Otitis media among high-risk populations: can probiotics inhibit *Streptococcus pneumoniae* colonisation and the risk of disease?

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Abstract

Otitis media is the second most common infection in children and the leading cause for seeking medical advice. Indigenous populations such as the Inuits, Indigenous Australians and American Indians have a very high prevalence of otitis media and are considered high-risk populations. *Streptococcus pneumoniae*, one of the three main bacterial causes of otitis media, colonises the nasopharynx prior to disease development. In high-risk populations, early acquisition of high bacterial loads increases the prevalence of otitis media. In these settings, current treatment strategies are insufficient. Vaccination is effective against invasive pneumococcal infection but has a limited impact on otitis media. Decreasing the bacterial loads of otitis media pathogens and/or colonising the nasopharynx with beneficial bacteria may reduce the prevalence of otitis media. Probiotics are live microorganisms that offer health benefits by modulating the microbial community and enhancing host immunity. Available data suggests that probiotics may be beneficial in otitis media. This review discusses the potential use of probiotics to reduce pathogen colonisation and decrease the prevalence of otitis media, providing justification for further investigation.

Keywords

Otitis media, probiotics, pneumococcal colonisation, nasopharynx, alpha-hemolytic, prevention

Otitis media

Otitis media (OM) is the second most common childhood infection [1-3] and the leading cause for which children seek medical advice, both in developed and developing countries [1, 4, 5]. Children less than three years of age have a high prevalence of OM with peak incidence occurring around one year of age [1, 5, 6]. Children under two years of age with six or more episodes of acute otitis media (AOM) are termed otitis prone [1]. Though the prevalence of otitis media varies considerably between different population groups, the Indigenous Australians, Inuits and American Indians have a high prevalence of otitis media [1, 7-9] and are considered high-risk populations.

The burden of OM in Indigenous Australians: Epidemiological studies demonstrate a significant burden of chronic OM in different Indigenous populations [8, 10]. Australian Indigenous children are particularly susceptible to OM and have a prevalence that is amongst the highest in the world. In a systematic review of the burden of OM which included over 250,000 children from 108 studies, Gunasekara et al. concluded that the highest prevalence of the disease and its associated complications is seen in Australian Indigenous children, citing that 84% of these children had OM and 23% also suffered hearing impairment [9]. Morris et al. assessed the middle ear status of children in 29 remote Aboriginal communities and found that 50% of children between 6 to 30 months had suppurative ear disease and 25% had perforated tympanic membranes [11]. According to the World Health Organization (WHO), a prevalence of more than 4% of chronic OM in a defined population of children indicates a massive public health problem requiring urgent attention [12].

Pathogenesis and clinical course of OM: The interaction between bacteria, viruses and the host immune response play a role in the pathogenesis of AOM [1, 13]. AOM is usually initiated by respiratory viruses, and can be complicated by bacterial infection which worsens the clinical outcome [14]. *Streptococcus pneumoniae* (the pneumococcus), *Haemophilus influenzae* and *Moraxella catarrhalis* are the main causative bacteria for AOM [1, 2, 15-21]. These pathogenic bacteria colonise the nasopharynx prior to the development of OM [15, 21-23]. As such, children may be asymptomatic carriers of such pathogens, or may develop infections such as suppurative OM [15, 22, 23]. There are several factors that contribute to the complex process of disease development. Under normal conditions, the low density of bacterial colonisation in the nasopharynx may initiate a host response that regulates the inflammatory process and eradicates these bacteria without causing mucosal damage [12, 21, 24]. In contrast, high bacterial loads in the nasopharynx compounded by early exposure to OM pathogens can cause repeated inflammation, mucosal damage and persistence of infection [21, 24] (Figure 1).

Increased pathogen loads in the nasopharynx are linked to an increased risk of upper respiratory tract infections, including OM [15, 25]. Smith-Vaughan et al. quantified the nasal bacterial load of the three main OM pathogens in otitis prone Aboriginal children and non-Aboriginal children (the latter being at low risk for developing OM). High nasopharyngeal bacterial loads were significantly associated with severe OM, and were considered a sensitive measure of suppurative OM [15]. In a separate study, the early onset of OM (defined as occurring at three to six weeks of age) was significantly associated with increased bacterial loads of OM pathogens in comparison to other microbes in the nasopharyngeal microbiota in Aboriginal children [25]. Early (less than three months of age) colonisation of the nasopharynx with otitis media pathogens resulted in an increased risk of OM in a cohort of 306 US infants followed up from birth to one year of age [16].

The microbial community of the upper respiratory tract develops soon after birth and is influenced by the environment and contact with other persons [26]. There is a dynamic interaction of competition and regulation between potentially pathogenic bacteria and commensals in the nasopharynx. Host immune responses can further affect the persistence or clearance of some species of bacteria [27]. The nasopharyngeal microbiota of children varies considerably between individuals and seasons [28]. In children with AOM, exposure to antimicrobials and prior pneumococcal vaccination (PCV7) were associated with a decrease in the prevalence of certain commensals (Streptococcaceae and Corynebacteriaceae) in the nasopharyngeal microbiota [29]. A case study which explored the microbiota of the middle ear, adenoids and tonsils in a child with chronic suppurative otitis media (CSOM) suggested that the adenoids may be a source for the microbiota in middle ear and tonsil [30].

In approximately 75% of children with AOM, inflammatory symptoms including otalgia and fever resolve spontaneously within two days [21], although asymptomatic effusion may be observed in a quarter of children even after three months [21, 31, 32]. In contrast, children in high-risk populations are more prone to early onset, recurrent episodes of AOM and are more likely to develop chronic suppurative otitis media (CSOM) [31, 32]. CSOM causes recurrent ear discharge, perforation of the tympanic membrane and associated hearing impairment with poor speech and language development [5, 7, 33], resulting in long term impacts on cognitive and educational outcomes [33].

Analysis of the nasopharyngeal swab and/or the middle ear fluid have demonstrated the presence of certain respiratory viruses along with pneumococcus, *H. influenzae* and *M. catarrhalis* increased the risk of AOM in children [34, 35]. In addition, a high nasopharyngeal titre of RSV is associated with increased risk of AOM in children [13]. Viral infection of the upper airways is likely to play a role in the transmission of pneumococcal disease [19, 36-39], as evidenced by epidemiological studies that demonstrate an association

between concomitant viral upper respiratory infection and horizontal spread of pneumococci amongst family members [40]. Furthermore, pneumococcal colonisation in humans [41] and mice [19, 42-44] is increased by infection with influenza A virus (IAV). In an infant mouse model that investigated pneumococcal-influenza synergism, young mice were colonised with pneumococci and subsequently with IAV three days later. IAV inoculation increased pneumococcal colonisation densities, induced the development of pneumococcal disease, and was essential for pneumococcal transmission to contact mice [19, 43, 44]. This model was designed to mimic clinical aspects of pneumococcal nasopharyngeal colonisation, as it commonly occurs in young children with an immature immune system. Mice coinfected with pneumococci and IAV had high pneumococcal load in the middle ear with signs of middle ear inflammation when compared to mice infected with pneumococci alone [43].

The host immune system plays a complex role in determining the progression of infection [3, 21] and also the prevention of OM [45-47]. An immature immune system may fail to elicit an adequate antibody response [48] to OM pathogens, leading to recurrence and chronicity of the disease [31]. A deficiency of secretory IgA, which reflect on the bacterial and viral adherence to the nasopharynx, is associated with recurrent AOM [31]. Delayed development of the immune system and abnormalities of the complement system have also been associated with the development of OM [2, 49].

A number of other risk factors have been identified for OM among children. Lack of breast feeding, parental smoking, poor household sanitation [9], younger children aged 6-17 months attending day care [50], overcrowding, and exposure to charcoal smoke [51] have all been shown to contribute to an increased risk for developing otitis media. Lower socioeconomic status with poor access to a health system has also been associated with high prevalence of OM [31].

Indigenous children usually develop OM early in life [21], they experience frequent and severe episodes and are more likely to develop complications compared to non-Indigenous children [11, 31, 52-56]. Indigenous children may be more vulnerable to social disadvantage that may accompany longstanding hearing impairment [7, 57]. This dichotomy between Indigenous and non-Indigenous children in terms of incidence, pathogenesis, severity, complications and long-term outcomes of OM needs to be addressed in order to arrive at an effective management strategy for OM in high-risk populations [31].

Streptococcus pneumoniae prevention and treatment strategies

S. pneumoniae, a member of the commensal flora of the upper respiratory tract colonises the nasopharynx [22] in early childhood with the colonisation rates declining to less than 10% in adult population [23]. Children, the elderly and immunocompromised individuals are more susceptible to pneumococcal disease, which can range from localised infections such as otitis media and pneumonia to invasive disease such as septicaemia or meningitis [20, 22]. Various preventive strategies and treatment options have significantly reduced the burden of pneumococcal infections. The introduction of pneumococcal heptavalent conjugate vaccine (PCV7) led to a significant reduction of invasive disease and pneumonia caused by vaccine serotypes of pneumococcus [20, 22], mainly in developed countries, such as the USA [58]. However, the efficacy of PCV7 against OM has been limited [22]. Clinical trials of an 11-valent pneumococcal conjugate vaccine using a *H. influenzae*-derived protein D carrier showed reduced carriage of *H. influenzae* and vaccine serotypes pneumococcus and some benefit against otitis media [59, 60]. However, the 10-valent licensed version of this vaccine (PhiD-CV; PCV10) did not have a substantial effect on *H. influenzae* carriage [61]. Vaccination has also been associated with increased colonisation by pneumococcal serotypes not covered by the vaccine (serotype replacement) [62-64], which also have the potential to

cause OM [65]. A major limitation to vaccination is that the first dose is typically not administered until two months of age, by which point infants in high-risk populations may already be colonised by pneumococci [66]. Early life pneumococcal colonisation[25], the low vaccination coverage among Indigenous populations [67], and the high cost involved in vaccine production and delivery [66] are factors which call for more effective strategies to reduce the burden of OM in high-risk populations. Pneumococci are innately susceptible to the penicillin group of antibiotics, but overuse of antibiotics has contributed to development of resistant strains [22]. Treatment with antibiotics can disrupt the balance of the nasopharyngeal microflora, further facilitating colonisation with pathogens [68]. Both the long-term use of oral antibiotics [69] and pneumococcal vaccination [70] have been shown to decrease the prevalence of tympanic membrane perforation in young indigenous children, but did not affect the prevalence of OM significantly [57]. Maternal pneumococcal vaccination trials are currently underway as possible strategies against middle ear infection and pneumococcal carriage among high-risk populations [71].

As mentioned above, nasopharyngeal colonisation is considered a prerequisite for pneumococcal infection [16, 72]. Adherence of the bacteria to the epithelial cell of the respiratory tract initiates the colonisation process [22, 23]. Since children can carry large numbers of pneumococci in the nasopharynx, they play a major role in the horizontal dissemination of the bacteria in the community, particularly in overcrowded situations [73, 74]. Hence, research focusing on methods to prevent the nasopharyngeal colonisation of pneumococci especially during early stages of infancy [25] has been considered a promising strategy for controlling OM and improving herd immunity [22]. Many researchers have highlighted the need to decrease the bacterial load in the nasopharynx to bring about any significant change in the prevalence of OM in the Australian Indigenous population [12, 15, 31, 75].

Probiotics and OM

Probiotics as defined by the WHO are 'live micro-organisms, which, when administered in adequate amounts, confer a health benefit on the host' [76]. Probiotics play a role in preventing diseases and re-establishing the microbial equilibrium of the intestinal tract [77]. The mechanisms of probiotic action have been investigated using in vitro and in vivo models as well has human studies. Some of the mechanisms by which probiotics are thought to act include inhibition of pathogen colonisation by competition for nutrients and adhesion sites on the epithelium [78], production of bacteriocins (antimicrobial compounds that can kill or inhibit other closely related bacterial species) [79, 80] and immune modulation by enhancing mucosal and systemic immunity [78, 81]. Immunomodulatory effects of probiotics include increased IgA production [82, 83] and modification of cytokine levels [84, 85] as well as being effective vaccine adjuvants [66]. However, it is important to note that the effects of probiotics are dependent on the species and strain used [86].

Administration of probiotics has demonstrated some beneficial results on upper respiratory infections including otitis media [87, 88] (Table 1). A study in which healthy adults drank a mixture containing four probiotic species namely *Lactobacillus rhamnosus* GG (LGG), *Bifidobacterium* sp, *Lactobacillus acidophilus* and *Streptococcus thermophilus* found that this treatment significantly reduced the occurrence of nasal colonisation with potentially pathogenic bacteria such as *Staphylococcus aureus,* pneumococcus and beta-hemolytic streptococci [89]. The study authors suggested that the ingested probiotics stimulated the gut-associated immune system, which enhanced mucosal immunity of the upper respiratory tract. Hatakka et al. [90] assessed the effect of LGG on respiratory infections including otitis media, by feeding 571 healthy children milk with or without LGG for seven months. Respiratory infections including OM and antibiotic treatment for respiratory infections were reduced in the probiotic group, but the differences in infection rates were not significant

when adjusted for age. In a study in which 248 healthy children were given milk with or without *Lactobacillus rhamnosus* LB21 for 21 months, the number of days the children experienced OM was significantly lower in the treatment group [91]. However, when 309 otitis media prone children were given either a probiotic capsule (containing LGG, *L. rhamnosus* LC 705, LC705, *Bifidobacterium breve* 99 and *Propionibacterium freudenreichii* JS) or placebo daily for 24 weeks, the two groups did not show statistically significant variation in the occurrence or recurrence of OM or the nasopharyngeal carriage of pneumococcus and *H. influenzae*, although a trend towards reduced recurrence of upper respiratory infections in the probiotic group was observed [92].

Rautava et al. [93] assessed the effects of probiotics in reducing the risk of acute respiratory infection, including OM, in infancy. Infants less than two months in age requiring formula feeds were administered formula supplemented with the probiotics LGG and *Bifidobacterium* subsp. *lactis* Bb-12 (Bb 12) or with placebo daily, until the age of one year. The probiotic group experienced significantly fewer episodes of AOM and recurrent respiratory infections in the first 12 months of life. However, in another infant study, consumption of Bb12 was not associated with lower incidence of OM, although infants receiving Bb-12 did experience significantly fewer respiratory infections [94]. The mechanisms by which oral ingestion of probiotics may exert effects in the upper respiratory tract remain unclear.

Alpha-haemolytic streptococci (AHS) as pharyngeal probiotics: AHS are commensal inhabitants of the healthy nasopharynx that produce bacteriocins and have been investigated in clinical trials for their ability to inhibit OM pathogens through various mechanisms including bacterial interference [95-98]. Although some strains of AHS may cause infection [99], most strains are well tolerated [97, 100-102] and have been safely used as probiotic supplements in a number of clinical studies and are commercially available. Roos and

colleagues [95] investigated the effect of AHS administered as a nasal spray on the incidence of OM in 108 otitis prone children aged six months to six years. Their results showed that the spray was effective in reducing the incidence of both recurrent AOM and secretory otitis media [95]. Based on these findings, a nasal spray containing AHS was investigated for efficacy in children under four years of age with OM, but there was no significant change in the nasopharyngeal microbiota or the number of OM episodes compared to the control group [97]. Nonetheless, there was a trend towards reduced carriage of *H. influenzae* and a lower number of otitis media episodes in the AHS-treated group towards the end of the study. The authors speculated that a higher dose of the AHS with superior adherence properties may have yielded a better result. Furthermore, treatment with a course of antibiotics prior to the administration of the spray could have helped to reduce the pre-existing bacterial microbiota and promoted better adherence of the AHS to the nasopharyngeal mucosa. Both of these clinical studies used sprays consisting of five strains of AHS with *in vitro* activity against pneumococcus, *H. influenzae and M. catarrhalis.* Another study compared a nasal spray containing probiotics the *S. sanguinis* or *L. rhamnosus* with placebo in the treatment of established secretory otitis media in children with median age of six months, and reported that a ten-day administration of *S. sanguinis* containing nasal spray was associated with a reduction in the presence of middle ear effusion [101].

After studying the bacteriology of the adenoids, Bernstein et al. [96] concluded that AHS are the predominant microbiota within the adenoids in non-OM prone children compared to OM prone children [96], and further investigation *in vitro* suggested that *Streptococcus oralis*, a member of the AHS, inhibits the growth of pneumococcus [103]. This finding indicates that a nasal spray with AHS has the potential to recolonise the nasopharynx with safer streptococci and inhibit pathogenic bacteria.

Streptococcus salivarius, an AHS isolated from the pharynx of a healthy person is a potential pharyngeal probiotic, owing to its immunomodulatory and anti-inflammatory properties, good host adaptability, and ability to produce plasmid-encoded broad-spectrum bacteriocins [80, 104, 105]. *S. salivarius* is well tolerated and considered safe for consumption by adults and children [106, 107]. Administration of *S. salivarius* tablets was associated with a reduction in *Streptococcus pyogenes* throat infections in a study of 40 adults with a history of recurrent streptococcal pharyngitis or tonsillitis [108]. In a similar study in 82 children, administration of *S. salivarius* tablets for 90 days reduced AOM episodes and streptococcal throat infections during the six-month follow up period. This study also showed a reduction in otitis media during the treatment period compared to the previous year, but these findings need to be interpreted with caution, given the difference in time frames of the observation periods on and off treatment (3 vs 12 months respectively) [102]. In a pilot study of oral administration of *S. salivarius* in otitis-media prone children, only a third became newly colonised with *S. salivarius*, indicating that dosing strategies need further optimisation [109]. Further studies using *S. salivarius* as a probiotic in otitis prone children are worth considering, in addition to studies using lactic acid bacteria, which have also demonstrated the potential to prevent respiratory infections [110] and inhibit pneumococcal infections in mouse models [111, 112]. More data are also needed to determine which probiotic species and strains would be most effective in preventing colonisation by OM pathogens, and what would be the optimal dosing and administration strategies to evaluate clinical efficacy.

The evidence so far from various studies on the effect of probiotics on OM offers promising results and justifies further research in this field. Well-designed clinical trials can provide valuable information on widely used oral probiotics and more targeted AHS nasal spray in preventing otitis media, especially in high-risk populations.

Conclusions

OM and its complications cause a significant burden on the health and well-being of high-risk populations. Research focused on determining the optimal use of preventive and intervention strategies, along with public health measures and evidence-based treatment options early in life are warranted to reduce the prevalence of OM [12].

Probiotics offer promising benefits in reducing nasopharyngeal colonisation with pathogenic bacteria and enhancing mucosal immunity, thus potentially decreasing OM and upper respiratory infections. Due to the varied and limited data currently available, *in vitro* experiments together with animal studies could provide important information on the mechanisms of action and potential effectiveness of probiotics in this setting. Furthermore, well designed clinical trials are needed to assess the effect of probiotics on pneumococcal infection and evaluate their potential as a novel strategy to reduce OM, especially in high-risk populations.

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Conflict of Interest:

The authors declare that they have no conflict of interest.

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Figure Legends

Figure 1: A model of otitis media pathogenesis, with a focus on Indigenous children. Wiertsema S and Leach AJ. Med J Aust 2009; 191(9): S50-S54. © Copyright 2009. The Medical Journal of Australia - reproduced with permission [21]

Table 1: Characteristics and results of clinical trials of the use of probiotics on otitis media and nasopharyngeal colonisation of bacterial pathogens [a]

Reference	Study design	Study population	Type of probiotic	Dose and duration	Outcome measures	Results (probiotic versus placebo)
Hatakka et al. 2007 [64]	Double-blind, placebo-controlled	309 otitis-prone children (10 months to 6 years)	*L. rhamnosus* GG, *L. rhamnosus* LC 705, *Bifidobacterium breve* 99 and *Propionibacterium freudenreichii* JS (8-9 × 10^9 CFU/ capsule of each strain)	One capsule daily for 24 weeks	Occurrence or duration of AOM, number of recurrent upper respiratory infections	AOM (≥ 1 episode): 72% vs. 65%, P=NS) Recurrent AOM (≥ 3 episodes): (18% vs. 17%, P=NS) Trend showing a reduction in recurrent (> 4 to ≥ 6) respiratory infections in the probiotic group (P = 0.046)
Gluck et al. 2003 [87]	Open prospective trial	209 adult volunteers, assigned randomly	*Lactobacillus* GG (7 × 10^9 CFU/day), *Bifidobacterium* sp (8 × 10^9 CFU/day), *Lactobacillus acidophilus* 3 × 10^9 CFU/day), and *Streptococcus thermophilus* (3 × 10^{10} CFU/day)	One vial of probiotic drink daily for 3 weeks	Nasal microbial flora analyzed on days 1, 21, and 28	Significant reduction (19%; P < 0.001) in the occurrence of nasal potentially pathogenic bacteria in the probiotic group
Hatakka et al. 2001 [88]	Double-blind, placebo controlled	571 healthy children (1-6 years)	*Lactobacillus rhamnosus* GG (5-10 × 10^5CFU/ml)	250 ml of milk supplemented with probiotic, 5 days a week for 7 months	Respiratory infection including AOM, antibiotic treatment for respiratory infection during intervention	Respiratory infection including AOM: 39% vs 47% (P=0.05) Antibiotic treatment: 44% vs 54% (P=0.03) (Age adjusted: NS)
Stecksen-Blicks et al. 2009 [89]	Double-blind, placebo controlled	248 healthy children (1-5 years)	*Lactobacillus rhamnosus* LB21 (1 × 10^7 CFU/ml)	150 ml of milk supplemented with probiotic, 5 days a week for 21 months	Number of days with OM, number of days with antibiotic treatment	Number of days with OM: 0.4 vs 1.3 days (P<0.05) Days of antibiotic treatment: 1.9 vs 4.7 (NS)
Rautava et al. 2009 [90]	Double-blind, placebo-controlled	72 infants less than 2 months (who needed infant formula	*Lactobacillus rhamnosus* GG and *Bifidobacterium lactis* Bb-12 (1-10 × 10^9 CFU/ capsule of each	One capsule contents added to infant formula daily until the age of	Primary outcomes: Incidence of early respiratory infections, AOM before 7 months Secondary outcomes: Incidence of	Primary outcomes: Incidence of AOM 22% vs. 50% ; RR 0.44 (95% Cl 0.21, 0.90); P=0.014) Secondary outcomes: AOM 13% vs. 25% (RR 0.50; 95% CI 0.17, 1.45; P=0.183)

		supplement)	strain)	one year	recurrent (≥ 3) infections during the first year of life	Tympanostomy 0% vs. 10% (RR 0.31; 95% CI 0.04, 2.66; P= 0.066)
Taipale et al. 2011 [91]	Double-blind, placebo controlled	109 healthy newborn (1-2 months)	*Bifidobacterium animalis* subsp. *lactis* BB-12 (5×10^9 CFU/tablet)	1 tablet of probiotic (administered with pacifier or spoon) twice daily for 8 months	Incidence of AOM, incidence of respiratory infections, antibiotic treatment during study period	Incidence of AOM: 26% vs 17% (P=NS) Incidence of respiratory infection: 65% vs 94% (P=0.014) Antibiotic treatment: 29% vs 23% (P=NS)
Roos et al. 2001 [92]	Double-blind, placebo controlled	108 children prone to otitis media aged between 6 months and 6 years	Pre-treatment with antibiotics (phenoxymethylpenicillin or amoxicillin clavulanic acid) twice daily for 10 days followed by AHS solution spray	Spray three puffs each nostril twice daily for 10 days. Starting at day 55-60, spray for another 10 days	Recurrence of OM during until 3 month follow up visit	No recurrence of otitis media at 3 months: 42% vs. 22% (P=0.02)
Tano et al. 2002 [94]	Double-blind, placebo controlled	43 children, 4 years or younger with recurrent AOM	Spray containing five strains of AHS containing more than 10^7 CFU/ml	50 µl puff in each nostril daily for 4 months	No. of episodes of AOM during treatment, assessment of whether spray could be an alternative method to tympanostomy tube insertion	Number of episodes of AOM 44% vs. 40% (P=NS). Nasal spray as per schedule is not an alternative treatment for recurrent AOM
Skovbjerg et al. 2009 [97]	Double-blind pilot study	60 children (1 to 8 years) with middle ear effusion for at least 2 months	Three groups: *Streptococcus sanguinis* (5×10^9 CFU/ml), *Lactobacillus rhamnosus* (5×10^9 CFU/ml) or placebo	50 µl puff in each nostril twice daily for 10 days before surgery	Amount of middle ear fluid, detection of bacteria and cytokines in middle ear fluid	Clinical improvement 7/19 vs. 1/17 (P< 0.05) Spray treatment did not alter the composition of the nasopharyngeal flora or the cytokine pattern
Pierro et al. 2012 [104]	Pilot study	87 children between 3-12 years	*Streptococcus salivarius* K12 ATCC BAA-1 024 (5×10^9 CFU/tablet)	1 tablet daily for 90 days	Incidence of AOM during probiotic intake period compared to previous year, incidence of AOM and streptococcal pharyngitis at 6 month follow up	Reduction of AOM episode during probiotic intake 40% (NS when adjusted for time period) Reduction of OM episode during follow up period 65% (P=0.03)

[a] OM- otitis media; AOM- acute otitis media; NS- not significant; RR- risk ratio; AHS- alpha haemolytic streptococci; CFU- colony forming units

The extended vicious circle of inflammation hypothesis explaining high rates of otitis media and other respiratory infections among Indigenous infants and young children