A trial of an oral probiotic (*S.salivarius*) to reduce GAS pharyngitis in at risk children

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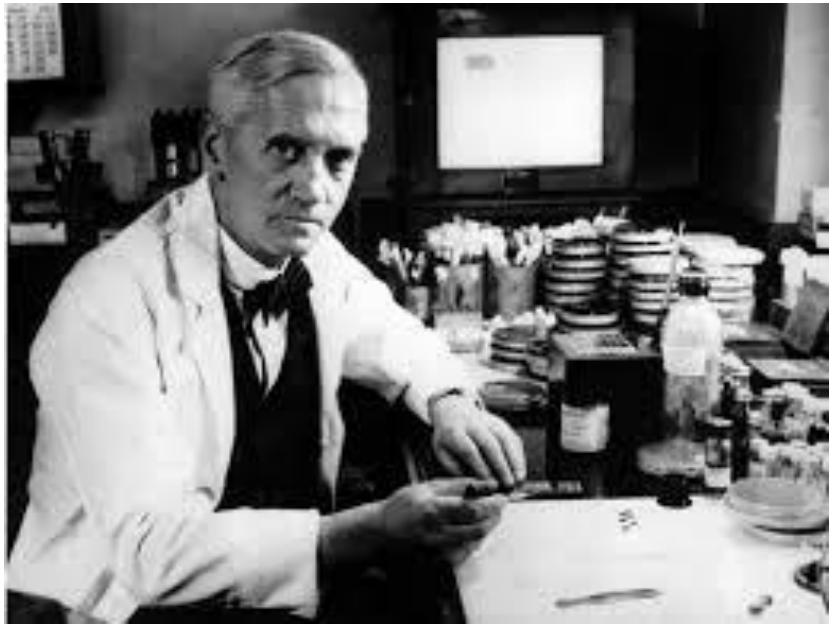
Funded by a partnership – HRC; Cure Kids; Heart Foundation; MoH
S.Salivarius provided by BLIS technologies Ltd (Gratis)

A trial of an oral probiotic to reduce GAS pharyngitis in children

- Probiotic
- Setting
- Methods
- Results

BLIS Bacteriocin-like Inhibitory Substances

10^8cfu *S. salivarius* K 12, isomalt, flavouring



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Enocin: An Antibiotic Produced by *Streptococcus salivarius* That May Contribute to Protection Against Infections Due to Group A Streptococci

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Clinical studies have indicated that certain constituents of the normal throat flora may play a role in resistance to group A streptococcal infections. Strains of *Streptococcus salivarius* were among the most active components of this protective flora. The present studies were designed to determine the mechanism responsible for the antagonism of group A streptococci by *S. salivarius*. Cell-free filtrates made at the end of the logarithmic growth phase of *S. salivarius* inhibited the growth of group A streptococci. The only other organisms susceptible to inhibition by these filtrates were those that require exogenous pantothenate, as group A streptococci do. The activity of filtrates was primarily bacteriostatic and could be specifically reversed by pantothenate. Activity was not due to a simple depletion of the vitamin but rather to the presence of a substance that interfered with the utilization of pantothenate. This substance, given the name enocin, was heat labile but was unaffected by proteolytic enzymes. Thus, strains of *S. salivarius* that appear to enhance the resistance of certain individuals to streptococcal infection may exert their protective effect through in situ production of the antibiotic enocin.

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ORIGINAL RESEARCH

Preliminary pediatric clinical evaluation of the oral probiotic *Streptococcus salivarius* K12 in preventing recurrent pharyngitis and/or tonsillitis caused by *Streptococcus pyogenes* and recurrent acute otitis media

Table 2 Episodes of streptococcal oral pathology during 90 days of treatment with BLIS K12 in children (n = 41) with recurrent streptococcal pharyngitis and/or tonsillitis

	Pharyngitis/ tonsillitis in the previous year	**Pharyngitis/ tonsillitis during BLIS K12**
Number of episodes	152 (1 year)	3 (90 days)
Incidence/month/child	0.309	0.024*
Delta (%)		–92.2

Notes: *$P < 0.0001$ considering 152 episodes and $P < 0.01$ considering 38 episodes (152/4).

Abbreviation: BLIS, bacteriocin-like inhibitory substance.

RCT BLIS in children enrolled in MoH Rh Fever prevention program

- MoH RFPP program
- ~2000 5-13 yr old children enrolled in Ministry program of swabbing and treatment in East Porirua
  - 12 schools in East Porirua
  - Commenced 2012
  - Self reported sore throat
    - Throat swab (twice weekly)
    - If positive for GAS 10 days Amoxicillin
  - Children away sick or during holidays – see GP or attend A/E

RCT BLIS

- Pragmatic trial (Daily Rx during term time only)
- 11/12 schools agreed to participate (decile 1-3)
- Consent from parents/caregivers through schools
- Children pseudo-randomised by birthdate (odd or even dates) High classroom and school mobility
- Two sets of swabs (combined throat and tongue) from all children for pre and post microbiology (qPCR)
- Daily witnessed administration of BLIS or placebo lozenges in school by school staff for 1 school year.
- Daily record of lozenge administration

Study Population

Ethnicity		Gender		Age	
Maori	492 **(36.7%)**	Male	661 **(49.3%)**	<=6	349 **(26%)**
Pasifika	780 **(58.2%)**	Female	679 **(50.7%)**	7-9	541 **(40.4%)**
NZ European	82 **(6.1%)**			>=10	450 **(33.6%)**
Others	89 **(6.6 %)**				
Total			1340		

Results

ITT	Negative	Positive GAS	% pos
BLIS	1406	119	7.8
PLACEBO	1278	124	8.8

P=0.34

11.4% reduction

≥3 lozenges in last 7/7	Negative	Positive GAS	% pos
BLIS	1052	81	7.1
PLACEBO	964	93	8.7

P=0.18

18.4% reduction

Results by ethnicity

	Maori	Pacific	Samoan	Asian	MELAA	NZE or European
Total ITT	1020	1866	1075	94	40	253
BLIS/Placebo	537/483	967/899	521/554	40/54	20/20	167/86
BLIS GAS +	50 **(9.3%)**	74 **(7.6%)**	46 **(8.8%)**	4 **(10.0%)**	2 **(10.0%)**	19 **(11.4%)**
Placebo GAS +	44 **(9.1%)**	83 **(9.2%)**	45 **(8.1%)**	4 **(7.4%)**	1 **(5.0%)**	13 **(15.2%)**
P value	0.99	0.25	0.75	0.94#	1#	0.52
≥3 lozenges in last 7/7	776	1367	778	75	28	202
BLIS/Placebo	409/367	702/665	366/412	29/46	13/15	132/70
BLIS *GAS+	38 **(9.3%)**	48 **(6.8%)**	31 **(8.4%)**	2 **(6.8%)**	1 **(7.7%)**	12 **(9.0%)**
Placebo *GAS+	34 **(9.2%)**	59 **(8.8%)**	33 **(8%)**	4 **(8.6%)**	1 **(6.7%)**	12 **(17.1%)**
P Value	1	0.19	0.92	1#	1#	0.15

Provenance of the swabs

		Negative	Gas Positive	P value
Keneperu	Blis	31	2	0.13#
14.8% GAS+ve	Placebo	38	10	
Med centres	Blis	197	40	0.96
17.1%	Placebo	165	35	
School swabs (ITT)	Blis	1178	77	0.53
6.5%	Placebo	1075	79	

Compliance

- 1314 children receiving regular lozenges
- 209 treatment days available
- 116 (2-190) mean lozenges/child
- 72% of available days
- 38% of total days

Why has BLIS failed to reduce GAS +ve swabs in this setting?

- Given in conjunction with broad spectrum Abs
- Baseline GAS positivity low (7-8% for children reporting a sore throat at school).
  - True clinical GAS pharyngitis – uncommon
  - +ve swabs = carriers?
  - Effect of Ab's?
- 2.5 years into program with regular Abs for positive swabs
- Daily at school (72% or 38%) not frequent enough exposure
- Prior antiseptics?
- Time of day, dissolves in the mouth; with or without food?
- 10^8 cfu's not enough?
- ?

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Provenance of the swabs

		Negative	Gas Positive	P value
Keneperu (ITT)	Blis	31	2	0.13#
14.8%(GAS +ve)	Placebo	38	10	
Keneperu*	Blis	20	1	0.25#
13.3%	Placebo	19	5	
Med centre (ITT)	Blis	197	40	0.96
17.1%	Placebo	165	35	
Med centre*	Blis	130	26	0.55
18.1%	Placebo	95	24	
School swabs (ITT)	Blis	1178	77	0.53
6.5%	Placebo	1075	79	
School swabs*	Blis	902	54	0.27
6.3%	Placebo	850	64	