertainment of milder ARF cases** may now be assessed potentially by subgroup analysis of the data base prepared both for Lakes BOP ARF register loading and a North Island data base presented by Dr Te Aro Moxon and Diana Lennon at World Congress Cardiology 2014 . Such studies of ARF and RHD in NZ increasingly use the NHF criteria of clinical severity 2006 and echocardiographic measures of cardiac severity and standardized reporting format [[64](#_ENREF_64)]

**Subclinical RHD;** International RHD echocardiograph screening criteria were validated in 2012[[46](#_ENREF_46)] Echocardiographic screening studies for RHD of 3500 NZ children have been performed [[45](#_ENREF_45)] Remenyi and Wilson, the same investigators in 2010 showed that BOP echocardiographic screening predicts in high risk Maori school pupils **one undiagnosed child with RHD for each one known in a study of more than 500 local primary school children** peak age 9 years Kawerau and Ngai Tuhoe and Murupara. They identified 1; 135 Rheumatic Heart Disease on screening mainly Maori pupils from Decile 9-10.[[35](#_ENREF_35)] An HRC study of echocardiographic screening impacts is underway 2014-5 in which this team is participating.. Whakatane primary school pupils are likely to have the same findings of asymptomatic RHD.

**Echocardiography access;** Echocardiography became increasingly accessible to Whakatane patients 2013 with the doubling of Echocardiographer staffing and the establishment of twice weekly Echocardiographic clinics in Whakatane obviating the need to travel to Tauranga with improved and timely access and utilization. Future intervention studies, using these epidemiological and echocardiographic tools, will be able to identify if ARF cases identified have increasingly mild cardiac involvement RHD or not. Hence future programme efficacy, where numbers permit may be assessed by both ARF incidence and severity.

Despite local areas of improvement, **total** **BOP ARF acute incidence** is variable year to year, but stable over recent 5 year epochs. In BOP Toi Te Ora reports ARF cases are slightly older age some intermediate and early high school [[13](#_ENREF_13)]. The increasing mean age of ARF cases mean that measures and programmes reaching at least third and fourth forms high school, adapting ARF school primary prevention programmes as has occurred in Kawerau and such as Rapid response clinics proposed for Whakatane are needed and are being implemented locally and regionally.

**ARF incidence rate** continues to increase for New Zealand Maori and Pacific overall Lennon and Milne.[[2](#_ENREF_2)] A BOP audit of ARF ethnicity coding showed under reporting of Maori[[65](#_ENREF_65)] in keeping with other diseases. [[14](#_ENREF_14), [66](#_ENREF_66), [67](#_ENREF_67)] The ethnicity trends and Decile findings [[68](#_ENREF_68)] mean that our study targeting mainly Maori Education Decile 1 pupils is increasingly appropriate.

**Our study focuses on the three Whakatane primary schools with highest Maori roll. If effective a wider rollout may be possible.**

## Rationale for Bliss K12 trial site focus; 3 Whakatane primary schools.

Whakatane TLA is a significantly socially and clinically heterogeneous area with respect to GAS and ARF risk. Within Whakatane TLA for school children, there is variable ARF risk, likely significant diversity of GAS exposure, [[35](#_ENREF_35)] housing, NZ Deprivation centiles, Maori and Pakeha proportionate ethnicities at schools and a range of community ARF interventions, GP intervention and health access.

Some census areas within Whakatane town e.g. Oriini Census Area and surrounding areas have as high ARF numbers and rates as those in Opotiki and Kawerau [[12](#_ENREF_12), [13](#_ENREF_13)]. There have been no ARF cases for example over 10 years from Ohope Census area and several from Oriini Census Area, West Whakatane. The much larger Whakatane TLA includes both significantly more affluent and low risk areas as well as higher deprivation areas where more at ARF risk students live.

Whakatane town has no ARF primary prevention in school programmes hence targeted ARF strategies within this Territorial Land Authority to high risk areas, schools and pupils are appropriate, as well the usual background generic sore throats ARF health promotion and GP swab and treat approaches, to a lesser extent implemented by ED Whakatane. A Whakatane ARF rapid response clinic is soon to be established increasing school pupil rapid access.

The trial of a BLIS K12 a probiotic as a universal intervention to all the class of high risk mainly Maori pupils in three Whakatane primary schools is to be offered to pre-symptomatic pupils not currently served by a sore throat in schools strategy. The intervention does not rely on self-presentation to CHW or GP with a sore throat. It offers a preventive intervention more proximally to challenge GAS colonization and alternatively colonize children’s throats with Streptococcus salivarius.

The three primary schools to be offered this study intervention are mainly Maori, the at risk population ,with highest education challenges Education decile 1 and 2 which has a close correlation with socioeconomic challenges where they live NZ Deprivation Decile Index 9 and 10 from whence most but not all ARF cases currently emerge.[[2](#_ENREF_2), [7](#_ENREF_7), [68](#_ENREF_68)] The school areas map the NZ Dep Quintile 5.[[69](#_ENREF_69)] The numbers are sufficient for statistically meaningful results and the currently available funding, EBPHA innovation grant.

## Rationale for intervention duration; of ONE MONTH Blis K12

One month BLIS K12 has been successfully trialled in an open intervention study at the end of a ten day antibiotic course for RECURRENT **GAS sore throats in Kawerau. It was conducted WITHIN a Primary school sore throat swabbing ARF prevention programme**. It was evaluated mainly by **re-presentations with GAS sore throats, which were significantly less in the following 3-5 months, with a smaller subset confirmed GAS negative following Blis K12 treatment**. This successful trial in 2013 was by the Kawerau EBPHA ARF prevention team for a small group of children n 23 with recurrent GAS sore throats ( three to five Group A strep sore throats episodes in 4 months).[[29](#_ENREF_29)]

When BLIS K12 was taken every night immediately after a ten day antibiotic course for one month it was found to be **well tolerated, acceptable and effective** at significantly diminishing recurrence of GAS sore throats. It was more effective limiting GAS sore throat recurrence, than the previously used NZ Ministry of Health recommended antibiotic regimens alone.

Statistically there was a highly significant reduction (p<0.001) in these children’s GAS sore throats in the 3 months following, compared to three months preceeding ONE month Bliss K12. For most no GAS sore throats recurred up to five months after BLIS K12. A protocol for future GAS recurrence prevention studies has been defined in part from the recurrence patterns seen in that study. That research project aims to evaluate the regimen’s efficacy in significantly greater numbers in all four of the Eastern BOP school ARF programmes.

The Kawerau GAS recurrence trial suggests one month is sufficient to colonize a person with Streptococcus Salivarius the protective bacteria in BLIS K12. Hence this trial seeks to achieve similar GAS prevention with a short one month trial of BLIS K12. Both trials treat GAS with 10 day antibiotics when identified prior to the month of BLIS K12.

The Italian day care trial of BLIS K12 was 90% effective for the 90days taken and of the order of 60% effective protecting for the 6 months to follow. [[25](#_ENREF_25)] The Italian study duration of protection to follow the course is similar to the Kawerau study though exposure length shortened to one month.[[29](#_ENREF_29)] The current Porirua trial Crane is for 12 months BLIS K12.[[26](#_ENREF_26)]

**Why is this study innovative? How could it add value, adding to GAS knowledge?**

1. Firstly; GAS **carriage prevention is the primary outcome of this study**. We will be measuring for the first time that we are aware of, the impact on GAS colonization of all children before and, following a **one month course at the end and 3 months** after commencement. Some children had follow-up swabs in the Kawerau study after BLIS K12. They were GAS negative. (If additionally funded, a 5 month Throat swab would assist further).
2. Secondly Context ;We propose a 30 day BLIS K12 trial in whole primary schools a **primary prevention of GAS carriage intervention, outside a current school primary prevention ARF programme.** On the other hand the current HRC funded year long BLIS K12 Porirua study sits within a current school primary prevention programme with Public Health Nurse /community health worker, twice or thrice weekly school visits for sore throat swabbing**. Trialing outside a primary prevention CHW swabbing “sore throats in schools” programme, shifts swabbing from schoolroom to General Practice, both a risk of distance requiring 2 points of pupil contact at school then GP practice, and an opportunity, testing potential GP practice delivery in an era and area of increased sore throat awareness.** The design costs need evaluation but possibly this programme design lessens some programme expenditure The Whakatane school study differs in many other respects too from other studies; **The advent of accessible Rapid Response ARF clinics treating sore throats with one such clinic to be started in Whakatane in 2015 adds another dimension.**
3. **Thirdly, the duration 30 days BLIS K12 is a further very important point of difference compared to the Porirua programme of Blis K12 duration** taken for **one year that is 12 months** Both the prior three month 90 day Italian (Pierra Italy 2012) and current Porirua studies (Crane Porirua 2013-15) have focussed on the remarkable 90% protection while taking the probiotic while we have noted also the 65% GAS protection to follow in the Italian and Kawerau studies..

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1. Fourthly, we are evaluating with this one month trial a probiotic to prevent Group **A Streptococcal sore throats as a secondary outcome**. **GAS sore throat point prevalence information is gained at three points, before, after one month treatment and 3 months after commencing.** In contrast in the Kawerau GAS recurrence study we evaluated by documenting sore throat reports from twice weekly CHW school visits, and then confirmed GAS status after reviewing swab reports. Between school swabs in Whakatane, their GPs will see, swab and treat or they may be treated by the RRC the Rapid response ARF clinic.
2. **Acceptance** ;We will also in effect be evaluating **probiotic prevention acceptance, whether primary school pupils, most of whom have NOT had sore throats and their whanau, find short course BLIS K12 an appealing and useful preventive intervention**. Two short questions are proposed at the end of the BLIS course. Most of the children, (80%), will not have colonization let alone a sore throat at the point of commencing the probiotic. For these children it is hoped the probiotic with lessen the chance of colonization and infection in the months to follow. For the 20% colonized with Group A streptococcus they will be offered a 10 day course of antibiotics followed by a month of BLIS K12 to prevent suppurative complications, GAS sore throat and to limit recolonization. **This group taking probiotic pre- known infection is in marked contrast to the much smaller group of children 23 from Kawerau whose parents and community health workers were highly motivated to treat recurrent GAS symptomatic sore** throats which at the time of commencing BLIS K12 had usually had 3 and sometimes 5 symptomatic episodes in 3 months.
3. **Probiotic timing;** The parents in Kawerau GAS recurrence study administered BLIS K12 in the evening at bedtime, the most effective time for its use with possibly 10-12 hours sleep hours to establish Salivarius colonization. To achieve school wide adherence five days of BLIS K12 will be **administered towards the end of the school day** with an evening meal likely to follow with less time of exposure without competing influences. The weekend BLIS K12 will be taken home.
4. Follow-up; The GAS recurrence BLIS intervention Kawerau study had a median of 5 months follow-up but some as short as 2 months hence this study with consistent follow-up aimed at least for 3 months will be consistent and in significant numbers which if effective will increase the confidence with which this study’s findings might be generalized

**This Whakatane study proposes a one month 30 day BLIS K12 trial for children whether they have complained of a sore throat or not and whether they are colonized at that point with Group A streptococcus or not.**

**Implications for future studies**

If this shorter course of BLIS K12 ( than 12 month Porirua proposal) used in GAS primary prevention area could achieve six month GAS protection or sufficiently decrease in GAS prevalence to significantly decrease pathogenic GAS carriage and fewer GAS sore throats, it would obviate longer BLIS K12 courses, associated supervision needs and raise the possibility that 6 monthly supervised or home one month BLIS K12 from or in schools may be an effective and more easily manageable GAS and ARF primary prevention intervention perhaps taken in 2 courses March and September or February and August each year..

If effective the approach might be more generalizable than longer courses within current school models of primary prevention. If partially successful one month BLIS K12 twice a year might be combined with primary school swabbing where the costs saved for fewer throat swabs at $17 each might pay for BLIS K12 courses.

## Ethics considerations addressed include.

The authors have aimed to frame this study within the Ethical Principles for Medical Research involving Human Subjects of the World Medical Association Declaration of Helsinki, [[70](#_ENREF_70)] the NZ Health Research Council guidelines for Ethics in Health Research [[71](#_ENREF_71)]and Guidelines for Health Researchers on Health Research involving Maori [[72](#_ENREF_72)]which have been reviewed and applied. Ethics and site approval are being sought from the HDEC and BOPDHB Ethics committees

Informed consent; Parents’ and whanau consent is needed, (as well as tumuaki/ principal kaiako/ teachers Board of trustees) considering the school age of the children; Children of this age 5- 15 years, control to a considerable extent what they swallow so their age appropriate understanding and compliance is also needed. Comprehensive information is on the consent form, will be provided and discussed in the preceeding hui, meetings, principals and Board of Trustees including benefits outcomes and safety; The partnership between Te Tohu o te Ora o Ngati Awa ,NASH and EBPHA staff ensures iwi health provider Hauora and GP Practice PHA scrutiny both from proposal stage and ongoing as is reporting to funder EBPHA.. There is no personal or whanau financial gain from participating or loss from withdrawal, and withdrawal is simple and without compromise of usual care;

**Probiotic trial “equipoise”;** there is both the reasonable possibility of significant benefit / effectiveness and also sufficient uncertainty about BLIS K12 effectiveness in the primary school preventative setting for this duration, outside a primary prevention ARF school swabbing project for this proposed trial to be ethical to conduct (has equipoise).

 **Whanau and kura access to study research team** provide feedback in the event of unlikely, as yet unmet adverse reactions Sequential monitoring of throat swabs monitor benefits accurately **The probiotic has FDA GRAS status meaning generally regarded as safe** and for Kawerau school children experience is of a pleasant taste, without any problems or untoward effects in keeping with this status.[[29](#_ENREF_29)]

### Important point of information for community consultation

One major issue is that the intervention, unless later funded by Ministry of Health, is likely to be a one off intervention study .While no guarantee of availability long term, their interest in this and the longer duration Porirua study can be stated. Families will be informed of this at the outset at the time of community consultation. An extension of funding for a second course would provide data over a whole year. The hope that if effective it may be funded in the long term may be sufficient .While available OTC through pharmacies the cost appears to have historically limited widespread use.

**Further** Ethical consideration; Asymptomatic and symptomatic children with GAS will be treated lest asymptomatic GAS goes on to cause complications. Support for this approach, acknowledging the effects of subclinical infection or colonization comes from Eastern Bay school echocardiographic screening study 2010 showing one new child with RHD for each one already known.[[35](#_ENREF_35)] These children usually had no history of sore throats.[[35](#_ENREF_35)] Several children with severe RHD presenting in heart failure had no elevation of acute phase reactants nor history of preceding sore throats which means that asymptomatic ARF can be severe. [[48](#_ENREF_48)] Hence on balance not treating colonization appears currently unethical. Interventions addressing asymptomatic carriage may prevent RHD pathology.

Dissemination to whanau, Kura/ schools and community through panui and newspaper articles will be done at the end of the trial, to Te Tohu o Te Ora o Ngati Awa, NASH EBPHA including local GPs, regional BOPDHB Rheumatic Fever Steering Group and later through publications.

Data access and protection. Personal Health information throat swab results with NHI will be uploaded by the local Pathlab to the DHB personal information system, and the GP system accessed from EBPHA, GP and DHB staff access where appropriate with usual confidential safeguards where there is a clinical need to know. The research team will access the results from the Pathlab to facilitate treatment of GAS positive throat swabs.

Further more detailed discussion including ethical aspects are in the sections headed consent, safety, treatment of asymptomatic GAS found on pre study throat swabs, the selection of schools and implications for other Whakatane schools.

## Responsiveness to Maori

The study will take place in Ngati Awa rohe/ area. This proposal is a joint one between Te Tohu o te Ora o Ngati Awa, Ngati Awa Social and Health Services and EBPHA Clinical Lead ARF with Senior Nursing and Management of both organizations planning and implementing this study with Paediatric support. All partners will be actively involved in implementation analysis and write-up. The principles of partnership, participation, protection will be applied and consultation with local Kura, whanau incorporating consultation. All the partners have actively participated submitting this proposal to EBPHA innovation awards, since conception and application in the design and have ongoing roles in the governance, management, implementation process, analysis, write-up, local feedback and dissemination. The consent process discussed with schools, will be open, offer Te Reo Maori options for consent and design implementation and dissemination aspects. Data sharing limited to specific throat swab data is specified clear and safeguards for confidentiality of personal information maintained. The anonymity of personal findings will be maintained. Each Kura’s kawa, custom and practice are and will be respected. Individual and collective rights for example around consent or not and withdrawal, will be respected.

The tumuaki/ principals and kaiako/ teachers of these Kura/schools have health teams with interests in health issues of their pupils and will discuss with their boards of trustees and whanau their views on these projects.

Te Tohu o te Ora o Ngati Awa NASH, are widely respected as the provider of primary child health well child services, Family Start, contributing to Well Child forum, Otago University paediatric community medical student training as examples of their child health work with their nurses tangata whenua and embedded in this local community of Whakatane and surrounds including these Kura.

The team from EBPHA brings significant local experience from Maori community health projects and these processes. EBPHA ARF Clinical Lead Nurse supports four ARF primary prevention projects three with iwi providers Te Wheke Atawhai for Whakatohea, Te Ika Whenua in Murupara and Ngai Tuhoe provider Te Kaokao o Takapau Taneatua and with its own local team in Kawerau. The EBPHA ARF Clinical Lead Nurse also coordinates the ARF sector group of community organizations working for ARF including Toi te Ora public Health which in the Bay affects mainly Maori.

While the research does not take place on BOPDHB premises the complication of GAS sore throats especially ARF are diagnosed and treated within Whakatane Hospital, BOPDHB. BOPDHB contributes to the funding of the two lead organizations and employer of the Paediatrician. There is a close working relationship with BOPDHB Maori Health, Amohaere Tangitu, Lani Marama ,Marama Tauranga with whom we have ongoing ARF discussions and presentations. Maori Health BOP approval has been sought and given (March 2015) before BOPDHB Site Agreement, alongside this ethics application;

**RESEARCH DESIGN AND METHODS.**

### Aims To assess primarily if one Month of BLIS K12 Probiotic with Streptococcus Salivarius taken by Whakatane Primary School children prevents or limits colonization with Group A Streptococcus GAS pathogens, and secondly decreases GAS Sore throats. While the latter is more challenging logistically, we believe in Whakatane than Porirua, it is achievable with caveats. A third aim to assess if one Month of BLIS K12 Probiotic with Streptococcus Salivarius taken by Whakatane Primary School children prevents Acute Rheumatic Fever ARF is a longer term worthy goal but will not be assessable in this study duration and numbers of participating pupils (nor Porirua).

**Methodology** An open non- randomized one month Intervention study, is proposed of probotic BLIS K12 efficacy on GAS carriage in primary school children at high risk of GAS and ARF; GAS carriage will be assessed with full school throat swab sweeps for GAS. Swabs will be checked before and after the month of BLIS K12 and three months after commencing the BLIS K12 month. On pre and post BLIS K12 throat swab screening those who have a GAS positive swab, will be noted and treated with 10 day courses of appropriate antibiotics. . A stepped wedge, staggered start design approach will enable comparisons of GAS rates with contemporaneous local controls, the yet to start schools and follow one school for a further month checking duration of benefit for four months. GAS colonization rates in these schools will be compared with pre-study rates and duration of BLIS K12 effect noted.

Comparisons with adjacent areas historical rates before and after primary prevention of ARF sore throat programmes, (which use a sore throat and treat GAS approach) will also be of interest and noted. In the case of Kawerau and Ngai Tuhoe recent GAS school community rates are known from school sweeps checking for GAS prevalence.

Point prevalence of **GAS carriage, sore throats and GAS sore throats** will be available at pre BLIS K12 , one month after starting, three months after starting, that is two months later and possibly if funded an extra swab for about 200 children a further month later; Some months before and during the 4 month study, education about sore throats will occur and pupils encouraged to inform parents and to check sore throats with their family doctors and practice nurses The schools will be advised of resources available will receive panui/ notices to parents, advising to present with sore throats to their family GP practices or ARF Rapid response clinics. (ARF RRC) .The General Practices, and ARF RRC presentations of sore throats and GAS found and treated prior to and over the study period will be monitored with consent for these pupils of consenting whanau via Pathlab. The study team will consult General Practices.

On taking swabs, children will be asked if they have a sore throat and GAS findings noted. A fuller Sore Throat Assessment template was used in South Auckland studies [[73](#_ENREF_73)] and the correlation between sore throat, symptoms, additionally appearance and GAS carriage noted;

On parental whanau consenting we will ask permission to participate, children’s demographics names date of birth , family doctor GP name or name of practice and permission to follow up positive GAS findings prescription of appropriate antibiotics in conjunction with their GPs,with phone calls or visits, and refer sore throats between swabs for treatment with panui; The consent will include consent to be asked about sore throats , and BLIS tolerance and acceptability at the end of the study.

A month of BLIS K12 will be given to all consented pupils daily in the classroom and two extra tablets given on Fridays for the weekend. For those with GAS positive sore throats, BLIS K12 will be given as 10 days antibiotic treatment finishes. If BLIS K12 is given 5 days a week at school before leaving for home and the two weekend doses at home may be given at bed time. This model of school adherence will be reliable and monitored.

While Prof Tagg’s original work and subsequent product advice recommended giving at night as the child or adult goes off to sleep, after a chlorhexidine gargle we have found BlLIS K12 efficacious in Kawerau without the chlorhexidine given at night.. The Whakatane timing of dosage at school late afternoon is clearly a new variable.

While the benefits of ease of recall with blister packs is acknowledged, the cost of preparing blister packs is significant and individual containers of tablets will be issued for weekends.

General Practice Acute sore throat culture numbers and Acute GAS sore throat positivity and rates in the previous three and six months (historic controls) and three and six month following will be compared.

## Stepped wedge design; a staggered start method giving controls.

1. Separates BLIS K12 effect from GAS season variation, compares GAS rates with untreated contemporaneous control (pre treatment children before intervention in schools using BLIS K12 )
2. Provides opportunity to check for longer protection in subgroup
3. This option staggers swabbing and maybe most manageable for staffing and schools
4. It provides the opportunity for a longer follow-up duration for a subset a possible 4/12 swab Te Kura Kaupapa Maori o Te Oriini if feasible and parents, pupils and school permitted

Timetable



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**Intervention BLIS K 12 lozenges characteristics** (copied with permission Prof J Crane study with some deletions and occasional amendment for the Whakatane study[[26](#_ENREF_26)]**)**

*The probiotic is provided in the form of a rapidly dispersible flavoured lozenge that is held in the mouth and dissolves in 3-5 minutes. It has a pleasant sweet taste,* (not sour or bitter, personal experience of Whakatane team) *and comes in a variety of flavours. The sweetening agent is isomalt. There is no association of isomalt and dental caries (as there is for sucrose and glucose). Indeed S salivarius K12 is active against mouth organisms (S mutans and S sobrinus) that are associated with dental caries.*

*Additionally, isomalt has been shown to increase tooth mineralisation in short term studies and has been suggested as an addition to fluoride in toothpaste to increase tooth mineralisation.*

*The lozenges are produced commercially for national and international sale to the standards of ISO 9001:2000 requirements and will be supplied from BLIS Technologies Ltd. Each lozenge will contain 2 x 109 colony forming units of S. Salivarius K12 plus the lyoprotectant agents trehalose, lactitol and maltodextrin, which are added to enhance the stability and viability of the bacteria.*

*The lozenges may be prepared in blister pack or container (for optimal hygiene and ease of handling), labelled and provided to each classroom .The shelf life of the lozenges at <25 degrees Centigrade is certified for 2 years.*

***Safety*** *Studies have shown S Salivarius K12 to lack pathogenicity and has Generally Regarded as Safe GRAS status with the USA Federal Drug Administration, FDA. >>*

*(Generally* **Recognised as Safe status by the Federal Drug Administration, USA)**

Treatment of GAS

GAS carriage and GAS sore throats on the study swabs will be treated by Paediatrician and those between, by usual GP practice or Rapid Response ARF clinics all with reference to GP allergy history. This will apply to the four planned throat swabs and those extras from sore throats between. Those with recurrent GAS three episodes in three to four months will be offered MOH Primary Care Guideline 2012 Co-amoxy-clavulonic acid marketed often as Augmentin ten days, or equivalent if penicillin allergic, then a further course of Blis K12 for one month. Those with further GAS sore throats within a month will be offered Amoxil 10 days with Rifampicin in the last 4 days, with a further one month of BLIS K12 to follow.

### Recruitment;

School and community engagement

The **school principals have been initially consulted. The subsequent sequence will vart between schools including the principal or research team presenting to the Boards of Trustees ( as with Te Kura o Te Paroa), school Hui** for teachers, **whanau** families to discuss the proposal and implementation and modifications needed;

Te Tohu o Te Ora or Ngati Awa NASH, staff, Eastern Bay Primary Health Alliance EBPHA ARF clinical Lead and Paediatrician specified will consult and meet with Kura Hui, school meetings or after school information and enrolment sequentially or in parallel as preferred. Te Tohu o Te Ora or Ngati Awa NASH’s Nurses, kaiawhina, community health workers and public health nurses are highly respected in the three school communities as are EBPHA and Community Health Workers ARF staff who have a record of highly successful engagement with the community of Kawerau. The EBPHA Rheumatic Fever Clinical Lead Co-ordinator , meets regularly with Bay wide ARF sector at Opotiki, Murupara and Taneatua Kawerau, and full Sector Hui including Te Tohu o Te Ora or Ngati Awa NASH staff Rotorua and Tauranga ARF staff..

**Experience with consent process;** Consent processes for BLIS K12 at school will be similar to enrolment processes for acute rheumatic fever primary prevention undertaken by EBPHA in Kawerau and which EBPHA ARF Clinical Lead, has supported also in Whakatohea, Ngai Tuhoe and Murupara primary prevention. Both processes engage with whanau and involve information sharing about purpose goals and the detail, consenting for swabs, in this study also consenting for BLIS K12 lozenges, both aiming to prevent and treat Group A Streptococci in order to prevent Acute Rheumatic Fever. Pupils and parents opting out and in will be noted and wishes respected. Parents changing their mind will withdraw their pupil/ akonga or for those making a late enrolment will have their pupil enrolled up to 2 weeks into the BLIS K12 course and the timing noted.

**Community, whanau current awareness is the foundation;**

**BLIS K12 information is additional.**

Rheumatic fever awareness in the community comes from whanau experience, community newspaper and iwi radio Te Manuka Tutahi, Toi te Ora Public Health promotions and now television commercials from Ministry of Health. The Project Management Group of NASH, EBPHA and paediatrician expect to attend Hui.

**Ethical considerations and Responsiveness to Maori see p 23 and 24**

**Consent process and forms**

Written information and consent; Panui and hui in English and/or Te Reo Maori after consultation with community, will describe the project informing in clear English and Maori where appropriate and preferred, the proposed study, benefits and safety, the confidentiality of findings, how families will be informed of results, their preferred contacts and preferred GP practice, discussion of appropriate antibiotics (allergies will be discussed with whanau and GP , prior to antibiotic prescribing ), and links to own GPs if abnormal results. How to ask, how to opt out, and rejoin the study will be detailed. Baseline data for consenting children will include their names; school, parents and contacts, ethnicities and family doctor General Practice enrolled or attended.

Family Practices and ARF RRC (Rapid Response clinics ) will be consented prior to beginning the study; Antibiotic allergies will be sought prior to antibiotic prescribing with GPs

Consent will be for pre and post Bliss K 12 throat swabbing, release by Path Labs of these findings, asking tamariki, children if sore their child taking BLIS K12, receiving notices for whanau, ARF Rapid response clinics and GP if children have sore throats, and preceding and follow-up GAS swab rates and outcomes with their GP. We will ask consent from whanau for Pathlab/ GP preceding 6 month throat swabs, GAS positives and consent to access both pre 6/12 and post 6/12 swabs with GP or Pathlab.

### Quality assurance;

Partnership preparation and presentations will identify and confirm approaches most acceptable and helpful for school communities, assessments of information for parents and school in appropriate languages English, Te Reo Maori and health literacy; Quality assurance standards of swab taking will be part of Te Tohu o Te Ora o Ngati Awa, NASH and EBPHA collaboration and pre swab training . Pathlab is Telarc certified. Recurrent GAS will be documented and repeat BLIS K12 given following appropriate antibiotics as per NZ primary care guideline 2012. Feedback to schools written and by word of mouth at Hui with parental evaluation potentially noted during and at the end of BLIS K12 and feedback to schools and parents within 2-3 months of the end of BLIS month.

### Dissemination

Follow-up and dissemination of results will be possible with individual parents where appropriate, by team GPs and investigators, and school Hui and panui meetings and notices planned. The findings will be circulated to Te Tohu o Te Ora o Ngati Awa, NASH and EBPHA to schools in panui or Hui as agreed at the time of consultation and consenting. The findings will also be summarized to the parent organizations Te Tohu o Te Ora o Ngati Awa, NASH and EBPHA, the Lakes BOPDHB Rheumatic Fever Steering group, presented to Paediatrics Department Whakatane, Professors Dr Julian Crane and Michael Baker of the University of Otago. It may be appropriate to present to local conferences in NZ including PHA, Whakapiripiri HRC, NHF, PSNZ and later Lancefield International Symposium on Streptococci, in 2017. Ministry of Health has shown interest and will be kept informed. An article will be submitted to NZ Medical Journal, NZ Family Physician, Kaitiaki (NZNO Journal) Journal of Paediatric and Child Health, RACP, Australasian Journal of Public Health or others as appropriate. A summary will be included in future BLIS K12 funding and ethics applications.

A summary will be disseminated to participating parents, schools, Whakatane community, and ARF sector group of all the ARF primary prevention teams in the Bay by the Te Tohu o Te Ora o Ngati Awa, NASH and EBPHA team.

Eligibility

All the school pupils at each school of all ages and ethnicities will be eligible for enrolment. It is expected that almost 100% of the pupils potentially enrolled at Te Kura o Paroa and Te Kura Kaupapa Maori o Te Oriini are Maori and 75% at James St School; Close to 100% of the Opotiki, Kawerau and Ngai Tuhoe pupils participate in ARF primary prevention in schools programmes. We hope for similar consent rates in Whakatane schools. We will attempt to enrol pupils currently away on their return.

Exclusions

Children who have consented but are away for a few days will be offered BLIS K12 or time appropriate swabbing on their return. These pupils and new pupils will be included, their BLIS K12 duration noted if possible, lest the effect of Blis K12 is dose dependent. Those who shift to local other schools are anticipated to be few in number and will not able to be followed unless they shift to participating schools. There may be circumstances such if the Bliss trial was complete where this may not be logistically possible. Children leaving the district during the month of BLIS K12 will be excluded.

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We will discuss with parents of children with recent serious illnesses and admissions their participation. We do not anticipate problems but in the context of preceding and possibly continuing symptoms for such children discussion about participation or not with their parents will be appropriate. While it is not anticipated that we will meet such children, children with immune deficiencies and significantly immune -compromised will be excluded. Children receiving short course steroids for example for asthma will be included.

### Where project will run;

### it is proposed to offer to the following schools,

The three Whakatane area primary schools which appear the most appropriate candidate schools with whom initial enquires have been made with the principals are; Te Kura o Te Paroa to the west of Whakatane on the outskirts, Te Kura Kaupapa o Te Oriini (at Taiwhakaia out near the airport), and James Street in the western suburbs.

We will discuss with these three schools, management and whanau to seek engagement.

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Primary aged students in specific schools have been selected; the schools are of Education Decile 1 and 2 and the parent residential areas NZ deprivation index 9, 10, with full or high percentage of Maori students on their roll. The population to be directly served is 534 primary aged school students of whom 473 are identified by their parents Maori.[[74](#_ENREF_74), [75](#_ENREF_75)]

(All Whakatane school rolls were tabulated by student numbers, ages, education Decile and ethnicity of pupils, planning to enrol pupils mainly ages 5-15years as relative risk factors for Acute Rheumatic Fever which are continuous variables. The number of eligible pupils approaching 500 consented from 3 schools will be manageable with the funds allocated .and results interpretable and meaningful. Similar consent rates in the high 90% area, close to 100% have occurred with the other primary prevention of ARF local programmes

### Schools and student numbers

Most ARF cases, if not all recent ARF cases in BOP and with one exception in the last 7 years in EBOP are Maori. The schools selected for this public health project, are with significant mainly Maori rolls and Education Decile one and NZ Deprivation index 9, 10. In this area of Eastern BOP recent ARF cases imply there is currently almost an exclusively Maori ethnicity risk of rheumatic fever. There are certainly a few exceptions, so that full 10 day courses of appropriate antibiotic with once day Amoxicillin as first line, are expected for GAS pharyngitis regardless of ethnicity and Deprivation index between ages of 0-30 years .

General Practice case management of Whakatane children presenting with sore throats of all ethnicities and residential Deprivation index is likely to factor in their GAS school classroom, playground exposure and contacts e.g. with a “swab and inform if positive” approach for some and “swab and prescribe immediately” for others as the MOH Sore throat guideline 2014 advises. The Ministry of Health rapid response ARF clinic approach is likely to be similar to the latter (as has been practiced for some years with Rotorua adolescent High school clinics).

This is a study, a trial rather than a programme, trialling BLIS K12 a likely effective short new intervention which might be generalized to other areas if the outcome was significant, reproducible, and affordable.

**Other Whakatane primary schools**

We know ARF risks are relative and continuous variables, and few if any absolute. While the most intensive studies focus on the highest risk pupils, enhanced but less intensive programmes, with enhanced GP practice and high school access, may improve GP and school GAS coverage and management.

GP practice access has increasingly MOH funded access for those less than 13 years planned from July 2015 after this study begins, which may increase GP practice GAS management for example, for other Whakatane primary and intermediate school pupils. The **Rapid Response ARF clinics** treating sore throats will be close to, implemented possibly some months before free GP visits for under 13 year pupils (i.e. primary and intermediate pupils). (In Kawerau one practice offers free GP visits for patients less than 18 years of age)

Whakatane **Secondary schools;** This study with current funding does not address Whakatane Intermediate and High schools with the same Blis K12 intervention or primary prevention school based community health worker visits or clinics as elsewhere in EBOP.. GP practice / practice nurse utilization, is encouraged and increasingly responsive high school nursing with BOP **Rapid Response drop** in clinics at or nearby the EBOP high schools starting in 2015 may address those schools pupils sore throat treatment needs. Minister Tariana Turia announced such clinics for eight Auckland sites in October 2013 and further BOP ones start in 2015.

The EBPHA data analysis and linkage with Pathlab has analyzed GP throat swabbing in the recent past. It may identify if an increase in childhood throat swabbing occurs or not, within Whakatane primary practices in general, those serving these schools and the school pupils consented and at Whakatane Hospital if time permits . While GAS treatments are expected to be in the intervention trial and General Practices, numbers of children treated at Rapid response clinics will also be relevant when assessing the main points of contact utilized for GAS treatment during the course of the study. The impact on GAS will most easily be documented within the trial and to a lesser extent the impact on swabbing and treatment through the other sites.

Whakatane Hospital ARF admissions, then Toi Te Ora Public Health Service Episurv ARF notifications monitor and are a measure of the **impact of community interventions on new ARF cases and their schools of origin over time**. The MOH ARF root cause analysis process implemented locally at Whakatane Hospital, reviews process and steps leading to new ARF cases, identifying potentially avoidable steps and generates programme adaptation where indicated. The findings are fed back to Toi Te Ora Public Health Service. These processes provide potential continuing quality assurance to both the planned study and adjacent EBOP areas.

Data Management and Statistical analysis is likely to closely parallel that of EBPHA and Hauora ARF primary prevention documentation frameworks, established in four rohe, areas between 2009 and 2011.; Te Tohu o Te Ora o Ngati Awa NASH and EBPHA will adapt and design Excel sheet frameworks for documentation from parents consents of pupils and whanau data, schools names date of birth address GP practice ethnicities, BLIS K12 uptake over 4 weeks, swab results over time, post swab and three months, Te Tohu o Te Ora o Ngati Awa NASH findings when swabbing sore throats and actions taken will be documented and confidentiality maintained. The EBPHA Medtech links will track Pathlab reports

Results analysis; EBPHA collaboration with Te Tohu o Te Ora o Ngati Awa, NASH using Excel possibly Pivot data. Anonymized group data will be collated by schools then aggregated by EBPHA data analyst and Te Tohu o Te Ora o Ngati Awa, NASH,

Calculations of GAS carriage and tests of significance of change of GAS rates, will be done with Russell Ingram Seal Evaluator EBPHA and statistical colleagues;

### Analysis and sample size

Baseline and changein GAS carriage will be the main outcome statistic. It is anticipated there will be a maximum of 531 pupils. Through the stepped wedge (staggered start) design half 260 pupils intitially act as controls ( till their BLIS 12 starts) to check that the rate of fall of GAS carriage is statistically greater than seasonal or monthly variation. We will compare the change in GAS carriage of approximately 250 pupils, The half of the group the first two schools who start BLIS K12 with the third school having GAS swabs a month pre starting then their own starting swabs checked

**For the whole group of maximum 531 pupils we aim to have 85 to 95% consent (the school ARF primary prevention programmes in the EBOP achieve the latter or better. Should there be** a similar or greater than 61% -90 % drop in GAS carriage to the Italian and GAS sore throats (86 % drop in our Kawerau studies) from the initial swabs to the immediate one month swabs the result is likely to be statistically significant. Duration of GAS carriage drop will be checked for 500+ pupils at three month from BLIS onset and for 250 pupils 4 month follow up ones, and such a change would be detectable and significant,

We will note and compare the outcome GAS colonization and GAS sore throat rates to adjacent areas school pupils in Kawerau and Ngai Tuhoe. We will also compare these recent GAS colonization rates and GAS carriage changes in adjacent communities with other ARF interventions as noted.( Kawerau ASID 2015)

The use of a **stepped wedge design or staggered starts over** Term 2, 2014 will complete the BLIS K12 month for all schools but permit comparison of immediate before and after BLIS K12 GAS rates with yet to be started adjacent schools, a contemporaneous rather than historical control effectively a short term placebo but without treatment being withheld in the longer term.. The design addresses seasonal variation in GAS rate. It is also efficacious for staffing. It lengthens the duration of programme for schools to 4 months and one week.

**Consultations**; Principals School Boards and whanau will be the main local consultations. We discussed with Professors Julian Crane and Michael Baker given their BLIS K12 Porirua study our proposed open study, duration, enrolment method, goals and supported these as achievable outcome measures, Dr Nevil Pierce statistician commented on sample size as likely to be adequate to detect the likely outcomes. Professor Chris Frampton ,Biostatistician more recently suggested the stepped wedge design achieving controls within the study. Dr Jo Scott Jones GP Opotiki made suggestions after reviewing the proposal December 2014.

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### Methods of Measuring intended outcomes

## GAS carriage Positivity and other Primary Outcomes

1. **Impact of BLIS K12 on GAS carriage rates**

GAS positives over total consenting pupils, by schools, then aggregated, will be compared prior to, after one month BLIS K12 **and 2 months later that is** 3 **months and for 250 pupils 4 months after commencement; The primary outcome or impact will be the comparison of these rates.** These rates **will be compared** with the change, if any, in the control pre treatment adjacent schools, through the stepped wedge, staggered start model.

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1. **Impact of BLIS K12 on point prevalence of GAS sore throats.**

The GAS positive sore throats, per that school’s consented pupils and total GAS positive sore throats / total consented pupils provides a point prevalence of GAS sore throats and the change in GAS positivity a second outcome . While this may reflect the likely change were BLIS K12 targeted just to those with sore throats such a calculation does not acknowledge unless explicitly stated the possibility of a herd effect through protection of the asymptomatic GAS carriers also given a month of BLIS K12. Hence this measure is better described as the **Impact of BLIS K12 on point prevalence of GAS sore throats in a school GAS primary prevention project.**

1. The core four swabs are achievable within the study design and budget The addition of early swabs in school three suggested by the stepped wedge design start have been budgeted and funded too.. They establish controls and **exclude seasonal variation within the first months of the study** and let the first school outcome be compared with controls for whom no BLIS intervention has yet occurred.
2. A further swab checked one month after the last, that is 4 months after the BLIS K12 commencement for the first school Te Kura Kaupapa Maori o Te will test further **duration of benefit.**
3. (Future study designs;, In the event of two courses of BLIS K12 being available in the year, a further throat swab sweep prior to the second subsequent course would effectively be also a 5-6 month post initial course swab. i.e. A second course also provides an opportunity to measure whether there is a longer duration of effect on GAS carriage from one month BLIS K12. More likely future programme designs could be two courses of one month of BLIS K12 over the school year)

## .Secondary outcome measures and data interpretation considerations

1. From Pathlab data, a comparison of the Throat swabbed numbers from the school age population particularly 5-15 years and the GAS positives from the wider Whakatane primary practices in the six months prior to and following the study will be made if possible as a measure of wider study and public health impact on throat swab utilization..

As covered in Outcome 2 Kaiawhina, Community Health Workers at the time of the students ‘pre BLIS K12 throat swab and also when taking one and three month follow-up swabs checks will ask the students and document if tamariki children report sore or not **Sore throats;** Those swabbing throats record comments of pupils of “sore throat” “he mamae o tona korokoro”, converting to rates/ consented pupils at the time of before BLIS K12 throat swabs, and after intervals on completion of the 1 month BLIS K12 and 2 months later that is 3 months after commencement; The sore throats numbers/ consenting swabbed pupils will give a sore throat rate; In addition **Between community surveillance swabs, we propose programme staff encourage “ Sore throat reporting” to General Practice and Rapid Response Clinics at these schools.**. **It is hoped to improve GP sore throat access also alerting parents that Rapid Response clinics will be available in Whakatane too April May June 2015**. The numbers who reach GP or **ARF RRC will be noted if possible**. Intensification of school GAS sore throat promotion in high risk schools and pupils will translate we hope for most if not all into ARF RRC treatment or GP practice swabbing of these pupils in response to school notices. The publicity will we hope assist **school pupils from other schools attend GP and RRC too**.

1. We will incorporate evaluation of tolerance of the probiotic BLIS K12 at the follow-up swab after the month of Blis possibly in English and Te Reo Maori

Q How was your Probiotic ? OK Yes No

Q Any problems or comments ?

Population comparisons

1. The **GAS prevalence** identified by the throat swabbing undertaken and **GAS sore throat point prevalence** pre, one and three months after commencing BLIS K12 will be **compared with the rates in the EBOP regions ARF primary prevention school programmes** ;The impact of BLIS K12 on GAS colonization and GAS sore throat rates will be noted and compared with other known interventions for effect size. While not a formal comparison with full statistical rigour it will be indicative and of interest whether more formal comparisons are needed. The BOP is unique that both school based throat swabbing[19], General Practice GAS treatment with updated 2014 guideline and algorithm [27] approaches will at that time be in place while BLIS K12 is offered in different schools .Kawerau school sweeps showed 20% GAS baseline GAS colonization rates 2010 decreasing to close to 11% by 2013 after 3 years sore throat swabbing in schools then by 2014 after additional skin sepsis intervention 7 % [32, 45] ; Whether GAS colonization dropped by as much, similar or greater amounts in Whakatane BLIS K12 schools would be noted.
2. GP’s in the EBOP have found 20% of their sore throat swabs GAS positive..[[30](#_ENREF_30)] Primary prevention community health workers in school based ARF prevention often start with 20% sore throats swabs GAS positive initially and 10% after programmes establish; At three points in the Whakatane schools BLIS K12 study firstly prior to study, then one and 3 months later, the “GAS sore throat rate” that is the percentage GAS positive within those with sore throats which are mainly viral ( as well as GAS sore throat point prevalence within the whole school population) will be compared .

Group A strep sore throats and Acute Rheumatic Fever awareness secondary outcomes ;Surveyed outcomes

1. ARF prevention knowledge of students and caregivers pre and post interventions

This survey will be undertaken by EBPHA; 100 children and 75 caregivers surveyed per phone interviews

1. Post survey of children and caregivers includes BLIS K12 adherence and tolerance see point 7 above .

### Outcomes for possible Qualitative analysis

### Benefits for these and other schools

While this project is to be delivered in specific schools, through publicity, word of mouth, radio and community newspaper, it is intended to inform Whakatane primary and secondary schools and whanau of GAS sore throat prevention and treatment to prevent ARF. The awareness generated may increase whanau knowledge, older siblings awareness and GP practice utilization for GAS sore throats at a time of Government support for free GP access for all children under 13 years from 1 July 2015 .(Until then GP is free under 6 years). The publicity is likely to increase utilization of the Rapid Response GAS ARF clinic too to be established in 2015.

### Population benefit

The GP practices where these tamariki are enrolled will be informed of this project, anticipated awareness, potential new knowledge re local prevalence and BLIS K12 one month efficacy and targeted for education re relevant best practice, as this will benefit their wider enrolled population.

### Additional benefits; The proposed study will;

1. Complement Te Tohu o Te Ora o Ngati Awa NASH’s Sore throats promotion programme whilst distinguishing GAS community carriage and undertaking active prevention.
2. Identify Whakatane GAS community carriage which is important for **effective regional advocacy.** Linking these findings to local case numbers of ARF in recent years and awareness of local especially young people with RHD will emphasize potential prevention.
3. Support the school based providers who have children presenting with repeat GAS positive throat swabs. (The BLIS K12 research identifies that if the oral cavity is colonised by Streptococcus salivarius the risk of a GAS throat infection is significantly reduced. Parental commitment to use antibiotics can wane with GAS repeat positives. This study may provide further opportunity to offer BLIS K12 also as an additional strategy to support treatment. A proposal is being prepared to further establish the role and optimal protocol to use BLIS K12 as an antibiotic adjunct treatment for those students suffering repeat GAS episodes in other BOP areas.)
4. The knowledge gained from this study will benefit the regional and national RF prevention projects; It will clarify if one month BLIS can provide sustained benefits similar to three month and one year courses

## Additional benefits to current service provision;

Collaboration;

Within the EBOP there are ARF prevention projects school based sore throat management in Opotiki (delivered by Whakatohea Iwi and Social Health Services),Ngai Tuhoe (Te Kaokao O Takapau), Murupara (Te Ika Whenua Hauora) and Kawerau (Eastern Bay Primary Health Alliance). These projects are provided clinical leadership from EBPHA.

In this project EBPHA and Te Tohu o Te Ora o Ngati Awa NASH collaborate and a further area and its children offered a GAS intervention. This collaboration may be a model for other projects. This project complements Te Tohu o Te Ora o Ngati Awa who are contracted by BOPDHB to deliver ARF prevention health promotion to the Whakatane district schools from July 1st 2014.

### Health literacy need addressed

This project supports the development of health literacy re acute rheumatic fever (ARF) prevention through sore throat awareness, effective sore throat management pathway at school and family practice. These are whanau, Te Tohu o Te Ora o Ngati Awa GP, EBPHA, BOPDHB and MOH goals.

GAS throat carriage is anticipated to reduce using a combination of best practise antibiotic for both GAS carriage and GAS sore throats then BLIS K12 probiotic treatment. Students and whanau will become more familiar with both, especially accessing antibiotics for GAS sore throats, and the possible role for BLIS K12 probiotic. The population targeted is regarded as having the highest health needs within the Whakatane community and vulnerable to Acute Rheumatic Fever.

### Problems anticipated;

If adverse outcomes are perceived (though not anticipated) the route for discussion can include Te Tohu o Te Ora o Ngati Awa NASH and EBPHA nursing, Dr J Malcolm, Paediatrics and local GP. Dr Jo Scott Jones Opotiki GP who has contributed significantly previously is willing to assist where able and appropriate.

### Responsibility for Service delivery and Project management

NASH will deliver the study in the three schools with support from EBPHA who will provide practical support, coordination, clinical leadership and evaluation Project Management

Pareake O’Brien R/N, Tui Edwards, Maude Takarua Manager Sandra Ball R/N Melissa Bennett Russell Ingram Seal Evaluator EBPHA, Dr J Malcolm Paediatrician. BOPDHB

### Duration

The active programme in schools is likely to go from consultation and discussion to feedback over one year October 2014 to October 2015, though the intervention period at schools from first swab to last will be four months one week, April 2015 to August 2015.

### Team track record

**Sandra Ball R/N** works part-time as a District Nurse in Opotiki and also provides clinical leadership for the EBOP ARF School based Primary Prevention projects.

She began this mahi in 2008 whilst undertaking post graduate nursing studies, spurred by Toi Te Ora Public Health Sevice registrar Dr Belinda’s Loring’s report on the incidence of ARF in the BOP and Lakes districts. Her awareness of the full implications of ARF resulted in her advocating with the local PHO to take an active stance against ARF in the Opotiki community. This led to her employment by the Maori PHO Te Ao Hou representing Whakatohea, Ngai Tai, Ngai Tuhoe and Whanau a Apanui; initially researching and submitting a successful proposal to the BOPDHB funding and planning unit (for a school –based sore throat swabbing pilot to be delivered in the Opotiki district) creating forums for the community and Public Health discussions that preceded these projects. She subsequently supported the project into the Kawerau community in 2010, 2011 Ngai Tuhoe and Murupara and 2013 Ruatahuna.

Since 2010 she has been funded by the BODHB via EBPHA to provide clinical leadership to the four ARF primary prevention projects based at Opotiki (Whakatohea Iwi and Social Health Services), Kawerau (Eastern Bay Primary Health Alliance), Taneatua for Ngai Tuhoe rohe (Te Kaokao o Takapau) and Murupara (Te Ika Whenua Hauora). All ARF prevention projects and their staff across the Bay have had her support alongside Toi Te Ora Public Health including Lindsay Lowe RF and Infectious Disease nurse, DHB and Iwi providers.

She liaised initially with Helen Herbert (Ngati Hine Health Trust), Professor Diana Lennon, RN Lizzie Farrell and Dr Jo Scott-Jones (Opotiki GP and recent President of Rural GP network) to explore programme design and implementation. She worked with BOPDHB Funding and Planning to facilitate and co-ordinate the monitoring of these programmes and with Ministry of Health to help build an EBOP ARF prevention profile. She has worked effectively with GPs across the EBOP to establish and maintain relationships in order to support best practice including co-ordinating specific CME sessions.

Sandra led the Whakatohea and Te Kaokao o Takapau CHW to play a practical part assisting the Echocardiographic screening research led by Dr Nigel Wilson (including the pre-programme Kawerau GAS prevalence studies 2010). Other research activities advocated for and facilitated have been the Kawerau GAS prevalence full school role swabbing 2013 (post three years of ARF prevention programme) and 2014 (post skin sepsis intervention). This data gathered has informed part of HRC funded study lead by Prof Diana Lennon regarding the impacts of GAS sore throat treatment and most recently skin sepsis programmes on GAS throat prevalence presented at ASID 2015 in poster form.

Sandra submitted an abstract on the impact on the Kawerau ARF primary prevention sore throat swabbing in schools and more recently skin sepsis interventions on GAS rates to the BOPDHB Clinical Research Awards 2014 and most recently she and EBPHA authors have distributed a full report on the skin sepsis interventions.. The EBPHA Kawerau team with J Malcolm were finalists with BLIS K12 for recurrent GAS in Kawerau ARF primary prevention project . Sandra also contributes actively to the Lakes BOPDHB Rheumatic Fever Steering Group.

**Pareake O’Brien RGON, MN**

Pare is currently a Nurse Practitioner in training, delivering a community based Kaupapa Maori Primary Health Care service within a whanau ora framework. The service has a focus on chronic care, children at risk and has a population base across the lifespan. Pare affiliates to Ngati Awa, Ngati Porou and Te Arawa iwi. She has a passion for Maori Health, whanau ora and the development of the Maori nurses.

Following a distinguished nursing career as a senior nurse at Whakatane Hospital she joined Te Tohu O Te Ora O Ngati Awa in 2008 to develop and lead the Kaupapa Maori Nurse Led community service. She provides clinical leadership to the organisation supervises the nursing contracts and oversees a number of community initiatives.

Pare has completed her Master of Nursing qualification and has a keen interest in supporting workforce development. She mentors and leads student placement’s within Te Tohu O Te Ora O Ngati Awa including the community paediatric student sites visits from University of Otago Wellington Clinical School, Waiariki Polytech nursing school and the Rural Immersion programme for all health and allied health students BOPDHB. She also provides clinical supervision to senior nurses from within the primary health care community at a local and regional level.

She has consultative roles with a number of health and community organisations. Pare is a member of the clinical advisory group to the Eastern Bay Primary Health Alliance, EBPHA. She sits as a member of the Clinical Board BOPDHB. She is a member of the advisory board to the Bachelor of Health Science (Maori) nursing at Awanuiarangi and she contributes to the Lakes & BOP DHB Rheumatic Fever Steering Group. She contributes and affiliates to local and regional nurses forums including the respiratory nurses forum, diabetes nurses forum, paediatric nurses forum, nurse practitioners forum BOPDHB, Ukaipo breast feeding coalition, NGO national forum and the Maori Providers forum for the BOPDHB.

Pare has professional affiliations to the New Zealand Nurses Organisation, College of Primary Health Care Nurses, Te Kaunihera o Nga Neehi Maori, and Te Runanga o Aotearoa.

**Melissa Bennett**

Melissa Bennett has worked for four years with Liisa Wana, and Sandra Ball with the Kawerau schools ARF primary prevention school sore throat swabbing programme visiting the schools of Kawerau, Te Teko and Te Mahoe on twice weekly basis checking those with sore throats providing education about sore throats and ARF in age appropriate formats to primary and secondary schools. The Kawerau team documented community GAS carriage since 2010,adding a programme for Kiri Ora skin health in 2014 which was presented at ASID 2015 showing significantly decreased GAS with each step of the programme. She and Michelle Godfery and Lisa Wana, adapted ARF education programme for high schools. Melissa has developed skills in graphic design of information education packages and data entry which will be used for this programme, Melissa took part in the Kawerau teams work and presentation in BOP ARF sectors presentation to PHA 2013, Maori Public Health Otago Summer School seminar Wellington 2015 and the successful work using BLIS K12 in the prevention of GAS recurrences to the BOPDHB Clinical Research awards 2014.

**Tui Edwards MPH**

Tui Edwards graduated 2014 with Masters in Public Health, first class honours, from Auckland University of Technology and is currently contracted part-time by Te Tohu o te Ora o Ngati Awa to assist with co-ordination and implementation of this study, working along side Pare O’Brien, Sandra Ball, Dr Malcolm and Melissa Bennett. Tuis MPH thesis is titled, Ūkaipōtanga:A Grounded Theory on Optimising Breastfeeding for Māori Women and their Whānau.

Tui affiliates to Whakatohea, Ngati Awa, Ngai Tai, Nga Puhi, and Ngati Kahungungu. She has worked for more than 13 years in the health sector, commencing as a Health Promoter with Toi Te Ora Public Health, then returning to her community to work within Kaupapa Māori organisations. Her key strengths are in coordinating projects, and has been involved in organising many regional and local projects and events. She has also held positions on national and regional committee’s, including NZ Injury Prevention Committee, and is currently a member of the EBOP Ukaipo Committee (which she helped form and coordinate), and the communities site 2 Representative on the Kopeopeo Canal Remedial Community Liaison Committee.

**Maude Takarua** as Manager Te Tohu o Te Ora o Ngati Awa NASH administers and leads Well Child Tamariki Ora and the more intensive Family Start programmes amongst many contracts, some which go beyond Ngati Awa rohe itself.

**Russell Ingram-Seal**: Russell has worked within the BOP Rheumatic Fever Prevention Project for over 10 years as a researcher evaluator with Toi Te Ora Public Health Service and now with the EBPHA in the EBOP. He brings qualitative and quantitative research skills to the project and supports many organisations in the analysis and interpretation of information i.e. ARF prevalence and GAS rates. He lends evaluative expertise to all of the ARF programmes in the EBOP. He has worked closely with Sandra Ball, John Malcolm and James Beharry on an all age study on the impact of RHD in the Bay of Plenty 2005-9 presented to PSNZ 2011 and part of the PHA presentation 2013. He has created population data frameworks for the analysis of ARF and recently assisted James Scarfe Statistician TTO and Liam Walsh on ARF 2000-2014 in BOPDHB (like James Beharry a Summer Medical student).

**John Malcolm** is a Whakatane Paediatrician with secondary care ARF and RHD responsibilities and relationships including opportunities to collaborate and support ARF projects with Maori providers and communities. In Echocardiographic studies of undiagnosed RHD 2010 led by Dr Nigel Wilson and Dr Bo Remenyi he collaborated with Hauora PHO,in Kawerau Ngai Tuhoe and Ngati Manawa communities; Dr Malcolm followed up those diagnosed and is regional BOP investigator for Dr Wilsons HRC partnership funded echocardiographic follow-up study. Dr Malcolm contributed to preceding Community consultation with Kawerau community PHO, Noske Skog (News print mill owner in Kawerau) and with Te Kaokao o Takapau, Ngai Tuhoe rohe and Te Ao Hou PHO, who funded the Ngai Tuhoe arm. GAS prevalence was studied in the Kawerau community initiative of Lyn Hartley and colleagues. While Dr Malcolm has been nominated BOP investigator of GAS prevalence follow-up study (recipient of HRC Partnership funding led by Prof Diana Lennon) much planning and swabbing has been coordinated by Sandra Ball and her EBPHA ARF prevention team. He collaborated with Professor Diana Lennon and Te Aro Moxon in a detailed North Island ARF data base [[64](#_ENREF_64)]The impact of Rheumatic Heart Disease in EBOP, an all age study of morbidity and mortality of ARF and RHD in the Eastern Bay 2005-9 with a FHMS summer student James Beharry and Russell Ingram Seal was presented in poster format to Paediatric Society NZ PSNZ. Both this and the previous echocardiographic screening study were presented at BOPDHB Clinical research awards 2010, 2012 with Lyn Hartley Kawerau and Hana Harawira Te Kaokao o Takapau and at PHA Ngaruawahia 2010. He contributed to provisions for improved clinical follow-up in BOP Lakes proposed ARF register, detailed case reviews, ARF register preparation with Dr Lisiate Ulufonua and R/N Lindsay Lowe TTO and to the BOP ARF 2013-17 Strategic plan. “Tautoko Rheumatic Hearts” a presentation, with Sandra Ball, Sunshine Biddle, Liisa Wana, Melissa Bennett, and Jaqueline Godfery to Public Health Association 2013 summarized primary, secondary and tertiary prevention and outlined challenges for affected communities’ health sectors including Public Health published online by PHA Taranaki conference proceedings. A poster of Audits for Quality improvement in ARF and RHD for areas without ARF registers to RACP Congress 2014 summarized audits over seven years using DNS Benzathine Penicillin, Bicillin and clinic notes as the database as quality improvement tool for diagnostic improvement, Bicillin analgesia, Clinical care and follow-up. Many of the insights of these audits are through collaboration with members of the District Nursing Service who administer Benzathine Penicillin secondary prophylaxis IM for those who have had ARF. Dr Malcolm has supported the ARF primary prevention projects speaking at the launch of the Te Ika Whenua, Murupara and Te Kaokao o Takapau Ngai Tuhoe Ruatoki projects alongside in the latter case local speakers, Professor Diana Lennon, Helen Herbert and Sandra Ball.; He suggested study design and presented Kawerau Blis findings for recurrent GAS with Sandra Ball and EBPHA team finalists at the 2014 BOPDHB Clinical Research awards. He supported the 5th year celebration of the Whakatohea schools ARF prevention project. Dr Malcolm works closely ensuring appropriate clinical follow-up for children and young adults with RHD needing Cardiology and medical and DNS follow-up the latter for Benzathine Penicillin Bicillin for secondary prevention of ARF. He has worked with DNS including Pamela Barke Nurse leader, Heather Thomas and Sandra Ball, on improving analgesia. Summer student projects for 2014-5 with Liam Walsh include reviews of ARF ethnicity coding, ARF primary prevention project impact and Bicillin analgesia preferences and utilization, the latter with Pamela Barke DNS Clinical Leader also one of the two BOPDHB Rheumatic Fever Champions. He is an active member of the Lakes BOPDHB ARF Steering Group after MBCHB Otago, completing post graduate qualifications including DTMH, DCH, PGCert Maori Studies Waikato, PGCert Public Health Auckland, MRCP UK and FRACP.

Schedule

|  |  |  |
| --- | --- | --- |
| **Milestone Name/** ***Reporting update***  | **Planned Completion Date**  | **How will this milestone be verified?**  |
|  Ethics research approval promotion  |  Submitted Jan 2015Likely March 2015  | Written feedback to EBPHA/Ngati Awa mgmt.Dr J Malcolm ethics approved , proceed or re-work/ re-submit. |
| ***Reporting***  |  | The ethics document has been written and submitted by Dr John Malcolm.  |
| Plan evaluation | Draft complete Attached  | Plan to EBPHA and Ngati Awa mgmt.Evaluator /Rheumatic Fever Clinical lead (RFCL)Evaluation plan draft complete submitted  |
| ***Reporting***  |  | Evaluation plan complete (attached)EBPHA |
| GP /GPPN engagement  | Feb 2015 | Plan to Yvonne Boyes EBPHA Dr J Malcolm / RFCLCME/NE session coordinated  |
| ***Reporting***  |  | WPMS session yet to be booked for 2015  |
| School leadership engagement  | Nov/Dec/Feb 2014-15 | 3 schools to be engaged Te kura o Te Paroa, Te Kura o Te Orini, James St Primary  |
| ***Reporting***  |  | Principals of the three schools have been consulted, BOT/whanau consultation to occur Feb. |
| Reporting to funder/management  | Jan 10 2015 | RFCL develop/complete reporting template in conjunction with funder requirements |
| ***Reporting***  | Jan 22 2015 | Filed S. Ball RFCL |
| ***Completed To date*** |  |  |
| Pre-knowledge survey  | Feb 2014 | Survey due Surveyed 75-100 (tamariki/ caregiver) data to evaluator RFCL |
| Consenting 85-100%  | Feb Mar 2015 |  Feedback due EBPHA/NA. 85-100% (children consented /data to evaluator) EBPHA |
| Pre-swab and treat positive GAS  | Feb-Mar 2015 (check following dates with Dr M) |  All consented children throat swabbed and positive GAS identified and GAS treated , data to evaluator EBPHA |
| BLIS K12 delivered  | Mar-April 2015 |  Feedback due NASH/ EBPHA All consented children commenced on 30 day BlisK12, data to evaluator  |
| Post BLIS K12 throat swab /treat  | April 2015 | Feedback due NA/ EBPHA CHW All children swabbed and those positive GAS treated per best practice , data to evaluator  |
| Positive GAS BLIS K12 |  |  Feedback due NASH / EBPHA CHWAll positive GAS children get Blis K12 post GAS positive , data to evaluator  |
| Reporting to funder /management |  | RFCL |
| 3&4 month post initial BlisK12 throat swab Extra swab round detail to be confirmed | July-Aug 2015 |  Feedback due NASH/EBPHA CHWAll children swabbed and those positive GAS treated per best practice, data to evaluator  |
| Positive GAS throat Treat antibioticsBlis K12 delivered to these children | June/July 2015  |  Feedback due NASH/ EBPHA CHW Those positive GAS treated per best practice , and Blis K12 provided data to evaluator |
| Post Knowledge survey  | July 2015 | Survey undertaken RFCLSurveyed 75-100 (tamariki/whanau ), data to evaluator  |
| Reporting to funder/management  |  | RFCL |
| Evaluation  | Aug –Sept 2015  | Written by Evaluator / review Dr J Malcolm Evaluation completed/submitted to mgmt. |

**BLIS study Whakatane 2015; throat swabbing regime/timetable /estimate of throat swab numbers due.** (Roll = Education Counts data 1 July 2014)

School: **Te Kura Kaupapa Maori o Te Orini ki Ngati Awa** Roll: 31

|  |  |  |
| --- | --- | --- |
| Swab regime | Dates to be confirmed | No. of throat swabs taken  |
| One month prior BLIS |  | 31 |
| Immediately prior BLIS |  | 31 |
| Immediately post BLIS |  | 31 |
| Three months post BLIS |  | 31 |
|  |  | Total swabs taken124 |

School: **James Street Primary** Roll: 251

|  |  |  |
| --- | --- | --- |
| Swab regime | Dates tbc |  Throat swabs taken  |
| One month prior BLIS |  | 251 |
| Immediately prior BLIS |  | 251 |
| Immediately post BLIS |  | 251 |
| Three months post BLIS |  | 251 |
|  |  | Total swabs taken1004 |

School: **Te Kura o Te Paroa** Roll: 249

|  |  |  |
| --- | --- | --- |
| Swab regime | Dates tbc |  Throat swabs taken  |
| Immediately prior BLIS |  | 249 |
| Immediately post BLIS |  | 249 |
| Three months post BLIS |  | 249 |
| Four months post BLIS |  | 249 |
|  |  | Total swabs taken996 |

**Budget**

|  |  |  |
| --- | --- | --- |
| **Item**  | **Basis of calculation**  | **Amount** excluding GST  |
| ***Establishment / One off costs***  |  |
| [name of expense item]  | [summarise how the amount was calculated, e.g. 0.5 FTE @ $xxx pa]   |   |
| GP, GPPN/ Principal/school Promotion  |  CME /CNE event $1,500-00School promotions $1,500-00 |  3000-00 |
| Laboratory cost 4 x 3 full school throat swab | Total 2124 swabs @ $ 15-00 | 31860-00 |
| BLIS K12  | 531 one month/30 tablet courses @ $7-50 | 3982-50 |
| Antibiotic estimated 15% GAS positivity over the four full school swabs swabs  | 319 antibiotic courses @$10-00 per course  | 3190-00 |
| *Subtotal*  | **42032-50** |
| ***Personnel costs***  |  |
| NASH CHW | 80 hours per month @$30-00 per hr x 6 months  |  14400-00 |
| EBPHA CL/ coordinator  | 16 hours per month @ 35-00 per hr x 6 months  |  3360-00 |
| EBPHA Evaluator  | 80 hours total @40-00 per hour  |  3600-00 |
| *Subtotal*  | **21360-00** |
| ***Administration costs***  |  |
|  Printing and stationary  |   |  2000-00 |
|   |   |   |
|   |   |   |
| *Subtotal*  |  **2000-00** |
| ***Travel related costs***  |  |
|  nil |   |   |
|   |   |   |
|   |   |   |
| *Subtotal*  |  nil |
| ***Overheads***  |  |
|  Met by each organisations related contract that will benefit  |   |   |
|   |   |   |
|   |   |   |
| *Subtotal*  |  nil |
| ***Other***  |  |
|   |   |  |
|  Management proportion | Contributed EBPHA |  nil |
|  Contributed funds EBPHA CHIFS fund  |   |  56025-00 |
| Contributed funds JM CME/CPD needed for 4th round of throat swabs ( $ 9367 and 633 for skin sepsis information/ packs for schools) | 10,000 |
|  **TOTAL** excluding GST  | 66,025-00 |

Glossary the meanings noted here are not exhaustive e.g. Akonga; Pupil

BLIS K12: Strep Salivarius with Bacteriocin like inhibitory substance marketed as BLIS K12

Episurv; the IT notification tool by which Medical Officers of Health within DHB notify notifiable diseases to the Ministry of Health.

Hauora: Maori health provider, often contracted to local region’s District Health Board

Hui; Meeting gathering with Maori kaupapa or protocol

Iwi; n. Tribe, a. tribal affiliation

Kaiako; school teacher

Kaiawhina; support staff, in this context Community health workers

Kaitiaki: guardian; in this context the journal of the NZ Nurses Organization

Kaupapa; protocol in context of Kura Kaupapa Maori school following Maori ways of teaching in Te Reo Maori

Kawa; Maori customary practice

Mamae o tona korokoro; pain/ soreness in his her throat

Maori: Indigenous people of New Zealand

Pakeha: non indigenous people of New Zealand usually applied to New Zealand European

Pacific; New Zealand people from Te Moana nui a Kiwa, the Pacific Ocean

Panui; a notice often an official one e.g. sent home from school

Pathlab: The sole contracted provider of pathology services to the BOPDHB

Porirua; a city west of central Wellington, part of greater Whanganui a Tara Wellington city

Probiotic; food product acting as a vehicle for safe bacteria taken for health benefits.

Rohe; area, in this context tribal area

Tamariki: children

Te Reo Maori; Maori Language

Tumuaki; School Principals

Whakapiripiri; Maori Health Hui of the Health Research council of New Zealand

Whanau; extended family

Whakatane largest town in Eastern Bay of Plenty others including Kawerau, Opotiki

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