

# Menzies School of Health Research

## Ear Health Projects

### September 2008

#### 1. Azithromycin v Placebo in the treatment of asymptomatic acute otitis media in young Aboriginal children. (AAAOM)

##### Primary Research Question

Among Aboriginal children with asymptomatic AOM, does azithromycin 30mg/kg/dose given on day 0 and day 7 (compared to placebo given at the same time) result in a reduction in the proportion of children with signs of persistent disease 14 days after starting treatment?

##### Secondary Aims

1. To describe the prevalence, natural history and clinical course of asymptomatic acute otitis media in young Aboriginal children living in the NT.
2. To assess the effectiveness of azithromycin in the treatment of asymptomatic acute otitis media and prevention of tympanic membrane perforation 1 week and 4-6 weeks after treatment.
3. To describe the impact of azithromycin on antibiotic resistance, nasopharyngeal colonisation, rhinosinusitis, and skin sores 1 week and 4-6 weeks after treatment.

##### Progress

Consultation phase. Aim to start collecting data in late September.

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#### 2. Implications of nonencapsulated streptococcus pneumoniae carriage for maintenance of Antibiotic resistance genes and the efficacy of pneumococcal conjugate vaccine (Prevanar) for pneumococcal disease. (SPINICA)

The pneumococcus is a bacterium that causes diseases such as pneumonia and middle ear infections, especially in children. All children in Australia now receive a vaccine called Prevanar which protects from disease caused by 7 types of pneumococcus. Studies have shown that the remaining types of pneumococcus not included in the vaccine will now become more prevalent (replacement types). The current proposal will look at non-encapsulated pneumococcus which is an important replacement type in Aboriginal children who have been vaccinated with Prevanar. Previously this type of pneumococcus received little attention, and little is understood about its epidemiology. This study will help us to understand its relationship to other pneumococci, and its potential role as a reservoir of antibiotic resistance for pneumococci

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#### **Progress**

Planned laboratory experiments completed. Antibigram data and molecular characterisation of 192 isolates (Box typing) is complete. The molecular analysis is made up of 5 pneumococcal PCRs (pneumolysin; autolysin; Spn gene 9828; Spn gene 9802; and the *wzg* capsule gene). MLST of the top three Box types has begun. Antibigrams of penicillin and erythromycin have been analysed and *mef/erm* analysis of erythromycin resistant isolated completed. Results from the *wzg* capsule gene analysis identified 23 capsule gene positive NCSpn isolates. The isolates have been referred to Lyn Gilbert's lab to try and determine serotype associations. Publications are in preparation.

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#### **3. Pilot study of a novel clinical application (metagenomics) for Indigenous health.**

Indigenous children experience excessive rates of otitis media. The disease is caused by many different bacteria. Previously, researchers have only been able to examine one bacterium at a time. Metagenomics is a new science which allows study of numerous bacteria simultaneously. Using metagenomic methods, we aim to understand how otitis media develops and why some children do not respond to therapy. This will allow design of better interventions to improve ear health for Indigenous children.

#### **Progress**

PhD student Robyn Marsh has commenced candidature and is preparing a literature review and study plan.

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#### **4. Mathematical modeling of bacterial carriage in children (MMAPS).**

Children exposed to larger numbers of other children are at risk of persistent bacterial infections. Such circumstances explain the high rates of ear and chest infections, and skin sores seen in children in historical times. Changing social circumstances (smaller families, better housing, nutrition and hygiene), as well as the introduction of antibiotics, explain the decline of such infections in affluent communities since the early 20th century. However, even today, in affluent countries, children attending group child care are at high risk of ear infections. As many bacteria are resistant, antibiotics are now much less effective than when they were first introduced. Furthermore, there is a continuing load of infection for children in Aboriginal communities, in PNG and other developing countries, causing hearing loss, chronic respiratory problems, and heart disease and renal disease in later life.

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Using data previously collected from other studies in Indigenous communities and children in child care, mathematical models allow us to ask "what if?", and answer important public health questions:

1. What environmental and public health measures can reduce the cycle of cross-infection in child-care and high-risk populations?
2. What coverage rates with pneumococcal vaccine will eliminate the vaccine-specific bacteria from child care centres, from the wider community, and from high risk populations?
3. Will infections with bacteria not covered by vaccine then increase?
4. Will the resistant bacteria tend to disappear if antibiotic use is restricted?
5. Under what circumstances will antibiotics help to control infection?

The modelling will promote understanding of the social and health costs of bacterial infection in Aboriginal communities and child care and use educational scenarios to promote uptake of the most cost-effective and socially acceptable interventions.

#### **Progress**

Data sets from several large longitudinal studies have been combined. Model parameters have been evaluated and assumptions tested on model data. The model has been applied to several of the research questions around clinical and microbiological outcomes of antibiotic treatment of otitis media. Presentations have been made at ISPPD6 (Iceland, June 2008).

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#### **5. Immunising Aboriginal mothers with pneumococcal polysaccharide vaccine to prevent infant ear disease and pneumococcal carriage. (PneuMum).**

The primary aim of the project, called PneuMum, is to determine if maternal vaccination with the 23-valent pneumococcal polysaccharide vaccine (23vPPV), given antepartum or immediately postpartum, can reduce nasopharyngeal carriage of vaccine type pneumococci and the prevalence of middle ear disease among Indigenous children at seven months of age. This is the first vaccine trial to be conducted among Indigenous Australians and the only maternal vaccine trial in the world that has been designed to assess impact against ear disease, a major public health problem for Indigenous Australians.

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#### Progress

The subject consent rate has been 57% (145/255), and has exceeded researcher expectations (33%). Following eligibility assessment, there were 87 women randomised as of 31 January 2008. To date, there have been 78 births with no evidence to date of increased risk from vaccination in pregnancy. Forty two infants have completed follow-up to age 7 months, at which point only 22 (52%) were still breast feeding. There have been two withdrawals from the study and, as yet, no subjects lost to follow-up. The immune response to vaccination has been promising. Preliminary data from maternal venous blood pre and post vaccination (n=45), cord blood (n=50) and infant blood at age 7 months (n=29) have been consistent with previous studies in other population groups and show:

- A good maternal immune response to 23vPPV
- Significantly higher cord blood antibody levels for infants of antenatal "vaccinees" than postnatal "vaccinees".
- No evidence of maternal antibody interference with the infant response to the 7-valent pneumococcal conjugate vaccine.

The primary endpoints of infant middle ear disease and nasopharyngeal carriage remain blinded but the overall rates are below those expected in both the vaccine and control groups. These preliminary results have been submitted for presentation at the 6<sup>th</sup> International Symposium on Pneumococci and Pneumococcal Diseases (ISPPD6), Iceland, 2008.

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#### 6. Viral Interactions and AOM Bacterial Load : a Longitudinal Evaluation (VIABLE)

The primary question of this project is "Do respiratory viruses explain high rates of acute otitis media with perforation (AOMwIP) in young Aboriginal children in remote Australia?" The VIABLE study is a retrospective analysis of clinical trial specimens and data. We are using stored nasopharyngeal swabs collected at monthly visits from children less than 18 months of age with AOM with perforation and from children without AOM to determine the prevalence of respiratory viruses (influenza A and B; respiratory syncytial virus; parainfluenza 1,2 & 3; rhinovirus, adenovirus, human metapneumovirus). We will also quantify the AOM-pathogen-specific load (*Streptococcus pneumoniae*, *Haemophilus influenzae* and *Moraxella catarrhalis*), and total bacterial load prior to and at the time of perforation. Mathematical models of bacterial load and viral infection will be applied to test the hypothesis that viral infection directly or indirectly increases the risk of AOMwIP.

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#### **Progress**

All laboratory methods for bacterial Real Time PCR and viral analyses have been developed and optimised. Stored nasopharyngeal swabs from completed longitudinal studies have been selected to meet criteria for association with AOM/wiP or AOM/woP.

#### **Contact**

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