Improving the management of children (especially Indigenous children) hospitalised with bronchiolitis

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Thesis submitted for the degree of

Doctor of Philosophy

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**Declaration**

I hereby declare that the work herein, now submitted as a thesis for the degree of Doctor of Philosophy of the Charles Darwin University, is the result of my own work, and all references to the ideas and work of other researchers have been specifically acknowledged. I hereby certify that the work embodied in this thesis has not already been accepted in substance for any degree, and is not being currently submitted in candidature for any other degree.

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Abstract

Bronchiolitis, a typically self-limiting illness causes significant morbidity and remains a leading cause of hospitalisation among infants globally. In some populations such as Northern Territory Indigenous infants, bronchiolitis is more severe and the incidence is higher. Despite being the most common acute lower respiratory infection worldwide, the current mainstay of treatment for hospitalised bronchiolitis is supportive.

This thesis presents findings of studies undertaken to improve the management of hospitalised bronchiolitis, with a particular focus on Indigenous children. The major hypothesis of my thesis was that azithromycin improves short and long term clinical outcomes of children hospitalised with bronchiolitis. Gaps in knowledge were addressed and the principal findings were:

1. Severity scoring systems are easy to use, reliable and repeatable and can be used with health staff of varying levels of experience.

2. Different doses of azithromycin (single or 3-weekly doses) did not improve short or long term clinical outcomes and should not be routinely used to treat children hospitalised with bronchiolitis.

3. Azithromycin reduced the proportion of bacterial carriage, but had no impact on viruses or atypical bacteria.

4. Non-traditional risk factors prolonged hospitalisation. Presence of persistent symptoms 3-weeks beyond hospitalisation increased the risk for ongoing morbidity, respiratory readmissions and developing bronchiectasis.
5. Mobile phones in conjunction with a culturally sensitive framework were an effective strategy to improve adherence and retention of participants in the largest randomised controlled trial.


The long term consequence of respiratory disease among Indigenous children is an important public health issue. Identifying target points that can lead to optimising clinical care and better lung health and prevention of subsequent bronchiectasis among Indigenous children are needed.
Acknowledgments

There are so many incredible people who have journeyed with me through this PhD. My heartfelt thanks to everyone who have laughed, cried and encouraged me during my PhD study.

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Publications during Candidature


6. Gabrielle B McCallum, Peter S Morris, Keith Grimwood, Carolyn Maclennan, Andrew V White, Mark D Chatfield, Theo P Sloots, Ian M Mackay, Heidi Smith-Vaughan, Clare C McKay, Lesley A Versteegh, N

Submitted papers

Statement of contributions to jointly authored works

This section lists authors' contributions to publications or submitted manuscripts included in this PhD thesis.


The protocol was written by Ms. McCallum and Professor Chang. Professor Morris reviewed the protocol. For the review, Ms. McCallum and Professor Chang independently reviewed the search, double entered data and wrote the manuscript. All authors have read and approved the manuscript.


Ms. McCallum set up and coordinated the study, performed the data analysis and drafted the manuscript. Professor Chang conceptualised the study, interpreted the data and edited the manuscript. Professor Morris assisted in data interpretation and contributed to the manuscript. Mr. Chatfield and Ms. Ward assisted in the data analysis and edited the manuscript. Mrs. Versteegh and Mrs. Mckay participated in recruiting participants and edited the manuscript. All authors have read and approved the manuscript.

3. McCallum GB, Morris PS, Chatfield MD, Maclennan C, White AV, Sloots TP, Mackay IM, Chang AB. A single dose of azithromycin does not

Professor Chang, Professor Morris and Dr. Macleannan conceived and designed the experiments: Ms. McCallum, Dr. Macleannan and Dr. White performed the experiments and standardised the management of bronchiolitis in their unit. Ms. McCallum set up and coordinated the study, recruited participants, performed the data analysis and drafted the manuscript. Professor Sloots and A/Prof Mackay assisted in the viral components of the study. Mr. Chatfield assisted in the data analysis. All authors contributed to reagents/materials/analysis tools and edited the manuscript.


Ms. McCallum set up and coordinated the study, recruited participants, performed the data analysis and drafted the manuscript. Mrs. Versteegh, Mrs. Mckay, Mrs. Jacobsen and Dr. White recruited participants and edited the manuscript. Professors Chang and Morris conceptualised the study, interpreted the data and edited the manuscript. Ms. Heather D’Antoine provided cultural integrity support.

The first review was primarily written by Ms. Bailey and Professor Chang who also reviewed the abstracts and articles. In this updated review, Ms. Bailey and Professor Chang reviewed the searches from 2008-2012; Ms. McCallum and Professor Chang reviewed search data from 2012-2014. Ms. McCallum and Professor Chang extracted and entered the data. Ms. McCallum updated this review, which was reviewed by all authors.


Ms. McCallum set up and managed the study, performed the data analysis and drafted the manuscript. Professor Chang conceptualised the study. Professor Chang and Professor Grimwood co-drafted the manuscript. Professor Chang, Professor Morris, Professor Grimwood, Professor Sloots, Dr. White and A/Prof MacKay co-designed the study and contributed to obtaining the grant, and edited the manuscript. A/Prof Byrnes was responsible for overseeing all aspects of the trial in New Zealand. Dr. Maclennan, Dr. White and A/Prof Byrnes were responsible for standardising the management of bronchiolitis in their units, recruiting participants and edited the manuscript. Mrs. McKay, Mrs. Versteegh, Mrs. Jacobsen and Dr. Maclennan were responsible for recruiting participants and edited the manuscript. Professor Sloots and A/Prof McKay assisted in the viral components of the study and edited the manuscript. A/Prof Smith-
Vaughan assisted in the microbiological components of the study and edited the manuscript. Ms. McCallum and Mr. Chatfield had full access to all the data in the study and took responsibility for the integrity of the data and the accuracy of the data analysis. Mr. Chatfield assisted in the data analysis and edited the manuscript. All authors have read and approved the final manuscript.


Ms. McCallum designed the data collection instruments, collected data, coordinated the study and carried out initial data analysis and manuscript. Professor Chang conceptualised the study with modifications by Professor Morris and Ms. McCallum.

Mr. Chatfield provided statistical support, assisted in further data analysis and edited the manuscript. All authors assisted in data interpretation, contributed to the manuscript and approved the manuscript as submitted.
Presentations by the candidate relevant to thesis

This section lists conference presentations made relevant to my PhD thesis.


List of awards/prizes relevant to thesis

This section lists awards/prizes received during my PhD candidature.

2. Winner of the CRE in Lung Health of Aboriginal and Torres Strait Islander Children – Australian Satellite of the Cochrane Airways Group Scholarship (2014).
7. Recipient of the National Health and Medical Research Council (NHMRC) post graduate scholarship (2012).
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### Abbreviations

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<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tr>
<td>ACCP</td>
<td>American College of Chest Physicians</td>
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<tr>
<td>ACTR</td>
<td>Australian Clinical Trials Registry</td>
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<tr>
<td>ALRI</td>
<td>Acute lower respiratory infection</td>
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<tr>
<td>aROC</td>
<td>Area under receiver operating curve</td>
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<tr>
<td>BTS</td>
<td>British Thoracic Society</td>
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<tr>
<td>CI</td>
<td>Confidence interval</td>
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<tr>
<td>CT</td>
<td>Computed Tomography</td>
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<tr>
<td>DSMB</td>
<td>Data safety monitoring board</td>
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<tr>
<td>ED</td>
<td>Emergency department</td>
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<tr>
<td>GP</td>
<td>General practitioner</td>
</tr>
<tr>
<td>GRADE</td>
<td>Grades of recommendation, assessment, development and evaluation</td>
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<tr>
<td>HREC</td>
<td>Human Research Ethics Committee</td>
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<tr>
<td>HRV</td>
<td>Human rhinovirus</td>
</tr>
<tr>
<td>hMPV</td>
<td>Human metapneumovirus</td>
</tr>
<tr>
<td>IDT</td>
<td>Institute of Drug Technology Australia Pty LTD</td>
</tr>
<tr>
<td>ITT</td>
<td>Intention to treat</td>
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<tr>
<td>IQR</td>
<td>Interquartile range</td>
</tr>
<tr>
<td>K</td>
<td>Kappa</td>
</tr>
<tr>
<td>Ki</td>
<td>KIPyV</td>
</tr>
<tr>
<td>LOS</td>
<td>Length of stay</td>
</tr>
<tr>
<td>MID</td>
<td>Minimum important differences</td>
</tr>
<tr>
<td>MD</td>
<td>Mean difference</td>
</tr>
<tr>
<td>NHS</td>
<td>National Health Service</td>
</tr>
<tr>
<td>NHMRC</td>
<td>National Health and Medical Research Council</td>
</tr>
<tr>
<td>NNTB</td>
<td>Number needed to treat for additional beneficial outcome</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Description</td>
</tr>
<tr>
<td>--------------</td>
<td>-------------</td>
</tr>
<tr>
<td>NPS</td>
<td>Nasopharyngeal swab</td>
</tr>
<tr>
<td>NT</td>
<td>Northern Territory</td>
</tr>
<tr>
<td>NZ</td>
<td>New Zealand</td>
</tr>
<tr>
<td>$O_2$</td>
<td>Oxygen</td>
</tr>
<tr>
<td>OR</td>
<td>Odds ratio</td>
</tr>
<tr>
<td>PC-QOL</td>
<td>Parent cough quality of life questionnaire</td>
</tr>
<tr>
<td>PedsQL</td>
<td>Pediatric quality of life questionnaire</td>
</tr>
<tr>
<td>PCR</td>
<td>Polymerase Chain Reaction</td>
</tr>
<tr>
<td>RACS</td>
<td>Respiratory assessment change in score</td>
</tr>
<tr>
<td>RCT</td>
<td>Randomised controlled trial</td>
</tr>
<tr>
<td>RDAI</td>
<td>Respiratory distress assessment instrument</td>
</tr>
<tr>
<td>RDH</td>
<td>Royal Darwin Hospital</td>
</tr>
<tr>
<td>RSV</td>
<td>Respiratory syncytial virus</td>
</tr>
<tr>
<td>SD</td>
<td>Standard deviation</td>
</tr>
<tr>
<td>SoF</td>
<td>Summary of findings</td>
</tr>
<tr>
<td>SMS</td>
<td>Short message service</td>
</tr>
<tr>
<td>SpO$_2$</td>
<td>Oxygen saturation measured on a pulse oximeter</td>
</tr>
<tr>
<td>UK</td>
<td>United Kingdom</td>
</tr>
<tr>
<td>USA</td>
<td>United States of America</td>
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<tr>
<td>WUPyV</td>
<td>WU</td>
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Chapter 1: Introduction and Literature Review

1.1 Chapter Overview
This review outlines the clinical syndrome of bronchiolitis in children (in particular Indigenous children), including the burden internationally and locally. Bronchiolitis is the most common acute lower respiratory infection (ALRI) worldwide, yet there are limited treatment options. This review outlines the etiology, diagnosis, assessment of severity and current treatment and management practices, focusing on the potential of macrolides as a treatment option for hospitalised bronchiolitis. This review then provides a summary of the impact of protracted respiratory symptoms beyond hospitalisation, and the contribution to ongoing respiratory morbidity. It concludes with a summary of the research hypothesis and aims addressed by this thesis.

1.2 Overview of bronchiolitis
Bronchiolitis as a clinical syndrome in children was first described in 1941 in the United Kingdom (UK), after an influenza epidemic affected a large number of young children.\textsuperscript{1} The authors, described; “acute bronchiolitis is the essential pulmonary lesion in epidemic influenza”.\textsuperscript{1}

Despite bronchiolitis now being the most common ALRI in young children globally, agreement on a “standard” definition across the paediatric community is lacking.\textsuperscript{2} It is agreed however, that diagnosis is essentially clinically based, yet will vary across and within countries.\textsuperscript{3-5} The definition of the syndrome is further discussed below in section 1.4.1.
Bronchiolitis is a seasonal illness affecting the very young (primarily infants) in the winter months, or the rainy season in tropical climates. The most common virus associated with bronchiolitis is respiratory syncytial virus (RSV). Most children can be effectively managed at home. However, those with moderate to severe illness may require hospitalisation for supportive therapies.

Bronchiolitis is a relatively short lived illness, usually resolving within 1-2 weeks. However, a proportion of children will have protracted symptoms beyond the acute illness, which may contribute to further respiratory morbidity and poorer long term respiratory outcomes.

### 1.3 Burden of disease

#### 1.3.1. Epidemiology and prevalence globally

Bronchiolitis is a global issue with approximately one third of children developing the illness before they are 2 years of age. Bronchiolitis is a leading cause of hospitalisation in children, implicated for more than 3 million cases annually. The incidence across and within countries is variable and therefore difficult to systematically evaluate. The authors Cheung et al describe this complexity, reporting a 15 fold variation in the incidence of hospitalisations, among infants in the UK (351–5140 admissions per 100 000). They speculate this is likely due to variations in clinical decision making. Similarly, in the United States of America (USA), bronchiolitis hospitalisations are widespread (19-65%) with more than a threefold difference observed. The authors of this study agree with Cheung et al that there is a need to standardise clinical care.

Nevertheless, in the USA and UK, around 3% of children are hospitalised annually. In Australia, approximately 1% of children are hospitalised yearly, of
which a majority are infants (80%). The incidence of bronchiolitis hospitalisations among marginalised groups, such as Indigenous children though consistently remains much higher and more severe than non-Indigenous children. Overseas studies have reported that being of Indigenous heritage is an independent risk factor for RSV hospitalisations, even after adjusting for socioeconomic risk factors. The burden of disease among Indigenous children is described in more detail in the following section.

During the 1980-1990s, hospitalisation rates significantly increased worldwide. In the USA, rates increased by 240% from 12.9 per 1,000 in 1980 to 31.2 per 1,000 in 1996 for reasons that are not fully understood. Possible explanations are likely to be multifactorial and include improved survival of neonates and possible reduction in thresholds to admit due to low oxygen saturations in first line care. In contrast, Hasegawa and colleagues reported a reduction of children ≤2 years admitted to USA hospitals in 2000-2009, from 17.9 to 14.9 per 1,000 person-years (17% decrease), yet an increase in hospital related costs from $6,380 to $8,530 (34% increase). Reasons for this declining trend are not yet known, however the authors speculate this may be due to decreased incidence and severity of disease, changes to diagnostic criteria for admission, or trends in child care practices. Other contributing factors may include the use of Palivizumab prophylaxis in high risk infants. Singleton et al found a significant reduction of RSV hospitalisations by over a third during 2001-2004 and suggest Palivizumab as a possible reason. Despite reduction in hospitalisations, bronchiolitis still causes substantial morbidity and hospital related costs.
Although the number of hospitalisations has fluctuated, deaths attributed to bronchiolitis in previously well children living in developed countries are rare. Deaths in USA infants are reported in 5.3 per 100,000 and 2.0 per 100,000 in the UK and are decreasing.\textsuperscript{27-29} Risk factors for death include low birth weight, increasing birth order, low Apgar score at 5 minutes, young maternal age, tobacco use during pregnancy and single status of the mother.\textsuperscript{30} Globally, ALRI still remains a main cause of morbidity among children less five years worldwide, and bronchiolitis is responsible for much of this burden of disease.\textsuperscript{31}

\subsection*{1.3.2 Epidemiology and prevalence among Indigenous children}

In Australia, the definition for Indigenous status include people who are of ‘Aboriginal origin, Torres Strait Islander origin or both Aboriginal and Torres Strait Islander origin’.\textsuperscript{32}

The burden of ill health from acute and chronic respiratory disease remains high among Indigenous populations globally.\textsuperscript{2,33,34} In developed countries, such as USA (Alaska), Canada, New Zealand and Australia, the incidence and severity of hospitalised bronchiolitis among Indigenous children exceeds that of non-Indigenous children.\textsuperscript{20-22,35} In American Indian and Alaska Native infants, rates are reported in 61.8 per 1,000 infants,\textsuperscript{18} compared to New Zealand Maori children (115.4 per 1,000) and Pacific Islander (168.9 per 1,000).\textsuperscript{36} The highest bronchiolitis hospitalisations reported are however among Canadian Inuit children in the Baffin region (484 per 1000 infants).\textsuperscript{20}

The incidence of bronchiolitis hospitalisations among Australian Indigenous children is high, but varies significantly between physical locations. In Mount Isa, reported rates are 71.3 per 1,000 children ≤24 months,\textsuperscript{37} Townsville 46 per 1,000 infants\textsuperscript{38} and
in Western Australia 70.6 per 1,000 infants.\textsuperscript{39} Yet amongst Northern Territory (NT) infants, the incidence is far higher than any other reported Australian region (352 per 1,000).\textsuperscript{22} Apart from Canadian Inuit population, these rates exceed any published data, including other Indigenous populations (i.e. American Indians, Alaskan Natives, New Zealand Maori and Pacific Islander and developing countries).\textsuperscript{18,20,36}

In addition to the high reported rates of bronchiolitis of Indigenous children in the NT, they are also more likely to be hospitalised than non-Indigenous, to have more severe disease, longer hospital stays, and to be re-hospitalised within 6-months with a respiratory illness.\textsuperscript{22}

Although bronchiolitis is common and severe in Australian Indigenous children, there were no prospective studies prior to the studies described in my thesis. Thus, one of the objectives of my thesis relates to addressing this gap (chapters 2 to 6).

1.4 Diagnosis and etiology of bronchiolitis

1.4.1 Clinical features and diagnosis of bronchiolitis

With the absence of a “gold standard” definition worldwide, there is widespread variability (across and within countries) in criteria for diagnosing bronchiolitis. Nevertheless, in all definitions of bronchiolitis, the condition is a clinical syndrome based on a typical history and findings on physical examination.\textsuperscript{3,5,40} In the UK and the USA, the upper limit of diagnosis is made in children up to 23-24 months\textsuperscript{3,5} but in Australia the diagnosis is based on the presence of tachypnoea (respiratory rate >60/min in infants aged <2 months, <50/min in 2 – 12 months), wheeze and/or crepitations.\textsuperscript{4,40} However, in some parts of Australia like the NT, children up to 18 months are included to capture those most at risk of more severe respiratory illness (i.e. Indigenous).\textsuperscript{2,4,22} Clinical diagnosis includes age-adjusted tachypnoea
(respiratory rate >60/min if aged <2-months; >50/min if 2-12-months; and >40/min if 13-24-months), with wheeze and/or crackles. In some countries, wheezing is regarded as an important clinical finding. Including older children however (up to 24 months) increases the risk of including those with reactive airways disease or asthma.

The term “bronchiolitis” means inflammation of the bronchioles. The American Academy of Paediatrics described bronchiolitis, as ‘a constellation of clinical symptoms and signs occurring in children younger than 2 years, including a viral upper respiratory prodome followed by increased respiratory effort and wheezing’. This clinical syndrome is usually characterised by 2-3 days of corzyal symptoms, such as rhinorrhea, cough, low grade fever, poor feeding preceding to other symptoms such as increased breathing difficulty (i.e. tachypnoea and dyspnoea).

Pathologically, necrosis of the respiratory epithelium and destruction of ciliated epithelial cells is followed by peribronchiolar infiltration with lymphocytes and neutrophils. Airway oedema and inflammation causes obstruction with mucus and plugging in the bronchioles, causing impaired exchange at the alveoli and increasing hyperinflation and respiratory effort. Cyanosis is generally only documented in a small proportion of children, due to high cardiac output. On chest auscultation, high pitched wheeze and/or fine inspiratory chest crackles are typically heard.

Radiologically, abnormalities such as hyperinflation of the lungs and atelectasis are most often observed in these children. Most guidelines however, do not suggest chest X-rays be performed, as lobar consolidation can be present found in <1% of films and misdiagnosed with pneumonia. However, children whose chest X-rays show consolidation and atelectasis have an increased risk of severe disease.
requirement for a chest X-ray therefore needs to be determined based on individual clinical symptoms and severity. In NT hospitals, it is standard management to have a chest X-ray on admission, due to the high incidence of bronchiolitis, severity of disease and possible complications of secondary pneumonia.22

1.4.2 Etiology of bronchiolitis

1.4.2.1 Viral associations

Bronchiolitis is caused by viral infections and hence is ‘a seasonal viral illness’, most frequently occurring in the winter months in temperate climates or the rainy season in tropical climates.3,5,16

The most common virus associated with bronchiolitis is RSV47 and was subsequently first isolated from chimpanzees.48 Two distinct subtypes (A and B) have been identified, yet disease severity does not appear to differ between each type.47,49 RSV accounts for 50-80% of cases and is often reported to cause more severe disease.6,49,50 RSV is a highly infectious virus, with most children infected by 2-3 years.51 The virus is carried and spread through air samples (e.g. by coughing, sneezing) and often touching infected surfaces (i.e. found on fomites for several hours and hand/eye contamination).3,5 Reinfection of RSV is common in children up to 2 years of age. Most infections occur within the first 12-months and after this time, infections are generally limited to the upper respiratory tract.47

Testing for viruses are generally reserved for hospital (i.e. for cohorting purposes to reduce nosocomial infections) or for research, by either nasopharyngeal swabs or aspirates.3,5 Improved molecular techniques over the last decade with polymerase chain reaction (PCR), have allowed quicker, more sensitive testing than conventional methods (e.g. viral culture and antigen detection), as well as the ability to detect new
and multiple viruses from one sample.\textsuperscript{52,53} A large number of new viruses have been identified and implicated in bronchiolitis in recent years.\textsuperscript{53} Human rhinovirus (HRV), a well described virus in upper respiratory tract infections and asthma studies,\textsuperscript{53,54} is the second most common virus reported (14-30\%).\textsuperscript{29} In a recent review of bronchiolitis, other viruses implicated in bronchiolitis include human bocavirus (14-15\%), human metapneumovirus (3-12\%), enterovirus, adenovirus, coronavirus and influenza viruses, ranging from (1-8\%).\textsuperscript{29}

Despite the large number of new viruses and studies, it still remains unclear whether single or multiple viruses are associated with more severe disease. A systematic review of viruses, reported single viruses in 30.9\% to 96.1\% (mean 68.2\%), compared to co-infections from 5\% to 62\% (mean 23\%).\textsuperscript{53} Different methodologies, number of viruses tested, seasonal and yearly variations may be contributing factors for these differences. There is also evidence emerging on the role of atypical bacteria (i.e. \textit{Mycoplasma pneumoniae} and \textit{Chlamydia} species) and their contribution in the development of chronic lung disease and altering lung maturation.\textsuperscript{55-58} \textit{Mycoplasma pneumoniae} is recognised as an important cause of community acquired lower respiratory tract infection and is most commonly reported in 5 to 20 year olds.\textsuperscript{59} However, \textit{Mycoplasma pneumoniae} has been reported in 10\% of children under 5 years presenting to hospital with an acute respiratory infection and was associated with more severe illness.\textsuperscript{60} \textit{Chlamydia} species are also suggested to be responsible for 10-15\% of community acquired pneumonia.\textsuperscript{61,62} Transmission of \textit{Chlamydia} is through vertical transfer from mother to infants, which can persist for many years and may result in increased risk of pneumonia.\textsuperscript{63} In Indigenous Australians, high rates of \textit{Chlamydia} are reported.\textsuperscript{64} Also, \textit{Simkani negevensis} (\textit{Chlamydia} species) has been reported among Canadian Inuit infants hospitalised with bronchiolitis.\textsuperscript{65}
Given the similar incidence of bronchiolitis hospitalisations among Canadian infants and the high respiratory morbidity (i.e. pneumonia) among Indigenous children in the NT, this is an important gap in knowledge. Further, in a retrospective study in Darwin (NT), infants with RSV bronchiolitis were more likely to be readmitted to hospital within a 6-month period. Yet, despite the high incidence of bronchiolitis hospitalisations among Indigenous children in the NT, there are no prospective studies in our setting exploring the diversity of viruses, atypical bacteria and associated disease severity. To fill this knowledge gap, nasopharyngeal swabs were collected as part of two randomised controlled trials (RCTs) at Royal Darwin Hospital (RDH), which examined the point prevalence of 17 viruses and atypical bacteria (chapters 3-4 and 6).

1.4.2.2 Bacterial associations

It is not routine management to test for respiratory bacteria in children with bronchiolitis, unless a secondary bacterial infection or sepsis is suspected. In the context of Indigenous children in the NT hospitalised with bronchiolitis, there are several reasons why bacteria may be important in the clinical management. Firstly, infants with severe bronchiolitis requiring admission to the intensive care unit (ICU) are more likely to have lower airway bacterial infections. Secondly, NT Indigenous children have earlier acquisition, dense carriage rates and multiple species of common respiratory bacteria, (i.e. Streptococcus pneumoniae, non-capsular Haemophilus influenzae (NTHi) and Moraxella catarrhalis) in their nasal space compared to non-Indigenous children. This is associated with higher rates of transmission and respiratory infections, and more severe bronchiolitis (described in section 1.3.2). Colonisation with respiratory bacteria has also been shown to be a risk factor for childhood pneumonia.
It is plausible that secondary bacterial infections occur post viral infections when the nasopharynx is colonised with bacteria.\textsuperscript{71} There are limited data on secondary bacterial infections in bronchiolitis. Of those published studies, co-infection with bacteria in children with RSV range from 3.5\% to 31\%.\textsuperscript{12,72,73}

In the absence of any published data on the possible role of bacteria contributing to the clinical profile of Indigenous children, a section of my thesis explored the role of common respiratory bacteria in disease severity in hospital (chapter 3-4) and beyond the hospitalisation period (chapter 6).

1.5 Assessing severity and risks of prolonged hospitalisation and post bronchiolitis syndrome

1.5.1 Assessing severity of bronchiolitis

Determining severity is an important part of clinical assessment and management of bronchiolitis. Many severity scoring systems are used in studies of bronchiolitis. However, despite their widespread use, many of these systems have not been validated or have limited validity when systematically evaluated.\textsuperscript{5,74-79}

The ability to predict disease severity is important and would benefit clinicians by altering care plans and management accordingly. A systematic review identified several studies which predicted disease severity. However, each study described different outcomes, thus focusing on different characteristics of the bronchiolitis process.\textsuperscript{2} Three of these studies focused on clinical predictors affecting disease progression which supported textbook diagnosis and risk factors of disease progression.\textsuperscript{45,80,81} Usen and colleagues described the importance of clinical signs and the relationship to hypoxic children.\textsuperscript{82} They identified key predictors which included pulse oximetry, cyanosis, head bobbing and respiratory rate.\textsuperscript{82} Others have
shown the use of pulse oximetry as the best guide to determine application of oxygen therapy.83 In the last decade, the introduction of pulse oximetry has seen a fivefold increase in the number of bronchiolitis hospitalisations.10,24 Yet, only 3 of 12 published clinical scores used oxygen saturations as outcome measures.84-86 The use of pulse oximetry has however shown to be useful in predicting cyanosis and clinical severity with the ability to detect worsening of disease at a 48-hour time point.10,87

The most widely used severity scoring system75 uses key respiratory signs, such as wheezing, retractions and respiratory rate. This system is complex and has been described for very short term assessment (i.e. hours).75,88 In current scoring systems, level of complexities include auscultation in segmental lobes, distinction of wheeze through parts of inspiratory and expiratory phases and other clinical parameters, which do not take into account SpO2 or cyanosis,74,75 thus making it difficult to evaluate across clinical research studies. While there is some level of subjectivity, several studies presented varying levels of agreement between observers for individual components such as respiratory rate, retractions and wheezing.75-79 Poor agreement in the detection of wheeze (kappa 0.29)89 and other clinical signs found on auscultation among general practitioners (kappa 0.12-0.39) is well known. This means scoring systems that describe wheeze are complex and are unlikely to be repeatable outside of specialist settings.90 In addition, many of the scoring systems have only looked at inter-rater agreement between doctors.91

A recent analysis of published severity systems for bronchiolitis identified only half were validated and had been modified for individual studies.74 Despite the widespread use, very little is known whether standardising a severity scoring system
will be useful for children hospitalised with bronchiolitis. Also, no scoring system has been used to predict oxygen requirement (like in asthma studies). The 2006 Scottish Intercollegiate Guidelines Network (SIGN) bronchiolitis guideline states there are “no good quality evidence on the use of formal clinical scoring systems in infants with acute bronchiolitis”. The lack of reliable tools to evaluate disease severity in clinical practice is therefore needed. Outside the hospital setting, identifying a useful clinical severity system that can be reliably used by non-medical staff (i.e. nurses, Indigenous Health Practitioners) in remote settings of the NT (where most of our Indigenous children reside) would be beneficial to improve assessment and clinical care. Chapter 2 describes a prospective observational study that systematically validated a modified clinical severity system to address this gap in the literature. Assessments were done by research nurses of varying levels of experience among children hospitalised with bronchiolitis.

1.5.2 Risk factors of prolonged hospitalisation for bronchiolitis

Those at risk for prolonged length of bronchiolitis hospitalisation include the very young (i.e. infants under 6-months of age) and born in the winter months. Other traditional clinical risk factors implicated for prolonged hospitalisation, include underlying medical conditions (i.e. prematurity, cardiac disease (CHD), immunodeficiency or underlying respiratory disease). Premature infants are more likely to be predisposed to more severe illness due to underdeveloped or damaged lungs and/or airway hyperactivity. The risk of apnea is also higher among infants (8%), and has been associated with prolonged length of hospitalisation (often due to admission to ICU and mechanical ventilation).
Other “non-traditional” risk factors likely to increase risk of bronchiolitis hospitalisations include: birth to a young mother, born in the first half of the RSV season, day care attendance, tobacco exposure, low birth weight, male gender, household crowding, and lack of breast feeding.\textsuperscript{23,95} International studies also report being Indigenous as an independent risk factor for hospitalisation compared to the general population.\textsuperscript{19,23,44,96} This may be due in large to socioeconomic factors such as overcrowding, environmental conditions and reduced access to health care services in remote regions. By the time these children are retrieved to tertiary care, their condition may have worsened and become more severe.\textsuperscript{35,42,97,98} Whether to admit or discharge a child in hospital is a complex decision. Many risk factors need to be considered, which include (but not limited to) the presence of co-morbidities, disease severity, geography and the caregiver’s ability to look after a child at home should their condition deteriorate.\textsuperscript{3,5}

Once hospitalised, determining which factors prolong hospitalisation remains challenging. Most hospital based studies have thus far focused on well known risk factors (i.e. age, underlying medical conditions etc.) and viruses such as RSV.\textsuperscript{35,53,93,99-101} In spite of RSV being the most dominant virus, improved molecular techniques over the last decade have identified a large number of other viruses.\textsuperscript{102-104} The clinical relevance of many of these however remains unclear, in particular when these non-classical viruses are commonly present in asymptomatic children (e.g. HRV, coronaviruses and bocaviruses).\textsuperscript{102-105} In a study from the USA, a virus (including non-classical viruses) was detected in 41.7\% in the nasopharynx of children hospitalised with no respiratory symptoms.\textsuperscript{105} In addition, whether single vs. multiple viruses influence clinical severity is also controversial.\textsuperscript{6,52,53,106-110} Reasons may be due to studies using different methodologies, yearly and seasonal variation,
sampling frame, age and number and type of viruses investigated, thus making it difficult to determine which viruses are associated with more severe disease in the wider population.\textsuperscript{52,53}

Among children in the NT, a retrospective study reported that Indigenous children experienced worse clinical outcomes than non-Indigenous children, yet specific risk factors associated with this increase was not known due to absence of data recorded in hospital records.\textsuperscript{22}

One of the objectives of my thesis was to determine what ‘non-traditional’ risk factors (clinical and microbiological), were associated with prolonging LOS, as part of two randomised controlled trials (chapters 3 to 4) and a cohort study (chapter 2) at RDH in the NT (chapter 6).

1.5.3 Post bronchiolitis symptoms

Bronchiolitis typically lasts from 3 to 7 days, yet a number of children will continue to have protracted symptoms beyond the acute clinical phase (i.e. >14 days).\textsuperscript{8} Most children will be asymptomatic by two weeks, however a small proportion will continue to have persistent symptoms up to four weeks.\textsuperscript{3} Cohort studies have reported persistent symptoms in 39\% of infants after 14-days, 18\% after 21-days and 9\% after 28-days after presentation to a primary health care setting.\textsuperscript{8} Other cohort studies have reported symptoms persisting between 15 to 25 days in up to 40\% of ambulatory children after presentation to hospital for bronchiolitis.\textsuperscript{3,5,53,111,112} The concept of post-bronchiolitis syndrome is therefore increasingly appreciated.\textsuperscript{3,8}

Children with severe disease may also be more likely to have persistent symptoms and signs such as wheeze and cough, which may be associated with ongoing
respiratory morbidity such as pneumonia. The potential role of antibiotics (in particular macrolides) may therefore benefit children with persistent symptoms and secondary bacterial infection, in the post-acute phase (>14 days). Further, data on the effectiveness of montelukast, (a cysteiny1 leukotrience receptor antagonist) for treating post-bronchiolitis syndrome (i.e. post-bronchiolitis wheeze) is inconsistent. A recent systematic review identified four RCT’s in children up to 24-months. The review concluded that montelukast reduced the frequency of post-bronchiolitis recurrent wheezing, but did not affect the incidence of recurrent wheezing or symptom free days. Reasons for variations in these results are likely multifactorial and include dose and duration of treatment, different methodologies (e.g. including children up to 24-months of age) and duration of follow up (6 to 18-months).

Presently, long term bronchiolitis studies in children focus on the development of asthma after a RSV and HRV bronchiolitis episode, rather than other respiratory symptoms (such as cough). Asthma will not be discussed any further in this thesis. Rather, I will focus on the importance of cough in post-bronchiolitis syndrome. Among Alaskan native children, a previous RSV bronchiolitis illness was predictive of chronic cough for children 5 to 8 years rather than development of asthma. The burden of persistent symptoms among Indigenous children beyond hospital (i.e. medium term) is not known. Given the high burden of respiratory disease in young children in our population, we suspect this would be substantial. Thus one of my objectives of my thesis was to determine the importance of persistent symptoms at 3-weeks, increased risk of respiratory readmissions 6-months and bronchiectasis 12-
months post hospitalisation. These knowledge gaps will be addressed in chapters 4 and 6.

Given that the damaged airway epithelium and respiratory cilia may persist for 13 to 17 weeks, secondary bacterial infections may occur during this phase. Under these circumstances, antibiotics may be beneficial. A Cochrane Review to examine the effectiveness of antibiotics compared to placebo to reduce or treat persistent respiratory symptoms following acute bronchiolitis was also undertaken (chapter 7).

Cough is the dominant symptom in bronchitis (an element of post-bronchiolitis syndrome). As part of my thesis, a second Cochrane Review was undertaken to evaluate whether using clinical pathways improves management and clinical care for children with chronic cough (≥4 weeks).

1.6 Treatment and management of bronchiolitis

1.6.1 Overview of current treatment and management guidelines

Although bronchiolitis is a typically self-limiting condition, effective treatment for bronchiolitis remains limited. The differences in the management of bronchiolitis transcend across borders and international countries and are widespread. The implementation of evidence based guidelines aims to improve management and reduce unnecessary investigations and therapies.

While most children can be managed at home, those with moderate to severe illness may require hospitalisation. Currently, no universal treatment is available, thus the mainstay for hospitalised bronchiolitis remains supportive, (e.g. supplemental oxygen, fluid replacement) until resolution of symptoms of the acute episode. Thresholds to commence supplemental oxygen vary widely across and within
countries. However, oxygen is usually provided in hypoxic infants when saturations fall below \( \leq 92\% \), until saturations are maintained between 92 to 95\%.\textsuperscript{3-5}

Infants with increased respiratory effort often have difficulty feeding.\textsuperscript{3,5,42} There are few studies addressing the most effective route of fluid therapy (i.e. intravenous or nasogastric feeding). Guidelines recommend infants should receive enough fluid to restore, maintain and avoid dehydration during acute periods of bronchiolitis.\textsuperscript{29} A number of therapies have been trialled with the aim to reduce the severity and/or length of the bronchiolitis episode.\textsuperscript{120} Current guidelines do not support treatments such as bronchodilators (albuterol, nebulised racemic epinephrine), systemic corticosteroids, montelukast, hypertonic saline, nasal suctioning, which respiratory support is best (i.e. continuous positive airway pressure, high-flow nasal cannula) chest physiotherapy, and antibiotics in otherwise previously well children hospitalised with bronchiolitis.\textsuperscript{3,5,121-124}

The only prophylactic treatment currently licenced to protect against RSV hospitalisation is palivuzumab.\textsuperscript{125} This humanised monoclonal antibody specifically targets RSV and can be given either intramuscularly or intravenously.\textsuperscript{51} Palivuzumab is given in five monthly doses to high risk (i.e. CLD of prematurity) or immunocompromised (CHD) infants prior to the bronchiolitis season in an attempt to reduce the number of RSV hospitalisations.\textsuperscript{3,5,51} Due to the high cost of this treatment, however (>£5,000 per child in the UK\textsuperscript{125} or $21,500 in Australia\textsuperscript{38}) prophylaxis is usually limited to infants at greatest risk for severe infection.

There is no proven clinical benefit of antiviral therapies such as ribavirin (which inhibits replication of the RNA and DNA of viruses such as RSV).\textsuperscript{51}
1.6.2 Antibiotic therapy in the treatment of bronchiolitis

Antibiotics are not routinely advocated in first line treatment of bronchiolitis due to its viral origins. They are recommended when the illness is severe or when a secondary bacterial infection is suspected (i.e. pneumonia or sepsis).\textsuperscript{3,5,42,126}

A Cochrane Review recently identified five antibiotic trials of children less than 2 years diagnosed with bronchiolitis.\textsuperscript{126} The review did not discriminate between different classes of antibiotics and thus included both beta lactam and macrolide antibiotics (e.g. intravenous ampicillin and oral erythromycin and azithromycin).\textsuperscript{127-131} A total of 543 participants were included, with only one small trial\textsuperscript{128} reporting benefits for antibiotics (e.g. clarithromycin) in reducing length of hospitalisation and clinical symptoms. This trial will be discussed in more detail below (section 1.6.3). The review concluded that antibiotics should be used cautiously in only the most severe children, to reduce potential side effects, costs and increased antibiotic resistance among bacterial pathogens.\textsuperscript{126}

In our setting, beta lactam antibiotics (e.g. amoxicillin, penicillin and ceftriaxone) are commonly prescribed in hospital for bronchiolitis.\textsuperscript{46} Reasons for this are several fold. Firstly, early and dense colonisation of common respiratory bacteria occurs in the nasopharynx\textsuperscript{132,133} and may lead to aspiration in young children with respiratory infections.\textsuperscript{71,134} These bacteria may overwhelm local lung defences (mucosal and innate immunity) already impaired by a viral infection.\textsuperscript{71,134} Secondly, associated bacterial infections such as otitis media are high among Indigenous children.\textsuperscript{135} Thirdly, bronchiolitis is often complicated by clinical and radiographic signs of pneumonia later in the bronchiolitis episode.\textsuperscript{136}
1.6.3 Macrolides

Indigenous children in the NT are at high risk for more severe disease and secondary bacterial complications, thus macrolide antibiotics are an attractive alternative treatment for bronchiolitis. Macrolides are a family of antibiotics which in addition to possessing antibacterial have immunomodulatory properties, anti-viral properties and are effective against *Mycoplasma pneumoniae* and *Chlamydiales* species.

The immunomodulatory effects of azithromycin were first noted in the 1960s in patients with severe asthma. In more recent years, macrolides have been used in the treatment of cystic fibrosis and bronchiectasis. Macrolides have been shown in laboratory studies to decrease airway inflammation by inhibiting neutrophil migration to the respiratory epithelium and blocking cytokines and other inflammatory mediators. With respect to anti-viral properties, clarithromycin reduces the RSV receptor on epithelial cells whereas azithromycin promotes interferon-stimulated genes in rhinovirus infected bronchial epithelial cells. Azithromycin is largely carried in cells, rather than blood, has a longer half-life and better tissue penetration at the site of infection than clarithromycin, and thus requires a much shorter treatment regime. Azithromycin also has been shown to reduce bacterial carriage and the risk of ALRI infections among African children following a mass trachoma prevention campaign.

Anecdotally, azithromycin has been commonly used in the NT for more than a decade to treat several diseases prevalent among remote Indigenous Australians, (i.e. sexually transmitted infections, trachoma and chronic suppurative respiratory infections). Most recently, in the first randomised controlled trial of Indigenous children diagnosed with non-cystic fibrosis bronchiectasis, researchers in Australia...
and New Zealand reported weekly azithromycin improved clinical outcomes. Weekly dosing was feasible and safe to use with few very adverse effects.\textsuperscript{146}

In Indigenous populations who have high nasal bacterial carriage and secondary infections (e.g. pneumonia and otitis media), macrolides such as azithromycin may help reduce airway inflammation and chronic infections, thus improving clinical outcomes.\textsuperscript{146} However, azithromycin is associated with increased pneumococcal resistance, thus needs to be monitored and used with caution.\textsuperscript{143}

At the start of my PhD, two randomised controlled trials (RCT) had been published on macrolides for bronchiolitis. The first was a small trial in Turkey, which involved 21 infants $\leq 7$ months with RSV bronchiolitis.\textsuperscript{128} This study had very small numbers and high attrition ($n=9$, 30%), nevertheless reported that a daily dose of clarithromycin (15mg/kg/day) for 3-weeks significantly reduced length of hospitalisation, supplemental oxygen and intravenous fluid requirements.\textsuperscript{128} The authors also reported a reduction in the number of respiratory readmissions within 6-months of hospital discharge.\textsuperscript{128}

The second was a larger European trial which included 71 infants $\leq 24$ months hospitalised with RSV bronchiolitis from the Netherlands.\textsuperscript{131} This trial was underpowered as it was stopped early due to logistical reasons, yet reported that 3 daily doses of azithromycin compared to placebo (10 mg/kg/day) was not associated with any clinical beneficial effects in reducing length of hospitalisation, duration of oxygen supplementation and clinical score.\textsuperscript{131}
At that point in time, there was insufficient evidence to determine whether macrolides would have any clinical benefit in children hospitalised with bronchiolitis. It was suspected that children in our setting would benefit from azithromycin as they had a similar clinical profile to the Turkish trial due to high rates of concomitant bacterial infections and respiratory disease (i.e. childhood bronchiectasis). Hence, a RCT on the use of azithromycin was planned. The pilot study (chapter 3) provided data for submission of a National Health and Medical Research Council (NHMRC) grant for a larger study, which formed chapter 4 of my thesis.

Since the above 2 studies and during the term of my PhD candidature, a further two studies have been published. These studies are described in chapter 3 and 4.

The larger study planned (forming chapter 4) extended the duration of azithromycin to 3 once-weekly doses, to determine if a longer course improved clinical outcomes in hospital (i.e. length of hospitalisation and duration of oxygen supplementation).

1.7 Hypothesis and aims

There are many gaps in the literature pertaining to the treatment and management of hospitalised bronchiolitis. To address these knowledge gaps, studies within my PhD aimed to contribute to the clinical management of hospitalised bronchiolitis among children. My primary aim was to improve the management of children, in particular, Indigenous children hospitalised with bronchiolitis.

The major hypothesis of my thesis was that azithromycin improves short and long term clinical outcomes of children hospitalised with bronchiolitis (Chapters 3 and 4).
The specific aims addressed by the studies included in this thesis are as follows:

1. To determine if a bronchiolitis scoring system (Tal et al.91 and its modification) undertaken by trained nurses is valid (inter-rater reliability and internal consistency) and a useful predictor of disease severity (need for supplementary oxygen at 12 and 24-hours post assessment) (Chapter 2).

2. To determine whether a single large dose of azithromycin (compared to placebo) reduced length of stay (LOS) and duration of O₂ requirement in children hospitalised with moderate to severe bronchiolitis. Secondary aims were to determine the influence of azithromycin on the incidence of respiratory readmissions and presence of bacteria and viruses in the nasopharynx (Chapter 3).

3. To determine whether a longer course (three large once-weekly doses) of azithromycin for Indigenous infants hospitalised with bronchiolitis improved clinical outcomes (LOS and duration of oxygen supplementation). Secondary aims were to: (i) determine the effects of azithromycin on respiratory symptoms and signs at day-21 and respiratory hospitalisations in the following 6-month period; (ii) assess the short-term impact of azithromycin upon nasopharyngeal carriage and respiratory virus shedding and; (iii) also describe the viruses, *M. pneumonia, Clamydiales* and *Simkani negevensis* species detected in these infants (Chapter 4).

4. Describe a novel approach to improve adherence, retention and clinical review rates of Indigenous children. The main outcome measure was rates of adherence to medications, retention in the RCT and self-presentation (with child) to clinic for a clinical review on day-21. This descriptive study was
nested within a placebo-controlled, randomised trial (RCT) on weekly azithromycin (or placebo) for 3-weeks (Chapter 5)

5. To determine factors (clinical and microbiological) on admission that were associated with; (i) prolonged LOS, (ii) presence of persistent symptoms 3 weeks after hospital discharge, (iii) whether presence of cough at 3 weeks was associated with bronchiectasis up to ~24 months post-hospitalisation and (iv) re-hospitalisation within 6 months for a respiratory illness.

6. To determine the effectiveness of antibiotics compared to a control (no treatment or placebo) to reduce or treat persistent respiratory symptoms following acute bronchiolitis (within 6-months of acute illness) (Chapter 7a).

7. To evaluate the effectiveness of using a clinical pathway in the management of children with chronic cough (Chapter 7b).

1.8 Thesis design

Studies were performed to address gaps in knowledge of specific aims. Chapter 2 describes our validated severity scoring tool. This study is embedded within two RCTs and a cohort study of children ≤24 months admitted to RDH with bronchiolitis. This severity scoring tool is important and will help monitor disease severity in hospitalised children as well in remote health settings where most health practitioners are nurses or Indigenous Health Practitioners.

Chapters 3 and 4 explore the role of different durations of azithromycin (single dose and 3-weekly doses) compared to placebo in an attempt to reduce short and long term clinical outcomes for children hospitalised with bronchiolitis. In chapter 5, a novel approach is described to improve adherence and retention of participants used
in our largest RCT using mobile phones and a culturally appropriate framework (chapter 4).

The point prevalence of different types of viruses, atypical bacteria, including concurrent bacterial infections are described in hospitalised children with bronchiolitis (chapters 3 to 4). The influence of viruses and bacteria on disease severity and recovery of acute bronchiolitis potentially provide data on strategies to prevent long term respiratory dysfunction (chapter 6).

Chapter 7 comprises of two Cochrane Reviews. Chapter 7a firstly examines the effectiveness of antibiotics to reduce persistent symptoms (i.e. cough and wheeze) following acute bronchiolitis. Chapter 7b evaluates the role of clinical pathways to improve management and clinical care of children with chronic cough.

The final chapter (chapter 8) summarises and discusses the research findings and discusses future research directions.

1.9 Summary of Chapter 1

Universally, bronchiolitis remains a leading cause of hospitalisation among infants. Although a typically self-limiting condition, there are significant knowledge gaps in how to treat and manage hospitalised children. This is of particular concern for Indigenous children, who have more severe disease and repeated hospitalisations in the first few years of life. The high incidence of respiratory disease among Indigenous children continues to drive early morbidity and mortality. Post-natally, the first two years of life is the most critical period for lung growth. Events such as severe ALRI's during this critical period are likely to have long term effects to the well-being, growth and development of Indigenous children.
This thesis aims to fill gaps in knowledge relating to the treatment and management of Indigenous children with bronchiolitis in an attempt to improve short and long term respiratory outcomes and prevent subsequent development of bronchiectasis.
Chapter 2: Severity Scoring Systems to Assess the Severity of Bronchiolitis

2.1 Chapter overview

This chapter addresses the gap in the assessment of bronchiolitis (described in section 1.5.1). The overall aim of this study was to determine the validity, responsiveness to change and reliability of two clinical severity scoring systems. The secondary aims were to determine if a bronchiolitis severity scoring system was a useful predictor of disease severity and the need for oxygen supplementation 12 to 24-hours after assessment.

Despite the numerous severity scoring systems available, very few have been systematically validated and have limited repeatability. This prospective cohort study of 115 children ≤24 months admitted to RDH with a clinical diagnosis of bronchiolitis was undertaken between October 2010 and December 2011. Three research nurses (two experienced, one junior) were trained in the assessment of scores, along with a standardised protocol. Two scoring systems were completed independently (i.e. nurses were blinded to each other’s score) by each nurse within 15 minutes of each other. Children were also assessed in a calm state. Standardised data collection forms were used to record demographic information and clinical data associated with the bronchiolitis episode (i.e. respiratory rate, accessory muscle use, degree of wheezing, cyanosis and oxygen saturations).

Section 2.2 consists of the published paper from this study, which supports our primary aim that severity scoring systems can used easily by nurses with varying levels of experience. However, the ability to predict oxygen use at 24-hours was limited.
2.2 Journal article - Severity Scoring Systems: Are they internally valid, reliable and predictive of oxygen use in children with acute bronchiolitis?
Chapter 3: Short Term Azithromycin Treatment to Improve Clinical Outcomes for Children Hospitalised with Bronchiolitis

3.1 Chapter overview

This chapter addresses the clinical gap in understanding the role of azithromycin in treating bronchiolitis (discussed in section 1.6.2 and 1.6.3). The overall aim of this pilot RCT was to determine if a large single dose of azithromycin (30mg/kg) compared to placebo reduced the length of hospital stay, duration of oxygen supplementation and respiratory readmissions within 6-months of hospital discharge. We also determined the effect on a broad panel of viruses, atypical bacteria and respiratory bacteria. We hypothesised that the anti-microbial and anti-inflammatory properties of azithromycin would improve clinical outcomes for children hospitalised with moderate to severe bronchiolitis. At the time of this pilot RCT, there was insufficient evidence from the two published trials, 128, 131 to determine the effectiveness of macrolides in the treatment of hospitalised bronchiolitis.

This RCT was conducted at RDH between June 2008 and December 2011, and the Townsville Hospital during October 2010 and December 2011. Townsville was included as a secondary site to assist with recruitment. 97 children ≤ 18 months, admitted to hospital with a clinical diagnosis of bronchiolitis were recruited and randomised (n=50 azithromycin, n=46 placebo) within 24-hours of admission. One participant was excluded from the primary analysis as they had received a macrolide in the previous 7-days, which was an exclusion criterion.

At enrolment, children received a single dose of azithromycin or placebo and had a nasopharyngeal swab collected and again 48-hours later. Children were monitored
every 12-hours using standardised data collection forms until their clinical endpoints were reached (i.e. off oxygen for 16-hours and feeding well). Respiratory hospitalisations within 6-months of discharge were recorded.

Section 3.2 consists of the published paper from this study. Despite azithromycin reducing carriage of bacteria in the nasopharynx, this study did not support our primary hypothesis that a large single dose of azithromycin improves clinical outcomes. When the data were grouped by ethnicity, Indigenous children had more severe disease, longer length of hospitalisation, oxygen requirement, and a higher proportion were readmitted with a respiratory illness within 6-months than non-Indigenous children. These data provide a clinical picture of Indigenous children in the NT population. The high rates of more severe respiratory illness, may be a precursor to chronic respiratory illness (i.e. bronchiectasis).

During the recruitment phase of this trial, we received funding from the NHMRC for our main RCT. This study extended the number of doses and duration of azithromycin to improve short and long term clinical outcomes. This RCT is described in chapter 4.
3.2 Journal article - A single dose of azithromycin does not improve clinical outcomes of children hospitalised with bronchiolitis: A randomised, placebo-controlled trial
A Single Dose of Azithromycin Does Not Improve Clinical Outcomes of Children Hospitalised with Bronchiolitis: A Randomised, Placebo-Controlled Trial

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Abstract

Objective: Bronchiolitis, one of the most common reasons for hospitalisation in young children, is particularly problematic in Indigenous children. Macrolides may be beneficial in settings where children have high rates of nasopharyngeal bacterial carriage and frequent prolonged illness. The aim of our double-blind placebo-controlled randomised trial was to determine if a large single dose of azithromycin (compared to placebo) reduced length of stay (LOS), duration of oxygen (O2) and respiratory readmissions within 6 months of children hospitalised with bronchiolitis. We also determined the effect of azithromycin on nasopharyngeal microbiology.

Methods: Children aged 1–18 months were randomised to receive a single large dose (30 mg/kg) of either azithromycin or placebo within 24 hrs of hospitalisation. Nasopharyngeal swabs were collected at baseline and 48hrs later. Primary endpoints (LOS, O2) were monitored every 12 hrs. Hospitalised respiratory readmissions 6-months post discharge was collected.

Results: 97 children were randomised (n = 50 azithromycin, n = 47 placebo). Median LOS was similar in both groups; azithromycin = 54 hours, placebo = 58 hours (difference between groups of 4 hours 95%CI -8, 13, p = 0.6). O2 requirement was not significantly different between groups; Azithromycin = 35 hrs, placebo = 42 hrs (difference 7 hours, 95%CI -9, 13, p = 0.7). Number of children re-hospitalised was similar 10 per group (OR = 0.9, 95%CI 0.3, 2, p = 0.8). At least one virus was detected in 74% of children. The azithromycin group had reduced nasopharyngeal bacterial carriage (p = 0.01) but no difference in viral detection at 48 hours.

Conclusion: Although a single dose of azithromycin reduces carriage of bacteria, it is unlikely to be beneficial in reducing LOS, duration of O2 requirement or readmissions in children hospitalised with bronchiolitis. It remains uncertain if an earlier and/or longer duration of azithromycin improves clinical and microbiological outcomes for children. The trial was registered with the Australian and New Zealand Clinical Trials Register. Clinical trials number: ACTRN12608000150347.

Introduction

Worldwide, bronchiolitis remains one of the most common reasons for hospitalisation of children [1]. Over 5 million children are diagnosed with bronchiolitis annually [2–3]. The incidence of bronchiolitis is higher in some populations, including Alaskan Native and Indigenous Northern Territory (NT) infants [1]. In the latter group, hospitalisation rates for bronchiolitis are higher [4] (352 vs. 62.6 per 1000) and infections are more severe than non-Indigenous children [5].

Bronchiolitis is a clinical syndrome that is diagnosed in children up to 24 months of age [6–8]. The most common infecting virus, respiratory syncytial virus (RSV) occurs in 50–80% of cases, [9] although an increasing number of viruses (e.g. human rhinoviruses...
(HRV), coronaviruses, bocavirus, [10,11] including multiple infections [12] are being identified. Current recommended therapies in hospitalised children are limited to oxygen (O2), fluids and hypertonic saline nebulisation [13]. However, semi-synthetic macrolides (e.g. azithromycin, clarithromycin) which have in vitro anti-viral effects, [15] which may be beneficial in children with bronchiolitis unless the illness is very severe or when a secondary bacterial infection is suspected [13]. However, semi-synthetic macrolides (e.g. azithromycin, clarithromycin) which have immunomodulatory, and/or anti-microbial properties [14] and in-vitro anti-viral effects, [15] which may be beneficial in children with bronchiolitis and high nasopharyngeal carriage rates of bacteria. Three randomised placebo-controlled trials (RCTs) have been published and these RCTs used different doses and duration of macrolides to treat hospitalised bronchiolitis [16] [17,18]. These studies also differed in adherence of settings which may reflect differences in the frequency and severity of acute respiratory infections in these populations [19]. Thus not surprisingly, results from the existing RCTs differed in the effect on reducing length of hospitalisation and O2 requirement. A Turkish [17] trial reported improved clinical outcomes. In comparison a European [16] and a Brazilian [18] trials showed no improvement.

Table 1. Demographic and clinical characteristics of 96 patients randomized to treatment of Azithromycin (n = 50) or placebo (n = 46) and by ethnicity.

<table>
<thead>
<tr>
<th></th>
<th>Azithromycin (n = 50)</th>
<th>Placebo (n = 46)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Indigenous (31)</td>
<td>Non Indigenous (19)</td>
</tr>
<tr>
<td></td>
<td>Indigenous (30)</td>
<td>Non Indigenous (16)</td>
</tr>
<tr>
<td>Age in months</td>
<td>5 (3–8)</td>
<td>5.6 (1.5–11)</td>
</tr>
<tr>
<td>Age ≥6 months</td>
<td>19 (81%)</td>
<td>9 (47.3%)</td>
</tr>
<tr>
<td>Boys</td>
<td>23 (74%)</td>
<td>11 (58%)</td>
</tr>
<tr>
<td>Gestational age (weeks)</td>
<td>39 (35–40)</td>
<td>38.3 (37–40)</td>
</tr>
<tr>
<td>Birth weight (kg)</td>
<td>3.15 (1.9–3.4)</td>
<td>3.38 (2.87–3.78)</td>
</tr>
<tr>
<td>Number from remote areas</td>
<td>19 (61%)</td>
<td>4 (21%)</td>
</tr>
<tr>
<td>Exposed to household smoke</td>
<td>20 (65%)</td>
<td>2 (11%)</td>
</tr>
<tr>
<td>Lethargy</td>
<td>16 (52%)</td>
<td>11 (58%)</td>
</tr>
<tr>
<td>Fever C</td>
<td>37 (36.3–37.2)</td>
<td>37 (36–37)</td>
</tr>
<tr>
<td>Antibiotics prescribed</td>
<td>27 (87%)</td>
<td>9 (47%)</td>
</tr>
<tr>
<td>Supplemental fluid administered</td>
<td>12 (39%)</td>
<td>7 (37%)</td>
</tr>
<tr>
<td>C/O taken</td>
<td>30 (97%)</td>
<td>14 (74%)</td>
</tr>
<tr>
<td>Skin infection</td>
<td>8 (26%)</td>
<td>2 (11%)</td>
</tr>
<tr>
<td>Anaemia</td>
<td>7 (23%)</td>
<td>1 (5%)</td>
</tr>
<tr>
<td>Failure to Thrive</td>
<td>1 (3%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Lobar Pneumonia/Collapse on CXR</td>
<td>8 (26%)</td>
<td>1 (5%)</td>
</tr>
<tr>
<td>Other</td>
<td>1 (3%)</td>
<td>0 (0%)</td>
</tr>
</tbody>
</table>

Median and IQR (25–75%) for continuous variables. Actual numbers for categorical variables and percentages. NB: Missing values described.

Azithromycin: Gestational age = 3 (6%). Birth weight = 6 (12%). Mother smoked during pregnancy = 3 (6%). Exposure to household smoke = 2 (4%). Placebo: Gestational age = 2 (4%). Birth weight = 3 (6.5%).

Indigenous children: Gestational age = 2 (3.3%). Birth weight = 4 (6.5%). Mother smoked during pregnancy = 2 (3%). Exposure to household smoke = 1 (1.6%).

Non Indigenous children: Gestational age: 3 (8.6%). Birth weight = 5 (14.3%) Mother smoked during pregnancy = 1 (3%). Exposure to household smoke = 1 (3%).

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Fever

Skin infections

Anaemia

Failure to Thrive

Lobar Pneumonia/Collapse on CXR

Other

-year-olds. Antibiotics are rarely advocated in the management of bronchiolitis unless the illness is very severe or when a secondary bacterial infection is suspected [13]. However, semi-synthetic macrolides (e.g. azithromycin, clarithromycin) which have immunomodulatory, and/or anti-microbial properties [14] and in-vitro anti-viral effects, [15] which may be beneficial in children with bronchiolitis and high nasopharyngeal carriage rates of bacteria. Three randomised placebo-controlled trials (RCTs) have been published and these RCTs used different doses and duration of macrolides to treat hospitalised bronchiolitis [16] [17,18]. These studies also differed in adherence of settings which may reflect differences in the frequency and severity of acute respiratory infections in these populations [19]. Thus not surprisingly, results from the existing RCTs differed in the effect on reducing length of hospitalisation and O2 requirement. A Turkish [17] trial reported improved clinical outcomes. In comparison a European [16] and a Brazilian [18] trials showed no improvement.

Bacterial infections in children with RSV positive acute lower respiratory infections range from 3.5% to 31% [2,20,21]. The higher rate is more likely in less-affluent settings and/or with those with more severe disease [22–24]. Viral-bacterial co-infections are more likely when the upper airways are densely colonised with bacteria or during repeated infections [25]. In the NT, children have early acquisition of bacteria in the nasal space [26]. This is more likely to be similar to Turkey where high rates of pneumonia and bronchiectasis are also reported [22]. Thus, we conducted a RCT on children hospitalised with bronchiolitis. Our primary objective was to determine whether a single large dose of azithromycin (compared to placebo) reduced length of stay (LOS) and duration of O2 requirement in children hospitalised
with moderate to severe bronchiolitis. We also determined the influence of azithromycin on the incidence of respiratory readmissions and presence of bacteria and viruses in the nasopharynx.

**Methods**

**Study design**

Our double-blinded, placebo-controlled, RCT was conducted at the Royal Darwin Hospital between June 2008 and December 2011 and the Townsville Hospital between October 2010 and December 2011.

**Trial registration**

The trial was registered with the Australian and New Zealand Clinical Trials Register. Clinical trials number: ACTRN12608000150347.

**Ethics statement**

The study was approved by the Human Research Ethics Committee of the Northern Territory Department of Health and Menzies School of Health Research (HREC 07/60) and The Townsville Health Service District Human Research Ethics Committee (HREC/10/QTHS/9). Individual written informed consent was obtained from children’s parents or legal guardian.

**Participants**

Children were enrolled if they were ≤18 months, admitted with a clinical diagnosis of bronchiolitis (according to standardised hospital protocols; ≤18 months, with cough and coryza, wheezing +/− crackles, respiratory distress with both tachypnoea (respiratory rate >50 beats/min) and retractions), required supplemental O₂ and consented within 24 hrs of hospitalisation. Children were excluded if they had: severe disease (admitted to intensive care unit), chronic lung disease, congenital heart disease, contraindica-
tions to macrolide use (e.g. liver dysfunction, hypersensitivity), diarrhoea (≥2 stools of watery consistency more than normal pattern), received macrolides (in last 7 days), or clinical and radiological features consistent with a primary diagnosis of pneumonia [27] at time of randomisation.

Protocol and interventions used across both sites

Study staff visited the paediatric wards twice daily to assess newly admitted children. After consent, children were randomised to receive a single large dose of oral liquid azithromycin (30 mg/kg) or placebo suspension (equal volume). The placebo suspension was made up of confectioner’s Sugar, Hydroxypropyl Cellulose, Xanthan Gum, Syloid 244, Sodium Phosphate Tribasic, Imitation Vanilla Creamy Flavour, Black Cherry Flavour, Quinine Sulphate (ground Quinate 300 mg Tablets). Children were managed by the paediatric team of each hospital according to the same clinical protocol for bronchiolitis (e.g. criteria for commencement and weaning of O2) that was standardised 6 months before commencement of the trial. Children were allowed to receive concurrent medications specified by the attending physician, except macrolide antibiotics. The protocol for this trial and supporting CONSORT checklist are available as supporting information; see Checklist S1 and Protocol S1.

Randomisation, allocation and blinding

Randomisation was stratified by age (<6 or >6 months), ethnicity (Indigenous or non-Indigenous) and site (Darwin or Townsville). Randomisation was by computer generated permuted blocks and treatment allocation concealed by opaque stickers. Upon enrolment, children were assigned the next treatment on the appropriate stratified list. Neither the study team (researchers, hospital staff) nor parents were aware of the assigned treatment group until the end of the trial.

The placebo medication was manufactured by the Institute of Drug Technology Australia Limited (Melbourne, Victoria). It had a similar smell and taste to active azithromycin. Azithromycin (Pfizer, Australia) was repackaged by IDT. Both medications were prepared as powder in identical opaque bottles and sealed with an aluminium foil.

Figure 2. Length of stay (LOS) in hospital – Azithromycin Vs Placebo and Ethnicity.
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Figure 3. Time on Oxygen (O2) in hospital – Azithromycin Vs Placebo and Ethnicity.
doi:10.1371/journal.pone.0074316.g003

Figure 4. Time to first readmission – Azithromycin Vs Placebo.
doi:10.1371/journal.pone.0074316.g004

Figure 5. Time to first readmission – Indigenous Vs Non-Indigenous.
doi:10.1371/journal.pone.0074316.g005
Clinical assessment and outcome measures

Standardised data collection forms were used to record demographic, medical history and clinical data from each child (Table 1). This included O2 requirement and level, respiratory rate, temperature and heart rate. Other therapies (intravenous fluids, antibiotics) and routine investigations (full blood count and chest x-ray) were also documented.

Children enrolled in the study were assessed twice daily by the attending doctor (blinded and not an investigator) for clinical signs inconsistent with bronchiolitis and associated with known azithromycin side effects. Outcome measures were collected every 12 hours until the study endpoint was reached. The primary endpoints were: LOS for respiratory illness and duration of O2 requirement. LOS was defined as time from admission to time for ‘ready for discharge’ (SpO2 consistently >94% in air for >16 hrs) and feeding adequately. ‘Ready for discharge’ differed from LOS, as discharge from hospital in our setting is often delayed due to other social factors, especially in children from remote Indigenous communities. Other outcomes were (i) any respiratory related readmissions within 6 months of discharge and (ii) identification of respiratory viruses and bacterial pathogens. Adverse events were monitored by study staff every 12 hours until discharge. Respiratory readmissions were collected from the medical charts; as there these children had no access to any other hospitals in the region, this is a reliable outcome.

Specimen collection and process

A nasopharyngeal swab (NPS) was taken prior to administration of study medication and 48 hrs later (or at discharge). NPS were placed in skim milk tryptone glucose glycerol broth media and were transferred on ice stored at 2-8°C in accordance to published guidelines [28,29].

Assessment for viruses and atypical bacteria were described previously [30–32]. Nucleic acids were extracted from 0.2 ml of each NPS using the High Pure Viral Nucleic Acid kit (Roche Diagnostics, Australia), according to the manufacturer’s instructions. Polymerase Chain Reaction (PCR) methods were used to detect RSV (A and B), adenovirus, parainfluenza (1, 2, 3), influenza virus (A and B), HRV and enterovirus, coronaviruses, bocavirus type 1, human metapneumovirus (hMPV), KI (KIPyV) and WU (WUPyV) polyomaviruses, Chlamydophila pneumoniae and Mycoplasma pneumoniae. For bacterial analysis, NPS were thawed and 10 μl aliquots cultured overnight on selective media at 37°C in 5% CO2; identification of Streptococcus pneumoniae, Haemophilus influenzae, Moraxella catarrhalis and Staphylococcus aureus used established techniques as previously described [26,28,33].

Statistical methods

We formally compared baseline characteristics of Indigenous vs. non-Indigenous children, with appropriate statistical tests. We did not formally do this between treatment groups in accordance with current CONSORT recommendations (available http://www.consort-statement.org/consort-statement/13-19-results/item15baseline-data/. Accessed 28th June 2013). Our pre-specified analysis plan, stated that non parametric methods be used if...
data were not normally distributed. Data were presented as medians and interquartile range (IQR) for LOS and O2. Differences between groups were tested using the Mann-Whitney test. A 95% confidence interval (CI) was obtained for the difference in medians between treatment groups [34]. Subgroup analysis was performed by ethnicity (Indigenous vs. non-Indigenous) and by age (≤6 and >6 months). Differences in proportions were tested with Fisher’s exact test. We looked at time to readmission within 6 months of hospital discharge using Kaplan-Meier survival plots.

Sample size
We calculated that a total sample of 92 children (equal numbers of Indigenous and non-Indigenous children recruited) would provide 90% power to detect a difference in the mean LOS of 24 hrs between each treatment for each ethnic group at the 5% significance level assuming the standard deviation was 24 hrs in each group. This study was underpowered to detect differences in rates of readmission between treatment groups.

Results
We recruited 97 children and data from 96 children were analysed (Figure 1). The major reason why 450 children did not meet the inclusion criteria was they did not require supplemental O2 or were admitted over the weekend. During recruitment, 21 children admitted into intensive care were excluded; 17 were Indigenous. One participant was excluded from the analysis of primary outcomes; they had received a macrolide in the previous 7 days (this child was randomised to placebo). This child was included in the analysis of secondary outcomes. Of the 96 remaining children, demographic and clinical characteristics were similar between the treatment groups (Table-1). No children received steroids during hospitalisation. Of the cohort, 10 children were previously hospitalised for a respiratory episode. In hospital, additional antibiotics were more often prescribed in Indigenous children (n = 52, 85%, p = 0.005) (Table-1).

LOS was similar in both treatment groups. The median LOS in the azithromycin group was 54 hrs, compared to 58 hrs in the placebo group (difference between groups of 4 hrs, 95%CI –8, 13, p = 0.6), figure 2. The median time on O2 in the azithromycin group was 35 hrs, compared to 42 hrs in the placebo group (i.e. reduction of 7 hrs 95%CI –9, 13, p = 0.7), figure 3. No child required admission into intensive care and there were no adverse or serious adverse events.

All children contributed to readmission data. There was no significant difference in the number of respiratory readmissions within 6 months (10 per group, OR = 0.9, 95%CI 0.3, 2, p = 0.8) or time to readmission (logrank p = 0.9) between treatment groups (figure 4). 70% of children readmitted, were reported to have a wheeze-associated illness.

Indigenous children (n = 61) had longer LOS; median 59 hrs compared to 51 hrs in non-Indigenous children (n = 35) (difference of 8 hrs, 95%CI –25, 1.3, p = 0.07). This was similar with duration of O2: 43 hrs in Indigenous children and 35 hrs in non-Indigenous children (difference of 8 hrs 95%CI 2-1, 1, p = 0.08). A higher proportion of Indigenous children were readmitted for a respiratory illness (n = 16 (26%) compared to non-Indigenous children (n = 4 (11%)), difference 15% (95%CI 0, 30%) p = 0.05. Indigenous children were more likely to be re-hospitalised earlier (Indigenous n = 16, non-Indigenous n = 4, OR = 2.8, 95% CI 0.9, 8.8), logrank p = 0.08 (figure 5). There was no evidence that the difference in either LOS or O2 between treatment groups varied according to ethnicity or age (table-2).

Viral and bacteria data
All but one child had a baseline NPS. NPS could not be obtained on all participants at 48 hrs due to discharge occurring during evenings or weekends. One participant’s family withdrew consent for NPS.

At baseline, viruses were not detected in 23 (24%) participants. One or more virus was detected in 54 (56%) children. Two or more viruses were detected in 19 (20%) of children. RSV was the most common (n = 48, 50%), followed by HRV (n = 16, 17%), bHPV (n = 5, 5%) and coronavirus (n = 5, 5%). Figure 6 depicts the frequency of virus detection at baseline and 48hrs. There was no reduction in the mean number of viruses detected per child from baseline to 48hrs; azithromycin 1.0 to 0.8 (95% CI = 0.2, 0.6, n = 34); placebo 0.9 to 1.0 (95% CI = 0.3, 0.2, n = 37).

Table-3 summarises NPS bacteria detected at baseline and 48 hrs. A reduction in the mean number of respiratory bacteria was detected per child; in the azithromycin group from 1.2 to 0.5

<table>
<thead>
<tr>
<th>Nasal carriage of pathogens</th>
<th>Azithromycin</th>
<th>Placebo</th>
<th>Azl vs. Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>48 hours</td>
<td>Baseline</td>
</tr>
<tr>
<td>Staphylococcus pneumoniae</td>
<td>N = 49</td>
<td>9 (19%)</td>
<td>2 (4%)</td>
</tr>
<tr>
<td>Haemophilus influenzae</td>
<td>N = 46</td>
<td>18 (37%)</td>
<td>3 (6%)</td>
</tr>
<tr>
<td>Moraxella catarrhalis</td>
<td>N = 46</td>
<td>21 (43%)</td>
<td>2 (4%)</td>
</tr>
<tr>
<td>Staphylococcus aureus</td>
<td>N = 37</td>
<td>4 (8%)</td>
<td>1 (2%)</td>
</tr>
</tbody>
</table>

Table 3. Bacteria outcomes at pre treatment (baseline) and post treatment (48 hours).
bacteria (difference 0.7 95%CI 0.25, 1.1, p = 0.01), and zero change in the placebo group; 1.3 to 1.3 bacteria.

Compared to those with a single dose of azithromycin alone (n = 14) (i.e. received no additional antibiotics in hospital) were less likely to have S. pneumoniae (3/14, vs. 0/11), M. catarrhalis (5/14 vs. 1/11), H. influenzae (6/14 vs. 1/11), and Staphylococcus aureus (3/14 vs.0/11) at 48 hrs. 3/14 children did not have NPS at 48 hrs.

Discussion

We found that a large single dose of azithromycin (compared to placebo), did not have large clinical effects on LOS, length of O₂ requirement or readmission within 6 months of discharge. Azithromycin reduced the proportion of children with respiratory bacteria in their NPS but had no significant effect on viral detection by PCR.

Of the 3 published RCTs on macrolides to treat hospitalised children with bronchiolitis, [16-18] only one [17] reported improved clinical effects i.e. reduced LOS, duration of O₂ requirement and lower readmission rates. Our findings are similar to the other two trials [16,18] showing that a single dose azithromycin does not shorten LOS and O₂ requirement. However, methodological differences among trials need to be considered. One of the larger trials [16] included only children with RSV-confirmed bronchiolitis, thus limiting generalisation to bronchiolitis caused by other pathogens. Other differences included: age, ethnic populations, concurrent use of antibiotics, treatment regimens and macrolide type and duration. The immunomodulatory difference between azithromycin and clarithromycin may also account for the differential results between Tahan et al’s study [17] with ours and the other 2 RCTs [16,18]. For example, azithromycin increased the production of IL-10 whereas clarithromycin inhibited the production of IL-6 by dendritic cells in animal work [35]. Tahan and colleagues [17] used a daily dose for 3-weeks of clarithromycin, but ours like Kasyber et al [16,18] (7-day daily dose) used a short course of azithromycin. However, Tahan et al’s [17] study had very small numbers (n = 21) and high attrition. Thus, it remains unknown if a longer course of azithromycin may be effective in reducing readmission rates.

Of the published RCTs on macrolides for bronchiolitis in children, our patient profile is most like that of the Turkish study [17]. However, unlike the Turkish RCT, [17] we did not find a beneficial effect of azithromycin on clinical outcomes. Possibly contributory reasons include the very high concomitant use of antibiotics in our group; different treatment regime used the density of bacterial carriage and secondary co-morbidities. The common use of antibiotics in children with bronchiolitis in our setting relates to the high rates of concomitant infections among children. A similar treatment practice occurs in Alaskan children [1]. 56% of Indigenous children in our trial received antibiotics before admission and 87% during hospitalisation. While the use of antibiotics is common practice in such settings, its effectiveness and possibly increased adverse events remains unknown. Ideally, concurrent antibiotics should have been disallowed in our study but it was not possible to alter clinicians’ practice and our a priori protocol allowed the concurrent use of antibiotics other than macrolides.

We used a single large dose of azithromycin, which is equivalent to one week of treatment for several reasons [36]. In our setting, early (as early as 2-weeks of age) nasopharyngeal colonisation of respiratory pathogens occurs in Indigenous children [37]. Azithromycin potentially has a beneficial microbiological effect on these pathogens [36]. Azithromycin also has the benefit of a long half life and tissue penetration requiring less frequent dosing, compared to other antibiotics [36]. This is important in our setting where adherence to treatment regimes can be challenging.

While our trial did not find significant differences between treatment groups for clinical outcomes, our study had some novel data. Firstly, none of the published RCTs on macrolides for children with bronchiolitis report data on the impact on viral detection or bacterial carriage. As viruses were identified by PCR, it is not surprising no difference in viral detection were found at 48 hrs (although azithromycin may have some anti-viral effect) [15]. Future research should look at the impact of azithromycin on viral load/copies. While our numbers were small, we showed a significant difference in the mean number of respiratory bacteria per child; from 1.2 to 0.5 bacteria (difference 0.7 95%CI 0.25, 1.1, p = 0.01) in the azithromycin group. This is important in our setting as NPS carriage of respiratory pathogens (e.g. S. pneumoniae, H. influenzae, M. catarrhalis) are among the highest reported globally (over 80%), compared to non-Indigenous children (50%) [26].

Secondly, our study provides a clinical picture of hospitalised cases of bronchiolitis in different geographical and ethnic groups in Northern Australia, where acute respiratory infections may be one precursor of high rates of chronic respiratory illness [5,30]. This is the first data published, showing NPS detection of viruses and bacteria from Indigenous children hospitalised with bronchiolitis. Wheezing and bacterial infections in young children have been shown to be associated in one prospective cohort study [39]. Thus our data may have implications in settings, where acute and chronic respiratory diseases are more prevalent and more severe, including Alaska and New Zealand [40-42].

We found that Indigenous children exhibited longer LOS, O₂ requirement and earlier time to hospital readmission than non-Indigenous children. The most likely reason why the latter aspects are different from our previous study [5] is because we excluded children managed in intensive care. In our cohort, Indigenous children were more likely to be readmitted for another respiratory illness. This is not surprising as Indigenous children in the NT are 5 times more likely to be hospitalised for pneumonia and influenza than non-Indigenous children [43]. Whether readmission is related to the insult from bronchiolitis can only be postulated. Recurrent hospitalisation for respiratory illness is an independent risk factor for developing bronchiectasis and/or respiratory dysfunction in adulthood [44,45]. In our region, bronchiectasis affects 1 in every 68 Indigenous children [46]. In the follow up of our cohort, 6/61 (10%) Indigenous children (3 in azithromycin group, 3 in placebo group) have subsequently been diagnosed with bronchiectasis and an additional 4 children are awaiting chest scans.

The prevalence of readmission for a respiratory illness within 6-months in our trial was 21%; 70% had a wheezing illness. This was similar to the Turkish trial at 24% (53% were wheezing) [17]. The two most common viruses found in our cohort, RSV and HRV have been implicated for ongoing wheezing [47-50]. New Zealand data have also recently described high prevalence (70%) of on-going intermittent wheezing 12-months post hospitalisation with acute lower respiratory infections [41]. In addition, wheezing and persistent cough can also be problematic post acute bronchiolitis [17]. Our trial (and the other published RCTs of macrolides for acute bronchiolitis) did not assess this, a known clinical research gap [7,31]. Despite providing new data, there are other several limitations to our study, in addition to the concurrent use of antibiotics. Having older children increased the risk of including asthma prone children. We also did not limit to the first bronchiolitis admission. Removing the children with recurrent disease in a secondary analysis made no difference to study outcomes. As our study was
limited to a single dose, it remains uncertain if any macrolides, or a longer macrolide treatment course, is beneficial in high risk children who do not receive any other antibiotics. Only having two sites, may also affect the generalisability of the results.

Conclusion

In children hospitalised with moderate to severe bronchiolitis and requiring supplemental O2, we found that a large single dose of azithromycin (compared to placebo) did not have any clinical benefit to reduce LOS, duration of O2 requirement or readmission rates within 6 months of hospital discharge. Azithromycin reduced the proportion of bacterial carriage, but had no significant effect on reducing proportion of viruses. Further research is required to determine whether earlier administration and longer duration of azithromycin is beneficial to improve the clinical and microbiological outcomes of acute bronchiolitis, associated co-morbidities and prevent ongoing respiratory morbidity in this population.

Supporting information

Checklist S1 CONSORT checklist. (PDF)

Protocol S1 Trial protocol. (PDF)

References

Chapter 4: Three Weekly Doses of Azithromycin to Improve Clinical Outcomes for Indigenous Infants Hospitalised with Bronchiolitis

4.1 Chapter overview

This chapter continues to address the clinical gap in understanding the role of azithromycin in the treatment of bronchiolitis within and beyond hospitalisation (discussed in section 1.6.2 and 1.6.3 and builds on chapter 3). At the time of commencing this trial, only two RCT’s were published. Clinical evidence suggested that a short course of azithromycin was not effective; however it remained unknown if longer courses improved clinical outcomes beyond hospitalisation. Furthermore, Indigenous children in affluent countries such as Australia and New Zealand are at high risk of more severe disease (i.e. determined by length of hospitalisation, oxygen requirement) and repeated respiratory readmissions within 6-months of discharge.22,35,94,149

Consequently, we conducted a multicentre international, double-blind RCT, to determine if 3-weeks of azithromycin (compared to placebo), improved clinical outcomes in Indigenous infants hospitalised with bronchiolitis. Our secondary aims were to: (i) determine the effects of azithromycin on respiratory symptoms and signs at day-21 and respiratory hospitalisations in the following 6-month period; (ii) assess the short-term impact of azithromycin upon nasopharyngeal carriage and respiratory virus shedding and; (iii) also describe the viruses, *M. pneumonia, Clamydiales* and *Simkani negevensis* species.

This RCT was conducted at RDH between June 2010 and September 2013, Townsville Hospital between August 2010 and June 2013 in Australia and Auckland Starship Children’s Hospital between November 2012 and September 2013 in New
Zealand. Two-hundred-and-nineteen infants ≤24 months (this trial defined infants ≤24-months) were randomised (n=106 azithromycin, n=113 placebo) within 24-hours of hospitalisation. The same eligibility criteria applied to infants in this RCT as chapter 3, other than caregiver’s requirement to have a mobile phone (described in further detail in chapter 5).

Infants were randomised to three once-weekly doses of oral azithromycin or placebo. The first dose was given in hospital, whereas the final two doses were either directly supervised by study nurses (urban-based participants) or given at home by caregivers (remote-based participants). Parents received education prior to hospital discharge in how to prepare medication and research nurses also contacted caregivers at the time when medication was due, to help ensure adherence to trial medication and compliance to the study protocol.

A nasopharyngeal swab was collected at enrolment (and again 48-hours later) to determine the presence of a broad panel of viruses and respiratory bacteria. Hospital management was identical to that described in chapter 3. Infants were monitored by study staff every 12-hours using standardised data collection forms until their clinical endpoints were reached (i.e. off oxygen for 16-hours and feeding well). Infants were clinically reviewed at day-21 to determine the presence of persistent respiratory symptoms and signs. Hospitalised respiratory readmissions within 6-months of discharge were also recorded.

Section 4.2 consists of the manuscript from this study has been submitted for publication. Despite reducing nasopharyngeal bacterial carriage, three large once-weekly doses of azithromycin did not have any short or long term clinical benefit over placebo during the bronchiolitis illness at day-21 review or 6-months post-
hospitalisation. Our data are consistent with the published RCTs. Azithromycin should not be recommended to treat infants hospitalised with bronchiolitis.
4.2 Journal article - Three-weekly doses of azithromycin for Indigenous infants hospitalised with bronchiolitis: A multicentre, randomised, placebo-controlled trial (manuscript submitted for publication)
Three-weekly doses of azithromycin for Indigenous infants hospitalized with bronchiolitis: a multicentre, randomized, placebo-controlled trial

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Background: Bronchiolitis is a major health burden in infants globally, particularly among Indigenous populations. It is unknown if 3 weeks of azithromycin improve clinical outcomes beyond the hospitalization period. In an international, double-blind randomized controlled trial, we determined if 3 weeks of azithromycin improved clinical outcomes in Indigenous infants hospitalized with bronchiolitis.

Methods: Infants aged ≤24 months were enrolled from three centers and randomized to receive three once-weekly doses of either azithromycin (30 mg/kg) or placebo. Nasopharyngeal swabs were collected at baseline and 48 h later. Primary endpoints were hospital length of stay (LOS) and duration of oxygen supplementation monitored every 12 h until judged ready for discharge. Secondary outcomes were: day-21 symptom/signs, respiratory rehospitalizations within 6 months post-discharge and impact upon nasopharyngeal bacteria and virus shedding at 48 h.

Results: Two hundred nineteen infants were randomized (n = 106 azithromycin, n = 113 placebo). No significant between-group differences were found for LOS (median 54 h for each group, difference = 0 h, 95% CI: −6.8; p = 0.8), time receiving oxygen (azithromycin = 40 h, placebo = 35 h, group difference = 5 h, 95% CI: −8; 11; p = 0.7), day-21 symptom/signs, or rehospitalization within 6 months (azithromycin n = 31, placebo n = 25 infants, p = 0.2). Azithromycin reduced nasopharyngeal bacterial carriage.

Abbreviations: CI, confidence interval; DSMB, data safety monitoring board; HRV, human rhinovirus; LOS, length of stay; NHMRC, National Health and Medical Research Council; NPS, nasopharyngeal swab; PCR, polymerase chain reaction; RCT, randomized controlled trial; RSV, respiratory syncytial virus.
(between-group difference 0.4 bacteria/child, 95% CI: 0.2, 0.6; \( p < 0.001 \)), but had no significant effect upon virus detection rates.

**Conclusion:** Despite reducing nasopharyngeal bacterial carriage, three large once-weekly doses of azithromycin did not confer any benefit over placebo during the bronchiolitis illness or 6 months post-hospitalization. Azithromycin should not be used routinely to treat infants hospitalized with bronchiolitis.

**Clinical trial registration:** The trial was registered with the Australian and New Zealand Clinical Trials Register: Clinical trials number: ACTRN12610000360999.

**Keywords:** bronchiolitis, Indigenous, viruses, bacteria, respiratory syncytial virus, macrolides, azithromycin, randomized controlled trial

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**Introduction**

Bronchiolitis is the most common acute viral lower respiratory infection in infants worldwide causing more than three million hospitalizations annually (1). Indigenous children from affluent countries, such as Australia and New Zealand, are at particular risk. They are more likely than non-Indigenous children to be hospitalized (2, 3), to have longer hospital stays (2), to receive antibiotics for pneumonia (2, 4), and to be rehospitalized in the next 6 months with a respiratory illness (5). Indigenous children also have high rates of pneumonia and bronchiectasis (the latter related to recurrent pneumonia) (6, 7) and their upper airways are colonized with bacterial pathogens from an early age (8).

Supportive care, including supplemental oxygen, respiratory support, and fluid replacement, underpins bronchiolitis management. Clinical trials have shown bronchodilators, mucolytics, anti-viral, and anti-inflammatory agents to be ineffective (9). However, macrolide antibiotics pose as an attractive alternative, especially for Indigenous infants with their high risk of severe disease and secondary bacterial complications (5). In addition to possessing direct antibacterial actions, including activity against *Mycoplasma pneumoniae* and *Chlamydiales* species, macrolides modulate macrophage, neutrophil, and epithelial cell function in vitro and in experimental models (10), and possess potential anti-viral properties. Clarithromycin reduces respiratory syncytial virus (RSV) receptor numbers on epithelial cell surfaces; while azithromycin induces interferon-stimulated genes in rhinovirus (RV)-infected bronchial epithelial cells (11, 12). Finally, a single azithromycin dose decreases nasopharyngeal bacterial loads (5) and transiently reduces the risk of acute lower respiratory infections in African children following mass trachoma prevention campaigns or when contributing to combination therapy for malaria (13, 14).

Four placebo, double-blind, randomized controlled trials (RCTs) have evaluated the efficacy of macrolides in children hospitalized with bronchiolitis (5, 15–17). The first trial from Turkey (15), involving 21 infants aged ≤7 months with RSV, found that clarithromycin daily for 3 weeks significantly reduced hospital length of stay (LOS) and supplemental oxygen and intravenous fluid requirements compared to placebo. In contrast, 3 later RCTs (5, 16, 17) involving a total of 352 infants (up to age 2 years) with clinically diagnosed bronchiolitis from Australia, the Netherlands, and Brazil failed to demonstrate any clinical benefit using azithromycin for 1, 3, or 7 days, respectively. The Turkish trial was also the only one where treatment extended beyond the period in hospital where just 1 of the 12 infants in the clarithromycin group was re-hospitalized compared with 4 of 9 receiving placebo (15).

At the time we started our study, only the RCTs from Turkey (15) and the Netherlands (16) had been completed. We believed Indigenous infants were more like high-risk children in Turkey and might also benefit from a longer treatment course (the Turkish study was the only one to have addressed this question) (15).

This is of considerable importance for Indigenous infants where respiratory symptoms and recurrent hospitalized respiratory illnesses are major risk factors for developing bronchiectasis (5–7). As administering twice-daily clarithromycin on an ambulatory basis is impractical in our setting (18), we took advantage of azithromycin’s long half-life and favorable pharmacokinetics by opting to determine whether a longer course (three large once-weekly doses) of azithromycin for Indigenous infants hospitalized with bronchiolitis improved clinical outcomes (LOS and duration of oxygen supplementation). Secondary aims were to: (i) determine the effects of azithromycin on respiratory symptoms and signs at day-21 and respiratory hospitalizations in the following 6-month period; (ii) assess the short-term impact of azithromycin upon nasopharyngeal carriage and respiratory virus shedding and; (iii) describe the viruses, *M. pneumoniae* and *Chlamydiales* species detected in these infants.

**Materials and Methods**

**Study Design and Setting**

This was a multi-center, randomized, double-blind, placebo-controlled trial. Infants were recruited at the Royal Darwin (June 2010–September 2013) and Townsville Hospitals (August 2010–June 2013), Australia and the Auckland Starship Children’s Hospital (November 2012–September 2013), New Zealand. Human Research Ethics Committees at all participating institutions approved the study and caregivers provided written, informed consent. The study was registered with the Australian and New Zealand Clinical Trials Register: ACTRN12608000150347 and monitored by an independent data safety monitoring board (DSMB).
Participants
As described in detail previously (19), eligible infants were aged ≤ 24 months and hospitalized with a standardized clinical diagnosis of bronchiolitis (age-adjusted tachypnea with wheeze or crackles), had parent-assigned Indigenous ethnicity (Australian Aboriginal, Torres Strait Islander, Maori, and/or Pacific Islander), were consented within 24 h of hospitalization and had caregivers with a mobile phone (see supplement for exclusion criteria and tachypnea definitions).

Randomization, Allocation and Blinding, and Medications
An independent statistician used a computer-generated, permuted block design to generate randomization sequences. Sealed opaque envelopes (selecting one of the eight different bottle codes) concealed the treatment allocation. Infants were allocated in a 1:1 ratio, stratified by age (≤ 6 or > 6 months), oxygen supplementation on presentation (yes/no) and site (Darwin, Townsville, or Auckland), to once-weekly doses of oral azithromycin or placebo for 3 weeks. Neither the study team (researchers, hospital staff) nor parents were aware of assigned treatment groups until data analysis was completed.

The first dose was given in the hospital (30 mg/kg azithromycin) or equal volume of placebo. The remaining two doses were supervised directly by study nurses (urban-based participants) or given at home by caregivers (remote-based participants) at weekly intervals. Study nurses contacted families via mobile phones to help ensure adherence (20).

Clinical Assessment, Management, and Outcomes
Demographic, medical history, and clinical data were recorded on standardized data collection forms. A validated severity score was employed (see Supplementary Material). Infants with bronchiolitis were managed at each site according to a common protocol, which outlined when supplementary oxygen was indicated (SpO₂ < 94%) and when nasogastric feeds or intravenous fluids were required. The protocol was in place for several months before commencing the trial. Infants received additional therapies (other than macrolides) at the discretion of the treating pediatrician.

The primary endpoints of LOS for respiratory illness and duration of oxygen requirement (where applicable) were monitored every 12 h. LOS was the time from admission to time "ready for discharge" from respiratory care as defined by SpO₂ > 94% in air for > 16 h and feeding adequately. In our setting, "ready for discharge" from respiratory care can differ from LOS, as discharge from hospital may be delayed because of non-medical factors (such as waiting for air transport back to remote communities). For the other clinical outcomes, the day-21 review was conducted by study nurses (urban-based participants) and local health clinic staff (remote-based). Respiratory rehospitalization within 6 months of discharge was recorded through community and hospital electronic records. Adverse events were monitored daily in hospital by research staff and following discharge with weekly phone calls until the day-21 review.

Specimen Collection and Processing
Nasopharyngeal swabs (NPS) taken before initial study medications were administered and repeated 48 h later, and were processed as described previously (21-23) for viruses and atypical bacteria (C. pneumoniae, Simkania negevensis, M. pneumoniae) using real-time polymerase chain reaction (PCR) assays (see Supplementary Material for list of viruses). NPS were cultured for respiratory bacterial pathogens that also underwent antibiotic susceptibility testing (24).

Sample Size and Analysis
Based upon our previous data where the mean LOS in Indigenous infants with bronchiolitis was 96 (SD 24) hours (2), we estimated a total sample of 200 infants (100 in each age sub-group: ≤ 6 months and > 6 months) would provide 94% power to detect a difference in the mean LOS of 12 h between treatment groups at the 5% significance level (two-tailed) and 95% power to detect a reduction in respiratory rehospitalization within the next 6 months from 30 to 10% (19).

Data were analyzed according to our published protocol. Data were analyzed according to the group the child was allocated to. Only available data were analyzed. Between-group differences were tested using Fisher's exact test (for proportions) and Mann–Whitney U test (for continuous variables). A 95% confidence interval (CI) was obtained for the difference in medians between treatment groups (25). Subgroup analysis was performed by age (≤ 6 and > 6 months) as planned (19), and also for groups based on oxygen requirement when enrolled, remoteness, antibiotic use, and previous respiratory hospitalizations for the three clinical outcomes. These post hoc subgroup analyses were conducted that might inform clinical practice. p-Values are reported for the subgroup × treatment interaction term in a linear regression model (for log-transformed LOS and duration of supplemental oxygen) and in a logistic regression model (for any readmissions within 6 months) with main effects for just treatment group and subgroup. Data were also analyzed adjusting for significant between-group differences at baseline.

Results
We recruited 219 infants (106 randomized to azithromycin, 113 to placebo (Figure 1). Overall, 218 received dose-1 in hospital; 102 (azithromycin) and 111 (placebo) received dose-2 and 94 (azithromycin); and 106 (placebo) received dose-3. Demographical and clinical characteristics were similar between treatment groups, apart from household smoke exposure involving more infants in the azithromycin (69%) than the placebo (50%) group, χ² = 0.01; see Table 1. Of the study cohort, 133 (61%) required oxygen during hospitalization. Non-macrolide antibiotics were prescribed in 93 (43%) infants before hospitalization (see Supplementary Material) and none received steroids or required intensive care management. Thirty-eight infants were hospitalized previously for a respiratory illness (azithromycin: 18; placebo: 20). Retention was high (≥ 97%) for the clinical endpoint at day-21.
Clinical Outcomes
No significant between-group differences were found for LOS or duration of supplemental oxygen (Figures 2A,B). The median LOS of 54 h was identical in both groups (difference = 0 h, 95% CI: −6, 8; p = 0.8), while the median time receiving oxygen was 40 h in the azithromycin group and 35 h in the placebo group (difference = 5 h, 95% CI: −8, 11; p = 0.7).

Day-21 Clinical Review and 6-Month Readmission
Two hundred ten (97%) infants completed the day-21 review (Figure 1). Although persistent symptoms or signs were more common in placebo group, the between-group differences were not significant (Table 2).

Overall, 81 (azithromycin n = 47, placebo n = 34) respiratory rehospitalizations were recorded from 56 participants (azithromycin n = 31, placebo n = 25). No significant between-group differences were found (odds ratio for any hospitalization 1.5, 95% CI: 0.8, 3.0, p = 0.2). Sixty (74%) rehospitalizations were for wheezing-associated illness.

There was no evidence of a differential effect of azithromycin on any of the main three clinical outcomes for any of the subgroups (see Tables S2–S4 in Supplementary Material). Adjustment for household smoking exposure had negligible effect on the trial’s main analyses (see Table S5 in Supplementary Material).
TABLE 1 | Demographic and clinical characteristics of 219 patients randomized to treatment with either azithromycin (n = 106) or placebo (n = 113).

<table>
<thead>
<tr>
<th></th>
<th>Azithromycin (n = 106)</th>
<th>Placebo (n = 113)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (months)</td>
<td>5.7 (3–10)</td>
<td>5.6 (3–9)</td>
</tr>
<tr>
<td>≤6 months</td>
<td>56 (52%)</td>
<td>61 (54%)</td>
</tr>
<tr>
<td>6–24 months</td>
<td>50 (48%)</td>
<td>52 (46%)</td>
</tr>
<tr>
<td>Male</td>
<td>64 (60%)</td>
<td>72 (64%)</td>
</tr>
<tr>
<td>Indigenous Australians</td>
<td>92 (87%)</td>
<td>95 (84%)</td>
</tr>
<tr>
<td>New Zealand Maori/Pacific Islander</td>
<td>14 (13%)</td>
<td>18 (16%)</td>
</tr>
<tr>
<td>Gestational age (weeks)</td>
<td>38 (36–40)</td>
<td>38 (36–40)</td>
</tr>
<tr>
<td>Birth weight (kg)</td>
<td>3.03 (2.3–3.3)</td>
<td>3.00 (2.5–3.4)</td>
</tr>
<tr>
<td>Remote region</td>
<td>74 (70%)</td>
<td>71 (63%)</td>
</tr>
<tr>
<td>Currently breastfed</td>
<td>82 (77%)</td>
<td>87 (75%)</td>
</tr>
<tr>
<td>Mother smoked during pregnancy</td>
<td>54 (51%)</td>
<td>58 (51%)</td>
</tr>
<tr>
<td>Exposed to household smoke</td>
<td>72 (69%)</td>
<td>57 (50%)</td>
</tr>
<tr>
<td>Previously hospitalized for acute respiratory infection</td>
<td>18 (17%)</td>
<td>20 (18%)</td>
</tr>
<tr>
<td>Symptoms leading up to admission</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nasal discharge</td>
<td>93 (89%)</td>
<td>96 (85%)</td>
</tr>
<tr>
<td>Cough</td>
<td>104 (99%)</td>
<td>110 (97%)</td>
</tr>
<tr>
<td>Breathing difficulties</td>
<td>102 (97%)</td>
<td>111 (98%)</td>
</tr>
<tr>
<td>Poor feeding</td>
<td>48 (46%)</td>
<td>63 (56%)</td>
</tr>
<tr>
<td>Lethargy</td>
<td>52 (50%)</td>
<td>52 (46%)</td>
</tr>
<tr>
<td>Baseline clinical severity score [see Supplementary Material]</td>
<td>5 (4–7)</td>
<td>5 (4–7)</td>
</tr>
</tbody>
</table>

Enrolment observations

| Number receiving oxygen | 59 (56%) | 74 (65%) |
| Level of supplemental oxygen (L/min) | 1 (0.5, 2.5) | 1 (0.5, 1.5) |
| Heart rate (bpm)        | 152 (137, 164) | 147 (136, 156) |
| Temperature (°C)        | 36.6 (36.4, 36.9) | 36.7 (36.4, 37.0) |
| Non-macrolide antibiotics prescribed prior to hospital | 47 (45%) | 46 (42%) |
| Non-macrolide antibiotics prescribed during hospital | 64 (61%) | 68 (60%) |
| Supplemental intravenous fluid administered | 24 (23%) | 23 (20%) |
| Chest radiograph taken  | 87 (83%) | 88 (78%) |
| Co-morbidities          |                     |
| Any otitis media         | 21 (20%) | 18 (16%) |
| Otitis media with perforation | 4 (4%) | 6 (5%) |
| Skin infection           | 32 (30%) | 27 (24%) |
| Anemia                   | 9 (9%) | 4 (4%) |
| Failure to thrive        | 5 (5%) | 6 (5%) |
| Lobar pneumonia/atelectasis on Chest X-ray | 21 (20%) | 13 (12%) |
| Any virus detected       | 82 (79%) | 92 (83%) |
| Any respiratory bacterial pathogen detected | 73 (70%) | 83 (73%) |

Microbiology

Nasopharyngeal swabs were collected from 217 infants at baseline and 215 at 48 h. At baseline, at least 1 virus was detected in 174 (81%) infants (see Figure S1 in Supplementary Material). RSV was detected in 91 (42%), followed by HRV (79%, 37%) and adenovirus (14% 7%). The mean number of viruses detected per infant hardly changed from baseline to 48 h; azithromycin: 1.0–0.9 viruses (difference 0.1, 95% CI: −0.2, 0.2; p = 0.4); placebo: 1.1–1.0 viruses (difference 0.1, 95% CI: −0.02, 0.3; p = 0.09). Nasopharyngeal swabs isolations of S. pneumoniae, non-typable H. influenzae, and M. catarrhalis at 48 h were less common in the azithromycin group than in the placebo group (Table 3). On average, there were 0.4 (95% CI: 0.2, 0.6; p < 0.001) fewer bacterial species per infant in the azithromycin group.

Adverse Events

Three adverse events were reported to our DSMB. In the azithromycin group, one infant presented to hospital with vomiting and diarrhea and another vomited the trial medication. In the placebo group, one infant presented to hospital with wheezing and a rash. All recovered and none discontinued the trial.

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TABLE 2 | Persistent respiratory symptoms/signs at day-21 review.

<table>
<thead>
<tr>
<th></th>
<th>Azithromycin N = 100 (%)</th>
<th>Placebo N = 110 (%)</th>
<th>Risk difference (95% CI)</th>
<th>p-value*a</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wet cough</td>
<td>12 (12%)</td>
<td>17 (15%)</td>
<td>−4% (−12%, 0%)</td>
<td>0.4</td>
</tr>
<tr>
<td>Crackles/crepitations</td>
<td>7 (7%)</td>
<td>15 (14%)</td>
<td>−6% (−14%, 1%)</td>
<td>0.1</td>
</tr>
<tr>
<td>Chest recession</td>
<td>0 (0%)</td>
<td>2 (2%)</td>
<td>−2% (−4%, 0.7%)</td>
<td>0.2</td>
</tr>
<tr>
<td>Wheeze</td>
<td>11 (11%)</td>
<td>11 (10%)</td>
<td>1% (−7%, 9%)</td>
<td>0.9</td>
</tr>
<tr>
<td>Any of the above</td>
<td>23 (23%)</td>
<td>35 (32%)</td>
<td>−8% (−20%, 3%)</td>
<td>0.2</td>
</tr>
</tbody>
</table>

*aFisher’s exact test.

TABLE 3 | Nasal swab bacteriology pre- and 48 h post-treatment.

<table>
<thead>
<tr>
<th></th>
<th>Azithromycin</th>
<th>Placebo</th>
<th>OR Azithromycin vs. placebo (95% CI)</th>
<th>p-value**</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre-treatment (baseline)</td>
<td>Post-treatment (48 h)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Azithromycin n = 104 (%)</td>
<td>Placebo n = 113 (%)</td>
<td>Azithromycin n = 102 (%)</td>
<td>Placebo n = 113 (%)</td>
</tr>
<tr>
<td>S. pneumoniae</td>
<td>24 (23%)</td>
<td>32 (29%)</td>
<td>6 (6)</td>
<td>24 (21)</td>
</tr>
<tr>
<td>Penicillin intermediate resistant</td>
<td>11 (11)</td>
<td>11 (10)</td>
<td>3 (3)</td>
<td>8 (7)</td>
</tr>
<tr>
<td>Penicillin resistant</td>
<td>1 (1)</td>
<td>0 (0)</td>
<td>1 (1)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Azithromycin resistant</td>
<td>6 (6)</td>
<td>6 (6)</td>
<td>3 (3)</td>
<td>6 (6)</td>
</tr>
<tr>
<td>Non-typable H. influenzae</td>
<td>38 (37)</td>
<td>43 (38)</td>
<td>10 (10)</td>
<td>34 (30)</td>
</tr>
<tr>
<td>Azithromycin resistant</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Ampicillin resistant</td>
<td>8 (8)</td>
<td>8 (7)</td>
<td>1 (1)</td>
<td>9 (9)</td>
</tr>
<tr>
<td>Beta-lactamase positive</td>
<td>9 (8)</td>
<td>8 (7)</td>
<td>1 (1)</td>
<td>9 (9)</td>
</tr>
<tr>
<td>M. catarrhalis</td>
<td>33 (32)</td>
<td>50 (44)</td>
<td>12 (12)</td>
<td>41 (36)</td>
</tr>
<tr>
<td>Beta-lactamase positive</td>
<td>30 (29)</td>
<td>50 (44)</td>
<td>12 (12)</td>
<td>41 (36)</td>
</tr>
<tr>
<td>S. aureus</td>
<td>11 (11)</td>
<td>15 (13)</td>
<td>10 (10)</td>
<td>17 (15)</td>
</tr>
<tr>
<td>Erythromycin non-susceptible</td>
<td>2 (2)</td>
<td>6 (5)</td>
<td>4 (4)</td>
<td>7 (6)</td>
</tr>
<tr>
<td>MRSA</td>
<td>2 (2)</td>
<td>4 (4)</td>
<td>1 (1)</td>
<td>6 (5)</td>
</tr>
</tbody>
</table>

OR, odds ratio.

Four infants not counted in table results (i.e., refused, missed).

Minimum inhibitory concentrations determine for S. pneumoniae and non-typable H. influenzae (NTHs), and breakpoints defined using European Committee on Antimicrobial Susceptibility Testing (EUCAST) (http://www.eucast.org). S. pneumoniae, intermediate penicillin resistant, MIC >0.06–2 mg/L, penicillin resistant, MIC >2 mg/L, and azithromycin resistant MIC >5 mg/L, and for H. influenzae, azithromycin resistant, MIC >4 mg/L and amoxicillin resistant, MIC >1 mg/L.

**Logistic regression = difference between treatment groups at post-treatment (48 h).

*p-value from Fisher’s exact test.

Discussion

This is the first international, multicentre, double-blind RCT of an extended course of macrolides in bronchiolitis. In this study involving 219 Indigenous infants, we found that three once-weekly doses of azithromycin (compared to placebo), conferred no benefit in terms of LOS, duration of oxygen supplementation, day-21 symptom/signs, or respiratory rehospitalizations within 6 months post discharge. Azithromycin significantly reduced the mean number of nasopharyngeal bacteria per infant, but not the mean number of viruses per infant.

Our study is larger than the four preceding published studies on macrolides in bronchiolitis (5, 15–17) and involved a group of infants from populations at high risk for chronic suppurative lung disease (6). Our findings on the lack of beneficial effect of azithromycin for hospital-based outcomes (LOS and duration of oxygen supplementation) are concordant with three of these studies (5, 16, 17). To date, the Turkish study is unique (15) where 3 weeks of clarithromycin reported reduced LOS, oxygen supplementation, and respiratory rehospitalization within the following 6 months. Possible reasons for the difference between the Turkish (15) and other studies (5, 16, 17) include: using clarithromycin with its greater lung penetration and potential anti-RSV activity (11), differences in sample size, attrition population characteristics, the role of chance, and increased risk of bias associated with small studies.

We used a longer course of azithromycin than the other studies (5, 15–17) and did not find any clinically significant between-group outcomes. Azithromycin had no significant effect on the presence of persistent symptoms/signs on day-21 review and the proportion with persistent respiratory symptoms or signs (14–24%) are similar to another report of 25% infants remaining symptomatic after 21 days (26). Furthermore, the importance of the symptoms beyond hospitalization of persistent cough and wheeze was highlighted in a guideline on bronchiolitis (27).

The proportion of respiratory rehospitalizations within 6 months of discharge (25%) was also similar to other trials (5, 15). Rehospitalization for respiratory illness is an important outcome because it is an independent risk factor for bronchiectasis in Indigenous children (6). We targeted this high-risk group, as respiratory diseases are prevalent and more severe and persistent in this population (5, 28).

The mean number of nasopharyngeal respiratory bacteria was reduced more in the azithromycin than the placebo arm, as seen in our previous short-term RCT (5). Although the number of macrolide-resistant bacteria at 48 h also declined, this was not to the same extent as found in susceptible strains. Meanwhile,
detection rates for respiratory viruses between treatment groups changed little over the 48 h following enrollment, though PCR detects nucleic acids, it is not possible to determine whether differences in viable viruses existed with azithromycin treatment.

Our study has several other limitations, which may have resulted in the negative results of our RCT. First, including an older age group increased the risk of including those with asthma. However, our cohort’s median age of 6 months (IQR 3, 9) reduced this possibility. Further, in both the UK and USA bronchiolitis guidelines, the upper age limit is 23–24 months. Second, in the Australian centers, we included those hospitalized previously for an acute respiratory infection, which may have contributed to the number of respiratory rehospitalizations (27, 29). Third, the concurrent use of antibiotics in two-thirds of infants with bronchiolitis may limit the ability of additional macrolide treatment to improve outcomes. We were unable to influence the clinical practice of physicians on this matter. However, subgroup analyses on previous respiratory hospitalization, or antibiotic use did not show any significant differences on any of our outcomes (see Supplementary Material). Fourth, our strategy of using three large once-weekly azithromycin doses may have produced sub-optimal results. This, however, is unlikely as prior RCTs of daily azithromycin found no benefit (16, 17). Moreover, in children, single doses of azithromycin can successfully treat otitis media (18), while for several weeks after its mass distribution within rural African villages for controlling trachoma, azithromycin reduced the risk of acute lower respiratory infections by more than one-third (13). Although our RCT (18) used the same regime for long-term therapy of children with bronchiectasis and showed that azithromycin significantly reduced the exacerbation rate by 50% (compared to placebo), the different disease and younger age group in this RCT meant an alternative dose and/or regime for optimal efficacy may have been required. Finally, even though parents reported verbally that doses-2 and 3 were given, we were unable to directly observe these for remote-based infants (n = 145). However, the day-21 follow-up rate of >97% at the local health clinic implies that parents are likely to have adhered to the study protocol. This is supported by feedback from research nurses who interviewed parents throughout the trial.

Our study was aimed at infants at high risk of future bronchiectasis and employed a 3-week equivalent course in a multicentre setting. This design was to maximize the chances of demonstrating a clinical benefit for azithromycin in our target population, by reducing subsequent hospitalization and shortening hospital stay (both are independent risk factors for later development of bronchiectasis). Despite this, no advantage from receiving azithromycin was identified. Moreover, there are now growing concerns over the increasing global consumption of antibiotics and rising rates of antibiotic resistance, especially when few new anti-microbial agents are in the developmental pipeline (30, 31). Much of this antibiotic resistance is being driven by antibiotics prescribed for viral respiratory infections, most notably long-acting, broad-spectrum agents, including azithromycin (32, 33). An emerging fear for this young age group is that antibiotics may also adversely affect the developing intestinal “microbiome” with potential deleterious long-term effects upon gastrointestinal, immunological, and metabolic programming (34). Thus, given our study’s negative findings and the concerns over the association between azithromycin and increased carriage of macrolide-resistant pathogens (35), the increasing need for anti-microbial stewardship, potential immediate and long-term adverse events, and associated costs, it is clear that these factors outweigh any postulated, but still unproven benefits of macrolides in this patient population.

Conclusion

In this RCT of Indigenous infants hospitalized with bronchiolitis, we found that three once-weekly doses of azithromycin significantly reduced nasopharyngeal bacterial carriage, but did not have any significant impact on viruses or short (reduced LOS or duration of oxygen supplementation) or long-term (decreased odds of persistent symptoms at day-21 or respiratory rehospitalization within 6 months of discharge) clinical benefits compared with placebo. In light of these results, similar findings in other studies, and fears over rising antibiotic resistance, azithromycin should not be used to treat infants hospitalized with viral bronchiolitis.

Author Contributions

GM set up and managed the study, recruited participants, performed the data analysis, and drafted the manuscript. AC conceptualized the study. AC and KG co-drafted the manuscript. AC, PM, KG, TS, AW, IM co-designed the study and contributed to obtaining the grant, interpreted the data, and edited the manuscript. CB was responsible for overseeing all aspects of the trial in NZ. CM, AW, and CB were responsible for standardizing the management of bronchiolitis in their units, recruiting participants, and edited the manuscript. CM, LV, NJ, CM were responsible for recruiting participants and edited the manuscript. TS and IM assisted in the viral components of the study and edited the manuscript. HS-V assisted in the microbiological components of the study and edited the manuscript. MC assisted in the data analysis and edited the manuscript. All authors read and approved the final manuscript.

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to reduce the morbidity of bronchiolitis in Indigenous infants: a protocol.

Supplementary Material

The Supplementary Material for this article can be found online at http://journal.frontiersin.org/article/10.3389/fped.2015.00332

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Allman Douglas MD, Bryant Trevor, Gardner Stephen. Statistics with Confi-


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Three-weekly doses of azithromycin for Indigenous infants hospitalised with bronchiolitis: A multicentre, randomised, placebo-controlled trial

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1. Supplementary Data

METHODS

Exclusions were: severe disease (admitted to the intensive care unit); underlying chronic lung or congenital heart disease, contraindications to macrolides (e.g. hypersensitivity or liver dysfunction,); diarrhoea (>2 two watery stools above the normal daily pattern), received macrolides within last seven-days, or clinical and radiographic features of a primary pneumonia. In New Zealand, infants with previous wheezing illnesses were excluded due to the high incidence of asthma in Maori and Pacific Islander children.

Age-adjusted upper levels of normal respiratory rates were (i) respiratory rate ≥60/min if aged <2-months; (ii) ≥50/min if 2-12 months; and (iii) ≥40/min if 13-24 months.

Clinical assessment

A previously validated severity score was assigned to each infant, and consisted of four components (respiratory rate, accessory muscle use, degree of wheezing and pulse oximetry saturation reading). Each component scored between 0 and 3, providing a composite score between 0–12 (Supplementary Table-1).
Specimen collection and processing
NPS were processed for a broad panel of viruses RSV A and B; adenovirus, parainfluenza (1-3), influenza A and B, rhinovirus, human metapneumovirus, human coronaviruses (OC43, HKU1, 229E, NL63), human bocavirus, C. trachomatis, C. pneumoniae, Simkania negevensis and M. pneumoniae).

Medications
The placebo, manufactured by the Institute of Drug Technology (IDT) (Melbourne, Victoria, Australia), had a similar look, smell and taste to active azithromycin. Azithromycin (Pfizer, Australia) was purchased and repackaged by IDT. Both medications were prepared as a powder in identical opaque bottles and sealed with an aluminium foil.

RESULTS
Antibiotics given prior to hospital include intramuscular ceftriaxone (n=47, 44%) and procaine penicillin (n=21, 20%) and oral amoxicillin (n=12, 11%). Additional non-macrolide antibiotics were also prescribed commonly during hospitalisation (n=132, 61%); oral amoxicillin was the most common (n=75, 33%), followed by parenteral benzylpenicillin (n=65, 29%) and oral amoxicillin-clavulanate (n=26, 11%).

References
### 2.1 Supplementary Tables

Supplementary Table-1. Validated clinical severity score

<table>
<thead>
<tr>
<th>Points</th>
<th>Respiratory Rate (breaths/min)</th>
<th>Wheezing</th>
<th>SpO2 (in air after 1 min)</th>
<th>Accessory respiratory muscle utilisation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>&lt;30</td>
<td>None</td>
<td>&gt;95</td>
<td>None</td>
</tr>
<tr>
<td>1</td>
<td>30-45</td>
<td>Expiration only</td>
<td>94-95</td>
<td>+</td>
</tr>
<tr>
<td>2</td>
<td>46-60</td>
<td>Entire expiration and inspiration with stethoscope only</td>
<td>90-93</td>
<td>++</td>
</tr>
<tr>
<td>3</td>
<td>&gt; 60</td>
<td>Entire expiration and inspiration without stethoscope</td>
<td>&lt;89</td>
<td>+++</td>
</tr>
</tbody>
</table>

#### Definitions

<table>
<thead>
<tr>
<th>Points</th>
<th>Component</th>
<th>Instructions</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Respiratory rate (breaths per minute)</td>
<td>Count the number of time the infant’s chest rises and falls for a period of 60-seconds</td>
</tr>
<tr>
<td>0</td>
<td>&lt; 30</td>
<td>Nil wheezing heard</td>
</tr>
<tr>
<td>1</td>
<td>30-45</td>
<td>Wheezing heard on expiration</td>
</tr>
<tr>
<td>2</td>
<td>45-60</td>
<td>Wheezing on inspiration and expiration</td>
</tr>
<tr>
<td>3</td>
<td>&gt;60</td>
<td>Wheezing on inspiration and expiration observed (standing at bedside)</td>
</tr>
<tr>
<td></td>
<td>SpO2</td>
<td>Oxygen saturation in blood measured by pulse oximeter</td>
</tr>
<tr>
<td>0</td>
<td>&gt;95</td>
<td>Work of breathing assessed when off oxygen</td>
</tr>
<tr>
<td>1</td>
<td>94-95</td>
<td>No chest in-drawing i.e. absence of lower chest wall (intercostal) retraction during inhalation (mild) = presence of mild intercostal retraction (just visible), no head bobbing or tracheal tug</td>
</tr>
<tr>
<td>2</td>
<td>90-93</td>
<td>(moderate) = moderate amount of intercostal retraction, no head bobbing or tracheal tug</td>
</tr>
<tr>
<td>3</td>
<td>&lt;89</td>
<td>(severe) = moderate or marked intercostal retraction with presence of head bobbing or tracheal tug</td>
</tr>
</tbody>
</table>

WHO definition of chest retraction = chest in drawing in a calm child, lower part of the chest moves in or retracts when inhalation occurs (i.e. all or none phenomena)
### Supplementary Table-2. Subgroup analysis of hospital length of stay (LOS) until ‘ready for hospital discharge’

<table>
<thead>
<tr>
<th></th>
<th>Median LOS in hours (IQR)</th>
<th>Difference (Azithromycin-placebo) (95% CI)</th>
<th>Interaction P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Azithromycin n=106</td>
<td>Placebo n=113</td>
<td></td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 6-months</td>
<td>56 (40, 82)</td>
<td>64 (44, 96)</td>
<td>8 (-4, 21)</td>
</tr>
<tr>
<td>&gt; 6-months</td>
<td>53 (46, 70)</td>
<td>52 (40, 63)</td>
<td>-1 (-11, 4)</td>
</tr>
<tr>
<td><strong>Oxygen supplement requirement</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>56 (40, 78)</td>
<td>54 (40, 92)</td>
<td>-2 (-9, 11)</td>
</tr>
<tr>
<td>No</td>
<td>53 (46, 73)</td>
<td>56 (44, 78)</td>
<td>3 (-6, 11)</td>
</tr>
<tr>
<td><strong>Location</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Remote</td>
<td>55 (46, 76)</td>
<td>62 (44, 91)</td>
<td>7 (-13, 14)</td>
</tr>
<tr>
<td>Urban</td>
<td>53 (38, 62)</td>
<td>50 (38, 69)</td>
<td>-3 (-10, 11)</td>
</tr>
<tr>
<td><strong>Antibiotics in hospital</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study drug + beta-lactam</td>
<td>54 (44, 82)</td>
<td>62 (45, 95)</td>
<td>8 (-4, 17)</td>
</tr>
<tr>
<td>Study drug only</td>
<td>53 (41, 62)</td>
<td>48 (38, 64)</td>
<td>-5 (-9, 8)</td>
</tr>
<tr>
<td><strong>Respiratory hospitalisation prior to enrolment</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>54 (49, 75)</td>
<td>54 (37, 74)</td>
<td>0 (-21, 9)</td>
</tr>
<tr>
<td>No</td>
<td>53 (40, 74)</td>
<td>54 (43, 82)</td>
<td>1 (-5, 11)</td>
</tr>
</tbody>
</table>
### Supplementary Table-3. Subgroup analysis of time of oxygen requirement (where applicable)

<table>
<thead>
<tr>
<th></th>
<th>Median duration of oxygen in hours (IQR)</th>
<th>Difference (Azithromycin-placebo) (95% CI)</th>
<th>Interaction P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Azithromycin n=59</td>
<td>Placebo n=74</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 6-months</td>
<td>37 (24, 73)</td>
<td>50 (24, 80)</td>
<td>13 (-9, 23)</td>
</tr>
<tr>
<td>&gt; 6-months</td>
<td>41 (30, 59)</td>
<td>28 (21, 39)</td>
<td>-13 (-21, -1)</td>
</tr>
<tr>
<td>Location</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Remote</td>
<td>41 (24, 77)</td>
<td>35 (22, 76)</td>
<td>-6 (-16, 11)</td>
</tr>
<tr>
<td>Urban</td>
<td>38 (20, 52)</td>
<td>35 (26, 53)</td>
<td>-3 (-7, 12)</td>
</tr>
<tr>
<td>Antibiotics in hospital</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study drug + beta-lactam</td>
<td>41 (26, 77)</td>
<td>42 (26, 77)</td>
<td>1 (-13, 16)</td>
</tr>
<tr>
<td>Study drug only</td>
<td>38 (24, 50)</td>
<td>29 (20, 44)</td>
<td>-9 (-16, 7)</td>
</tr>
<tr>
<td>Respiratory hospitalisation prior to enrolment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>54 (35, 77)</td>
<td>26 (16, 33)</td>
<td>-28 (-46, -2)</td>
</tr>
<tr>
<td>No</td>
<td>37 (23, 62)</td>
<td>38 (24, 72)</td>
<td>1 (-9, 12)</td>
</tr>
</tbody>
</table>
Supplementary Table-4. Subgroup analysis of respiratory-related rehospitalisation within 6-months of discharge

<table>
<thead>
<tr>
<th></th>
<th>Azithromycin n/N (%)</th>
<th>Placebo n/N (%)</th>
<th>Odds Ratio (95% CI)</th>
<th>Interaction P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 6 months</td>
<td>12/55 (22%)</td>
<td>14/61 (23%)</td>
<td>0.9 (0.4, 2)</td>
<td>0.2</td>
</tr>
<tr>
<td>&gt; 6 months</td>
<td>19/50 (38%)</td>
<td>11/52 (21%)</td>
<td>2.3 (1.0, 5)</td>
<td></td>
</tr>
<tr>
<td><strong>Oxygen supplement requirement</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>20/56 (36%)</td>
<td>15/66 (23%)</td>
<td>2 (1, 4)</td>
<td>0.4</td>
</tr>
<tr>
<td>No</td>
<td>11/49 (22%)</td>
<td>10/47 (21%)</td>
<td>1 (0.4, 3)</td>
<td></td>
</tr>
<tr>
<td><strong>Location</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Remote</td>
<td>21/74 (28%)</td>
<td>15/71 (21%)</td>
<td>2 (0.7, 3)</td>
<td>0.9</td>
</tr>
<tr>
<td>Urban</td>
<td>10/31 (32%)</td>
<td>10/42 (24%)</td>
<td>2 (0.6, 4)</td>
<td></td>
</tr>
<tr>
<td><strong>Antibiotics in hospital</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study drug + beta-lactam</td>
<td>19/64 (30%)</td>
<td>13/68 (19%)</td>
<td>2 (0.8, 4)</td>
<td>0.5</td>
</tr>
<tr>
<td>Study drug only</td>
<td>12/41 (29%)</td>
<td>12/45 (27%)</td>
<td>1.1 (0.4, 3)</td>
<td></td>
</tr>
<tr>
<td><strong>Respiratory hospitalisation prior to enrolment</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>11/18 (61%)</td>
<td>5/20 (25%)</td>
<td>5 (1, 18)</td>
<td>0.07</td>
</tr>
<tr>
<td>No</td>
<td>20/87 (23%)</td>
<td>20/93 (22%)</td>
<td>1 (0.5, 2)</td>
<td></td>
</tr>
</tbody>
</table>
Supplementary Table-5.

<table>
<thead>
<tr>
<th></th>
<th>Azithromycin vs placebo</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Multiplicative effect on geometric mean* (95% CI)</td>
<td></td>
</tr>
<tr>
<td>Length of stay (hours) (unadjusted)</td>
<td>0.9 (0.8, 1.1)</td>
<td>0.4</td>
</tr>
<tr>
<td>Length of stay (hours) (adjusted)</td>
<td>0.9 (0.8, 1.1)</td>
<td>0.2</td>
</tr>
<tr>
<td>Time receiving oxygen (hours) (unadjusted)</td>
<td>0.9 (0.7, 1.3)</td>
<td>0.9</td>
</tr>
<tr>
<td>Time receiving oxygen (hours) (adjusted)</td>
<td>1.0 (0.7, 1.3)</td>
<td>0.8</td>
</tr>
<tr>
<td></td>
<td>Odds Ratio (95%CI)</td>
<td>P-value</td>
</tr>
<tr>
<td>Respiratory rehospitalisation (unadjusted)</td>
<td>1.5 (0.8, 3.0)</td>
<td>0.2</td>
</tr>
<tr>
<td>Respiratory rehospitalisation (adjusted)</td>
<td>1.2 (0.6, 2.3)</td>
<td>0.5</td>
</tr>
</tbody>
</table>

One person was missing household smoke status and was excluded from the above analyses.
2.2 Supplementary Figures

Supplementary Figure-1. Frequency and distribution of viruses and atypical bacteria detected in nasopharyngeal swabs: Baseline and 48-hours later

![Graph showing frequency and distribution of various viruses and bacteria detected in nasopharyngeal swabs.](image-url)
Chapter 5: Mobile Phones Support Adherence and Retention Of Indigenous Participants in a Randomised Controlled Trial: Strategies and Lessons Learnt

5.1 Chapter overview

Indigenous children in the NT have among the highest hospitalisation rates for bronchiolitis (352 per 1,000) and more severe disease. Most Indigenous children live in remote communities (defined as more than 100km from a tertiary hospital) and are retrieved to tertiary hospitals for clinical care. Hospitalisations in the first few years of life increase the risk of ongoing respiratory morbidity and development of chronic suppurative lung disease. This study is embedded in our RCT (chapter 4) and aims to improve short and long term clinical outcomes for Indigenous children hospitalised with bronchiolitis during 2010 to 2013. A novel approach using mobile phones and a culturally sensitive framework was developed. This study aimed to help support families, improve adherence to the trial medication and strengthen retention and clinical follow-up at day-21. In this study, only children from Australia (Darwin and Townsville), were included (n=186). The New Zealand cohort were urban based (and faced different challenges) and therefore were excluded.

5.2 Development of educational resources to support randomised controlled trial

As part of a needs analysis undertaken by our respiratory health group in 2010 and supported by key local and national stakeholders, we identified a lack of appropriate educational resources concerning respiratory illness amongst Indigenous children. A set of culturally appropriate educational flipcharts were subsequently developed. We targeted three common respiratory conditions e.g. bronchiolitis, pneumonia and...
chronic suppurative lung disease (i.e. bronchiectasis). Each flipchart was pictorially based and included education on how the respiratory system worked, disease progression and health promotion information for each condition in the prevention and improvement of lung health (see appendix 1).

The bronchiolitis flipchart was used in conjunction with our culturally sensitive framework. Our aim was to improve parents’ knowledge and understanding of bronchiolitis prior to recruiting study participants into our RCT, and to ensure true informed consent was obtained (chapter 4). The suite of resources has been placed online and can be downloaded for free at:

http://www.menzies.edu.au/page/Resources/?keywords=&research-area%5B%5D=Lungs&resource-type%5B%5D=Flipchart+or+Presentation

Section 5.3 consists of the published paper of our strategy to use mobile phones within a culturally sensitive framework. The paper demonstrates that this is an effective strategy to improve adherence and retention in our RCT among urban and remote families in the NT and Queensland.
5.3 Journal article – Mobile phones support adherence and retention of Indigenous participants in a randomised controlled trial: strategies and lessons learnt
Mobile phones support adherence and retention of indigenous participants in a randomised controlled trial: strategies and lessons learnt

Gabrielle B McCallum1*, Lesley A Versteegh1, Peter S Morris1,2, Clare C McKay1, Nerida J Jacobsen3, Andrew V White3, Heather A D’Antoine1 and Anne B Chang1,4

Abstract

Background: Ensuring adherence to treatment and retention is important in clinical trials, particularly in remote areas and minority groups. We describe a novel approach to improve adherence, retention and clinical review rates of Indigenous children.

Methods: This descriptive study was nested within a placebo-controlled, randomised trial (RCT) on weekly azithromycin (or placebo) for 3-weeks. Indigenous children aged ≤ 24-months hospitalised with acute bronchiolitis were recruited from two tertiary hospitals in northern Australia (Darwin and Townsville). Using mobile phones embedded within a culturally-sensitive approach and framework, we report our strategies used and results obtained. Our main outcome measure was rates of adherence to medications, retention in the RCT and self-presentation (with child) to clinic for a clinical review on day-21.

Results: Of 301 eligible children, 76 (21%) families declined participation and 39 (13%) did not have access to a mobile phone. 186 Indigenous children were randomised and received dose one under supervision in hospital. Subsequently, 182 (99%) children received dose two (day-7), 169 (93%) dose three (day-14) and 180 (97%) attended their clinical review (day-21). A median of 2 calls (IQR 1–3) were needed to verify adherence. Importantly, over 97% of children remained in the RCT until their clinical endpoint at day-21.

Conclusions: In our setting, the use of mobile phones within an Indigenous-appropriate framework has been an effective strategy to support a clinical trial involving Australian Indigenous children in urban and remote Australia. Further research is required to explore other applications of this approach, including the impact on clinical outcomes.

Trial registration: ACTRN12608000150347 (RCT component).

Keywords: Mobile phones, SMS, Adherence, Randomised controlled trial, ALRTI, Bronchiolitis, Indigenous

Background

In the Northern Territory (NT), Indigenous children have high hospitalisation rates of bronchiolitis (352 per 1000) and more severe disease. Most children admitted are retrieved from remote communities [1,2]. Hospitalised episodes of lower respiratory infections are associated with later development of chronic lung disease [3,4]. In an attempt to improve clinical outcomes, we conducted a double blind randomised controlled trial (RCT) (using azithromycin) [5] within an evidence-based framework for assessing and prioritising health interventions. RCTs are accepted as the highest level of evidence available. However, the lack of appropriate RCTs may contribute to poor participation, attrition and treatment inequalities in minority groups [6]. While some progress has been made in reducing health disparities, there is a continued need for intervention studies, both prevention and treatment trials, that focus on minority population(s) [7].

There are several possible methods that can be used to increase the adherence and reduce attrition (increase retention) in RCTs. One such method is the use of mobile phones as a means of communication. Mobile phones...
offer the advantage of real time communication, do not require high skills to function, are easily accessible, affordable and not restricted to computer or land line access [8]. The number of published research using the short message service (SMS) component of mobile phones to evaluate a range of health conditions has increased. However, the conditions studied have commonly focused on adult disease surveillance and chronic diseases [9-12]. Data on SMS outcomes in paediatric conditions; [13] i.e. acute illnesses, Indigenous populations or remote areas are limited.

In this study, we report on a novel approach to improve adherence, retention and clinical follow-up post-hospitalisation in 186 Australian Indigenous children participating in a RCT.

Methods
Study design
This study is embedded within a double-blinded, placebo-controlled, RCT conducted at the Royal Darwin Hospital and The Townsville Hospital between June 2010 and September 2013. We briefly describe the RCT below as the protocol has been published [5]. The RCT examines the question: ‘amongst children hospitalised with acute bronchiolitis, does azithromycin (compared to placebo) given once/week for three doses improve clinical outcomes?’ For this study, we describe the cohort of children enrolled in this RCT, strategies used and results obtained in ensuring adherence, retention and presentation to the clinic for follow-up. The trial was approved by each institution’s Human Research Ethics Committee and was registered with the Australian and New Zealand Clinical Trials Register. Clinical trials number: ACTRN12608000150347.

Study population
Children were eligible if they were Indigenous, aged ≤24 months, admitted to hospital with a clinical diagnosis of acute bronchiolitis, recruited within 24 hours of admission. There was also a requirement for the parent to have a mobile phone.

Recruitment and retention approach
Research nurses visited the paediatric wards twice daily to screen recently admitted children. Only parents whose child met eligibility criteria were approached. A summary of our frame work is presented in Table 1. Often parents had come to hospital in the early hours of the morning, were sleep deprived and had not retained information hospital staff provided. Therefore, research nurses always provided additional education on bronchiolitis using a pictorial-based flipchart (http://www.menzies.edu.au/page/Resources/Bronchiolitis_Lower_respiratory_tract_infection/). Time was spent with parents discussing the treatment and management of bronchiolitis and what to expect post discharge, regardless of the decision to be involved in the RCT. This appeared to enhance relationships and trust. Only when parents understood what bronchiolitis was, did research nurses proceed with discussion about the RCT. A pictorial consent flipchart was used in conjunction with a plain language information booklet (endorsed by the Menzies Child Health Indigenous Reference Group), to assist in the consent process. The time from screening to enrolment was recorded.

Once written informed consent was obtained from the parent or guardian, children were randomised to receive either azithromycin or placebo. The first dose was directly supervised in hospital; the remaining two doses were supervised by research nurses (urban-based children) or given at home by parents (remote-based children) (between days 5–9 and 10–12). The endpoint was a clinical review on day-21 (between days 20–30) by research nurses (urban-based children) or at the local health clinic (remote-based children) to determine presence of persistent respiratory symptoms and signs. Remoteness was defined as more than 100 km from a tertiary hospital.

Standardised assessment forms were used to collect clinical information from each child. Prior to discharge, parents were shown how to constitute the medication and were given the remaining medications in a sealed plastic bag which included syringes, 10 ml sterile water vials and a fridge magnet (with reminders when each medication and the clinical review was due).

We advised parents that we would ring or SMS when children were due to receive the medications and attend the clinic for their clinical review (remote-based children) or visit at home (urban-based children). For remote-based children, a phone call was also made to the local health clinic explaining the child’s involvement in the RCT and follow up required as part of routine clinical care post hospitalisation. A template was faxed to the health clinic and faxed back after the clinical review was completed. The number of contacts and reasons why contact could not be made were recorded (if applicable). A $20 mobile recharge voucher was sent via SMS after the third dose (but before clinical review) to thank parents for their participation.

Other strategies used
A number of strategies were implemented to help maintain contact with parents throughout the RCT. Firstly, research nurses called parent’s mobile phones prior to discharge. This ensured the number was transcribed correctly and started mobile phone contact while still meeting in person. Secondly, we obtained an additional mobile number for occasions when we were unable to contact the parent. Thirdly, we identified that parents would rarely answer phone calls from a blocked (unknown) number. Research nurses therefore called from
Table 1 Framework used in our study

<table>
<thead>
<tr>
<th>Pre study discussion</th>
<th>On the ground</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indigenous Reference Group (IRG) (consultation and endorsement of study)</td>
<td>Clinical Nurses with broad experience working in</td>
</tr>
<tr>
<td>Data Safety Monitoring Board (DSMB) (endorsement of study plan)</td>
<td>Indigenous health</td>
</tr>
</tbody>
</table>

Research team

- Paediatrics
- Clinical research
- Remote health settings

Project specific

- Briefings to IRG on study progress.
- DSMB updates on recruitment and retention.
- Providing education on bronchiolitis to parents using pictorial flipchart.
- Research nurses spending time discussing child's treatment and management in hospital and home.
- Consent process: using a pictorial flipchart in conjunction with a plain language information booklet.
- Education on how to prepare, when to give medication and attend health clinic for 21 day review.
- Education to nursing staff on paediatric wards to improve awareness and understanding of bronchiolitis.

Mobile phone specific

- Calling parent in hospital (number transcribed correctly and enabled two way communication).
- Obtaining additional number (if able).
- Calling parent from personal/study mobiles.
- Providing parents with option of calling from free 1800 number.

their personal mobiles (or a study mobile). Parents also had the option to call research nurses on the free 1800 number if they had any questions or concerns. However, we did not receive any call on this number. Parents preferred to call the personal mobiles of the research nurses.

Statistical analysis

Data were entered on an Access database and analysed using Stata version 12 (Statacorp College Station, Texas, USA). Data are presented as numbers and percentages, median and interquartile range (IQR 25-75% and or range). We describe feedback from parents and staff experiences in text.

Results

Demographics

Of 301 eligible children, 76 (21%) families declined participation and 39 (13%) did not have access to a mobile phone. A total of 186 children were enrolled; 161 in Darwin and 25 in Townsville. The median time taken to enrol participants was 30 minutes (range 20 minutes – 5 hours). The median age was 5.4 months (IQR 3–9); 111 (60%) boys, and 75 (40%) girls. Four children were withdrawn from receiving further medications (n = 3 for dose 2 and n = 4 for dose 3) by the paediatric team at site hospitals due to other medical reasons. The remaining children were followed up until they reached their endpoint (day-21 clinical review). More than two thirds of the children 144 (70%) lived in remote Indigenous communities. Of the Darwin-based cohort, 139 (85%) children were from remote-based communities.

In contrast, only 5 (20%) children enrolled in Townsville were remote-based. Figure 1 illustrates approximate locations of all communities and distances from site hospitals.

Medication and clinical review

All children 186 (100%) received the first dose of medication in hospital. A small number of children received dose-2 (n = 17 (8%)) and dose-3 (n = 3 (1%)) in hospital. For the remainder, research nurses made contact with parents on their mobiles when medication(s) and the clinical review were due. The adherence, retention and follow-up rate for the entire cohort was very high. Overall, 182 (99%) children received dose two (day-7), 169 (93%) received dose three (day-14) and 180 (97%) children attended their day-21 clinical review. Table 2 summarises the number of medication doses received, clinic reviews attended, missed and the median number of phone calls required to contact the carer.

Discussions

In our setting, it appears that mobile phones, combined with a culturally sensitive approach, were a simple and
effective tool to facilitate adherence in a clinical trial. To our knowledge, this is the first RCT involving Indigenous children that has used mobile phones to support adherence to research protocols. The success of our strategies is documented by a 97% retention rate, the highest we have ever achieved in a setting that involved children in the community.

The use of mobile phones in studies is not new. Previous research has shown mobile phones can have important benefits for clinic attendance, adherence to medications and treatment plans [14-17]. However we found only 3 studies involving children and none were relevant to Indigenous Australians or in acute illnesses [13,18,19]. Two of the 3 studies related to immunisations, [13,18] and the third was on reminders for appointments before and after cataract surgery in a large Chinese city hospital [19]. Two studies reported an improvement in the intervention group, compared to controls 43% vs. 39.9% [18] and 91% vs. 62% respectively [19]. The third study reported similar adherence in both groups using an intention to treat analysis 66% vs. 68% [13]. In contrast to the above studies, our study is not a RCT on mobile phones but a unique report on how we achieved an exceptional high retention and follow-up rate in a study setting where adherence to medications and follow-up has been reported to be generally difficult. While we were unable to observe adherence with doses 2 and 3 for remote-based children (we were reliant on parents providing this information), the day-21 follow-up rate of >97% at the local health clinic provides evidence of the success of our approach.

Including minorities in RCTs is important in addressing health gaps [20]. Adherence has been reported to be particularly challenging in those who are socially disadvantaged communities [7]. Improving adherence and reducing attrition is important in all clinical trials.

Table 2 Medication doses and clinic review by site

<table>
<thead>
<tr>
<th>Trial procedures</th>
<th>Darwin</th>
<th>Townsville</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Given</td>
<td>Missed N (%)</td>
</tr>
<tr>
<td>Dose 1</td>
<td>161 (100%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Dose 2*</td>
<td>157 (98%)</td>
<td>4 (2%)</td>
</tr>
<tr>
<td>Dose 3*</td>
<td>147 (91%)</td>
<td>14 (9%)</td>
</tr>
<tr>
<td>Clinical review</td>
<td>156 (97%)</td>
<td>5 (3%)</td>
</tr>
</tbody>
</table>

*3 children withdrawn from dose 2, 4 children withdrawn from dose 3 by the medical team.
#Combination of phone calls/SMS.
Strategies to reduce attrition have the potential to increase power and generalisability of results [21]. Our study has also shown that adherence to medications in the community setting is feasible, thus the opportunity for community based clinical care and follow-up can be highly successful. In addition to our mobile phone strategies, appropriate measures include: (i) building relationships and trust with parents; (ii) using culturally appropriate educational material; and (iii) personal contact with parents. It may also be important that all research staff were paediatric-trained with experience in working with Indigenous parents and children.

Our mobile phone strategy not only included obtaining multiple phone numbers but also calling from a mobile that displayed a number that could be identified by the parent. Over the past 14 years, network coverage in remote Australia has substantially improved. A study in the NT reported that mobile phones have become an essential part of relaying information to family members who were travelling or away from home [22].

Our strategies and findings have to be interpreted in the context of our target population and study settings. We recruited only children whose parents had a mobile phone as geographical remoteness limited our options to ascertain adherence. Although we did not expect the high number of mobile phone ownership, we found that only a small number of parents (13%) did not have access to a mobile phone at time of recruitment. It was not feasible for us to request community health clinics to supervise medication dosing as most of the children come from remote clinics with very high workloads. The clinical review was attended by health clinic staff as part of best practice guidelines for routine clinical care post hospitalisation for a respiratory infection in Australia and many affluent countries.

Families received a $20 mobile recharge voucher after the final medication dose, to thank them for their participation. While we provided this incentive, we do not feel this was fundamental to the adherence and retention of participants in our trial. Importantly, the incentive was provided before the day-21 clinical review, where the presentation rate was 97%. Previously, incentives in clinical trials have only reported small improvements in participant retention between 2-13% [21,23]. One RCT involved SMS reminders and provided a $20 gift card at time of enrolment [24]. The RCT [24] described that gift cards were not important to 22% of participants, somewhat important in 50%, and very important to 28% with regard to their participation in the RCT [13].

We speculate that building relationships and trust were fundamental to our high success of adherence and retention in this trial. In general, parents expressed how they felt supported in hospital and at home, knowing that our staff were there to talk to if they had queries or concerns about their child. In our setting, displacement to a major teaching hospital from a remote community can be distressing for Indigenous people. The approach used by our research nurses helped alleviate parent’s anxiety by providing support and understanding of bronchiolitis and thus we feel fundamental to them
continuing in the trial until the child’s endpoint. This was part of our culture-appropriate framework (Table 1). Our framework is supported by a similar strategies used to enhance participation of Maori people in a cardiovascular-based RCT in New Zealand. The NZ study outlined the importance of involving experienced Maori researchers at each time point of the trial, employing experienced Maori researchers, who used culturally specific processes for participation and retention of Maori participants and ongoing contact with Maori researchers and participants [24]. Such frameworks are important and highlight the effectiveness of strategies that are culturally appropriate, thus improving the participation and retention rates in minority populations.

Within our framework, we implemented multiple strategies to support adherence and retention of participants. It is difficult to ascertain the relative contribution to these strategies. This study was embedded within an RCT, thus is complex with the possible interaction between both a treatment intervention (azithromycin or placebo) and enhancing support (implementing cultural framework). Future treatment trials should account for these factors. One of our study’s limitations includes the lack of in-depth qualitative data to explore this issue. Also, our intervention period is relatively short (3 weeks). Whether or not these strategies will also be successful in longer term interventions remains unknown. Although the data presented are not high-level evidence (i.e. not a RCT), we have shown that the use of strategies employed here has led to an exceptionally high adherence and retention rate. This may have implications for clinical service in remote Indigenous settings and may improve health outcomes. It should be further studied as provision of high quality clinical service and ensuring adherence is a challenge in many settings, particularly in remote Indigenous settings.

Conclusions

Our data have provided important and novel data that the use of mobile phones, in conjunction with a culturally sensitive approach, is an effective strategy to support clinical trial protocols in Indigenous children living in urban and remote Australia. There is an opportunity to use these strategies to support health service delivery in remote communities that may improve adherence to medications and clinic attendance. Further research is required to explore the feasibility in these setting for health outcomes, cost effectiveness and long term sustainability using our described framework.

Competing interests

The authors declare that they have no financial competing interests.

Authors’ contributions

GBM set up and coordinated the study, recruited participants, performed the data analysis and drafted the manuscript. LAV, CCM, NJ, AVW recruited participants and edited the manuscript. ABC, PSM conceptualised the study, interpreted the data and edited the manuscript. HD provided cultural integrity support. All authors contributed to the study design and critically reviewed the manuscript and approved the final version.

Acknowledgments

We are grateful to all the children and families who participated in this study, and to the members of the Indigenous Reference Group for their advice (http://www.menzies.edu.au/page/About_Us/Board_and_Members_commmittee/Indigenous_Reference_Group/). We thank the medical and nursing staff for their support and helping identify children for the study and members of the DQMB (Dr Kerry Ann O’Grady, Dr William Fishman, Professor Alan Adsles, A/Prof Alan Ruben, Ms Linda Ward). We also thank the remote health clinics for their support. This study was funded by NHMRC (grant number 605899, on-going) and supported by a NHMRC Centre for Research Excellence in Lung Health of Aboriginal and Torres Strait Islander Children (grant number 1040830). GBM is supported by a NHMRC scholarship (grant 1055262). AC is funded by a NHMRC practitioner fellowship (grant 549216).

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References


Abbreviations

ACTRN: Australian New Zealand Clinical Trials Registry; IQR: Interquartile range; NT: Northern territory; RCT: Randomised controlled trial; SMS: Short message service.


Chapter 6: Outcomes of risk factors from Indigenous infants hospitalised with bronchiolitis

6.1 Chapter overview

This chapter addresses the gap in understanding of clinical risk factors and outcomes associated with bronchiolitis (described in section 1.5.2 and 1.5.3). Although bronchiolitis is a typical self-limiting condition, those at high risk for severe disease include infants with underlying medical conditions, such as prematurity, cardiac or respiratory disease. Despite a number of studies exploring disease severity in hospitalised bronchiolitis, it remains unclear whether non-traditional risk factors, viruses (single vs. multiple) and/or common respiratory bacteria influence disease severity within and beyond hospitalisation. There are also no prospective studies among Indigenous children extending the follow-up period beyond hospitalisation.

The overall aim of this study was therefore to describe the clinical severity of previously well Indigenous infants (i.e. excluding known clinical risk factors such as CLD of prematurity, CHD) hospitalised with bronchiolitis to determine what factors (clinical and microbiological) on admission that were associated with; (i) prolonged LOS, (ii) presence of persistent symptoms 3 weeks after hospital discharge, (iii) whether presence of cough at 3 weeks was associated with bronchiectasis up to ~24 months post-hospitalisation and (iv) re-hospitalisation within 6 months for a respiratory illness.

This study was nested in two RCT’s (chapters 3-4) and a cohort study (chapter 2) conducted at RDH between June 2008 and September 2013. For the purpose of this study, we excluded non-Indigenous children, as our previous work showed being Indigenous as an independent risk factor for more severe bronchiolitis. We used
data collected during hospitalisation to record demographic information and clinical data to determine disease severity, such as length of stay and oxygen requirement. Only infants in the second RCT (chapter 4), were clinically reviewed at day-21. 6-month respiratory readmission data was recorded on all children from both RCT’s (chapters 3-4).

Section 6.2 consists of the manuscript ready for submission, which identified that non-traditional clinical risk factors influence disease severity within and beyond hospitalisation. We report novel data that during hospitalisation, increased accessory muscle use on admission was associated with prolonged hospital stay. Moreover, persistent symptoms beyond hospitalisation were common and associated with an increased risk of respiratory morbidity and subsequent diagnosis of bronchiectasis. For populations at high risk for respiratory morbidity, our data will help optimise clinical care both in and beyond hospital to improve long term respiratory outcomes. This manuscript is ready for submission.
6.2 Journal article – Outcomes of risk factors of Indigenous infants hospitalised with bronchiolitis (manuscript ready for submission)
Title: Outcomes of risk factors of Indigenous infants hospitalised with bronchiolitis

Authors: Gabrielle B McCallum\textsuperscript{1} PhD, Mark D Chatfield\textsuperscript{1} MSc, Peter S Morris\textsuperscript{1,2} PhD, Anne B Chang\textsuperscript{1,3} PhD

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Keywords
Bronchiolitis, indigenous, risk factors, viruses, bacteria
Funding source and financial disclosure

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Short title: Outcomes of risk factors for bronchiolitis
Abstract

Background
Hospitalised bronchiolitis imposes a significant burden among infants, particularly among Indigenous children. Traditional or known risk factors for severe disease are well described, but there are limited data on risks for prolonged hospitalisation and persistent symptoms. Our aims were to determine factors (clinical and microbiological) associated with (i) prolonged length of stay (LOS), (ii) persistent respiratory symptoms at 3 weeks, (iii) bronchiectasis up to ~24 months post-hospitalisation and (iv) risk of respiratory readmissions within 6 months.

Methods
Indigenous infants hospitalised with bronchiolitis were enrolled at Royal Darwin Hospital between 2008-2013. Standardised forms were used to record clinical data. A nasopharyngeal swab was collected at enrolment to identify respiratory viruses and bacteria.

Results
The median age of 232 infants was 5 months (interquartile range 3-9); 65% male. On multivariate regression, our 12 point severity score (including accessory muscle use) was the only factor associated with prolonged LOS but the effect was modest (+3.0 hours per point, 95%CI: 0.7, 5.1, p=0.01). Presence of cough at 3 weeks increased the odds of bronchiectasis (OR 3.0, 95%CI: 1.1, 7.0, p=0.03). Factors associated with respiratory readmissions were: previous respiratory hospitalisation (OR 2.3, 95% CI: 1.0, 5.4, p=0.05) and household smoke (OR 2.6, 95%CI: 1.0, 6.3, p=0.04).
Conclusion

Increased severity score is associated with prolonged LOS in Indigenous children hospitalised with bronchiolitis. As persistent symptoms at 3 weeks post-hospitalisation are associated with future diagnosis of bronchiectasis, optimising clinical care beyond hospitalisation is needed to improve long-term respiratory outcomes for infants at risk of respiratory disease.
Introduction

Bronchiolitis is typically a self-limiting illness, but causes considerable morbidity and remains a leading cause for hospitalisation among infants worldwide.\textsuperscript{1} The cost of hospitalised bronchiolitis has risen substantially in the USA over the last decade (increase of 34\%).\textsuperscript{2} There are many studies that have reported on the risk factors for severe disease and length of stay (LOS) in hospital e.g. prematurity and cardio-respiratory disease.\textsuperscript{3} However, there is relatively little data on other factors (e.g. detection of bacteria with viruses) associated with LOS in hospital in an at-risk population (e.g. Indigenous children who have more severe bronchiolitis)\textsuperscript{4} and future bronchiectasis.\textsuperscript{5}

Factors associated with severe illness and/or prolonged LOS include: clinical severity (assessed by scoring systems), viruses\textsuperscript{1,3,6} and secondary bacterial infection.\textsuperscript{7} Respiratory syncytial virus (RSV) is implicated for 50-80\% of cases and is associated with more severe disease in some studies\textsuperscript{8-10} but not in others.\textsuperscript{6} Whether single vs. multiple viruses influence disease severity is also controversial.\textsuperscript{11,12} Further, a number of non-classical respiratory viruses (e.g. coronaviruses, bocaviruses) have been identified\textsuperscript{13} but the clinical relevance of these remains unclear, as these non-classical viruses are commonly present in asymptomatic children.\textsuperscript{14} In a hospital-based study, a virus (including non-classical viruses) was detected (42\%) in the nasopharynx of children who did not have any respiratory symptoms.\textsuperscript{14}

Children with severe bronchiolitis requiring intensive care are likely to have a secondary bacterial infection.\textsuperscript{7} However, studies on bronchiolitis to date have not examined whether the presence of respiratory bacteria in the upper airways
influences clinical outcomes in children hospitalised with bronchiolitis. Examination for bacteria is not routine in bronchiolitis management. However, it is plausible that secondary bacterial infection that occur post viral infections are more likely when the nasopharynx is colonised with bacteria, as found in some populations such as in Northern Territory Indigenous infants. In these children, early (at ~2 weeks of age), common (up to 90% of infants) and dense acquisition of respiratory bacteria (Streptococcus pneumoniae, Haemophilus influenza and Moraxella catarrhalis) have been documented. Thus, in study settings like ours, the presence of bacteria in the NP may be particularly relevant. Secondary bacterial infection may complicate bronchiolitis, and possibly contribute to poorer long-term outcomes such as chronic wet cough and bronchiectasis. It has been shown in children aged ≤3 years hospitalised with first time wheezing, co-detection of viruses (93%) and bacteria (60%) in nasopharyngeal aspirates resulted in prolonged LOS. Yet, it remains unknown whether co-detection of bacteria with viruses in the nasopharynx at the point of bronchiolitis hospitalisation contributes to LOS. This data is lacking and is especially important for populations at high risk of poorer outcomes (e.g. secondary bacterial pneumonia, chronic wet cough etc). Further rationale for assessing viruses and bacteria in the infants involved in our studies was described in a previous paper.

Beyond hospitalisation, persistence of respiratory symptoms (i.e. post-bronchiolitis syndrome) is increasingly appreciated. Cohort studies report symptoms in up to 40% of infants, 14-25 days post-hospitalisation. There are few data on what happens to these children in the medium term (4-weeks to 6 months). Determining the clinical relevance of symptoms beyond hospitalisation is particularly important in populations e.g. Indigenous children who have a high risk of bronchiectasis.
In the absence of any data from Indigenous children, we combined data from 3 prospective studies that included 232 Indigenous infants hospitalised with a clinical diagnosis of bronchiolitis, to examine factors (clinical and microbiological) on admission that were associated with (i) prolonged LOS (Aim-1), (ii) presence of persistent symptoms 3 weeks after hospital discharge (Aim-2), (iii) whether presence of cough at 3 weeks was associated with bronchiectasis up to ~24 months post-hospitalisation (Aim-3) and (iv) re-hospitalisation within 6 months for a respiratory illness (Aim-4). We hypothesised that co-detection of viruses and/or bacteria in the nasopharynx are associated with longer LOS, persistent respiratory symptoms and re-hospitalisation with a respiratory illness within 6 months of discharge.
Methods

Study design

Data from 3 prospective studies were combined (Figure-1) for the different aims; 2 studies were randomised controlled trials (RCT)\textsuperscript{5,23} and one a cohort study.\textsuperscript{24} Here, we briefly describe these studies as the methods have been published.\textsuperscript{5,23,24} Both RCTs aimed to determine if different durations of azithromycin, compared to placebo, improved clinical outcomes for infants hospitalised with bronchiolitis (i.e. LOS, oxygen requirement and respiratory readmissions within 6 months of hospital discharge). The cohort study aimed to determine the validity and reliability of a severity scoring system among infants presenting to Royal Darwin Hospital (RDH) with bronchiolitis (Figure-1).\textsuperscript{24} RDH is a 363 bed referral centre, servicing \textasciitilde150,000 people with geographical coverage of \textasciitilde400,000km.\textsuperscript{2} Studies were approved by the Human Research Ethics Committee of the Northern Territory Department of Health and Menzies School of Health Research (RCT-1:HREC 07/60; RCT-2 and cohort study: HREC-2010-1324). Written informed consent was obtained from the carer of each infant. Most children were involved in the two RCTs; Australian and New Zealand Clinical Trials Register: Clinical trials numbers: ACTRN12608000150347 (RCT-1) and ACTRN12608000150347 (RCT-2).

Study population

In this study, only Indigenous infants were included as our previous work showed being Indigenous as an independent risk factor for more severe bronchiolitis.\textsuperscript{5} Infants were eligible if they were from Darwin, \textless{}18 months (RCT-1)\textsuperscript{5} or \textless{}24 months old (RCT-2 and cohort study),\textsuperscript{23,24} and hospitalised with bronchiolitis. Infants were excluded if they had very severe disease (admitted to intensive care), chronic lung disease, congenital heart disease, contraindications to macrolide use (RCT-1 and
RCT-2), received macrolides (in last 7 days), diarrhoea, or clinical and radiological features consistent with a primary diagnosis of pneumonia (as diagnosed by the attending medical team). Infants contributed data only once for this study.

**Clinical assessment and specimen collection at enrolment**

Standardised data collection forms were used to record demographic, medical history and clinical data (Table-1). Other therapies and routine investigations were also documented. Infants who received additional trial medication (e.g. azithromycin) were treated the same for this analysis as those who received placebo, as no clinically significant differences in either RCT were observed.\(^5,23\) Severity was assessed using a score we validated in our setting.\(^24\) The score comprised of four components (respiratory rate, accessory muscle use, degree of wheezing and SpO2). Each component scored between 0 and 3, providing a composite score between 0-12. LOS was defined by the treating medical team as time from admission, to time for ‘ready for discharge’ (SpO\(_2\) consistently >94\% in air for >16hrs) and feeding adequately.

Infants were clinically reviewed by research nurses (urban-based infants) or at their local health clinic (remote-based infants) 3 weeks after hospital discharge, to determine presence of persistent respiratory symptoms and signs. Remoteness was described as more than 100km from a tertiary hospital. Any respiratory readmission and investigations for bronchiectasis were monitored by a hospital based study (HREC 07/63). As RDH is the only hospital our target population accesses, all hospitalisations were accurately captured.

A nasopharyngeal swab (NPS) at enrolment was tested for common respiratory bacterial pathogens (*Streptococcus pneumoniae*, *Haemophilus influenzae*, *Moraxella catarrhalis* and *Staphylococcus aureus*) and a broad panel of viruses and atypical
bacteria; RSV (A and B), adenovirus, parainfluenza (1, 2, 3), influenzavirus (A and B), human rhinovirus (HRV) and enterovirus, coronaviruses, bocavirus, human metapneumovirus (hMPV), KI (KIPyV) and WU (WUPyV) polyomaviruses, *Chlamydophila pneumoniae* and *Mycoplasma pneumoniae*. Common respiratory bacteria (other than *C. pneumoniae* and *M. pneumoniae*) were identified on culture and viruses identified by PCR.  

**Statistical analysis**

Data were entered on an Access database and analysed using Stata version 13 (StataCorp College Station, Texas, USA). As data was skewed, we log-transformed our main outcome measure LOS. Exponentiating linear regression coefficients of log LOS gave us the multiplicative effect of a risk factor on geometric mean LOS, which we re-expressed (by assuming the median LOS for the reference group was 58 hours) as the approximate increase in median LOS in hours. Logistic regression was used to examine the association of independent variables on presence of cough at 3 weeks, and respiratory readmissions within 6 months. All factors with univariate p<0.2 were included in multivariable regression models (except for viruses – RSV was entered and other variables relating to viruses were not). A two-tailed p≤0.05 was considered significant. As this was a secondary analysis of available data, sample size calculation was not undertaken.
Results

Demographic data is summarised in Table-1a for the 232 Indigenous infants included in this study (70% of the 232 were from RCT-1, RCT-218% and Cohort-12%, Figure-1). Most children were aged ≤12 months (90%), not born premature (75% born ≥37 weeks) and required O₂ supplementation (62%). No child required intensive care transfer.

From the NPS of 229 Indigenous infants (one refused, 2 did not provide consent for NPS), 175 (76%) had one or more viruses identified. RSV was the most common followed by HRV, WUPyV and adenovirus (Table-1b). At least one type of respiratory bacteria was detected in 155 (67%) infants. The most common bacteria cultured was Moraxella catarrhalis, followed by Haemophilus influenzae and Streptococcus pneumoniae. The NPS from 24 (10%) infants was negative for both bacteria and virus.

Factors on admission associated with prolonged LOS (Aim-1)

On univariate analysis, factors on admission significantly associated with prolonged LOS were age and severity score (Table-2a). Notably, antibiotics prior to hospitalisation, any virus and co-detection of virus/bacteria were not associated with longer LOS. On multivariate regression, the only factor that remained significant was severity score. Detection of RSV increased LOS by 10hrs (p=0.06), but this did not reach statistical significance. We then examined which component of the severity score contributed the most to LOS (Table-2b). In the univariate analysis, (considering each of the four components as single factors) all components except wheeze were significantly associated with prolonged LOS. On multivariate regression, only the ‘accessory muscle use’ component remained significant.
We repeated the main analyses, restricting the cohort to the n=181 infants who had no previous respiratory hospitalisations. On multivariate analysis, the only factor which significantly prolonged LOS was the severity score (p=0.02).

Presence of cough 3 weeks after discharge (Aim-2)

One hundred and fifty seven Indigenous infants who had a clinical review at 3 weeks contributed to this analysis (Figure-1). Persistent respiratory symptoms were frequent beyond hospitalisation (Table-1a). On univariate analysis, factors significantly associated with presence of cough 3 weeks after discharge was age and presence of ‘any bacteria’ cultured on NPS. No factors remained significant on multivariate regression.

Presence of cough 3 weeks after discharge and the relationship to bronchiectasis (Aim-3)

As of 7\textsuperscript{th} May 2015, 30/157 (19\%) infants had a chest CT scan requested by their treating paediatrician for clinical reasons when seen 7 months (interquartile range (IQR) 2-13) post-hospitalisation for bronchiolitis. All 30 (100\%) children had bronchiectasis documented in the CT scan, performed at median 13 months (IQR 7-18) post the index bronchiolitis hospitalisation. Infants with persistent cough at 3 weeks after hospitalisation were significantly more likely to have bronchiectasis compared to those without a cough (OR 3.0, 95\% CI: 1.1-7.0, p=0.03).

Respiratory readmissions 6 months after discharge (Aim-4)

On univariate analysis, factors that significantly increased the odds of respiratory readmission 6-months after discharge were previous respiratory hospitalisation and exposure to household smoke. Factors that significantly reduced the odds of readmission were detection of ‘any virus’, ‘any bacteria’, RSV and ‘RSV and HRV’
on NPS (Table-3). On multivariate regression, previous respiratory hospitalisation and exposure to household smoke were factors that significantly increased the odds of readmission but the presence of ‘any bacteria’ and RSV reduced the odds of readmission (Table-3). The presence of any respiratory abnormality (i.e. presence of cough, wheeze or crackles) at 3 weeks was not associated with the odds of respiratory readmissions (OR 1.2, 95% CI: 0.6-3.0, p=0.6).
Discussion

In our study involving 232 Indigenous infants hospitalised with bronchiolitis, we found that a higher severity score on admission, particularly use of accessory muscles, was associated with prolonged hospital stay. The presence of a virus or viruses detected on hospitalisation was not associated with poorer outcomes. Beyond hospitalisation, factors associated with presence of cough at 3 weeks were previous respiratory hospitalisation and presence of bacteria. By 6 months, infants previously hospitalised with a respiratory illness and exposed to household smoke had an increased odds of re-hospitalisation for a respiratory illness. In contrast however, infants with presence of RSV and culturable bacteria detected in NPS had decreased odds of re-hospitalisation at 6 months. Further, infants who were coughing at 3 weeks post-hospitalisation were significantly more likely to be diagnosed with bronchiectasis a median of 13 months later.

Our study involved only Indigenous children as recurrent hospitalisations for respiratory infections and chronic suppurative lung disease is prevalent in our setting.\cite{18} Indigenous children living in USA, Canada, Australia and New Zealand share many similarities with respect to the burden of respiratory illness.\cite{26} Thus, we were interested in finding factors associated with poorer clinical outcomes and possible future intervention points. Studies on hospitalised bronchiolitis in Canadian children found ethnicity, apnoea or respiratory arrest prior to hospitalisation or pulmonary consolidation to have more complicated hospitalisation.\cite{27} Further, previous RSV bronchiolitis hospitalisation was associated with chronic cough and recurrent respiratory infections in early childhood.\cite{17}
Well known or ‘traditional risk factors’ associated with severe bronchiolitis in infants include prematurity, cardio-respiratory disease, and being Indigenous. In contrast, there are a few prospective studies which examined other factors that prolonged LOS. In these studies, factors significantly associated with prolonged LOS were young age, increased work of breathing, heart rate, respiratory rate, dehydration, hypoxia on admission, SpO2 <94%, respiratory distress assessment instrument (RDAI) score >11, apnoea, weight, RSV, ethnicity and winter season. Retrospective studies have described that RSV, ethnicity, congenital syndromes, neuromuscular disorders and existing chronic respiratory diseases were associated with prolonged LOS. In our study, severity score on admission, particularly use of accessory muscles, was the only factor to prolong LOS, once other factors (n=21) were accounted for in the multivariate regression. None of the previous studies however had dissected which component of the scoring system contributed the most to LOS. Further, despite the many studies undertaken for bronchiolitis, most scoring systems used were not validated. Indeed the most commonly used system, the RDAI score, has limited validity when systematically examined. Within our study, we had validated the scoring system used and showed good inter- and intra-rater reliability.

The type and number of viruses (particularly RSV and HRV) did not significantly influence LOS in our study. Our results are similar to some studies, but dissimilar to others where RSV and/or HRV influenced disease severity. Reasons for these variations are likely multi-factorial including sample size, different methodologies, sampling frame, age, number and types of viruses investigated. We also found that although respiratory bacteria (H. influenza, S. pneumoniae and M. catarrhalis) and/or viruses were common (88%), their presence did not prolong LOS. While data
relating to LOS and type of virus detection has been previously examined, none of these studies have examined the influence of the presence of bacteria in the upper airways. We found that the presence of bacteria detected in the nasopharynx with or without concurrent viruses did not influence LOS. Our finding of high prevalence of concurrent bacteria with viruses (i.e. 88%) in the children’s nasopharynx is similar to that reported by Bisgaard and colleagues among young children of asthmatic mothers with acute wheeze in a non-hospitalised cohort.\textsuperscript{36}

Beyond the hospital phase, our study reported several novel outcomes. At 3 weeks post-hospitalisation, the prevalence of respiratory symptoms in our study (20%) was similar to other studies (18-25%).\textsuperscript{21,22,37} Few studies however have prospectively recorded respiratory symptoms post-hospitalisation, and no studies have examined for predictors of persistent respiratory symptoms otherwise known as ‘post-bronchiolitis syndrome’. While presence of bacteria in the NPS on admission was not significantly associated with persistence of cough at 3 weeks,\textsuperscript{36} chronic cough is the most common symptom of an underlying lung disease and causes poorer quality of life.\textsuperscript{38} Persistent cough was however a significant risk factor (OR 3.0, 95%CI 1.0-7.0, p=0.03) for CT-confirmed bronchiectasis 13 months later. Bronchiectasis is particularly common in Indigenous infants in the USA, Australia and New Zealand and hospitalisation for respiratory disease is an independent risk factor.\textsuperscript{18}

In the context that early treatment of bacterial infections in the lower airways prevents long-term lung damage,\textsuperscript{39,40} our post-hospitalisation data is both novel and important in high-risk population groups (e.g. Indigenous children).\textsuperscript{18} Post-bronchiolitis syndrome is likely highly important especially in high-risk populations. Our data raises an important public health issue with respect to follow-up of children with bronchiolitis, to optimise clinical care beyond the immediate hospitalisation...
phase to improve long-term respiratory outcomes for high-risk populations. We suggest that children should be clinically reviewed between weeks 3-4 after hospital discharge to assess for persistent symptoms and signs and managed accordingly. There is currently no high quality evidence on the most appropriate intervention in any groups of children with post-bronchiolitis syndrome.\textsuperscript{41} However, until further evidence is available, we suggest the use of antibiotics when the cough is wet and not improving in a group at high risk of chronic suppurative lung disease, in line with the treatment of protracted bacterial bronchitis.\textsuperscript{42}

Our post-hospitalisation data also showed that children exposed to environmental tobacco smoke and those previously hospitalised with a respiratory illness were twice as likely to be readmitted with a respiratory illness within 6 months of hospital discharge. Surprisingly, we found that presence of RSV on admission and ‘any bacteria’ significantly reduced the odds of re-hospitalisation by 6 months post index hospitalisation. Whether respiratory readmissions were related to the initial bronchiolitis episode or other causes can only be postulated. One possible reason for this RSV detection is a marker (as opposed to a cause) for future asthma (which does not lead to re-hospitalisation).

Our study has several limitations. Firstly, our sampling frame is restricted to Indigenous children without the well-known, traditional risk factors (e.g. chronic lung disease, cardiac disease) and who did not require intensive care. Reasons for our sampling frame were discussed above but it also means our data cannot be extrapolated to the general population or to non-hospitalised infants. Secondly, we did not exclude infants that had been hospitalised previously; however exclusion of these infants did not alter our main results. Thirdly, 87\% of children received
antibiotics during hospitalisation. This may have impacted on nasopharyngeal bacterial carriage, however removing these children did not alter our main results. Fourthly, the children were systematically reviewed only at one time point i.e. at 3 weeks post-hospitalisation. The decision by the treating paediatricians who reviewed these infants at a median of 7 months post-hospitalisation to subject the child to a chest CT scan was based on clinical assessments, not systemised and thus subject to external biases. Thus, we could not systematically analyse the factors on admission that are associated with future development of bronchiectasis. Also, while long-term, prospective, follow-up studies in high-risk populations are required, we cannot unethically subject all children to a chest CT (given the known risk of radiation in young children).

Conclusion
In the first prospective study of Indigenous infants hospitalised with bronchiolitis with post-hospitalisation data at 3 weeks and 6 months, we found that the severity score on admission, particularly accessory muscle use, was the sole factor associated with prolonged LOS once other factors (clinical and microbiological) were accounted for. Persistent respiratory symptoms at 3 weeks increased the risk of bronchiectasis and factors associated with persistent symptoms were prior hospitalisation for a respiratory illness and presence of bacteria on the NPS on admission. Thus, clinical review, with early treatment when necessary, should be undertaken in populations at high risk for chronic respiratory disease. Follow-up studies beyond 6 months are necessary to consolidate our findings and determine intervention points that can reduce the high burden of respiratory diseases in at-risk populations.
Acknowledgments

We are grateful for all infants and families who participated in this study. We thank the remote health clinics for their support and attending the clinical review. We thank Lesley Versteegh and Clare Mckay for enrolling participants and collecting the clinical data. We thank Vanya Hampton, Donna Woltring, Jemima Beissbarth, Jane Gaydon and Rebecca Rockett for processing the viral and bacterial samples.

Abbreviations

HREC: Human Research Ethics Committee; HRV: Human rhinovirus IQR: interquartile range; LOS: length of stay; NPS: nasopharyngeal swab; OR: odds ratio; O₂: oxygen; RCT: randomised controlled trial; RSV: respiratory syncytial virus; SpO₂: oxygen saturation

Conflict of interest

The authors declare that they have no conflicts of interest.

Contributors’ statement

Anne Chang conceptualised the study with modifications by Peter Morris and Gabrielle McCallum. Gabrielle McCallum designed the data collection instruments, collected data, coordinated the study and carried out initial data analysis and manuscript. Mark Chatfield provided statistical support, carried out further data analysis and edited the manuscript. All authors assisted in data interpretation, contributed to the manuscript and approved the manuscript as submitted.
References


FIGURE LEGEND

Figure-1. Studies where Indigenous infants were recruited at Royal Darwin Hospital

Infants from the three studies conducted at Royal Darwin Hospital during 2008-2013 used to answer different aims. ‘n’ refers to the number of infants included in this paper, rather than the actual number of infants in the original studies.
Figure-1: Studies where Indigenous infants were recruited from at Royal Darwin Hospital

**Study**

**Brief Description**

**Aims assessed**

**Cohort study**^{24}

Indigenous infants aged ≤24 months assessed for severity scoring study (n=28)

- **Aim-1**
  - Prolonged LOS

**RCT-1**^{5}

Indigenous infants aged ≤18 months randomised to receive a single large dose of azithromycin or placebo (n=42)

- **Aim-2 & 3**
  - Presence of persistent symptoms 3 weeks after hospital discharge
  - Cough at 3 weeks is associated with bronchiectasis ~24 months after discharge

**RCT-2**^{23}

Indigenous infants aged ≤24 months randomised to receive 3 large weekly doses of azithromycin or placebo (n=162)

- **Aim-3**
  - Re-hospitalisation within 6 months for a respiratory illness
### Table-1a Demographic and clinical characteristics of (n=232) Indigenous infants

<table>
<thead>
<tr>
<th>Demographics</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (months)</td>
<td>5 (3-9)</td>
</tr>
<tr>
<td>Boys</td>
<td>151 (65%)</td>
</tr>
<tr>
<td>Gestational age (weeks)</td>
<td>38 (36-39)</td>
</tr>
<tr>
<td>Birth weight (kg)</td>
<td>3.0 (2.5-3.3)</td>
</tr>
<tr>
<td>Premature (≤37 weeks)</td>
<td>59 (25%)</td>
</tr>
<tr>
<td>Remote</td>
<td>193 (83%)</td>
</tr>
<tr>
<td>Currently breastfed</td>
<td>195 (84%)</td>
</tr>
<tr>
<td>Previous respiratory hospitalisation</td>
<td>51 (22%)</td>
</tr>
<tr>
<td>Mother smoked during pregnancy*</td>
<td>130 (56%)</td>
</tr>
<tr>
<td>Exposed to household smoke*</td>
<td>145 (63%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Symptoms leading up to admission (parent reported)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Days with respiratory symptoms*</td>
<td>3 (2-4)</td>
</tr>
<tr>
<td>Nasal discharge</td>
<td>196 (85%)</td>
</tr>
<tr>
<td>Cough</td>
<td>228 (98%)</td>
</tr>
<tr>
<td>Breathing difficulties</td>
<td>228 (98%)</td>
</tr>
<tr>
<td>Poor feeding</td>
<td>95 (41%)</td>
</tr>
<tr>
<td>Lethargy</td>
<td>136 (59%)</td>
</tr>
<tr>
<td>Severity score (composite score (0-12))^23</td>
<td>5 (3-7)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Enrolment observations</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Number on oxygen</td>
<td>144 (62%)</td>
</tr>
<tr>
<td>Level of supplemental O_2 (L/min)</td>
<td>1 (0.5, 2)</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>143 (132-155)</td>
</tr>
<tr>
<td>Temperature (°C)</td>
<td>37.0 (36.0-37.0)</td>
</tr>
</tbody>
</table>
### Antibiotics prescribed prior to hospital

<table>
<thead>
<tr>
<th>Description</th>
<th>Count (Percentage)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antibiotics prescribed prior to hospital</td>
<td>116 (57%)</td>
</tr>
<tr>
<td>Antibiotics prescribed during hospital</td>
<td>201 (87%)</td>
</tr>
<tr>
<td>Supplemental IV fluid administered</td>
<td>64 (28%)</td>
</tr>
<tr>
<td>Chest X-ray taken</td>
<td>217 (94%)</td>
</tr>
<tr>
<td>Any virus detected</td>
<td>175 (76%)</td>
</tr>
<tr>
<td>Any bacteria present</td>
<td>155 (67%)</td>
</tr>
<tr>
<td>Any co-morbidity</td>
<td>131 (56%)</td>
</tr>
</tbody>
</table>

### Hospitalisation

<table>
<thead>
<tr>
<th>Description</th>
<th>Count (Percentage)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Length of stay (hours)</td>
<td>58 (43-85)</td>
</tr>
<tr>
<td>Supplemental O₂ required</td>
<td>144 (62%)</td>
</tr>
<tr>
<td>Time on supplemental O₂ (hours)</td>
<td>43 (23-74)</td>
</tr>
</tbody>
</table>

### Post-hospitalisation data

<table>
<thead>
<tr>
<th>Description</th>
<th>Count (Percentage)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cough present at 3 weeks post-hospitalisation</td>
<td>31/157 (20%)</td>
</tr>
<tr>
<td>Presence of any respiratory abnormality 3 weeks post-hospitalisation</td>
<td>32/157 (20%)</td>
</tr>
<tr>
<td>Presence of otitis media 3 weeks post-hospitalisation</td>
<td>21/143 (15%)</td>
</tr>
<tr>
<td>Re-hospitalisation for any respiratory illness within 6 months</td>
<td>48/204 (24%)</td>
</tr>
<tr>
<td>CT-confirmed bronchiectasis</td>
<td>30/157 (19%)</td>
</tr>
</tbody>
</table>

* Missing data – Gest age = 16, Weight = 22, Mother smoke = 4, Household smoke = 2, Days with respiratory symptoms = 3, Poor feeding = 1, Lethargy = 3, Pulse = 2, Temperature = 5, Ox (L/min) = 25, Nasopharyngeal swab = 3 refused/did not collect.

Severity score = 42 infants (one study did not collect). 3-week post hospital = 157 (only one study collected this data); n=5 did not complete review.

^ Co-morbidity = any otitis media, skin infection or lobar/collapse pneumonia.

Data presented as median and IQR for continuous variables, and actual numbers for categorical variables and percentages.
Table 1b. Distribution of viruses, atypical bacteria and bacteria detected at enrolment with NPS

<table>
<thead>
<tr>
<th>Virus and atypical bacteria</th>
<th>Number of children with micro-organism detected (% of N=229*)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No virus detected</td>
<td>54 (24%)</td>
</tr>
<tr>
<td>1 virus detected</td>
<td>123 (54%)</td>
</tr>
<tr>
<td>2 or more viruses detected</td>
<td>52 (23%)</td>
</tr>
<tr>
<td>RSV</td>
<td>98 (43%)</td>
</tr>
<tr>
<td>HRV</td>
<td>61 (27%)</td>
</tr>
<tr>
<td>Adenovirus</td>
<td>15 (7%)</td>
</tr>
<tr>
<td>WUPyV</td>
<td>15 (7%)</td>
</tr>
<tr>
<td>Influenza_AB</td>
<td>10 (4%)</td>
</tr>
<tr>
<td>hMPV</td>
<td>7 (3%)</td>
</tr>
<tr>
<td>Bocavirus</td>
<td>5 (2%)</td>
</tr>
<tr>
<td>Coronavirus</td>
<td>3 (1%)</td>
</tr>
<tr>
<td>Parainfluenza_123</td>
<td>4 (2%)</td>
</tr>
<tr>
<td>Enterovirus</td>
<td>4 (2%)</td>
</tr>
<tr>
<td>KIPyV</td>
<td>4 (2%)</td>
</tr>
<tr>
<td>C. Pneumoniae</td>
<td>4 (2%)</td>
</tr>
<tr>
<td>M. Pneumoniae</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>RSV/HRV</td>
<td>144 (63%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Bacteria</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>No bacteria detected</td>
<td>76 (33%)</td>
</tr>
<tr>
<td>1 type of bacteria detected</td>
<td>90 (39%)</td>
</tr>
<tr>
<td>2 or more bacteria detected</td>
<td>65 (28%)</td>
</tr>
<tr>
<td>Moraxella catarrhalis</td>
<td>89 (39%)</td>
</tr>
<tr>
<td>Haemophilus influenzae</td>
<td>88 (34%)</td>
</tr>
<tr>
<td>Streptococcus pneumoniae</td>
<td>50 (22%)</td>
</tr>
<tr>
<td>Staphylococcus aureus</td>
<td>24 (10%)</td>
</tr>
</tbody>
</table>

* Many children had more than one organism detected
Table 2a. Analysis of risk factors for LOS (n_{max}=232)

<table>
<thead>
<tr>
<th>Risk factors present on admission</th>
<th>Univariate</th>
<th></th>
<th></th>
<th></th>
<th>Multivariate</th>
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<tbody>
<tr>
<td></td>
<td>Difference in median LOS (hours)*</td>
<td>95% CI</td>
<td>P value</td>
<td>Difference in median LOS (hours)*</td>
<td>95% CI</td>
<td>P value</td>
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<td><strong>CONTINUOUS</strong></td>
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<td></td>
<td></td>
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<tr>
<td>Age (months)</td>
<td>-0.2</td>
<td>-1.2</td>
<td>(-2.1, -0.2)</td>
<td>0.02</td>
<td>-0.6</td>
<td>(-1.6, 0.5)</td>
<td>0.3</td>
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<tr>
<td>Gestational age (weeks)</td>
<td>0.09</td>
<td>0.7</td>
<td>(-0.7, 2.0)</td>
<td>0.3</td>
<td>0.3</td>
<td>0.3</td>
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<tr>
<td>Birth weight (kg)</td>
<td>0.03</td>
<td>-0.0</td>
<td>(-5.7, 6.2)</td>
<td>0.9</td>
<td>0.3</td>
<td>0.3</td>
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<tr>
<td>Severity score on admission (points)</td>
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<td>3.1</td>
<td>(1.1, 5.1)</td>
<td>0.002</td>
<td>3.0</td>
<td>(0.7, 5.1)</td>
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<td></td>
</tr>
<tr>
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<td></td>
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<tr>
<td>Female</td>
<td>61</td>
<td>-1.4</td>
<td>(-9.4, 8.0)</td>
<td>0.8</td>
<td>0.8</td>
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<td>Male</td>
<td>62</td>
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<td>0.8</td>
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<td>0.8</td>
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<td>Currently breastfed</td>
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<tr>
<td>Yes</td>
<td>62</td>
<td>1.9</td>
<td>(-8.9, 15.1)</td>
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<td>0.7</td>
<td>0.7</td>
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</tr>
<tr>
<td>Previous respiratory hospitalisation</td>
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<td></td>
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<td></td>
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</tr>
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<td>Yes</td>
<td>60</td>
<td>-2.0</td>
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<td>Item</td>
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<td>No</td>
<td>OR</td>
<td>95% CI</td>
<td>p-value</td>
<td>OR</td>
<td>95% CI</td>
</tr>
<tr>
<td>-------------------------------------------</td>
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<td>Mother smoked during pregnancy</td>
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<td>(-6.6, 11.4)</td>
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<td>0.2</td>
<td>(-8.0, 9.8)</td>
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<tr>
<td>Antibiotics before hospitalisation</td>
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<td>-7.1</td>
<td>(-14.4, 14)</td>
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<td>61</td>
<td>-2.4</td>
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<td>(-1.9, 21.3)</td>
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<td>RSV</td>
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<td>0.14</td>
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<td>10.0</td>
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<td>(-6.1, 14.6)</td>
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<td>RSV/HRV</td>
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<td>(-18.3, 14.3)</td>
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<td>Any bacteria detected</td>
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<td>No</td>
<td>3.1 (-5.7,13.4)</td>
<td>0.5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-----------------------</td>
<td>-----</td>
<td>----</td>
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<td>-----</td>
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<tr>
<td></td>
<td>63</td>
<td>59</td>
<td>(reference)</td>
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<td></td>
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</tr>
<tr>
<td>Virus/Bacteria Interaction</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Virus negative/Bacteria negative</td>
<td>58</td>
<td>(reference)</td>
<td>0.3</td>
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<td></td>
<td></td>
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<tr>
<td>Virus negative/Bacteria positive</td>
<td>53</td>
<td>-5.0 (-19.1,14.2)</td>
<td>0.6</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Virus positive/Bacteria negative</td>
<td>60</td>
<td>1.5 (-13.2, 21.0)</td>
<td>0.9</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Virus positive/Bacteria positive</td>
<td>65</td>
<td>7.0 (-7.9, 26.0)</td>
<td>0.4</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Arising as a re-expression of the multiplicative effect on the geometric mean from a linear regression on log (LOS)
Table-2b. Analysis of the different components of the severity score contributing to LOS (n=190)

* Arising as a re-expression of the multiplicative effect on the geometric mean from a linear regression on log (LOS)

<table>
<thead>
<tr>
<th>Points</th>
<th>Component</th>
<th>n</th>
<th>Geometric mean LOS</th>
<th>Difference in median LOS (hours)*</th>
<th>95% CI</th>
<th>P value</th>
<th>Difference in median LOS (hours)*</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Respiratory rate</td>
<td>&lt; 30</td>
<td>3</td>
<td>58</td>
<td>(reference)</td>
<td>1</td>
<td>30-45</td>
<td>73</td>
<td>54</td>
</tr>
<tr>
<td>2</td>
<td>Respiratory rate</td>
<td>45-60</td>
<td>70</td>
<td>60</td>
<td>2</td>
<td>(-26.0, 53.2)</td>
<td>0.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Respiratory rate</td>
<td>&gt;60</td>
<td>44</td>
<td>73</td>
<td>16</td>
<td>(-18.8, 80.0)</td>
<td>0.5</td>
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<tr>
<td>0</td>
<td>None</td>
<td>Wheeze</td>
<td>85</td>
<td>63</td>
<td>(reference)</td>
<td>1</td>
<td>Expiration only</td>
<td>37</td>
<td>56</td>
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<tr>
<td>2</td>
<td>Entire expiration and inspiration with stethoscope</td>
<td>30</td>
<td>52</td>
<td>-10</td>
<td>(-20.0, 1.9)</td>
<td>0.09</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Entire expiration and inspiration without stethoscope</td>
<td>38</td>
<td>66</td>
<td>3</td>
<td>(-8.4, 17.2)</td>
<td>0.6</td>
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<tr>
<td>0</td>
<td>&gt;95</td>
<td>SpO2</td>
<td>148</td>
<td>58</td>
<td>(reference)</td>
<td>1</td>
<td>94-95</td>
<td>14</td>
<td>59</td>
</tr>
<tr>
<td>2</td>
<td>90-93</td>
<td>24</td>
<td>69</td>
<td>11</td>
<td>(-3.1, 29.7)</td>
<td>0.1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>&lt;89</td>
<td>4</td>
<td>97</td>
<td>40</td>
<td>(-1.1, 109.3)</td>
<td>0.06</td>
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<td></td>
<td></td>
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<tr>
<td>0</td>
<td>None</td>
<td>Accessory muscle use</td>
<td>15</td>
<td>50</td>
<td>(reference)</td>
<td>1</td>
<td>+</td>
<td>64</td>
<td>53</td>
</tr>
<tr>
<td>2</td>
<td>++</td>
<td>66</td>
<td>60</td>
<td>12</td>
<td>(-5.9, 36.5)</td>
<td>0.2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>+++</td>
<td>45</td>
<td>76</td>
<td>31</td>
<td>(7.6, 63.9)</td>
<td>0.007</td>
<td></td>
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</tr>
</tbody>
</table>

Per one point increase per component

<table>
<thead>
<tr>
<th>Component</th>
<th>Respiratory rate</th>
<th>Wheeze</th>
<th>SpO2</th>
<th>Accessory muscle use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory rate</td>
<td>9.0</td>
<td>(2.7, 15.4)</td>
<td>0.004</td>
<td>4.7</td>
</tr>
<tr>
<td>Wheeze</td>
<td>-0.2</td>
<td>(-3.9, 3.7)</td>
<td>0.9</td>
<td>-1.8</td>
</tr>
<tr>
<td>SpO2</td>
<td>7.0</td>
<td>(0.5, 13.2)</td>
<td>0.03</td>
<td>4.5</td>
</tr>
<tr>
<td>Accessory muscle use</td>
<td>10.0</td>
<td>(4.4, 15.7)</td>
<td>0.0001</td>
<td>7.0</td>
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</table>
Table-3. Analysis of risk factors for respiratory readmissions within 6 months ($n_{\text{max}}=204$)

<table>
<thead>
<tr>
<th>Factors present on admission</th>
<th>Univariate</th>
<th>Multivariate</th>
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<tr>
<td></td>
<td>Median (respiratory readmit vs. first hospitalisation)</td>
<td>OR</td>
</tr>
<tr>
<td>CONTINUOUS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (months)</td>
<td>5.0 vs. 5.5</td>
<td>1.0</td>
</tr>
<tr>
<td>Birth weight (kg)</td>
<td>3.0 vs. 3.0</td>
<td>0.8</td>
</tr>
<tr>
<td>Gestational age (weeks)</td>
<td>38 vs. 38</td>
<td>0.9</td>
</tr>
<tr>
<td>Severity score on admission (points)</td>
<td>5 vs. 5</td>
<td>1.0</td>
</tr>
<tr>
<td>CATEGORICAL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td>Female 15/72 (21%)</td>
<td>0.8</td>
</tr>
<tr>
<td></td>
<td>Male 33/132 (25%)</td>
<td></td>
</tr>
<tr>
<td>Currently breastfed</td>
<td>Yes 42/173 (24%)</td>
<td>1.3</td>
</tr>
<tr>
<td></td>
<td>No 6/31 (19%)</td>
<td></td>
</tr>
<tr>
<td>Previous respiratory hospitalisation</td>
<td>Yes 16/41 (39%)</td>
<td>2.6</td>
</tr>
<tr>
<td></td>
<td>No 32/163 (20%)</td>
<td></td>
</tr>
<tr>
<td>Mother smoked during pregnancy</td>
<td>Yes 25/114 (22%)</td>
<td>0.8</td>
</tr>
<tr>
<td></td>
<td>No 23/87 (26%)</td>
<td></td>
</tr>
<tr>
<td>Exposed to household smoke</td>
<td>Yes 37/127 (29%)</td>
<td>2.4</td>
</tr>
<tr>
<td></td>
<td>No 11/76 (14%)</td>
<td></td>
</tr>
<tr>
<td>Antibiotics before hospitalisation</td>
<td>Yes</td>
<td>26/116 (22%)</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>22/88 (25%)</td>
</tr>
<tr>
<td>Any virus detected</td>
<td>Yes</td>
<td>31/154 (20%)</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>16/47 (34%)</td>
</tr>
<tr>
<td>RSV</td>
<td>Yes</td>
<td>9/89 (10%)</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>38/112 (34%)</td>
</tr>
<tr>
<td>HRV</td>
<td>Yes</td>
<td>14/54 (26%)</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>33/147 (22%)</td>
</tr>
<tr>
<td>RSV and HRV</td>
<td>Yes</td>
<td>23/128 (18%)</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>25/76 (33%)</td>
</tr>
<tr>
<td>Adenovirus</td>
<td>Yes</td>
<td>3/12 (25%)</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>44/189 (23%)</td>
</tr>
<tr>
<td>Any bacteria detected</td>
<td>Yes</td>
<td>25/138 (18%)</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>23/65 (35%)</td>
</tr>
<tr>
<td>Virus/Bacteria Interaction</td>
<td>Virus negative/Bacteria negative</td>
<td>8/20 (40%)</td>
</tr>
<tr>
<td></td>
<td>Virus negative/Bacteria positive</td>
<td>8/27 (30%)</td>
</tr>
<tr>
<td></td>
<td>Virus positive/Bacteria negative</td>
<td>14/44 (32%)</td>
</tr>
<tr>
<td></td>
<td>Virus positive/Bacteria positive</td>
<td>17/110 (15%)</td>
</tr>
</tbody>
</table>
Chapter 7: Clinical Care in Post Bronchiolitis Syndrome and Chronic Cough

7.1 Chapter overview

This chapter addresses gaps in knowledge as discussed in section 1.5.3 and 1.6.2. Antibiotics in the acute phase of bronchiolitis (≤14 days) are not routinely prescribed in children unless the illness is severe or there is a concern of a secondary bacterial infection. Bronchiolitis symptoms usually last from 3 to 7 days; however cohort studies have reported protracted symptoms beyond hospitalisation, with 25% of infants remaining symptomatic after 21-days. The importance of the symptoms beyond hospitalisation (i.e. post-bronchiolitis syndrome) in the form of persistent cough and wheeze has also been highlighted in the Scottish Intercollegiate Guidelines Network on bronchiolitis.

Section 7.2 is dedicated to a Cochrane Review that determined the effectiveness of antibiotics compared to placebo for persistent respiratory symptoms within 6-months of hospital discharge with acute bronchiolitis. Only one small RCT (n=30) met the inclusion criteria. This trial enrolled infants ≤7 months with RSV bronchiolitis and had high attrition (n=9, 30%). Despite the positive results of this trial, there is currently insufficient evidence to determine whether antibiotics should be given in the post-acute bronchiolitis phase. Further high quality RCTs are needed to evaluate the role of antibiotics for children with protracted respiratory symptoms, particularly in high risk populations (such as Indigenous children).

Section 7.3 is dedicated to a Cochrane Review that determined the effectiveness of a clinical pathway in the management of children with chronic cough. Only one RCT met the inclusion criteria. Children were randomised to early (2-weeks) or delayed (6-weeks) referral to respiratory specialists. Children in the early clinical
arm reported improved clinical outcomes by 6-weeks compared to those in the delayed pathway group.\textsuperscript{157} Evidence suggests a clinical pathway algorithm will improve clinical management of children with chronic cough in a specialist setting. However, further RCTs are needed to determine if cough management pathways are suitable in general practitioner and primary health care settings.

This chapter builds on gaps in knowledge as discussed in section 1.5.4 and 1.5.5 and data from chapter 4 and 6. This is relevant to my previous studies (as discussed in the multicentre RCT - chapter 4), with respect to persistent respiratory symptoms being common at day-21 (27\%) and associated with an increased risk of ongoing respiratory morbidity (i.e. bronchiectasis). Cough is one of the most important respiratory signs and is a common problem internationally.\textsuperscript{158-160} If not treated appropriately, chronic cough (≥4 weeks) may lead to delayed diagnosis and progression of respiratory morbidity.\textsuperscript{161} This is of particular importance in Indigenous populations where cough is poorly identified and seeking health care may be delayed.\textsuperscript{162}
7.2 Cochrane Review – Antibiotics for persistent cough or wheeze following acute bronchiolitis in children
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*Antibiotics for persistent cough or wheeze following acute bronchiolitis in children (Review)*

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Antibiotics for persistent cough or wheeze following acute bronchiolitis in children

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Editorial group: Cochrane Airways Group.


Review content assessed as up-to-date: 10 October 2012.

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ABSTRACT

Background
Bronchiolitis is a common acute respiratory infectious condition, with a high prevalence worldwide. It is a clinically diagnosed syndrome, manifested by tachypnoea (rapid breathing), with crackles or wheeze in young children. In the acute phase of bronchiolitis (< 14 days), antibiotics have only been recommended when a secondary bacterial infection is suspected. Although bronchiolitis is usually a self-limiting condition, a number of children have persistent respiratory symptoms such as cough and wheezing in post-acute bronchiolitis, and they present or re-present to secondary care.

Objectives
To determine the effectiveness of antibiotics compared to a control (no treatment or placebo) for persistent respiratory symptoms (within six months), following acute bronchiolitis.

Search methods
The following databases were searched, The Cochrane Airways Group Register of Trials, Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE (Ovid), EMBASE (Ovid) and ClinicalTrials.gov. We searched all databases from their inception to the present, and did not impose restriction on language of publication. The search was performed in October 2012.

Selection criteria
All randomised controlled trials (RCTs) comparing antibiotics with controls (placebo or no treatment) given in the post-acute phase of bronchiolitis (> 14 days) for children younger than two years of age diagnosed with bronchiolitis were included.

Data collection and analysis
Two review authors independently assessed studies against pre-defined criteria; and selected, extracted and assessed the data for inclusion. Several subgroup analyses were planned and this included when antibiotics commenced (early commencement classified as preventing; later commencement as treatment for post-bronchiolitis symptoms).
Main results
A single study met the inclusion criteria but had a high attrition rate. Thirty infants with respiratory syncytial virus (RSV)-confirmed bronchiolitis were randomised to receive either a daily dose of oral clarithromycin 15 mg/kg or placebo for three weeks. Using an intention-to-treat (ITT) analysis, there was no significant difference between groups for the proportion of children who had persistent symptoms (odds ratio (OR) 0.20; 95% confidence interval (CI) 0.02 to 2.02) or re-hospitalisation within six months (OR 0.11; 95% CI 0.01 to 1.29). There were no treatment studies of later commencement of antibiotics.

Authors’ conclusions
There is currently insufficient evidence to inform whether antibiotics should be used to treat or prevent persistent respiratory symptoms in the post-acute bronchiolitis phase. Future RCTs that evaluate the efficacy of antibiotics to reduce persistent respiratory symptoms are required, especially in areas where both acute and post-bronchiolitis morbidity is high such as in Indigenous communities in the US, New Zealand and Australia.

Plain Language Summary
Antibiotics for bronchiolitis after acute phase
Bronchiolitis is a common lung infection, affecting children across the world. It is usually caused by a virus called RSV (respiratory syncytial virus) but other viruses can cause this too. Young children with bronchiolitis normally have a cough, fast and difficult breathing, and poor feeding. Antibiotics are not normally prescribed to children with bronchiolitis unless there is concern of a secondary bacterial infection. However, some children continue to have ongoing problems (i.e. wheeze, cough) after the acute viral infection (> 14 days); increasing the risk of burden of disease and cost to the health system. These children often re-present for further medical care in the community (general practitioners and health providers) or in hospital (emergency departments). Antibiotics may help treat these ongoing symptoms and get rid of the bacteria in the lungs.

This review found only one eligible study looking at antibiotics compared to placebo for children in the post-acute bronchiolitis phase. This randomised controlled trial was from Turkey and enrolled 30 infants aged seven months or younger. There is currently not enough evidence to inform whether antibiotics should be used to treat or prevent persistent respiratory symptoms in the post-acute bronchiolitis phase. Randomised controlled trials that evaluate the efficacy of antibiotics to reduce persistent respiratory symptoms are needed, especially in countries where the morbidity of acute bronchiolitis is high such as in Indigenous populations.
SUMMARY OF FINDINGS FOR THE MAIN COMPARISON

Antibiotics compared with placebo or no treatment for persistent respiratory symptoms following acute bronchiolitis

Patient or population: children <24 months with ongoing symptoms (cough/wheeze) post-acute bronchiolitis
Setting: post-acute bronchiolitis phase > 14 days
Intervention: antibiotics
Comparison: placebo or no treatment

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Odds ratio effect (95% CI)</th>
<th>No of participants (studies)</th>
<th>Quality of the evidence (GRADE)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proportion of participants who were not cured at follow-up</td>
<td>OR 0.20 (95% CI 0.02 to 2.02)</td>
<td>30 (1 study)</td>
<td>⊕⊕⊕⃝⃝ low</td>
<td></td>
</tr>
<tr>
<td>Proportion of participants who were readmitted within 6 months</td>
<td>OR 0.11 (95% CI 0.01 to 1.29)</td>
<td>21 (1 study)</td>
<td>⊕⊕⊕⃝⃝ low</td>
<td></td>
</tr>
<tr>
<td>Adverse events</td>
<td>Not estimable</td>
<td>30 (1 study)</td>
<td>See comment</td>
<td>No adverse events were documented</td>
</tr>
</tbody>
</table>

OR: odds ratio; CI: confidence interval.
GRADE Working Group grades of evidence:
- High quality: Further research is very unlikely to change our confidence in the estimate of effect.
- Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
- Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
- Very low quality: We are very uncertain about the estimate.

1. There was a single study and we were not able to conduct analyses on the intention-to-treat population, therefore future trials are likely to alter the treatment effect, our confidence in the reported effect, or both.

BACKGROUND

Description of the condition

Bronchiolitis is a common acute respiratory infectious condition, with a high prevalence worldwide (Chang 2009). It is a clinically diagnosed syndrome manifested by tachypnoea (rapid breathing) with crackles or wheeze in very young children. However, the upper age limit of the clinical syndrome of bronchiolitis differs among continents (24 months in the US and 12 months in the UK). Multiple viruses and some bacteria can cause bronchiolitis, including respiratory syncytial virus (RSV), influenza, human metapneumovirus, rhinovirus, influenza, parainfluenza, adenovirus and mycoplasma.

In the acute phase (< 14 days), antibiotics have only been recommended in the treatment of bronchiolitis when a secondary bacterial infection is suspected. In acute bronchiolitis, one Cochrane review found “minimal evidence to support the use of antibiotics for acute bronchiolitis” (Spurling 2011). Although bronchiolitis is usually a self-limiting condition, typically lasting from three to seven days, a number of children continue to display respiratory symptoms following acute bronchiolitis. Swingler 2000 reported that 39% of infants were still symptomatic after 14 days, 18% after 21 days and 9% after 28 days.
Other studies have shown that 40% to 50% of those hospitalised have a “grumbling, sometimes protracted, respiratory syndrome of persistent cough and recurrent viral-induced wheeze” (SIGN 2006). While symptoms such as cough and wheezing in post-acute bronchiolitis may be mild, they have the potential to increase burden of disease and some children present or re-present to secondary care. Furthermore, in some settings, recurrent hospitalisations for bronchiolitis are common (Bailey 2009), thus increasing the burden (morbidity, social, economic, etc.) of disease. Also, cohort studies have suggested that bronchiolitis may trigger the development of asthma (Carroll 2009; Sigurs 2000). The possible biological mechanism giving rise to the persistent respiratory symptoms is likely to be multifactorial. In bronchiolitis, airway oedema occurs, the airway epithelium is affected and the ciliary damage can persist for 13 to 17 weeks (Wong 2005). Cilia are an important component of the airway’s clearance mechanism. Damage of airway cilia and the possible impairment of the innate immunity in severe bronchiolitis (Halfhide 2008) predispose these infants to secondary bacterial infection. Persistent or delayed resolution of airway oedema, or secondary bacterial infection in the airways (endobronchial infection) related to persistent ciliary damage can cause wheeze, cough or both.

**Why it is important to do this review**

A small but significant number of children with acute bronchiolitis have persistent problems after the acute viral infection (for a variety of reasons) and these children are usually referred to secondary and tertiary practice (i.e. outside of general practice). This group of children are clinically treated with a variety of medications such as antibiotics, bronchodilators, inhaled (Fox 1999) and oral corticosteroids (Bloom-Danielle 2007), and leukotriene receptor antagonists (Kim 2010). This clinical issue has been identified as an area that needs more research (SIGN 2006). Further, use of any medications may result in adverse events, and persistence of symptoms also influence burden of disease and health economics. Thus, a systematic review of the benefits, or otherwise, of using antibiotics in the post-acute bronchiolitis phase will be useful to guide clinical practice.

**Objectives**

To determine the effectiveness of antibiotics compared to a control (no treatment or placebo) to reduce or treat persistent respiratory symptoms following acute bronchiolitis (within six months of acute illness).

**Methods**

**Criteria for considering studies for this review**

**Types of studies**

All randomised controlled trials (RCTs) comparing antibiotics with controls (placebo or no treatment) given in the post-acute phase of bronchiolitis. Antibiotics could have been started in the acute phase (at start of illness to prevent post-bronchiolitis symptoms) or post-acute phase (i.e. treatment of post-bronchiolitis symptoms).

**Types of participants**

Inclusion criteria: previously healthy children (aged < two years) with bronchiolitis (as defined by study authors) who had been treated with antibiotics beyond the acute bronchiolitis period (>14 days).
Exclusion criteria: children with any underlying chronic disease such as lung disease (cystic fibrosis, bronchopulmonary dysplasia, bronchiectasis, aspiration, etc.), cardiac disease and immunodeficiency (primary or secondary).

Types of interventions
All types of antibiotics, given beyond the acute period (> 14 days). This included antibiotics prescribed for acute bronchiolitis that went beyond the acute phase of 14 days.

Types of outcome measures

Primary outcomes
1. Proportion of participants who were not cured at follow-up (up to six months).
2. Proportion re-admitted for a respiratory illness within six months.
We determined the proportion of participants who failed to improve on treatment (antibiotics or placebo), and the mean clinical improvement, using the following hierarchy of assessment measures (where two or more assessment measures are reported in the same study, we used the outcome measure that is listed first in the hierarchy).
1. Objective measurements of cough/wheeze indices (cough or wheeze recordings, cough receptor sensitivity and airway hyperresponsiveness).
2. Symptomatic measures, as assessed by parents or carers (quality of life, Likert scale, Visual Analogue Scale, level of interference of respiratory symptoms and diary cards).
3. Symptomatic measures, as assessed by clinicians (Likert scale, Visual Analogue Scale, level of interference of respiratory symptoms and diary cards).

Secondary outcomes
1. Proportion of participants who were not substantially improved at follow-up (up to six months).
2. Mean difference in cough or wheeze indices (diary, frequency, scores and quality of life).
3. Proportion of participants with recurrent wheeze (within six months of intervention).
4. Proportion of participants experiencing adverse effects of the intervention.
5. Proportion of participants experiencing complications (e.g. requirement for medication or pneumonia).
We selected complete resolution of symptoms as the primary outcome, as previously healthy children should completely recover after an episode of acute bronchiolitis. As different studies may use different outcome measurements to signify a cure, we defined a hierarchy of outcomes, where we considered objective markers superior to subjective measurements. Pneumonia and recurrent wheeze (some with requiring repeat hospitalisation) have been reported in cohort studies of bronchiolitis (Bailey 2009). Thus we considered re-admission for a respiratory infection and recurrent wheeze as important outcomes.

Search methods for identification of studies

Electronic searches
The Cochrane Airways Group’s Trial Search Co-ordinator performed the search; identifying trials using the following databases:
• the Cochrane Airways Group Register of Trials (CENTRAL), Issue 9 of 12, 2012;
• MEDLINE (Ovid) 1948 to Sept week 4 2012;
• EMBASE (Ovid) 1980 to week 40 2012;
• ClinicalTrials.gov.
The search strategies are listed in Appendix 1. We searched all databases from their inception to the present, and did not impose restriction on language of publication.
The search was performed by the Cochrane Airways Group (Elizabeth Stovold) on 10 October 2012.

Searching other resources
We checked reference lists of the included studies and relevant review articles for additional references. We also contacted authors of identified trials, where appropriate, to seek further identification of other published and unpublished studies.

Data collection and analysis

Selection of studies
Two review authors (GM, AC) independently assessed the potential studies from the search. We did not have any disagreements but had planned to resolve any disagreement through discussion, or if required adjudication from another review author (PM). Only one study met the eligibility criteria.

Data extraction and management
Two review authors (GM, AC) independently assessed risk of bias for each study using the criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2011). We did not have any disagreements but had planned to resolve any disagreement through discussion or by involving another review author (PM). We managed data in Review Manager 5.1 (RevMan...
2011) in accordance with the recommendations in the *Cochrane Handbook for Systematic Review of Interventions* (Higgins 2011).

**Assessment of risk of bias in included studies**

We assessed the risk of bias according to the following domains, using the Review Manager 5.1 (RevMan 2011) ‘Risk of bias’ tool and criteria set out in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011):

1. random sequence generation;
2. allocation concealment;
3. blinding of participants and personnel;
4. blinding of outcome assessment;
5. incomplete outcome data;
6. selective outcome reporting;
7. other bias.

We graded each potential source of bias as high, low or unclear. Two review authors (GM, AC) independently assessed the methodological quality of each trial. We did not have any disagreements but had planned to resolve any disagreement through discussion and if necessary by adjudication by a third review author.

**Measures of treatment effect**

For dichotomous variables, we calculated individual statistics as odds ratios (ORs) with 95% confidence intervals (CIs). Only one study met the eligibility criteria. Thus, measures of treatment effect were not applicable for other planned measures.

**Unit of analysis issues**

Cross-over and cluster-randomised trials are not appropriate for the target population and therefore were not included.

**Dealing with missing data**

We attempted to contact investigators of the sole included study (Tahan 2007) to verify some study characteristics and to obtain missing numerical outcome data; however, we were unsuccessful.

**Assessment of heterogeneity**

We planned to use the $I^2$ statistic to measure heterogeneity among the trials in each analysis. If we had identified substantial heterogeneity we planned to explore it by pre-specified subgroup analysis. We will consider levels of heterogeneity greater than 50% as substantial in future review updates. Only one study met the eligibility criteria. Thus, assessment of heterogeneity was not applicable.

**Assessment of reporting biases**

Where we suspect reporting bias, we planned to contact study authors and ask them to provide missing outcome data. If we felt missing data may introduce serious bias, we plan to explore the impact of including such studies in the overall assessment of results by conducting a sensitivity analysis in future updates. We planned to investigate publication bias by visually inspecting a funnel plot if we were able to meta-analyse 10 or more trials in a single outcome. We did not find evidence of publication bias or reporting bias.

**Data synthesis**

We created a ‘Summary of findings’ (SoF) table using the methods and recommendations described in Section 8.5 and Chapter 12 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011) and using GRADEpro software.

**Subgroup analysis and investigation of heterogeneity**

We had planned subgroup analysis based on:

1. type of control arm (placebo/no treatment);
2. severity (hospitalised versus non-hospitalised);
3. macrolides versus other types of antibiotics;
4. short ($\leq$ seven days) versus longer (> seven days) courses of antibiotics;
5. antibiotics commencement ($\leq$ 14 days or > 14 days of onset of bronchiolitis);
6. setting of study (affluent versus non-affluent setting).

As there was only one study, a subgroup analysis was not applicable.

**Sensitivity analysis**

We had planned to remove studies considered to be at a high or unclear risk of bias for methodological quality from the meta-analysis, and examine any change in the summary statistic. As there was only a single study, a sensitivity analysis was not applicable for this review.

**RESULTS**

**Description of studies**

See: Characteristics of included studies; Characteristics of excluded studies; Characteristics of ongoing studies.

See Characteristics of included studies and Characteristics of excluded studies for full details.
Results of the search
The search revealed a total of 265 articles. Once duplicates were removed a total of 231 articles were available for review; eight articles in CENTRAL, 69 in MEDLINE, 150 in EMBASE and one in TRIALS. Two review authors (GM, AC) independently assessed all potential abstracts for inclusion all the potential abstracts identified from the search strategy. Of these, 224 were rejected on title and abstract alone. Full-text articles were retrieved and reviewed independently by GM and AC. An additional two published articles were identified and one trial from the Australian and New Zealand Clinical Trials Registry were identified as potentially eligible. An update search in October 2012 identified 5 references, none of which were eligible for inclusion. Five studies did not meet inclusion criteria (ACTRN12608000150347; Friis 1984; Kabir 2009; Kneyber 2008; Mazumder 2009). One study met the inclusion criteria (Tahan 2007) and another is a study in progress (Chung 2011) (Figure 1).

Figure 1. Study flow diagram.

262 records identified through database searching
5 records identified from update search (October 2012)
3 additional records identified through other sources

236 records after duplicates removed
229 records excluded

7 records screened
5 records excluded

2 full-text articles assessed for eligibility

1 full-text article excluded. Study open to recruitment

1 study included in quantitative synthesis
Included studies

One study met the inclusion criteria (Tahan 2007). Tahan 2007 randomised 30 infants aged seven months or less. The trial included infants admitted to a paediatric hospital in Turkey with RSV confirmed bronchiolitis. Infants were randomised to receive either a daily dose of oral clarithromycin 15 mg/kg or placebo 15 mg/kg for three weeks. Nine infants were excluded during the analysis (six from clarithromycin group and three from the placebo group), as they were given corticosteroids while in hospital. Only 12 infants in the clarithromycin group and nine infants in the placebo group were analysed.

Excluded studies

We excluded five studies with reasons (ACTRN12608000150347; Friis 1984; Kabir 2009; Kneyber 2008; Mazumder 2009). In all five RCTs, the treatment phase did not go beyond the hospital or acute period (i.e. < 14 days).

Risk of bias in included studies

The risk of bias is summarised in Figure 2 and Figure 3.

Figure 2. Risk of bias graph: review authors’ judgements about each risk of bias item presented as percentages across all included studies.
Figure 3. Risk of bias summary: review authors’ judgements about each risk of bias item for each included trial.

Allocation
Tahan 2007 reported that participants were “randomised by a single study nurse”, but did not clearly describe how allocation was done and how concealment was maintained.

Blinding
Tahan 2007 adequately described that participants, families and investigators remained blinded to the randomisation until the end of the study.

Incomplete outcome data
Of the 30 infants enrolled, nine were excluded (three from the clarithromycin group and six from the placebo group) owing to receiving corticosteroid treatment in hospital (Tahan 2007). The attrition rate was high (31%) and data from these children were not described, but we remain uncertain of the impact of this bias on the results of the review.

Selective reporting
It was not clear if an intention-to-treat (ITT) analysis was used. It was also not clear if the trial had been registered.

Other potential sources of bias
No clear other potential source of bias.
Effects of interventions

See: Summary of findings for the main comparison Antibiotics compared with placebo or no treatment for persistent respiratory symptoms following acute bronchiolitis

Primary outcomes

Using ITT analysis, there was no significant difference between groups for the proportion of children who had persistent symptoms (OR 0.20; 95% CI 0.02 to 2.02) (Figure 4).

Figure 4. Forest plot of comparison: proportion of participants who were not cured at follow-up.

The group who received clarithromycin were less likely to be re-admitted to hospital within six months, but this was not statistically significant (OR 0.11; 95% CI 0.01 to 1.29) (Analysis 1.2). However, ITT analysis was not possible for this outcome as there were no data from the children who dropped out. Tahan 2007 reported that one (8.3%) infant from the clarithromycin group and four (44.4%) from the placebo group were re-admitted within six months with wheezing.

Secondary outcomes

Tahan 2007 stated that at the six-month telephone survey, parents of those children who were not re-admitted to hospital did not report any wheezing in their infants. Of five infants re-admitted to hospital within six months of discharge, one (8.3%) infant from the clarithromycin group and four (44.4%) from the placebo group had ongoing wheezing. There was no statistical significance between the groups (OR 0.11; 95% CI 0.01 to 1.29) (Analysis 1.3).

No adverse events were reported in either group.

DISCUSSION

Summary of main results

We found only one RCT that examined the efficacy of antibiotics on reducing persistent symptoms in the post-acute symptoms of bronchiolitis in young children. In the group of children who received a three-week course of clarithromycin, the proportion of children were not cured at six months was not significantly different to the group who received placebo. This analysis was based on ITT and thus the data presented here differ from that described in the Tahan 2007 paper, which did not use ITT. In the secondary outcome of ongoing wheeze, although fewer children randomised to clarithromycin had persistent respiratory symptoms compared to the placebo group, the difference between groups was not statistically significant.

Overall completeness and applicability of evidence

Treating bronchiolitis with antibiotics in the acute phase is only recommended when a secondary bacterial infection is suspected (SIGN 2006). The burden of ongoing respiratory symptoms such as wheezing, cough and respiratory re-admissions post bronchiolitis is increasingly appreciated. While the data presented in Tahan 2007 suggest that antibiotics may be an effective treatment in the prevention of ongoing respiratory symptoms post bronchiolitis, our review has shown that this was not statistically significant once ITT is used. Methodological challenges of the single trial included in this review relate to the small sample size, the high attrition rate and uncertain bias in many categories. It also remains unknown if a non-macrolide antibiotic would have resulted in similar findings. In addition to being an anti-microbial, macrolides have additional...
benefits (such as immunomodulatory) and thus data presented here cannot be extrapolated to non-macrolide antibiotics. As antibiotics were commenced at the onset of acute bronchiolitis, the sole included study (Tahan 2007) could be classified as ‘prevention’ of post-bronchiolitis syndrome. There were no studies that could be included for treatment of post-bronchiolitis syndrome.

Quality of the evidence
Given the sole study that could be included in this review, the quality of the evidence is poor. The included study had very small numbers and some methodological weaknesses. Allocation sequence and randomisation were not clearly described. Nine (30%) randomised infants were excluded from the final analysis, owing to corticosteroid use while in hospital, which limits the generalisability of the results.

Potential biases in the review process
We found only one trial and were unable to obtain the raw data (Tahan 2007). We do not feel that there were any biases in the review process.

Agreements and disagreements with other studies or reviews
We are not aware of any other reviews or studies to compare these results with. This review on post-bronchiolitis syndrome has similar findings to that for acute bronchiolitis (Spurling 2011), which found “minimal evidence to support the use of antibiotics for acute bronchiolitis”.

AUTHORS’ CONCLUSIONS

Implications for practice
There is currently insufficient evidence to inform whether antibiotics should be used to treat or prevent persistent respiratory symptoms in the post-acute bronchiolitis phase.

Implications for research
Future RCTs that evaluate the efficacy of antibiotics to reduce persistent respiratory symptoms are required, especially in areas where the morbidity of acute bronchiolitis is high such as in Indigenous communities in the US, New Zealand and Australia. These studies could be primarily preventive (i.e. antibiotics started in acute phase < 14 days) or treatment phase (when children have persistent symptoms). The RCTs should be parallel design, placebo controlled and double blind. Studies should address macrolide and non-macrolide antibiotics separately and the prevention of persistent symptoms should be considered separately from the treatment of ongoing symptoms. In the latter, it is likely that a longer course of antibiotics is required in light of the literature of Cochrane review on antibiotics for persistent wet cough in children (Marchant 2005) and current data on protracted bacterial bronchitis (Marchant 2012). Also, there are no trials that have used antibiotics after three weeks for persistent symptoms post bronchiolitis and there is a need for such research to inform clinical practice. Studies should also include microbiological data (both viruses and bacteria) that would complement clinical outcomes.

ACKNOWLEDGEMENTS
We thank Dr. Cates, Dr. Emma Welsh and Emma Jackson for support in the protocol and the review. We also thank Elizabeth Stovold from the Cochrane Airways Group for performing the searches.

REFERENCES

References to studies included in this review
Tahan 2007 [published data only]

ACTRN1260800150347 [unpublished data only]

Friis 1984 [published data only]

Kabir 2009 [published data only]
Kneyber 2008 [published data only]

Mazumder 2009 [published data only]

References to ongoing studies

Chang 2011 [published data only]

Additional references

Bailey 2009

Blom-Danielle 2007

Carroll 2009

Chang 2009

Didierlaurent 2008

Fox 1999

Giamarellos-Bourboulis 2008

Halflide 2008

Higgins 2011

Kim 2010

Leach 1994

Marchant 2005

Marchant 2012

McCallers 2006

RevMan 2011

SIGN 2006

Sigurs 2000

Spurling 2011
Spurling GK, Doust J, Del Mar CB, Erikson L. Antibiotics for bronchiolitis in children. *Cochrane Database of
Swingler 2000

Wong 2005

Zarogoulidis 2011

* Indicates the major publication for the study.
### Characteristics of included studies  
**ordered by year of study**

**Tahan 2007**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Methods</strong></td>
<td>Double-blind, placebo-controlled, parallel-group, randomised study</td>
</tr>
<tr>
<td><strong>Participants</strong></td>
<td>21 Infants ≤ 7 months hospitalised with respiratory syncytial virus-confirmed bronchiolitis</td>
</tr>
<tr>
<td><strong>Interventions</strong></td>
<td>Oral clarithromycin (15 mg/kg/day) or placebo (15 mg/kg/day) for 3 weeks</td>
</tr>
<tr>
<td><strong>Outcomes</strong></td>
<td>Length of hospital stay, Supplemental oxygen, Wheeze, Decrease in plasma concentrations (interleukin-4, interleukin-8, eotaxin), Enhanced production of interferon-gamma</td>
</tr>
</tbody>
</table>

| **Notes**                | -                                                                       |

**Risk of bias**

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors’ judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Unclear risk</td>
<td>No information on sequence generation provided. Paper describes that participants were &quot;randomised by a single study nurse&quot;</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Unclear risk</td>
<td>No information provided on how the study nurse randomised each participant and how concealment was maintained</td>
</tr>
<tr>
<td>Blinding of participants and personnel (performance bias) All outcomes</td>
<td>Low risk</td>
<td>Participants and families remained blinded to the randomisation until end of study</td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias) All outcomes</td>
<td>Low risk</td>
<td>Paper described that the investigators remained blinded to the randomisation until end of study</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias) All outcomes</td>
<td>Unclear risk</td>
<td>30 participants were enrolled and randomised. During the study phase, 9 were excluded (30%) owing to having received corticosteroids. The groups and outcomes of these infants were not reported</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Unclear risk</td>
<td>The result table appear to have only analysed the remaining children in the trial (21). No intention to treat had been used</td>
</tr>
</tbody>
</table>
Characteristics of excluded studies  [ordered by study ID]

<table>
<thead>
<tr>
<th>Study</th>
<th>Reason for exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACTRN12608000150347</td>
<td>Intervention involved a single large dose of azithromycin or placebo given on admission. Thus does not fulfil inclusion criteria</td>
</tr>
<tr>
<td>Friis 1984</td>
<td>This open randomised trial included children up to 62 months of age, pneumonia diagnosis, treatment up to 6 days and did not include antibiotics use beyond the acute period</td>
</tr>
<tr>
<td>Kabir 2009</td>
<td>In this RCT, the treatment period was only up to 7 days</td>
</tr>
<tr>
<td>Kneyber 2008</td>
<td>In this RCT, the treatment period was only up to 3 days</td>
</tr>
<tr>
<td>Mazumder 2009</td>
<td>It was not clear how long the treatment period was for this RCT. Analysis describes up to 5 days, thus not eligible for post-acute bronchiolitis</td>
</tr>
</tbody>
</table>

RCT: randomised controlled trial.

Characteristics of ongoing studies  [ordered by study ID]

**Chang 2011**

<table>
<thead>
<tr>
<th>Trial name or title</th>
<th>Randomized Placebo-Controlled Trial on Azithromycin to Reduce the Morbidity of Bronchiolitis in Indigenous Australian Infants: Rationale and Protocol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methods</td>
<td>Double-blind placebo-controlled randomised controlled trial</td>
</tr>
<tr>
<td>Participants</td>
<td>200 Indigenous infants aged &lt; 24 months hospitalised with acute bronchiolitis</td>
</tr>
<tr>
<td>Interventions</td>
<td>Azithromycin (30 mg/kg per dose) or placebo, once weekly for 3 weeks</td>
</tr>
<tr>
<td>Outcomes</td>
<td>Length of stay in hospital, duration of oxygenation and respiratory re-admissions within 6 months of discharge</td>
</tr>
<tr>
<td>Starting date</td>
<td>June 2010</td>
</tr>
<tr>
<td>Contact information</td>
<td>Professor Anne Chang - <a href="mailto:annechang@ausdoctors.net">annechang@ausdoctors.net</a></td>
</tr>
<tr>
<td>Notes</td>
<td>Ongoing prospective RCT</td>
</tr>
<tr>
<td>------------------</td>
<td>--------------------------</td>
</tr>
</tbody>
</table>

Chang 2011 (Continued)
## DATA AND ANALYSES

### Comparison 1. Prevention of post-bronchiolitis syndrome (antibiotics vs. placebo)

<table>
<thead>
<tr>
<th>Outcome or subgroup title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Proportion of participants who were not cured at follow-up</td>
<td>1</td>
<td></td>
<td>Odds Ratio (IV, Fixed, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>2 Proportion of participants who were re-admitted within 6 months</td>
<td>1</td>
<td></td>
<td>Odds Ratio (M-H, Fixed, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>3 Proportion with ongoing wheeze (between post discharge from hospital and 6 months)</td>
<td>1</td>
<td>21</td>
<td>Odds Ratio (M-H, Fixed, 95% CI)</td>
<td>0.11 [0.01, 1.29]</td>
</tr>
<tr>
<td>4 Adverse events</td>
<td>1</td>
<td></td>
<td>Odds Ratio (M-H, Fixed, 95% CI)</td>
<td>Totals not selected</td>
</tr>
</tbody>
</table>

### Analysis 1.1. Comparison | Prevention of post-bronchiolitis syndrome (antibiotics vs. placebo), Outcome | Proportion of participants who were not cured at follow-up.

Review: Antibiotics for persistent cough or wheeze following acute bronchiolitis in children

Comparison: 1 Prevention of post-bronchiolitis syndrome (antibiotics vs. placebo)

Outcome: 1 Proportion of participants who were not cured at follow-up

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Antibiotic</th>
<th>Placebo</th>
<th>Odds Ratio</th>
<th>Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>n/N</td>
<td>IV,Fixed,95% CI</td>
<td>IV,Fixed,95% CI</td>
</tr>
<tr>
<td>Tahan 2007</td>
<td>1/15</td>
<td>4/15</td>
<td>0.20 [0.02, 2.02]</td>
<td></td>
</tr>
</tbody>
</table>

Favours antibiotic | Favours placebo
### Analysis 1.2. Comparison 1 Prevention of post-bronchiolitis syndrome (antibiotics vs. placebo), Outcome 2
Proportion of participants who were re-admitted within 6 months.

Review: Antibiotics for persistent cough or wheeze following acute bronchiolitis in children

Comparison: 1 Prevention of post-bronchiolitis syndrome (antibiotics vs. placebo)

Outcome: 2 Proportion of participants who were re-admitted within 6 months

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Antibiotic n/N</th>
<th>Placebo n/N</th>
<th>Odds Ratio M-H,Fixed 95% CI</th>
<th>Odds Ratio M-H,Fixed 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tahan 2007</td>
<td>1/12</td>
<td>4/9</td>
<td>0.11 [0.01, 1.29]</td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: not applicable

Test for overall effect: $Z = 1.75$ ($P = 0.080$)

Test for subgroup differences: Not applicable

### Analysis 1.3. Comparison 1 Prevention of post-bronchiolitis syndrome (antibiotics vs. placebo), Outcome 3
Proportion with ongoing wheeze (between post discharge from hospital and 6 months).

Review: Antibiotics for persistent cough or wheeze following acute bronchiolitis in children

Comparison: 1 Prevention of post-bronchiolitis syndrome (antibiotics vs. placebo)

Outcome: 3 Proportion with ongoing wheeze (between post discharge from hospital and 6 months)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Antibiotic n/N</th>
<th>Placebo n/N</th>
<th>Odds Ratio M-H,Fixed 95% CI</th>
<th>Odds Ratio M-H,Fixed 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tahan 2007</td>
<td>1/12</td>
<td>4/9</td>
<td>0.11 [0.01, 1.29]</td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>12</td>
<td>9</td>
<td>0.11 [0.01, 1.29]</td>
<td></td>
</tr>
</tbody>
</table>

Total events: 1 (Antibiotic), 4 (Placebo)

Heterogeneity: not applicable

Test for overall effect: $Z = 1.75$ ($P = 0.080$)

Test for subgroup differences: Not applicable
Analysis 1.4. Comparison 1 Prevention of post-bronchiolitis syndrome (antibiotics vs. placebo), Outcome 4
Adverse events.

Review: Antibiotics for persistent cough or wheeze following acute bronchiolitis in children

Comparison: 1 Prevention of post-bronchiolitis syndrome (antibiotics vs. placebo)

Outcome: 4 Adverse events

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Antibiotic</th>
<th>Placebo</th>
<th>Odds Ratio M-H,Fixed,95% CI</th>
<th>Odds Ratio M-H,Fixed,95% CI</th>
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</thead>
<tbody>
<tr>
<td>Tahan 2007</td>
<td>0/12</td>
<td>0/9</td>
<td>0.01</td>
<td>0.0</td>
</tr>
</tbody>
</table>

Favours experimental Favours control

APPENDICES

Appendix 1. Database search strategies

CENTRAL (The Cochrane Library)
#1 MeSH descriptor Bronchiolitis explode all trees
#2 MeSH descriptor Respiratory Syncytial Virus Infections explode all trees
#3 bronchiolitis*:ti,ab,kw
#4 RSV*:ti,ab,kw
#5 (#1 OR #2 OR #3 OR #4)
#6 MeSH descriptor Cough, this term only
#7 MeSH descriptor Respiratory Sounds explode all trees
#8 cough*:ti,ab,kw
#9 wheez*:ti,ab,kw
#10 post-viral*:ti,ab,kw
#11 post-acute*:ti,ab,kw
#12 Any MeSH descriptor with qualifier: CO
#13 MeSH descriptor Recurrence explode all trees
#14 (#6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13)
#15 (#5 AND #14)
#16 post-RSV*:ti,ab,kw
#17 post-bronchiolit*:ti,ab,kw
#18 (#15 OR #16 OR #17)
#19 MeSH descriptor Anti-Bacterial Agents explode all trees
#20 antibiotic*:ti,ab,kw
#21 MeSH descriptor Macrolides explode all trees
#22 (macrolide* or azithromycin or clarithromycin or erythromycin or roxithromycin or spiramycin):ti,ab,kw
Antibiotics for persistent cough or wheeze following acute bronchiolitis in children (Review)

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EMBASE (Ovid)

1. exp bronchiolitis/
2. respiratory syncytial virus infection/
3. RSV$.tw.
4. bronchiolitis$.tw.
5. or/1-4
6. exp coughing/
7. wheezing/
8. cough$.tw.
9. wheez$.tw.
10. post-viral$.tw.
11. post-acute$.tw.
12. co.fs.
13. recurrent disease/
14. or/or-13
15. and 14
16. post-RSV$.tw.
17. post-bronchiolitis$.tw.
18. or/16 or 17
19. exp antibiotic agent/
20. antibiotic$.tw.
21. exp macrolide/
22. (macrolide$ or azithromycin or clarithromycin or erythromycin or roxithromycin or spiramycin).tw.
23. (penicillin$ or amoxicillin or amoxycillin or ampicillin or bencylpenicillin or cloxacillin or dicloxacinil or flucloxacinil or piperacillin
or ticarcillin or sulbactam).tw.
24. (cephalosporin$ or cephalexin or cephaclor or cefaclor or cefepime or cefotaxime or cephamycin$ or cefotetan or cefoxitin or cefmetazole or cefpirome or cepodoxime or cefpodoxime or ceftriaxone or cefepoxide or cefuroxime or cefuroxime or cefuroxime or ceftazidime or ceftriaxone).tw.
25. (fluoroquinolone$ or ciprofloxacin or enoxacin or norfloxacin or ofloxacin or fleroxacin or levofloxacin or moxi-
flloxacin).tw.
26. (tetracycline$ or doxycycline or methacycline or minocycline).tw.
27. (amikacin or gentamicin or neomycin or netilmicin).tw.
28. (clindamycin or lincomycin).tw.
29. (chloramphenicol or amantadine or cotrimoxazole or trimethoprim).tw.
30. or/19-29
31. 18 and 30
32. child/
33. exp pediatrics/
34. infant/
35. adolescent/
36. (paediatric$ or paediatric$ or child$ or adolescent$ or infant$ or young$ or preschool$ or pre-school$ or newborn$ or new-born$ or neonat$ or neo-nat$).tw.
37. or/32-36
38. 31 and 37
39. Randomized Controlled Trial/
40. randomisation/
41. Controlled Study/
42. Clinical Trial/
43. controlled clinical trial/
44. Double Blind Procedure/
45. Single Blind Procedure/
46. Crossover Procedure/
47. or/39-46
48. (clinical adj3 trial$).mp.
49. ((singl$ or doubl$ or trebl$ or tripl$) adj3 (mask$ or blind$ or method$)).mp.
50. exp Placebo/
51. placebo$.mp.
52. random$.mp.
53. ((control$ or prospectiv$) adj3 (trial$ or method$ or stud$)).mp.
54. (crossover$ or cross-over$).mp.
55. or/48-54
56. 47 or 55
57. exp ANIMAL/
58. Nonhuman/
59. Human/
60. 57 or 58
61. 60 not 59
62. 56 not 61
63. 38 and 62

Clinicaltrials.gov
Search terms=bronchiolitis
Study type= Interventional Studies
Interventions= antibiotics
HISTORY
Review first published: Issue 12, 2012

CONTRIBUTIONS OF AUTHORS
The protocol was written by GM and AC. PM reviewed the protocol. For the review, GM and AC independently reviewed the search, double entered data and wrote the manuscript. PM reviewed the manuscript.

DECLARATIONS OF INTEREST
All authors are involved in an RCT on the efficacy of azithromycin to reduce the respiratory burden of bronchiolitis in indigenous children hospitalised with bronchiolitis (Chang 2011).

SOURCES OF SUPPORT

Internal sources

• No sources of support supplied

External sources

• National Health Medical Research Council, Australia. Project grant number 605809
• National Health Medical Research Council, Australia. Salary support for AC, practitioner fellowship grant number 545216
• NHMRC Centre of Research Excellence Grant, Australia. CRE in respiratory health in Aboriginal and Torres Strait Islander children grant number 1040830

DIFFERENCES BETWEEN PROTOCOL AND REVIEW
We clarified the inclusion criteria.
7.3 Cochrane Review – Clinical pathway for chronic cough in children.
Clinical pathways for chronic cough in children (Review)

McCallum GB, Bailey EJ, Morris PS, Chang AB

This is a reprint of a Cochrane review, prepared and maintained by The Cochrane Collaboration and published in The Cochrane Library 2014, Issue 9

http://www.thecochranelibrary.com
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Clinical pathways for chronic cough in children

Gabrielle B McCallum1, Emily J Bailey1, Peter S Morris1, Anne B Chang1,2,3

1Child Health Division, Menzies School of Health Research, Charles Darwin University, Darwin, Australia. 2Queensland Children's Respiratory Centre, Royal Children's Hospital, Brisbane, Australia. 3Queensland Children's Medical Research Institute, Queensland University of Technology, Brisbane, Australia

Contact address: Gabrielle B McCallum, Child Health Division, Menzies School of Health Research, Charles Darwin University, Darwin, Northern Territory, 0810, Australia. gabrielle.mccallum@menzies.edu.au.

Editorial group: Cochrane Airways Group.

Publication status and date: New search for studies and content updated (conclusions changed), published in Issue 9, 2014.

Review content assessed as up-to-date: 8 January 2014.


ABSTRACT

Background

Chronic cough (a cough lasting longer than four weeks) is a common problem internationally. Chronic cough has associated economic costs and is distressing to the child and to parents; ignoring cough may lead to delayed diagnosis and progression of serious underlying respiratory disease. Clinical guidelines have been shown to lead to efficient and effective patient care and can facilitate clinical decision making. Cough guidelines have been designed to facilitate the management of chronic cough. However, treatment recommendations vary, and specific clinical pathways for the treatment of chronic cough in children are important, as causes of and treatments for cough vary significantly from those in adults. Therefore, systematic evaluation of the use of evidence-based clinical pathways for the management of chronic cough in children would be beneficial for clinical practice and for patient care. Use of a management algorithm can improve clinical outcomes; such management guidelines can be found in the guidelines for cough provided by the American College of Chest Physicians (ACCP) and the British Thoracic Society (BTS).

Objectives

To evaluate the effectiveness of using a clinical pathway in the management of children with chronic cough.

Search methods

The Cochrane Register of Controlled Trials (CENTRAL), the Cochrane Airways Group Specialised Register, MEDLINE, EMBASE, review articles and reference lists of relevant articles were searched. The latest search was conducted in January 2014.

Selection criteria

All randomised controlled trials of parallel-group design comparing use versus non-use of a clinical pathway for treatment of chronic cough in children (< 18 years of age).

Data collection and analysis

Results of searches were reviewed against predetermined criteria for inclusion. Two review authors independently selected studies and performed data extraction in duplicate.
Main results

One study was included in the review. This multi-centre trial was based in five Australian hospitals and recruited 272 children with chronic cough. Children were randomly assigned to early (two weeks) or delayed (six weeks) referral to respiratory specialists who used a cough management pathway. When an intention-to-treat analysis was performed, clinical failure at six weeks post randomisation (defined as < 75% improvement in cough score, or total resolution for fewer than three consecutive days) was significantly less in the early pathway arm compared with the control arm (odds ratio (OR) 0.35, 95% confidence interval (CI) 0.21 to 0.58). These results indicate that one additional child will be cured for every five children treated via the cough pathway (number needed to treat for an additional beneficial outcome (NNTB) = 5, 95% CI 3 to 9) at six weeks. Cough-specific parent-reported quality of life scores were significantly better in the early-pathway group; the mean difference (MD) between groups was 0.60 (95% CI 0.19 to 1.01). Duration of cough post randomisation was significantly shorter in the intervention group (early-pathway arm) compared with the control group (delayed-pathway arm) (MD -2.70 weeks, 95% CI -4.26 to -1.14).

Authors’ conclusions

Current evidence suggests that using a clinical algorithm for the management of children with chronic cough in hospital outpatient settings is more effective than providing wait-list care. Further high-quality randomised controlled trials are needed to perform ongoing evaluation of cough management pathways in general practitioner and other primary care settings.

PLAIN LANGUAGE SUMMARY

Clinical pathways for chronic cough in children

Background

Clinical pathways serve as a tool or algorithm (like a flow chart) that can be used in the treatment of patients with various chronic diseases. They provide a clear guide that assists doctors in diagnosing an illness and in making decisions with the patient about what treatment is needed or which specialists should be seen or tests ordered at each stage of progression of the disease. Overall the aim of clinical pathways is to provide efficient care for patients. Examples of patient decision aids are provided by the National Health Service (NHS) in the UK at http://www.rightcare.nhs.uk/index.php/shared-decision-making/about-the-pdas/.

Chronic cough in children is a significant medical problem that in some situations warrants thorough investigation. This review examined whether using clinical pathways was effective for evaluating and managing children with chronic cough (cough lasting longer than 4 weeks).

Study characteristics

Only a single multi-centre study could be included in this review. Evidence is current to January 2014. This study was funded by the National Health and Medical Research Council of Australia.

Key results

This study of 272 children in five Australian hospitals reported that those randomly assigned to earlier treatment according to a clinical pathway showed improved clinical outcomes (cough resolved earlier and quality of life was better) compared with those who were randomly assigned to later use of the pathway. No adverse events were reported.

Quality of the evidence

The quality of evidence was graded as moderate. Evidence is limited, as only one study could be included in this review. This study was unable to completely blind participants to the clinical pathway.
### Summary of Findings for the Main Comparison

**Clinical pathway compared with usual care for treatment of children with chronic cough**

**Patient or population:** children with chronic cough of unknown origin lasting longer than 4 weeks  
**Settings:** paediatric hospital outpatient clinics  
**Intervention:** clinical pathway algorithm (clinical review within 2 weeks)  
**Comparison:** usual clinical care (clinical review at 6 weeks)

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Illustrative comparative risks* (95% CI)</th>
<th>Relative effect (95% CI)</th>
<th>No. of participants (studies)</th>
<th>Quality of the evidence (GRADE)</th>
<th>Comments</th>
</tr>
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<tr>
<td></td>
<td>Assumed risk</td>
<td>Corresponding risk</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Standard care group</td>
<td>Clinical pathway</td>
<td>Clinical failure</td>
<td>71 per 100 (34 to 59)</td>
<td>47 per 100 (34 to 59)</td>
<td>OR 0.35 (0.21 to 0.58)</td>
</tr>
<tr>
<td>Follow-up: 6 weeks</td>
<td></td>
<td><strong>Primary outcome</strong> (by intention-to-treat analysis)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PC-QOL mean score at 6 weeks</td>
<td>5.01 (SD 1.63)</td>
<td>5.61 (5.2 to 6.02)</td>
<td>Mean difference between groups: 0.60 (0.19 to 1.01) weeks</td>
<td>226 (1 study)</td>
<td>⊕⊕⊕⃝ moderate</td>
</tr>
<tr>
<td>PC-QOL is a 27-item questionnaire. Each question has a 7-point score ranging from 1 (worst quality of life) to 7 (best quality of life). Scores for each item were added and the average taken.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration of cough post randomisation</td>
<td>Mean duration of cough was 9.1 (SD 6.6) weeks</td>
<td>Mean duration of cough was 6.4 (4.84 to 7.96) weeks</td>
<td>Mean difference between groups: -2.70 (-4.26 to -1.14) weeks</td>
<td>226 (1 study)</td>
<td>⊕⊕⊕⃝ moderate</td>
</tr>
</tbody>
</table>

*Cough resolution was defined as total resolution of cough or ≥ 75% improvement in cough scores for ≥ 3 days.*
<table>
<thead>
<tr>
<th>Proportion of adverse events experienced</th>
<th>Follow-up: 6 months</th>
<th>0 per 1000</th>
<th>0 per 1000</th>
<th>Not estimable</th>
<th>See comments</th>
<th>⊕⊕⊕⃝ moderate*</th>
<th>No adverse events were reported</th>
</tr>
</thead>
</table>

| Proportions of participants experiencing adverse events or complications | Follow-up: 6 months | 0 per 1000 | 0 per 1000 | Not estimable | See comments | ⊕⊕⊕⃝ moderate* | No adverse events were reported |

*The basis for the **assumed risk** was the mean control group risk in the included study. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; OR: Odds ratio; PC-QOL: Parent-reported cough-specific quality of life questionnaire; RR: Risk ratio; SD: Standard deviation.

GRADE Working Group grades of evidence.

**High quality:** Further research is very unlikely to change our confidence in the estimate of effect.

**Moderate quality:** Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

**Low quality:** Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

**Very low quality:** We are very uncertain about the estimate.

*A single study was identified, and complete blinding was not possible for this type of intervention.*
BACKGROUND

Description of the condition

Cough is the most common symptom presenting to primary care internationally (Britt 1999; Cherry 2003; Irwin 2006). In Australia, 5.8 of every 100 visits to general practitioners are result of cough (Britt 2008). Chronic (prolonged) cough is also one of the most common symptoms presenting to respiratory physicians (Fitzgerald 2006). Thus, in Australia alone, these visits on a population level would equate to millions of dollars per year in Medicare rebates for general practitioner (GP) visits. Further, studies have shown that more than 80% of children who have seen specialists for chronic cough have had more than five medical visits, and over 20% had seen a doctor more than 20 times (Chang 2012; Marchant 2008). The burden of chronic cough (defined in children as cough lasting longer than four weeks) (Chang 2006b; Marchant 2006) is significant, both in terms of personal cost and impaired quality of life (Marchant 2008) and at a societal level when medication costs are substantial (Irwin 2006).

Chronic cough in children causes a significant burden of distress for parents (Marchant 2008). Furthermore, although cough may be seen as a merely troublesome symptom with no serious consequences, ignoring cough that may be the sole presenting symptom of an underlying respiratory disease may lead to delayed diagnosis and progression of serious illness or chronic respiratory morbidity (Barr 2005; Karakoc 2002). Thus for the management of chronic cough in children, it is important for clinicians to define which patients will benefit from which interventions and treatment approaches (including ‘watchful waiting’) (Gupta 2007).

The major aim of clinical pathways or guidelines is to improve diagnosis and/or management of the specific condition or symptom. They provide a step-by-step approach for the clinician that is based on preceding criteria. Currently, treatment recommendations for cough vary among published guidelines (Irwin 2006; Kohno 2006; Shields 2007), but none have been evaluated in a randomised controlled trial (RCT). We (Chang 2005; Chang 2006a; Marchant 2006) and others (Shields 2006) have argued that children with chronic cough should be evaluated and treated in accordance with guidelines specific to children, as both causative factors and treatment in children are significantly different from those in adults (Chang 2006b).

How the intervention might work

Clinical guidelines have been shown to provide more efficient and effective patient care (Fessler 2005) and, if well designed, can facilitate clinical decision making. This approach in turn should reduce variations in delivery of care and delays in diagnosis or treatment (Kwan 2004). Cough guidelines, which were first provided by Irwin (Irwin 1990), were designed to facilitate the management of chronic cough. Subsequent cough guidelines have been published by various societies.

Why it is important to do this review

Cohort studies suggest that use of cough clinical pathways or algorithms improves outcomes (resolution of cough and accurate diagnosis) in children (Aslaksen 2008; Karabel 2013; Rehman 2009) and adults (Irwin 1990). However, use of guidelines is not universally popular in medical circles (Preiser 2004) and may arguably result in negative outcomes (e.g. from missed or delayed diagnosis). Clinical guidelines are regarded by some as ‘cook-book medicine,’ as bothersome and as negating critical thinking (Berg 1997). Examination, through a systematic review, of the effectiveness of using a clinical pathway in treating children with chronic cough would be useful for guiding clinical practice (Elbourne 2002). This is an update of a Cochrane review (Bailey 2004).

OBJECTIVES

To evaluate the effectiveness of using a clinical pathway in the management of children with chronic cough.

METHODS

Criteria for considering studies for this review

Types of studies

All RCTs of parallel-group design comparing use versus non-use of a clinical pathway for the treatment of children with chronic cough.

Types of participants

Inclusion criteria: children (< 18 years of age) with chronic (lasting longer than four weeks) cough of unknown origin.

Exclusion criteria: known preexisting respiratory illness causing cough.

Types of interventions

All randomised controlled comparisons of use of a clinical pathway. Review authors planned that trials examining use of other medications or interventions would be included if all participants were given equal access to such medications or interventions.
Types of outcome measures

Primary outcomes
Proportions of participants who were not cured or were not substantially improved at follow-up (clinical failure).

Secondary outcomes
1. Proportions of participants who were not cured at follow-up.
2. Proportions of participants who were not substantially improved at follow-up.
3. Mean difference in cough indices (cough diary, cough frequency, cough-specific quality of life scores, cough duration).
4. Proportions of participants experiencing adverse effects of the intervention (e.g. Cushing’s syndrome from steroid overdose).
5. Proportions of participants experiencing complications (e.g. acute hospitalisations, chronic lung disease resulting from delayed diagnosis).

Proportions of participants who failed to improve while receiving treatment and mean clinical improvement were determined using the following hierarchy of assessment measures (Note: When two or more assessment measures were reported in the same study, the outcome measure listed first in the hierarchy was used).
1. Objective measurements of cough indices (cough frequency, cough receptor sensitivity).
2. Symptomatic assessment by participant (adult or child) (quality of life, Likert scale, visual analogue scale, level of interference of cough, cough diary).
3. Symptomatic assessment by parents/caregivers (quality of life, Likert scale, visual analogue scale, level of interference of cough, cough diary).
4. Symptomatic assessment by clinicians (Likert scale, visual analogue scale, level of interference of cough, cough diary).

Search methods for identification of studies

Electronic searches
Trials were identified from the following sources.
1. The Cochrane Central Register of Controlled Trials (CENTRAL) (2014, Issue 1).
2. The Cochrane Airways Group Specialised Register.
3. MEDLINE (Ovid) (1950 to January 2014).

Full search strategies are listed in Appendix 1. Conference abstracts were handsearched and grey literature was searched through the CENTRAL database.

Searching other resources
In addition to the electronic search, we checked the reference lists of relevant publications and contacted the authors of the included trial to ask for further information.

Data collection and analysis

Selection of studies
Retrieval of studies: Using article titles, abstracts or descriptors, two review authors (EJB and ABC in original review and search from 2009 to 2012; GBM and ABC in search from 2012 to 2014) independently reviewed literature searches to identify potentially relevant trials for full review. They conducted searches of bibliographies and texts to identify additional studies. From the full-text articles obtained, the same two review authors independently assessed trials for inclusion on the basis of specific criteria. It was planned that disagreements would be resolved by third party adjudication (PM), but no disagreement was reported.

Data extraction and management
We had no disagreements but had planned to resolve disagreements through discussion with another review author (PSM). We extracted data using a standardised data collection form and managed them in Review Manager 5.2, in accordance with recommendations provided in the Cochrane Handbook for Systematic Review of Interventions (Higgins 2011). When required, we requested further information from trial authors.

Assessment of risk of bias in included studies
Two review authors (GBM and ABC) independently assessed risk of bias for each study using the criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2011). It was planned that disagreements would be resolved by discussion or by third party adjudication. We assessed risk of bias according to the following domains:
1. Allocation sequence generation (selection bias).
2. Concealment of allocation (selection bias).
3. Blinding of participants (performance bias).
4. Outcome assessment (detection bias).
5. Incomplete outcome data (attrition bias).
6. Selective outcome reporting (reporting bias).

Measures of treatment effect
For the dichotomous outcome variables of each individual study, odds ratios were calculated using a modified intention-to-treat analysis. This analysis assumes that children not available for outcome assessment have not improved (and probably represents a conservative estimate of effect). Other indices were assumed to
be normally distributed continuous variables, so the mean difference in outcomes could be estimated (weighted mean difference). It was planned that if studies reported outcomes using different measurement scales, the standardized mean difference would be used.

Unit of analysis issues
Cross-over trials are not appropriate for this intervention and therefore were not planned for inclusion in any meta-analysis performed. It was planned that cross-over trials that met other review inclusion criteria would be described in the text.

Dealing with missing data
It was planned that Investigators or study sponsors would be contacted to verify key study characteristics and to provide missing numerical outcome data when necessary.

Assessment of heterogeneity
It was planned that heterogeneity between study results would be described and tested using the I² statistic to ascertain whether it reached statistical significance (Higgins 2003). Heterogeneity is considered significant when the P value is less than 0.10 (Higgins 2011). As only one study was suitable for inclusion in the review, assessment of heterogeneity was not necessary.

Assessment of reporting biases
If reporting bias was suspected (see ‘Selective reporting bias’ in the ‘Risk of bias’ table below), we planned to contact study authors to ask them to provide missing outcome data. It was planned that if missing data were not provided, and if this was thought to introduce serious bias, the impact of including such studies in the overall assessment would be explored through a sensitivity analysis. As a single study with complete outcome reporting was included in this review update, sensitivity analysis was not required.

Data synthesis
An initial qualitative comparison of all individually analysed studies was planned to examine whether pooling of results (meta-analysis) was reasonable. This comparison would have taken into account differences in study populations, inclusion/exclusion criteria, interventions, outcome assessment and estimated effect size. Results from studies that met the inclusion criteria and reported any of the outcomes of interest would have been included in subsequent meta-analyses. However, as only one study was suitable for inclusion (based on study characteristics and inclusion criteria of this review), a qualitative comparison of studies was not required. We created a ‘Summary of findings’ table (SoF) (Summary of findings for the main comparison) in accordance with methods and recommendations described in Section 8.5 and Chapter 12 of the Cochrane Handbook for Systematic Review of Interventions (Higgins 2011) and using GRADEpro software.

The summary weighted odds ratio (OR) and 95% confidence interval (95% CI) (fixed-effect model) were calculated using RevMan. Numbers needed to treat for an additional beneficial outcome (NNTB) were calculated from the pooled OR, and its 95% CI was applied to a specified baseline risk with use of an online calculator (Cates 2003). Sensitivity analyses were planned to assess the impact of potentially important factors on overall outcomes.

1. Analysis by type of clinical pathway (e.g. continent-specific).
2. Analysis by setting, whereby frequency of causes of chronic cough may be different (e.g. general practitioners vs specialists, affluent vs non-affluent countries, indigenous vs mainstream communities).
3. Analysis using a random-effects model.
4. Analysis by “treatment received.”
5. Analysis by “intention-to-treat.”

As only a single study was included, subgroup (described above) and sensitivity analyses were not performed.

RESULTS

Description of studies
See Characteristics of included studies and Characteristics of excluded studies.

Results of the search
Combined searches (original and update reviews) performed by the Cochrane Airways Group identified 727 potentially relevant titles. After the abstracts were assessed, 10 studies were considered for inclusion in the review, and one study (Chang 2013) fulfilled the eligibility criteria of the review (Figure 1).
471 of records identified through original database searching

256 additional records identified from updated search (January 2014)

717 records after duplicates removed

10 records screened

9 records excluded

1 full-text article assessed for eligibility

1 study included in quantitative synthesis
Included studies

The sole study included in the review was a multi-centre study supported by a competitive, non-commercial grant (National Health and Medical Research Council of Australia). The study protocol was published previously (Chang 2010). Study authors described the trial as a pragmatic RCT (Chang 2013) utilising a standardised clinical management pathway for management of chronic cough in children (i.e. two weeks (early) vs six weeks (delayed) of referral by their referring physician). Children were randomly assigned by their referring physician to an early management pathway (within three weeks of referral to the specialist practice) or to usual care (i.e. later management with the pathway around the six-week waiting period required to obtain a regularly scheduled specialist appointment) (Chang 2013). The RCT did not strictly explore intervention versus standard care (i.e. use vs non-use of a clinical pathway), as all participants received the intervention within the timing of the intervention (i.e. merely delayed). Study authors justified the study design by stating that a cluster-blind RCT would not be feasible, as all centres involved in the study had similar standard clinical practices, in line with current recommendations (upon which the cough pathway was designed), and physicians were not comfortable withholding treatment for the purpose of a study. Similarly, the study authors acknowledged that strict time point adherence (rather than “early” and “delayed” use of the pathway) would introduce greater rigour to the study but stated that a pragmatic design was required for the real-life clinical settings in which the study operated (Chang 2013). This study was conducted in paediatric hospital outpatient clinics at five centres in Australia, and investigators recruited children who were newly referred with chronic cough (lasting longer than four weeks). A total of 272 participants were included in the study; 152 were male. The mean age of study participants was 4.5 (standard deviation (SD) 3.7) years, and the median duration of cough at enrolment was 16 (interquartile range (IQR) 8 to 32) weeks (Chang 2013).

Nineteen children were not treated according to the clinical pathway, as they did not attend their first scheduled appointment with the respiratory physician (n = 8 from the intervention group; n = 11 from the control group). A further 22 children were withdrawn from the study (parents withdrew n = 3; lost to follow-up n = 17; protocol violation n = 1; non-adherence n = 1). Baseline data for 253 participants were therefore available, as were complete primary outcome data for 226 participants. Although the study was undertaken to evaluate outcome measures four weeks post use of the pathway in the early-pathway arm and before use of the pathway in the delayed-pathway arm, participating children were seen (hence the pathway was used) at 1.9 (SD 1) weeks and 5.1 (SD 1.8) weeks, respectively. Outcomes of the study were likely diluted. The study used proportions of cough-free (> 75% improvement in cough or total resolution of cough for three or more days according to cough diary) children and parent-proxy quality of life score, both measured at week six, as the primary outcome measures. Excluded were children with a known chronic respiratory illness (previously diagnosed by a respiratory physician or confirmed on objective tests) such as cystic fibrosis or bronchiectasis. For further details, see Characteristics of included studies.

Excluded studies

Nine studies were excluded (see Characteristics of excluded studies) because they used a non-RCT design or did not use a specific management protocol for cough treatment.

Risk of bias in included studies

Risk of bias in the included study is summarised in Figure 2 and Figure 3.
Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.
**Allocation**
Assessed as low risk of bias. Study authors clearly described computer-generated randomisation sequencing with concealed allocation.

**Blinding**
Assessed as low risk of bias. Although participants and research personnel collecting data were not specifically informed about the study arm to which they were allocated, the design of the study made complete blinding not feasible. At the time the study was conducted, the usual wait time to see a clinician in the public health setting was used as the time frame for the delayed-pathway arm (control) (i.e. around six weeks) and usual wait time for private clinics was used as the time frame for the early-pathway arm (intervention) (one to three weeks). Regarding the objective character of outcome measures, we did not expect high risk of bias with clinical failure. With regards to subjective outcome measures, we do not expect high risk of bias for parent-reported cough-specific quality of life score (PC-QOL), as a standardised approach was implemented for all study participants.

**Incomplete outcome data**
Assessed as low risk of bias. Study authors (Chang 2013) stated that complete outcome data were obtained in more than 90% of participants.
Selective reporting
Assessed as low risk of bias, with study authors clearly describing in the published manuscript the progress of all randomly assigned participants. Limitations of the study were identified and discussed by the study authors.

Other potential sources of bias
The number of potentially eligible participants who were not enrolled (declined participation or were not approached for participation) is not stated by the study authors. This may introduce an unclear assessment of recruitment selection bias.

Effects of interventions
See: Summary of findings for the main comparison
As only one study met the criteria for inclusion in this review, no meta-analysis could be performed. The effects of intervention presented below are reported by the single included study (Chang 2013).

Primary outcome
Proportions of participants who were not cured or were not substantially improved at follow-up (clinical failure)
Intention-to-treat analysis revealed that clinical failure was significantly lower in the early-pathway arm (intervention) compared with the delayed-pathway arm (control) (OR 0.35, 95% CI 0.21 to 0.58; Analysis 1.1), as presented in Figure 4. The control event rate (i.e. the number of clinical failures reported from the control group) was 70.5% versus the intervention event rate of 46% (Chang 2013). These results indicate that one child will be cured for every five children treated by using the cough pathway at six weeks (NNTB = 5, 95% CI 3 to 9; Cates plot, Figure 5).

Figure 4. Forest plot of comparison: 1. Primary outcome, outcome: 1.1. Clinical failure-primary outcome (by intention-to-treat analysis).
Figure 5. In the control group, 71 of 100 participants were not cured at follow-up over 6 weeks compared with 46 of 100 (95% CI 33 to 58) for the active treatment group.

Secondary outcomes

Proportions of participants who were not cured at follow-up

The proportion of participants not cured at follow-up (secondary outcome) is the same as the proportion of participants with clinical failure (see primary outcome above) (Analysis 1.2).

Mean differences in cough indices (cough diary, cough frequency, cough-specific quality of life scores, cough duration)

The parent-reported cough-specific quality of life score (PC-QOL) at week six was significantly better (i.e. higher) for those in the early-pathway arm compared with those in the delayed-pathway arm (MD 0.60 points, 95% CI 0.19 to 1.01; Analysis 1.3). Duration of cough post randomisation was significantly shorter in the intervention group (early-pathway arm) compared with the control group (delayed-pathway arm) (MD -2.70 weeks, 95% CI -4.26 to -1.14; Analysis 1.4).

Proportions of participants who were not substantially improved at follow-up

The study reported only on participants cured or not cured at follow-up. Participants not substantially improved were considered not cured.

Proportions of participants experiencing adverse effects of the intervention or complications

Study authors reported that none of the participants in the intervention (pathway) group and none in the control (standard care) group experienced adverse events.
Other outcomes
Once the cough algorithm was used, irrespective of whether it was applied early or was delayed, the duration of cough was similar. Also, in contrast to results reported for a cough-specific quality of life, no differences were noted between groups in terms of generic health-related quality of life (PedsQL) score at six weeks (early arm: median 92.5, IQR 81 to 96.5; delayed arm: median 87, IQR 76 to 96.3).

DISCUSSION
Summary of main results
Only a single study fulfilled the inclusion criteria. This multi-centre study involved 272 children enrolled from hospital outpatient departments in Australia. This body of evidence was graded as moderate quality through the GRADE (Grades of Recommendation, Assessment, Development and Evaluation) approach. An ITT analysis revealed that clinical failure was significantly lower in the early-pathway arm (clinical review within two weeks) compared with the control arm (delayed use of pathway; clinical review at six weeks) (OR 0.35, 95% CI 0.21 to 0.58). For the secondary outcome of mean score for cough-specific parent-reported quality of life, the score was significantly better in the early-pathway group (0.60 units, 95% CI 0.19 to 1.01) compared with the control group. This is seen just at the minimum important difference (MID) (using the distribution method for calculating MID) (Newcombe 2010; Newcombe 2010b). The intervention group also had significantly shorter duration of cough post randomisation compared with the control group (MD -2.70, 95% CI -4.26 to -1.14). No adverse events were reported.

Overall completeness and applicability of evidence
Clinical pathways are used for various chronic diseases to facilitate diagnosis; aid decision making; and provide efficient care to patients. Chronic cough in children is a significant medical problem that in some situations warrants thorough investigation. This review is limited, as only data from a single study are available. Nevertheless, data support the use of clinical management pathways for chronic cough in children in a tertiary care setting. Although the RCT in this review planned to compare outcomes four weeks post use of the pathway in the early-pathway arm and before use of the pathway in the delayed-pathway arm (i.e. within six weeks of referral), pragmatically this was not feasible, and children entered the protocol at times that were not strictly adhered to, resulting in treatment of children by respiratory paediatricians in accordance with the pathway at 1.9 (SD 1) weeks and 5.1 (SD 1.8) weeks, respectively. This flexibility in treatment time means that study results are likely to be diluted, as children in the delayed-pathway arm received treatment before measurements were undertaken.

Limitations
The algorithm applied in the included study was used by respiratory physicians (all but one person was a respiratory physician); therefore, any effect that might be attributed to expertise required to use the algorithm cannot be identified. However, steps within the algorithm are simple and explicit, and most (85%) of the children had diagnoses that could be made easily in primary care. For example, key steps such as distinguishing between wet and dry cough (Chang 2005b) and categorising specific versus non-specific cough (Marchant 2006b) are both feasible and reliable. Thus, although the same pathway could be used in general practice, treatment outcomes may be different, as the pathway is dependent on thorough history taking and examination (including identifying the presence of crepitations). In general practice, agreement of items in preschool children (most children with chronic cough are of preschool age) such as wheeze and chest examination findings has been shown to be poor (kappa values range from 0.12 to 0.39) (Hay 2004). Thus, applicability of the pathway (without concurrent education) in general practice cannot be ascertained. Further education for primary care providers on how to use the algorithm is likely required for the algorithm to be as successful as was reported in the included study. A wait-list RCT pragmatic approach was used in the included study. The design of this study is similar to the wait-list approach used for some RCTs, such as those examining psychological interventions or paediatric surgery (e.g. tonsil-adenoidectomy for obstructive sleep apnoea), for which primary outcomes are selected before the intervention is decided. Arguably, early versus delayed use of the algorithm represents an alternative valid approach (c.f. use vs non-use of an algorithm) that can be used to determine whether the algorithm is efficacious, as effectively timing the primary outcome (at week six) tests use versus non-use of the algorithm.

Quality of the evidence
Given that only one study could be included in this review, the extent of the evidence is limited. Other than the unclear risk of bias associated with blinding of participants, the risk of bias for other criteria was low. This multi-centre study involved a relatively large number of participants (i.e. for cough-related studies). The consistency of favourable outcomes in the intervention arm (including duration of cough post randomisation) supports the unlikely presence of bias. Also, the generic quality of life measure used (PedsQL), which is a less sensitive measure for cough, was not significantly different between groups, but the cough-specific quality of life score (PC-QOL) was significantly better in the early-
pathway arm. Arguably, if quality of life was subject to clinically important bias, PedsQL score would also be significantly better in the intervention group (early-pathway arm) compared with the control group (delayed-pathway arm).

In addition to significant differences between groups in primary outcomes (PC-QOL and proportion ‘cough-free’), the duration of cough post randomisation was significantly different between groups (early-pathway vs delayed-pathway groups). Cough duration at baseline (Table 1 in the included study) and post use of the algorithm was similar in the two groups. Thus, it is most likely that use of the algorithm accounted for differences between groups.

**Potential biases in the review process**

Two of the authors of this review are co-authors of the sole RCT that was included in this review. However, we took steps to reduce bias by double-entering data, and the primary author of this review was not involved in the included RCT.

**Agreements and disagreements with other studies or reviews**

Data from cohort studies (Asilsoy 2008; Karabel 2013; Rehman 2009) are concordant with results of this review, which included only RCTs. These cohort studies used a cough algorithm that is similar to the one described in the included study. We are not aware of any other systematic reviews with which these results can be compared.

**Authors’ Conclusions**

**Implications for practice**

The limited available evidence presented here suggests that use of management protocols in the diagnosis and treatment of children with chronic cough (lasting longer than four weeks) is effective in improving clinical outcomes (cough-free, shorter duration of cough and improved parent-proxy cough-specific quality of life).

**Implications for research**

Further high-quality randomised controlled trials are needed for ongoing evaluation of the use of clinical pathways for the management of chronic cough in children. In these trials, settings should include general practitioner and other primary care settings and use of the cough algorithm should be compared with non-use of the algorithm. A cluster-randomised trial design is likely the most feasible study design in general practice. Use of validated cough outcome measures is essential. The ascribed diagnostic criteria and the definition of cough resolution should be decided a priori. Ideally, an objective cough outcome (such as cough counts) should also be included as an outcome.

**Acknowledgements**

We thank Chris Cates, Toby Lasserson and Emma Welsh for their advice and for providing support and comments on the protocol and the review. We also thank Susan Hansen and Elizabeth Stovold for performing the searches and for obtaining the relevant articles.

Christopher Cates was the editor for this review and commented critically on the review.

**References**

- **Asilsoy 2008** (published data only)

- **Dettmar 2009** (published data only)

- **English 2006** (published data only)

- **Flores-Hernandez 1999** (published data only)
Clinical pathways for chronic cough in children (Review)

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Hover 2000 {published data only}

Nagel 2009 {published data only}

Norton 2007 {published data only}

Rehman 2009 {published data only}

Rutten 1991 {published and unpublished data}

Spelman 1991 {published data only}

Additional references

Barr 2005

Berg 1997

Beir 1999

Beir 2008

Cates 2003

Chang 2010

Chang 2005

Chang 2005b

Chang 2006a

Chang 2006b

Chang 2012

Cherry 2003

Elbourne 2002

Fessler 2005

Fitzgerald 2006

Fukta 2007

Hay 2004
References to other published versions of this review

Marchant 2006

Marchant 2006b

Marchant 2008

Newcombe 2010

Newcombe 2010b

Preiser 2004

Shields 2006

Shields 2007

References to other published versions of this review

Bailey 2004

* Indicates the major publication for the study

Clinical pathways for chronic cough in children (Review)
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### Characteristics of included studies (ordered by study ID)

**Chang 2013**

<table>
<thead>
<tr>
<th>Methods</th>
<th>Randomised controlled trial</th>
</tr>
</thead>
</table>
| **Participants** | Inclusion criteria: children (< 18 years of age) with chronic cough (> 4 weeks) newly referred to specialist paediatric respiratory clinics at 5 Australian sites (Brisbane, Darwin, Melbourne, Sydney, Canberra)  
Exclusion criteria: children with known respiratory illness previously diagnosed by a respiratory physician or confirmed on objective testing (e.g. cystic fibrosis, bronchiectasis) before the time of referral  
Children assessed: n = 346 (n = 30 did not meet inclusion criteria, n = 44 declined participation)  
Children randomised: n = 272 (early use n = 140, delayed use n = 132) |
| **Interventions** | 1. Early or delayed use of an algorithm for management of cough in children (2 vs 6 weeks of referral)  
2. Children randomly assigned to the early intervention arm were seen by a respiratory specialist and were managed according to the algorithm within 3 weeks of referral and study enrolment  
3. Children randomly assigned to the delayed intervention arm were seen by a respiratory specialist and were managed according to the algorithm between 6 and 8 weeks of referral and study enrolment |
| **Outcomes** | Primary outcomes:  
1. Proportion of children who were cough-free (considered to be 75% improvement in cough score, or total resolution for 3 consecutive days)  
2. Quality of life measure (PC-QOL: cough-specific, parent-reported quality of life) at week 6 |
| **Notes** | Because of the nature of the study, data collected up until the week 6 time point have been selected for inclusion in this review, as this represents use (early arm) vs non-use (delayed arm) of the algorithm. Information beyond week 6 of the study has not been included in this review |

### Risk of bias

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors’ judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Low risk</td>
<td>Study authors refer to previously published trial protocol (Chang 2010): Study authors clearly describe computer-generated randomisation sequence using permuted blocks of 4 or 6, stratified according to participant age and study site location</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Low risk</td>
<td>Study authors state concealed allocation</td>
</tr>
</tbody>
</table>
Blinding of participants and personnel (performance bias)
All outcomes
Unclear risk
Complete blinding was not possible. Participants and research personnel collecting data were not specifically informed about the arm to which they were allocated. However, the allocated arm could easily be determined if these individuals made the effort to look at time between random assignment and clinical review.

Blinding of outcome assessment (detection bias)
All outcomes
Low risk
Study authors clearly describe (in previously published protocol (Chang 2010)) outcomes measured by blinded assessor and provide a description of how this was achieved.

Incomplete outcome data (attrition bias)
All outcomes
Low risk
Complete outcome data were measured in > 90% of participants.

Selective reporting (reporting bias)
Low risk
Progress of all randomly assigned participants was clearly described.

Characteristics of excluded studies  [ordered by study ID]

<table>
<thead>
<tr>
<th>Study</th>
<th>Reason for exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asilsoy 2008</td>
<td>Evaluation of chronic cough using American College of Chest Physicians (ACCP) guidelines. Excluded from review, as not a randomised controlled trial (RCT)</td>
</tr>
<tr>
<td>Dettmar 2009</td>
<td>Study excluded, as not an RCT and not examining use of a management pathway. Study was a prospective cohort study of an online diagnostic website for adult patients with chronic cough. The diagnostic website allowed participants to provide information about their likely diagnosis that was based on a predetermined algorithm, which differentiated among 3 common causes of chronic cough (reflux, asthma and rhinitis) according to European Respiratory Society guidelines for chronic cough</td>
</tr>
<tr>
<td>English 2006</td>
<td>Study excluded, as not RCT and not examining use of a pathway for chronic cough. Study was a cross-sectional evaluation of the accuracy of guidelines for screening patients for tuberculosis. Study found that with implementation of clinical guidelines for nurse practitioner screening of patients for suspected tuberculosis infection, a 68% increase in the rate of tuberculosis case detection was reported</td>
</tr>
<tr>
<td>Flores-Hernandez 1999</td>
<td>Study excluded, as not RCT and not examining use of a clinical pathway for chronic cough in children. Before and after study of clinical guidelines for the management of acute respiratory infection, findings show that after implementation of management guidelines, inappropriate prescribing of antibiotics and cough syrups was decreased</td>
</tr>
<tr>
<td>Hover 2000</td>
<td>Study excluded, as not RCT and not examining chronic cough in children. Study was an evaluation performed via pretreatment and post-treatment analysis and randomised chart review of implementation of principles of the American Academy of Pediatrics for the management of common office infections. Study did not utilise a clinical pathway and did not treat children with chronic cough</td>
</tr>
<tr>
<td>Reference</td>
<td>Description</td>
</tr>
<tr>
<td>-----------</td>
<td>-------------</td>
</tr>
<tr>
<td>Nagel 2009</td>
<td>Review article presenting diagnostic pathway and treatment options for chronic (&gt; 4 weeks) cough in children (published in German). Excluded, as not a research study. Paper presented a diagnostic and management pathway similar to those presented by Chang 2013 and Rehman 2009, and reiterated that cough lasting longer than 4 weeks in a child warrants thorough investigation for underlying pathology.</td>
</tr>
<tr>
<td>Norton 2007</td>
<td>Prospective cohort study examining the effectiveness of a clinical pathway in reducing hospitalisation for acute asthma episodes in children presenting to the emergency department of a children’s hospital. Study showed that after the clinical pathway had been implemented, hospital admissions in children with moderate to severe asthma were reduced by &gt; 50% with no increase in re-presentations. Excluded, as not RCT and pathway designed for acute asthma care, not chronic cough.</td>
</tr>
<tr>
<td>Rehman 2009</td>
<td>This study was excluded, as it was not an RCT. This prospective cohort study of a management algorithm for diagnosis of causes of chronic cough in children 6 to 59 months of age was specifically designed for developing countries. Investigators aimed to establish the positive predictive value of the algorithm. This study found that the positive predictive value of the algorithm in predicting clinical diagnosis was 0.921.</td>
</tr>
<tr>
<td>Rutten 1991</td>
<td>RCT examining use of an educational programme (participant handout) on cough and effects on the consulting behaviour of participants after they had received the intervention. Study excluded, as reported participant numbers did not specify numbers of children included in the study. We contacted the study author to obtain the numbers relevant for children; these data were not available. Study also excluded, as the intervention used was not a clinical pathway, and the intervention was used for participants presenting for acute cough episodes, not for chronic cough.</td>
</tr>
<tr>
<td>Spelman 1991</td>
<td>Prospective cohort study examining the hypothesis that children with chronic cough will develop asthma. 106 participants with chronic cough, younger than 10 years of age, from Irish general practitioners, were treated according to an asthma protocol for 16 weeks. Follow-up 2 years later showed that 71 children had been subsequently diagnosed with asthma. Study excluded, as not RCT, and the protocol used was not specific to the treatment of children with chronic cough.</td>
</tr>
</tbody>
</table>
**DATA AND ANALYSES**

Comparison 1. Clinical pathway versus wait-list control

<table>
<thead>
<tr>
<th>Outcome or subgroup title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Clinical failure - primary outcome</td>
<td>1</td>
<td></td>
<td>Odds Ratio (M-H, Fixed, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>2 Proportion of participants who were not cured at follow-up</td>
<td>1</td>
<td></td>
<td>Odds Ratio (M-H, Fixed, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>3 PC-QOL mean score at 6 weeks</td>
<td>1</td>
<td></td>
<td>Mean Difference (IV, Fixed, 95% CI)</td>
<td>Subtotals only</td>
</tr>
<tr>
<td>4 Duration of cough post randomisation</td>
<td>1</td>
<td></td>
<td>Mean Difference (IV, Fixed, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>5 Proportion of adverse events experienced</td>
<td>1</td>
<td>272</td>
<td>Odds Ratio (M-H, Fixed, 95% CI)</td>
<td>0.0 [0.0, 0.0]</td>
</tr>
<tr>
<td>6 Proportions of participants experiencing adverse events or complications</td>
<td>1</td>
<td></td>
<td>Odds Ratio (M-H, Fixed, 95% CI)</td>
<td>Totals not selected</td>
</tr>
</tbody>
</table>

**Analysis 1.1. Comparison 1 Clinical pathway versus wait-list control, Outcome 1 Clinical failure - primary outcome.**

Review: Clinical pathways for chronic cough in children

Comparison: 1 Clinical pathway versus wait-list control

Outcome: 1 Clinical failure - primary outcome

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Early use of pathway n/N</th>
<th>Delayed use of pathway n/N</th>
<th>Odds Ratio M-H (Fixed, 95% CI)</th>
<th>Odds Ratio M-H (Fixed, 95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chang 2013</td>
<td>64/140</td>
<td>93/132</td>
<td>—</td>
<td>0.35 [0.21, 0.58]</td>
</tr>
</tbody>
</table>

Favours early use Favours delayed use
### Analysis 1.2. Comparison 1 Clinical pathway versus wait-list control, Outcome 2 Proportion of participants who were not cured at follow-up.

**Review:** Clinical pathways for chronic cough in children  
**Comparison:** 1 Clinical pathway versus wait-list control  
**Outcome:** 2 Proportion of participants who were not cured at follow-up

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Early use of pathway</th>
<th>Delayed use of pathway</th>
<th>Odds Ratio M-H,Fixed 95% CI</th>
<th>Odds Ratio M-H,Fixed 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chang 2013</td>
<td>64/140</td>
<td>93/132</td>
<td>0.35 [ 0.21, 0.58 ]</td>
<td></td>
</tr>
</tbody>
</table>

### Analysis 1.3. Comparison 1 Clinical pathway versus wait-list control, Outcome 3 PC-QOL mean score at 6 weeks.

**Review:** Clinical pathways for chronic cough in children  
**Comparison:** 1 Clinical pathway versus wait-list control  
**Outcome:** 3 PC-QOL mean score at 6 weeks

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Early use of pathway</th>
<th>Delayed use of pathway</th>
<th>Mean Difference IV,Fixed 95% CI</th>
<th>Weight</th>
<th>Mean Difference IV,Fixed 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chang 2013</td>
<td>123 5.61 (1.49)</td>
<td>103 5.01 (1.63)</td>
<td>0.60 [ 0.19, 1.01 ]</td>
<td></td>
<td>0.00 [ 0.00, 0.00 ]</td>
</tr>
</tbody>
</table>

**Subtotal (95% CI):**  
Heterogeneity: not applicable  
Test for overall effect: Z = 0.0 (P < 0.00001)
### Analysis 1.4. Comparison 1 Clinical pathway versus wait-list control, Outcome 4 Duration of cough post randomisation.

Review: Clinical pathways for chronic cough in children

Comparison: 1 Clinical pathway versus wait-list control

Outcome: 4 Duration of cough post randomisation

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Early use of pathway</th>
<th>Delayed use of pathway</th>
<th>Mean Difference Mean(95% CI)</th>
<th>Early use of pathway</th>
<th>Delayed use of pathway</th>
<th>Mean Difference Mean(95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chang 2013</td>
<td>123</td>
<td>103</td>
<td>-2.70 [ -4.26, -1.14 ]</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Favours early use Favours delayed use

### Analysis 1.5. Comparison 1 Clinical pathway versus wait-list control, Outcome 5 Proportion of adverse events experienced.

Review: Clinical pathways for chronic cough in children

Comparison: 1 Clinical pathway versus wait-list control

Outcome: 5 Proportion of adverse events experienced

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Early use of pathway</th>
<th>Delayed use of pathway</th>
<th>Odds Ratio M-H,Fixed 95% CI</th>
<th>Weight</th>
<th>Odds Ratio M-H,Fixed 95% CI</th>
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</thead>
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<tr>
<td>Chang 2013</td>
<td>0/140</td>
<td>0/132</td>
<td>Not estimable</td>
<td></td>
<td>Not estimable</td>
</tr>
</tbody>
</table>

Total events: 0 (Early use of pathway), 0 (Delayed use of pathway)

Heterogeneity not applicable

Test for overall effect: not applicable

Test for subgroup differences: Not applicable
### Analysis 1.6. Comparison 1 Clinical pathway versus wait-list control, Outcome 6 Proportions of participants experiencing adverse events or complications.

**Review:** Clinical pathways for chronic cough in children

**Comparison:** 1 Clinical pathway versus wait-list control

**Outcome:** 6 Proportions of participants experiencing adverse events or complications

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Early use of pathway</th>
<th>Delayed use of pathway</th>
<th>Odds Ratio M-H,Fixed,95% CI</th>
<th>Odds Ratio M-H,Fixed,95% CI</th>
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<tr>
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<td>0/140</td>
<td>0/132</td>
<td>0.01</td>
<td>Not estimable</td>
</tr>
</tbody>
</table>

Favours early use

Favours delayed use

### APPENDICES

**Appendix 1. Search strategies**

**CENTRAL**

#1 MeSH descriptor Cough explode all trees
#2 MeSH descriptor Bronchitis explode all trees
#3 cough* or bronchit*
#4 (#1 OR #2 OR #3)
#5 MeSH descriptor Critical Pathways, this term only
#6 MeSH descriptor Clinical Protocols, this term only
#7 MeSH descriptor Guidelines, this term only
#8 MeSH descriptor Practice Guidelines, this term only
#9 (clinical path* or clinical guide* or critical path* or care map* or care path* or pathway*)
#10 (#5 OR #6 OR #7 OR #8 OR #9)
#11 MeSH descriptor Pediatrics explode all trees
#12 MeSH descriptor Child explode all trees
#13 MeSH descriptor Infant explode all trees
#14 MeSH descriptor Adolescent explode all trees
#15 child* or paediat* or pediat* or adolesc* or infan* or toddler* or bab* or young* or preschool* or “pre school” or pre-school* or newborn* or “new born” or new-born* or neo-nat* or neonat*
#16 (#11 OR #12 OR #13 OR #14 OR #15)
#17 (#4 AND #10 AND #16)
MEDLINE (Ovid)
1 exp COUGH/
2 exp BRONCHITIS/
3 (cough$ or bronchit$).
4 or/1-3
5 clinical pathways/ or Clinical Protocols/
6 guidelines/ or practice guidelines/
7 exp "guideline [publication type]"/
8 (clinical path$ or clinical guide$ or critical path$ or care map$ or care path$ or pathway$).mp.
9 or/5-8
10 adolescent/ or exp child/ or exp infant/
11 exp pediatrics/
12 (child$ or paediat$ or pediat$ or adolesc$ or infan$ or toddler$ or bab$ or young$ or preschool$ or pre school$ or pre-school$ or newborn$ or new born$ or new-born$ or neo-nat$ or neonat$).mp.
13 or/10-12
14 4 and 9 and 13

RCT filter
1. (controlled clinical trial or randomised controlled trial).pt.
2. (randomised or randomised).ab,ti.
3. placebo.ab,ti.
4. dr.fs.
5. randomly.ab,ti.
6. trial.ab,ti.
7. groups.ab,ti.
8. or/1-7
9. Animals/
10. Humans/
11. 9 not (9 and 10)
12. 8 not 11

EMBASE (Ovid)
1 exp COUGHING/
2 exp BRONCHITIS/
3 (cough$ or bronchit$).tw.
4 or/1-3
5 clinical pathway/
6 practice guideline/ or clinical pathway/ or clinical protocol/ or consensus development/ or good clinical practice/ or nursing care plan/ or nursing protocol/
7 (clinical path$ or clinical guide$ or critical path$ or care map$ or care path$ or pathway$).mp.
8 or/5-7
9 exp adolescent/ or exp child/ or exp infant/ or exp newborn/
10 (child$ or paediat$ or pediat$ or adolesc$ or infan$ or toddler$ or bab$ or young$ or preschool$ or pre school$ or pre-school$ or newborn$ or new born$ or new-born$ or neo-nat$ or neonat$).tw.
11 exp pediatrics/
12 or/9-11
13 4 and 9 and 12

RCT filter
1. Randomized Controlled Trial/
2. randomization/
3. controlled clinical trial/
4. Double Blind Procedure/
5. Single Blind Procedure/
6. Crossover Procedure/
7. (clinica$ adj3 trial$).tw.
8. ((singl$ or doubl$ or trebl$ or tripl$) adj3 (mask$ or blind$ or method$)).tw.
9. exp Placebo/
10. placebo$.ti,ab.
11. random$.ti,ab.
12. ((control$ or prospectiv$) adj3 (trial$ or method$ or stud$)).tw.
13. (crossover$ or cross-over$).ti,ab.
14. or/1-13
15. exp animals/ or exp invertebrate/ or animal experiment/ or animal model/ or animal tissue/ or animal cell/ or nonhuman/
16. human/ or normal human/ or human cell/
17. 15 and 16
18. 15 not 17
19. 14 not 18

Cochrane Airways Group Register of Trials (CAGR)

#1 MeSH DESCRIPTOR cough
#2 (cough*) AND (INREGISTER)
#3 COUGH:MISC1
#4 #1 OR #2 OR #3
#5 guideline* or pathway* or protocol*
#6 (care NEXT map*) or (care NEXT path*)
#7 #5 or #6
#8 #4 and #7

WHAT'S NEW

Last assessed as up-to-date: 8 January 2014.

<table>
<thead>
<tr>
<th>Date</th>
<th>Event</th>
<th>Description</th>
</tr>
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<tr>
<td>8 January 2014</td>
<td>New search has been performed</td>
<td>Literature search updated</td>
</tr>
<tr>
<td>8 January 2014</td>
<td>New citation required and conclusions have changed</td>
<td>One new study included; conclusions updated</td>
</tr>
</tbody>
</table>
CONTRIBUTIONS OF AUTHORS
The first review was written primarily by EJB and ABC, who also reviewed the abstracts and articles. In this updated review, EJB and ABC reviewed the searches from 2008 to 2012; GBM and ABC reviewed search data from 2012 to 2014. GBM and ABC extracted and entered data for the 2014 update and drafted the review. All review authors approved the review before submission.

DECLARATIONS OF INTEREST
ABC and PSM are authors of the included trial of a management protocol for the treatment of children with chronic cough. EJB was involved in the early conduct of this trial (for the first year of the trial) but was not involved in development of the study protocol, data analysis or manuscript production.

SOURCES OF SUPPORT

Internal sources
- Royal Children's Hospital Foundation, Brisbane, Australia.

External sources
- National Health and Medical Research Council, Australia.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW
Differences between the protocol and the review are described throughout the text. We updated the risk of bias tool and other methods to bring the review in line with current recommendations provided in the Cochrane Handbook for Systematic Reviews of Interventions and added a summary of findings table. We removed many of the sensitivity analyses specified in methods used previously for this review.
INDEX TERMS

Medical Subject Headings (MeSH)
*Critical Pathways; Chronic Disease; Cough [*therapy]

MeSH check words
Child; Humans
Chapter 8: Discussion and Conclusion

8.1 Thesis overview

Bronchiolitis, although a typically self-limiting illness, causes significant morbidity and remains a leading cause of hospitalisation among infants globally.\(^{31}\) In some populations such as NT Indigenous infants, the incidence of bronchiolitis is higher and more severe.\(^{22}\) Respiratory readmissions within 6-months of discharge are frequent\(^{22,151}\) and secondary bacterial complications are postulated to be common. It is also known that recurrent respiratory tract infections increase the risk of bronchiectasis.\(^{163}\)

Current mainstay treatment for hospitalised bronchiolitis is supportive care. Antibiotics are not advocated in first line treatment of bronchiolitis due to its viral origins. They may be recommended when the illness is severe or when a secondary bacterial infection is suspected.\(^3\) However, the effectiveness of macrolides in bronchiolitis management was inconclusive\(^{128,131,148}\) prior to studies undertaken within this thesis. My overarching aim was therefore to improve the management of children (in particular Indigenous children) hospitalised with bronchiolitis.

This final chapter summarises the main study findings, relating to the treatment and management of children hospitalised with bronchiolitis, important limitations of the studies and suggestions for future research. The chapter ends with the final conclusion from this thesis.
8.2 Main study findings and its significance

Accurate and good clinical assessment is an important part the management of any condition including bronchiolitis. Despite the number of clinical assessment severity scoring systems used widely for RCTs on bronchiolitis, few studies had undertaken inter and intra-rater assessments within their studies. Indeed, it is often unappreciated that bronchiolitis scoring systems have limited validity when systematically validated.\textsuperscript{74,75} To address this, a study was conducted at RDH to validate a modified clinical severity scoring system\textsuperscript{91} to assess the severity of bronchiolitis (chapter 2). We found this system was reliable, repeatable and can be validly used with ease by nurses of varying levels of experience.\textsuperscript{150} Incorporating this scoring system in clinical practice will likely facilitate the improvement of clinical assessment and thus bronchiolitis management, particularly in settings where non-medical practitioners are the first point of acute care (i.e. remote settings).

Improving clinical outcomes of children (in particular Indigenous children) hospitalised with bronchiolitis in our setting is important. Two RCTs were undertaken among children hospitalised with bronchiolitis to assess use of azithromycin to improve clinical outcomes (chapters 3-4). The two RCTs were different in the duration (single dose and 3 once-weekly doses) of therapy and sampling frame. The first RCT included both Indigenous and non-Indigenous children and was a single large dose compared to placebo. It also provided pilot data for funding for the second RCT for only Indigenous children (NHMRC project grant 605809).

In both RCTs, the use of azithromycin did not improve short or long term clinical outcomes (length of hospitalisation, duration of oxygen supplementation) or
respiratory readmissions within 6-months of hospital discharge. Additionally, for the first time in our setting, the point prevalence of a broad panel viruses, atypical and bacteria in nasopharyngeal swabs were described and influence of azithromycin examined (chapters 3-4). While azithromycin did not significantly improve clinical outcomes or proportion of viruses and atypical bacteria, it significantly reduced the mean number of respiratory bacteria per swab (chapter 4). Despite reducing bacterial carriage in the nasopharynx, these RCTs (chapters 3-4) have conclusively shown that azithromycin should not be recommended to treat children hospitalised with bronchiolitis. It is anticipated that the data will be incorporated into evidence based guidelines.

In chapter 5, a novel method using mobile phones and a culturally sensitive approach to improve adherence and retention of participants outside of hospital and clinic structures was reported. This was used in the second RCT (Chapter 4) and resulted in high medication adherence (>93%) and retention of >97% participants until their clinical endpoint at day-21. This method has the potential to improve adherence to medications and appointments in primary health care settings. Our method was used in conjunction with our bronchiolitis pictorial educational flipchart which included education on how the respiratory system worked, disease processes, health promotion and improving lung health (see appendix-1).

The presence of persistent symptoms 3-weeks after hospital discharge was frequent, regardless of what treatment group children were assigned (chapter 4). This was the first multicentre trial to extend follow up beyond the immediate hospitalisation phase in Indigenous children with bronchiolitis. The analysis of risks associated with prolonged LOS and poorer outcomes beyond hospitalisation (chapter 6), included
children who had cough at 3-weeks, who were significantly (OR 3.0 95% CI 1.1-7.0, 
p=0.03) more likely to have a subsequent diagnosis of bronchiectasis compared to 
those without cough (see section 6.2). This data establishes the need to review 
children post-hospitalisation and if necessary treat ongoing symptoms. Intervention 
at this point potentially reduces the long term consequences and may improve 
respiratory outcomes for Indigenous children. As a result of these findings (chapter 
4) and research translation activities, policy, clinical systems and process change are 
currently taking place in the NT. It is now recommended that children discharged 
from the hospital are clinically reviewed in their usual health clinic 3 to 4 weeks after 
hospitalisation. Prior to this, children were not systematically reviewed.

Two Cochrane systematic reviews were also undertaken. Chapter 7a was a review that 
examined the efficacy of antibiotics for persistent symptoms beyond the acute 
bronchiolitis phase. Some children will have ongoing symptoms beyond 
hospitalisation,3,8 thus the importance of the symptoms beyond hospitalisation (i.e. 
post-bronchiolitis syndrome) of persistent symptoms is increasingly appreciated.3,8 in 
this Cochrane Review, only a single RCT was included. As the sole included study 
had very small numbers and a high attrition rate,128 there is currently insufficient 
evidence to inform whether antibiotics in the post-acute bronchiolitis phase are 
effective in the management of persistent respiratory symptoms.155

The second Cochrane Review examined the efficacy of using clinical pathways for the 
treatment of chronic cough (≥4 weeks) in children. Chronic cough in children is a 
substantial medical problem resulting in 1.38 million general practitioner visits per 
year in Australia,159 and often requires further investigation.165 These data are
particularly important for Indigenous children in our setting, who have persistent symptoms and poorer long-term respiratory outcomes.

8.3 Limitations of the thesis

The limitations for each study are stated within the published or submitted papers contained in the respective chapter. The below summarises these important limitations.

The severity scoring study (chapter 2) would have been strengthened if children in the emergency department (ED) were enrolled from the onset of the study. Due to logistical reasons, we were unable to access ED until the latter half of the recruitment period. Furthermore, enrolling children in the ED who were later discharged home would have increased the generalisability of the severity of cases. We attempted to do this, however all children were eventually admitted to the paediatric wards.

Several limitations were present in both RCTs (chapters 3-4). At the start of the first RCT (chapter 3), study participants were only recruited during the working week; thus we missed a large number of children admitted over the weekend. Enrolling only within normal working hours may limit the generalisability of our findings. Subsequently, employment of a research nurse to cover the weekends was a successful strategy.

Including older children ≤18-months (chapter 3) and ≤24-months (chapter 4) in both RCTs increased the risk of including those with asthma. However, as the majority (n=282, 90%) of participants were aged ≤12 months in both RCTs, the likelihood of this is small.
The concurrent use of antibiotics other than macrolides in both RCTs (chapters 3-4) is a substantial limiting factor. As we were unable to influence the treating medical team on this, our protocol allowed the use of non-macrolide antibiotics at the discretion of the treating paediatrician. Thus, it remains uncertain if macrolides without concurrent antibiotics improves clinical outcomes. Importantly, when concurrent antibiotics were taken into account in a multivariate model, no significant between-groups difference was found.

In all the studies included in this thesis, we did not restrict to first respiratory hospitalisation (chapters 2-6), which may have contributed to the number of respiratory readmissions. However, removing these children in subgroup analyses made no differences to the end points of these studies.

The chapter on the risks of prolonged hospital stay and readmissions (chapter 6) would have been strengthened had we had included data from the other sites. This however was not feasible as different factors and complexities at other sites would have reduced the quality of the data.

Both Cochrane Reviews (chapter 7a and 7b) were limited by the absence of available studies. Only a single study was included in each review, thus limiting the evidence to inform clinical practice. An update is required for the first Cochrane Review (chapter 7a).

In this thesis, even though both RCTs and the mobile phone strategy (chapters 2, 5 and 6) were multicentre, most children were enrolled from a single site in Darwin. Thus, generalisability of these results may be reduced. Nevertheless, the studies
provide a clinical picture relevant to other Indigenous populations at high risk of severe and prolonged hospitalisation for bronchiolitis.

None of the studies in this thesis included objective measurements, such as markers of inflammation or atopy.\textsuperscript{111} Parents/guardians were asked about atopy, yet this was poorly understood and answered. Also, as most children (90%) were <12-months of age, lung function was not performed. The lack of specialised respiratory facilities also meant this was not possible.

The use of CXRs was frequent among study children. Current guidelines do not recommend the use of CXR for bronchiolitis.\textsuperscript{3,5} There are also no accepted radiological signs to confirm bronchiolitis as CXR features of bronchiolitis and bronchopneumonia overlap.

8.4 Future research

While studies within this thesis have addressed the clinical gaps described in chapter 1, many questions remain. Some of these are briefly mentioned below.

8.4.1 Improving the management of children hospitalised with bronchiolitis

Data from this thesis (chapter 3-4, and 6) have shown that Indigenous children have more severe hospitalised bronchiolitis and are at high risk for ongoing respiratory morbidity beyond hospitalisation. As outlined in recent bronchiolitis guidelines,\textsuperscript{5} improved assessment of risk factors and impact on clinical scores to determine disease severity during hospitalisation is needed.\textsuperscript{5} A possible future study would be the integration of a clinical pathway algorithm that focuses on improving assessment of risk factors at admission and subsequent management of the bronchiolitis episode (i.e. using the severity scoring system discussed in chapter 2).
8.4.2 What are the long term consequences of children hospitalised with bronchiolitis

As discussed in this thesis (chapter 4 and 6), presence of persistent symptoms beyond hospitalisation increased the risk for ongoing morbidity, respiratory readmission and subsequent diagnosis of bronchiectasis. Determining the long term clinical outcomes for Indigenous children who experience acute respiratory infections is of great importance. Presently, long term studies in children with bronchiolitis are focused on the development of asthma, rather than suppurative lung disease. Similarly, there are no long term data relating to bronchiolitis among Indigenous children. To address this clinical gap, a long term follow-up study of children previously enrolled in the RCTs (chapter 3 to 4) and a comparable (not hospitalised aged-matched children from the same community) should be undertaken.

The specific research objectives in this study should evaluate long term outcomes of Indigenous children previously hospitalised or treated in the community for bronchiolitis so as to:

(a) determine the risk factors (demographic, medical and microbiological) for the development of bronchiectasis; and

(b) identify possible intervention points that may prevent future lung disease.

8.4.3 Improving the management of bronchiolitis in primary health care settings

Improving clinical management pathways for Indigenous children with bronchiolitis in primary health care settings is important, in particular where acute clinical care is predominantly done by non-medical practitioners (i.e. nurses, Indigenous Health Workers). In line with 8.4.1, improved assessment and management of children in...
primary health care settings is needed for Indigenous children. A possible study could involve integrating a clinical pathway in remote health settings, for children diagnosed with a respiratory illness so as to:

(a) determine the acceptability of severity scoring systems in routine practice to improve clinical assessment and management of children with acute bronchiolitis (discussed in section 2.2).

(b) determine if the implementation of a culturally appropriate framework (discussed in section 5.2) for children with ALRI improves health outcomes (i.e. adherence to medication and appointments).

(c) determine the acceptability of a clinical pathway for chronic cough and interventional points that may prevent ongoing respiratory morbidity (discussed in section 7.3).

8.4.4 Indigenous children worldwide have poorer lung health.

As discussed in section 1.3.2, the incidence and severity of hospitalised bronchiolitis among Indigenous children in developed countries (e.g. USA (Alaska), Canada, New Zealand and Australia), remains disproportionately higher than non-Indigenous children. The studies in this thesis were limited to Northern Australia and to a lesser extent, Auckland. They have highlighted the importance of larger international studies for bronchiolitis, similar to those undertaken for bronchiectasis. These studies compared and contrasted Indigenous children at risk for bronchiectasis, to identify common interventional points to improve future lung health.
8.4.5 Is there a subset of children who benefit from adjunctive macrolide use?

As discussed in 1.6.3, macrolides were suggested as an attractive treatment for children hospitalised with bronchiolitis to reduce airway inflammation and chronic infections, thus improving clinical outcomes. Yet, despite azithromycin not improving clinical outcomes for either RCT (chapters 3-4), the differences in length of LOS and O2 requirement shown in figures (3 and 4 in journal article 3.2) and figures (2a and 2b in section 4.2), is substantial. Thus, it is possible, (but remains unknown) if a subset of children will benefit from adjunctive macrolide use and whether these children can be identified.

8.5 Final conclusions

In this chapter, the overall findings from this thesis are presented, conclusions drawn and possible future work outlined. Overall, work from this thesis has had translational research impacts.

Firstly, the bronchiolitis severity scoring system validated was reliable, repeatable and can be used by nurses of varying levels of experience. This system can potentially be incorporated into clinical systems. Secondly, a novel method of recruiting and successful retention (>97%) of Indigenous children in a study was described. This method can be used for future research and clinical studies. Thirdly, findings from the RCTs have conclusively shown that despite reducing bacterial carriage, azithromycin does not improve short or long term clinical outcomes. Thus, azithromycin should not be used routinely to treat infants hospitalised with bronchiolitis. The reduction in use of azithromycin would also improve anti-microbial stewardship, reduce potential adverse events, and reduce cost. It is expected this data will be incorporated in future guidelines on the management of bronchiolitis.
Fourthly, combining children from the studies above, risks of prolonged hospitalisation were examined. Severity score on admission, particularly accessory muscle use, was the sole factor significantly associated with prolonged LOS. Further, persistent symptoms at 3-weeks beyond hospitalisation were common and associated with an increased risk of respiratory morbidity and future diagnosis of bronchiectasis. As a result of these findings and research translation activities, clinical systems and process changes are currently taking place in the NT post-discharge.

Finally, two Cochrane Reviews that inform clinical management of post-bronchiolitis syndrome and chronic cough were presented. The data from the chronic cough review can be translated in the management of children who are reviewed post-bronchiolitis.

The long term consequence of respiratory disease among Indigenous children is an important public health issue. The significance of identifying target points is needed to optimise clinical care to improve future lung health and prevent subsequent development of bronchiectasis among Indigenous children.
Bibliography


51. Turner TL, Kopp BT, Paul G, Landgrave LC, Hayes D, Jr., Thompson R.  


evidence-based clinical practice guidelines. Chest. 2006;129(1 Suppl):1S-23S.


Appendix 1 – Bronchiolitis flipchart
Bronchiolitis
(Lower respiratory tract infection)
The lungs
You have two lungs.
They sit inside your chest, above your stomach and surround your heart.
The lungs have a very important job inside your body.
The lungs

- When we breathe in air it enters our body as oxygen.
- The air enters in through our mouth/nose and travels down our main windpipe (trachea).
- The wind pipe then divides into two smaller air tubes.
- One air tube goes into the left lung and one into the right lung (left and right bronchus).
- The air tubes then branch out into smaller air tubes (bronchioles).
The lungs

- The smaller air tubes (bronchioles) look like the branches of an upside down tree. At the end of the bronchioles are tiny little air sacs that look like tiny bunches of grapes, these are called alveoli.

- The air sacs (alveoli) have an important job of giving the good air (oxygen) to our blood and taking the used air (carbon dioxide) out.
- We breathe in good air called **oxygen** and we breathe out used air called **carbon dioxide**.

- The good air (**oxygen**) we breathe goes into our lungs then goes into our blood. **Oxygen** gives our body energy to work properly.
What is bronchiolitis?

- Inflammation of the small breathing tubes (bronchioles) in the lung.
- It is the most common lower respiratory tract infection in young children.
- Bronchiolitis can happen all year round.
What causes bronchiolitis?

- Bronchiolitis is usually caused by a virus called RSV (respiratory syncytial virus). But other viruses can cause bronchiolitis.
- This virus can be spread to other people by coughing, sneezing and touching surfaces that have the germs on it.
Signs and symptoms

- Runny nose.
- Cough.
- Temperature.
As children get worse they may show other signs:

- Fast and noisy sounds when they breathe.
- Their chest sucks in when they breathe.
- They find it hard to feed.
- They are restless - not sleeping well.
Some things we do for bronchiolitis

- Sometimes chest x-ray.
- A nose swab.
- Listen to your baby’s chest with a stethoscope.
Some babies need to come into hospital.
Some of the treatment for these babies are:

- Oxygen
- Close observation
- Lots of rest
- IV fluids or naso gastric feeds if baby is unable to feed
- Suction to keep the nose clear
- Sometimes antibiotic medicine and puffers
How long will my baby be sick?

- Some babies start to get better within 3-4 days.
- Some babies need to come into hospital and receive oxygen for a few days.
- Sometimes babies get worse and their chest infection may need antibiotics and their stay in hospital is longer.
- Most babies have a full recovery from bronchiolitis.
- Some babies will have wheeze attacks again.
What should I do if my child does not get better?

If your baby has any of the below problems, you need to visit your doctor or clinic:

- Has a cough for a long time, and it will not go away.
- Get short wind when they play.
- Always tired.
- Not eating and drinking well.
Ways to help improve your child’s lungs

- Breastfeeding to help make your baby strong.
- Keep immunisations up-to-date.
- Eating plenty of good tucker will help your child to grow.
Things to remember

- Nose blowing and coughing can help get rid of spit. Use tissue or toilet paper to stop germs from spreading.

- Keeping hands, face and skin clean will help stop germs from spreading.

- Avoid smoking around children, especially in cars and inside the house.

- Keep children away from open fire/smoke.
Why are healthy lungs important?

- The lungs in children are still growing, so we have to look after them.
- Lung sickness is one of the most common reasons why Aboriginal and Torres Strait Islander people need to go to hospital.
- Having strong lungs helps children to grow, live longer, play and learn.
Acknowledgments

The Bronchiolitis flipchart was developed in consultation with Menzies School of Health Research, The Australian Lung Foundation, Asthma Foundation Northern Territory and the Menzies School of Health Research Indigenous Reference Group.

To order more resources or to provide feedback please email: lunginfonet@menzies.edu.au or phone (08) 89228196.