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Published in:
Chest

DOI:
10.1016/j.chest.2016.06.030

Published: 01/11/2016

Document Version
Peer reviewed version

Link to publication

Citation for published version (APA):

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Protracted Bacterial Bronchitis in Children: Natural History and Risk Factors for Bronchiectasis

Short title: Risk factors for bronchiectasis in children with PBB

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Potential conflicts of interest: The authors declare no conflicts of interest in relation to this manuscript.

Funding Sources: This work was supported by the National Health and Medical Research Council (NHMRC) [project grant 1042601 and Centre of Research Excellence grant 1040830] and the Financial Markets Foundation for Children [project grant 2010-005]. DW was supported by scholarships from the Thoracic Society of Australia and New Zealand/Allen and Hanbury’s, Queensland Children’s Medical Research Institute and NHMRC [1039688]. AC and HSV are supported by NHMRC fellowships [1058213 and 1024175]. The views expressed in this publication are those of the authors and do not reflect the views of the NHMRC. The funders played no role in the conduct of the study or preparation of the manuscript.


Abbreviations: BAL = bronchoalveolar lavage; CT = Computed tomography; HRCT = High-resolution computed tomography; NTHi = non-typeable H. influenzae; PBB = protracted bacterial bronchitis.

Key words: Bacterial infection, bronchiectasis, paediatric lung disease, respiratory infection, viral infection
ABSTRACT

**Background:** Protracted bacterial bronchitis (PBB) and bronchiectasis are distinct diagnostic entities that share common clinical and laboratory features. It is postulated, but remains unproven, that PBB precedes a diagnosis of bronchiectasis in a subgroup of children. In a cohort of children with PBB, our objectives were to: (a) determine the medium-term risk of bronchiectasis and (b) identify risk factors for bronchiectasis and recurrent episodes of PBB.

**Methods:** 161 children with PBB and 25 controls were prospectively recruited to this cohort study. A subset of 106 children was followed for 2 years. Flexible bronchoscopy, BAL and basic immune function tests were performed. CT chest was undertaken if clinical features were suggestive of bronchiectasis.

**Results:** Of 161 children with PBB (66% male), 13 (8.1%) were diagnosed with bronchiectasis over the study period. Almost half (43.5%) with PBB had recurrent episodes (>3/year). Major risk factors for bronchiectasis included: *H. influenzae* lower airway infection (in BAL) (p=0.013) and recurrent episodes of PBB (p=0.003). *H. influenzae* infection conferred >7 times higher risk of bronchiectasis [HR 7.55 (95%CI 1.66 - 34.28), p= 0.009] compared to absence of *H. influenzae*. The majority of isolates (82%) were nontypeable *H. influenzae*. No risk factors for recurrent PBB were identified.

**Conclusions:** PBB is associated with a future diagnosis of bronchiectasis in a subgroup of children. *H. influenzae* lower airway infection and recurrent PBB are significant predictors. Clinicians should be cognisant of the relationship between PBB and bronchiectasis and appropriate follow-up measures should be taken in those with risk factors.
INTRODUCTION

Protracted bacterial bronchitis (PBB), first described in 2006, is a major cause of chronic cough in children.\textsuperscript{1,2} PBB has been studied by research groups in Australia,\textsuperscript{1-3} Europe\textsuperscript{4} and the US with similar findings.\textsuperscript{5,6} PBB is characterised by persistent wet cough, response to 2-weeks of appropriate antibiotic therapy and absence of indicators to suggest an alternative cause for cough.\textsuperscript{1,7} PBB is more common in young boys and children who have attended childcare.\textsuperscript{8} When compared to controls, children with PBB are more likely to have lower airway infection with common respiratory bacteria and viruses.\textsuperscript{8}

Currently, there are limited published data,\textsuperscript{9} and no prospective follow-up studies, evaluating the outcomes of children with PBB. This research gap limits the clinician’s ability to prognosticate on the likely natural history of PBB in any given child. Anecdotally, many otherwise healthy children experience recurrent episodes of PBB without appreciable longer-term consequences. However, in a subgroup of children, recurrent PBB appears to be associated with a future diagnosis of bronchiectasis.

PBB and bronchiectasis share many common features, spanning from respiratory symptoms (i.e. chronic wet cough) to intense neutrophilic lower airway inflammation and innate immune system activation.\textsuperscript{10-12} Lower airway microbiota,\textsuperscript{13} including presence of adenovirus type C\textsuperscript{14} and predominance of non-typeable \textit{Haemophilus influenzae} (NTHi)\textsuperscript{1,8} are also alike. These similarities underpin the notion that PBB and bronchiectasis represent a clinical continuum.\textsuperscript{15,16}

To date, the accuracy of this proposed continuum is uncertain and warrants evaluation in a prospective cohort study.
Hence, in 161 children with PBB and 25 controls, we aimed to determine: (a) the 2-year outcomes of children with PBB with respect to a diagnosis of bronchiectasis and; (b) risk factors for bronchiectasis and for recurrent episodes of PBB.

MATERIALS AND METHODS

Study participants

Participants were enrolled as part of a larger prospective cohort study aimed at evaluating the long-term outcome of children with chronic cough. Written informed consent was obtained from all parents/guardians and ethics approval granted by The Queensland Children’s Health Services (RCH) Human Research Ethics Committee (HREC/03/QRCH/17).

Between March 2008 and October 2012, 343 children were enrolled. Of these, 161 fulfilled criteria for PBB and 25 were recruited as control participants (15 undergoing evaluation for respiratory symptoms other than chronic cough, and 10 healthy controls). Data from the 15 children undergoing respiratory evaluation have previously been described\(^8\) (e-supplement 1). The 10 healthy controls were recruited from colleagues and friends.

All children (excluding the 10 healthy controls) underwent flexible bronchoscopy and broncho-alveolar lavage (BAL) as per clinical indication, and were recruited prior to their bronchoscopy. BALs were processed for cellularity and microbiology. Bacterial infection was defined as bacterial load of \( \geq 10^4 \) colony-forming units (cfu)/ml BAL.\(^8,11\) Laboratory tests for suppurative lung diseases were performed, as described previously.\(^14\) \textit{Haemophilus influenzae} characterisation was undertaken at a research laboratory (Menzies School of Child Health Research, Darwin) when BAL was available (e-supplement 2).
Follow-up

Follow-up included monthly contact (phone-calls or emails by research nurses) to capture respiratory exacerbations. Parents completed cough diaries during periods of illness. Antibiotic therapy was usually prescribed by their family doctor when appropriate, as per usual clinical management. The majority of children were seen by their pediatric pulmonologist 3-4 monthly as part of routine clinical follow-up. At 2-years a subset (n=106) also underwent clinical assessment for bronchiectasis (DW and/or AC).

Given the ethical considerations pertaining to research-related CT chest in children,\textsuperscript{17,18} CT scans were only performed when clinical features of bronchiectasis were present.\textsuperscript{19} Clinicians had similar practices whereby CT chest was undertaken for: (a) chronic wet cough non-responsive to 4 weeks of antibiotic therapy;\textsuperscript{20} (b) persistent chest radiographic changes despite appropriate antibiotic therapy or (c) recurrent hospitalisations for acute respiratory events.

Definitions

PBB was defined as: (i) history of chronic (≥ 4 weeks) wet cough, (ii) prospective evidence (supported by cough diaries) of response to 2 weeks of treatment with amoxicillin-clavulanate and (iii) absence of clinical pointers suggesting an alternative cause for cough.\textsuperscript{1} Bronchiectasis diagnosis was based on pediatric radiological (CT) criteria,\textsuperscript{21} in the context of a child having clinical symptoms of bronchiectasis. Two respiratory physicians, blinded to each other’s assessment, reviewed all CT images. Recurrent PBB was defined as >3 episodes of PBB in the first year after enrolment.
Statistical analyses

Descriptive statistics were utilized to summarize demographic and clinical characteristics. Median and inter-quartile ranges were reported as data were non-normally distributed. Pearson’s chi-square (or Fisher’s exact test) was used for categorical and Mann-Whitney U for continuous variables. Logistic regression was employed to calculate odds ratios (OR) and 95% confidence intervals (95%CI). A survival analysis (using Cox’s proportional hazards regression) examined the relationship between time to diagnosis of, and risk factors for, bronchiectasis. A 2-tailed p-value of <0.05 was considered statistically significant. Statistical analyses were performed using SPSS (version 21.0, Armonk, NY: IBM Corp., USA) and STATA (version 12.1, StataCorp, Texas, USA).

RESULTS

Clinical and demographic characteristics of participants

Of the 161 children with PBB, 106 completed the 2-year follow-up period and had clinician assessment for bronchiectasis (Figure 1). The median duration of follow-up was 25 months (IQR 24, 28) in children with PBB and 27 months (IQR 26, 29) in controls undergoing bronchoscopy.

There was no difference between children who completed the 2-year follow-up and those who did not (Table 1), with regards to: length of cough at recruitment (p=0.807), H. influenzae status (p=0.518) or proportion with 2+ siblings (p=0.260). However, those completing the 2-year follow-up (n=106) were significantly more likely to have had recurrent PBB (p=0.003). Thus, to reduce the potential for bias, 161 was used as the denominator in subsequent analyses. The 55 additional children who did not complete 2-year follow-up were assumed to be bronchiectasis-free at the 2-year time-point. We assumed this as, when these families were contacted by phone,
the vast majority of children had had resolution of their chronic cough. Comparison of groups at baseline showed that children with PBB had a higher burden of doctor visits in the preceding 12 months, as compared to controls (Table 1).

At 2-year follow-up, compared to controls, children with PBB were more likely to be coughing (44% vs 12%, p=0.005) and to be receiving antibiotic therapy (20% vs 0, p=0.012). The burden of doctor visits (in previous 5 years) was higher in the children with PBB compared to controls (44% vs 5%, p=0.001) and those with PBB were more likely to have had parent-reported wheeze in the preceding 12 months (58% vs 16%, p=0.001). Of the 161 children with PBB, 154 had completed cough diaries until at least the 1-year time-point. Of these, 67 (43.5%) had recurrent PBB (>3 episodes/year).

**Bronchiectasis diagnoses on chest CT scan**

Multi-detector CT with HRCT reconstruction was performed in 25 of 161 children with PBB. Radiological evidence of bronchiectasis was present in 13 (8.1%) and all had mild (i.e. cylindrical bronchiectasis). CT was performed at median duration of 9 months (IQR 4, 19) post recruitment. Their median age was 38 months (IQR 27, 58).

Compared to those that did not undergo CT, children with PBB who underwent CT chest, had similar rates of lower airway infection with *H. influenzae* (p=0.142) and *S. pneumoniae* (p=0.135), however, those undergoing CT scan were less likely to have *M. catarrhalis* infection, than those that did not undergo CT (34.2% vs 17%, p=0.029) (likely to have been a chance occurrence.) Similar rates of ‘recurrent PBB’ status were recorded in those undergoing CT and those that did not (p=0.118).
No children in the control group developed clinical features of bronchiectasis. Of the control children, 3 had CT scan performed for other indications. None had bronchiectasis.

**Risk factors for bronchiectasis and recurrent PBB**

Univariate analysis showed that bronchiectasis was significantly more likely to be diagnosed during follow-up when the child had recurrent PBB, when *H. influenzae* infection was present (i.e. cultured at a clinically significant level of $\geq 10^4$ cfu/ml in BAL) or in children with two or more siblings (Table 2). There were no significant inter-group differences for other factors.

Multivariate logistic regression showed that recurrent PBB status and *H. influenzae* infection were significantly associated with bronchiectasis diagnosis [OR 11.48 (95%CI 2.33-56.50) p=0.003 and OR 7.60 (95%CI 1.53-37.79), p=0.013, respectively], whereas having $\geq 2$ siblings was no longer significant [OR 3.53 (0.98, 12.70), p=0.054]. Survival analysis, using Cox regression, concurred with logistic regression findings. Participants with *H. influenzae* lower airway infection were > 7 times more likely to be diagnosed with bronchiectasis per month of follow-up, compared to those without *H. influenzae*, and recurrent PBB status conferred > 9 times greater risk of bronchiectasis diagnosis per month (Table 3).

The percentage of lower airway neutrophils was similar in children with and without a subsequent diagnosis of bronchiectasis [BAL neutr% 35 (12, 75) vs 25 (10,55), p=0.35] in the BE present and absent groups respectively. Total cell counts, percentage macrophages and percentage lymphocytes were similar between groups. Although the percentage of eosinophils in BAL was slightly higher in those who developed bronchiectasis [BAL eosin% 1 (0, 2) vs 0 (0,0),
p=0.001], the median eosinophil count was within the normal range (i.e. <2.5%), and hence this finding was considered to be clinically insignificant. Further, the difference was no longer observed when the major outlier was removed.

In the examination of predictors for recurrent PBB, univariate and multivariate analysis showed no significant difference between children with and without recurrent PBB for the factors examined (sex, age, prior pneumonia, tobacco smoke exposure, maternal tobacco smoking in pregnancy, Indigenous status, number of children in household, childcare attendance and BAL cellularity and microbiology) (e-Table 1). Notably, *H. influenzae* infection in BAL did not predict recurrent PBB.

**H. influenzae typing**

Thirty-four of 55 (62%) *H. influenzae* positive samples were available for further characterization. Of these, *H. influenzae* from the majority of samples (n=28; 82%) were identified as NTHi; encapsulated *H. influenzae* were not identified. *H. influenzae* from the remaining 6 samples were reassigned as *H. haemolyticus* following species-specific PCR.

**DISCUSSION**

This is the first prospective longitudinal cohort study of children with PBB. In our cohort, based in a large tertiary paediatric hospital, almost 44% had recurrent episodes (>3 episodes in the first year after recruitment) and approximately 1 in 12 were diagnosed with bronchiectasis at 2-years. We identified 2 significant risk factors for bronchiectasis: recurrent (>3 /year) episodes of PBB and presence of *H. influenzae* infection of the lower airways. Further, *H. influenzae* infection, compared to no infection, conferred >7 times higher risk of bronchiectasis diagnosis.
Findings from this study, the first to investigate the 2-year outcomes of children with PBB, support the hypothesis that PBB and bronchiectasis represent a clinical spectrum. Children with PBB have endobronchial bacterial infection and neutrophilic airway inflammation, factors known to be injurious to the airways. Our findings suggest that, in a subset of children, receiving close follow-up by pediatric pulmonologists, recurrent episodes (>3 per year) of PBB precede a diagnosis of bronchiectasis. Further, although a cause-effect relationship cannot be concluded, an association between *H. influenzae* infection and bronchiectasis has been shown. This finding is in accordance with the increasing recognition of the role of *H. influenzae* in the pathogenesis of chronic respiratory diseases.

*H. influenzae* is the most common bacterial species infecting the lower airways of children with endobronchial suppuration, including PBB, recurrent or non-responsive community-acquired pneumonia and bronchiectasis. *H. influenzae* is also the major bacterial pathogen associated with chronic respiratory disorders in adults e.g. bronchiectasis and COPD. Although *H. influenzae* infection may be an important risk factor for bronchiectasis, there are likely to be other contributory factors.

Our earlier studies identified children with PBB to be significantly more likely than controls, to have attended childcare, and to have viral infection of their lower airways, particularly with adenovirus type C. It is plausible, although beyond the scope of this study, that co-infection with specific pathogens e.g. adenovirus C and *H. influenzae*, initiates the vicious cycle of lower airway infection and inflammation inherent to these conditions. Factors such as young age at
initial infection (and concomitant immune and respiratory system immaturity), may also play a key role in aetio-pathogenesis.  

In this study, bronchiectasis was diagnosed at an early age (median 38 months), similar to our other cohorts of children with bronchiectasis. Together with findings from earlier studies on PBB, this observation lends further support to the assertion that timing of airway infection (with bacteria and/or viruses), with respect to age, is likely to be important. All children had mild or early cylindrical bronchiectasis where it is potentially reversible if treated early and intensively, prior to development of severe (saccular or cystic) bronchiectasis.

In support of previous studies on PBB, the present study showed that PBB is characterised by active lower airway neutrophilic inflammation. Although the median neutrophil percentage in BAL was greater in children with PBB who were subsequently diagnosed with bronchiectasis, compared to those who were not (median 35 vs 25, respectively), this difference was not significant. This suggested that the degree of airway neutrophilia did not predict bronchiectasis. Regarding the inter-group disparity in airway eosinophil levels between those with and without bronchiectasis, this is unlikely to be of clinical relevance for two reasons. First, eosinophil levels in both groups were within normal reported ranges, and second, when the major outlier was removed (16% eosinophils in a child with features consistent with persistent asthma in addition to PBB), the difference was no longer significant.

Several limitations to this study merit discussion. The most significant limitation is the fact that we did not perform CT scans on all children at study entry and exit. Given the potential increased lifetime risk of cancer associated with exposure to CT scans (and the relatively common nature of
PBB in otherwise well children\textsuperscript{39} we could not justify performing 2 CT scans on every child.\textsuperscript{18}

The impact of this limitation is two-fold. First, bronchiectasis may have been missed in some children at recruitment and indeed at follow-up. Hence, we cannot conclude that PBB progresses to bronchiectasis per se. Rather, our findings indicate that, in children with PBB (who are followed closely by pulmonologists) a proportion (approximately 8%) will be diagnosed with bronchiectasis on CT chest at 2 years. Second, we acknowledge the fact that performing CT scan only in a select subgroup introduces the possibility of selection bias in that individual clinicians may have different indications for performing CT chest. To address this, we compared children with PBB undergoing CT chest to those who did not and found no significant differences between groups with respect to bronchiectasis risk factors.

To definitively address our major research question, an ideal study design would include a large cohort of healthy (cough-free) children. CT scan, to investigate for bronchiectasis, would need to be performed both at study entry and exit. Multiple lower airway samples, collected over time, in addition to clinical data on cough and episodes of PBB, would need to be obtained. This would elucidate the temporal sequence of lower airway infection, symptom onset and bronchiectasis. Additionally, study numbers would need to be very large. For example, to detect one child who develops bronchiectasis in New Zealand (where prevalence is estimated at 33 per 100,000 children aged 0-14 years)\textsuperscript{40} several thousand children would need to be enrolled. The ethical issues pertaining to performing CT chest and BAL are indeed significant. Thus, from a practical and ethical standpoint, it would be extremely difficult to justify a study with the ideal design.

The major strengths of this study are the longitudinal nature of data collection and the inclusion of lower airway inflammatory and microbiological findings. However, as we only performed
bronchoscopy and BAL at a single time-point, the temporal relationship between infection with *H. influenzae* and development of bronchiectasis remains unclear. This does not, however, diminish the utility nor relevance of our findings. Irrespective of whether *H. influenzae* is a cause (or consequence) of bronchiectasis in young children, its presence in a child with recurrent PBB should alert the pulmonologist to the increased possibility of bronchiectasis, suggesting the need for closer monitoring and/or further investigation. This is a novel finding with direct clinical relevance to those managing children with chronic cough.

Findings from this longitudinal cohort study provide further evidence to support a link between PBB and bronchiectasis in young children. We have shown that approximately 1 in 12 children with PBB are diagnosed with bronchiectasis at 2-year follow-up with many experiencing recurrent episodes of PBB. We have identified potential risk factors for bronchiectasis i.e. *H. influenzae* lower airway infection and recurrent episodes of PBB.

Clinicians should be cognisant of the need to monitor children with PBB over time and to consider CT chest in those with risk factors for bronchiectasis. Further longitudinal studies, examining the outcomes of children with PBB, ideally using novel (low-radiation dose) imaging techniques are needed. Lastly, further research into the potential role of *H. influenzae* in the pathogenesis of bronchiectasis in children is needed to inform future preventative and therapeutic interventions.
ACKNOWLEDGMENTS

We wish to thank the families that participated in this study. We also thank the Cough and Asthma Airways Research Group (CAARG) research team at the Department of Respiratory and Sleep medicine, Lady Cilento Children’s Hospital (formerly The Royal Children’s Hospital), Brisbane for their invaluable contribution including Sophie Anderson-James BN (data collection, patient recruitment, study coordination), Carol Willis (data entry), Sandra Goodwin (data entry), Joanne Tuppin BN (data collection and patient recruitment) and Samantha Gardiner BN (data collection and patient recruitment). We also thank Jemima Beissbarth BSc (Menzies School of Health Research, Charles Darwin University, Darwin, Australia) for her laboratory work in processing samples for NTHi data.

Author contributions: Dr Wurzel co-conceptualised the study, is responsible for the content of the manuscript including data analysis and manuscript preparation, and was involved in data collection. Dr Marchant co-conceptualised the study and contributed to data interpretation and manuscript preparation. Dr Yerkovich co-conceptualised the study and contributed to aspects of data analyses and provided critical review of the manuscript. Dr Upham co-conceptualised the study and provided critical review of the manuscript. Dr Petsky contributed to data acquisition and study coordination and provided critical review of the manuscript. A/Prof Smith-Vaughan was responsible for characterisation of H. influenzae isolates and provided critical review of the manuscript. Drs Masters and Buntain contributed to acquisition of the data and critical review of the manuscript. Prof Chang conceptualised the study and contributed to all aspects, including: hypothesis delineation, study design, data acquisition, interpretation of results and manuscript preparation.
COMPETING INTERESTS

None

FINANCIAL DISCLOSURES

This work was supported by the National Health and Medical Research Council (NHMRC) [project grant 1042601 and Centre of Research Excellence grant 1040830] and the Financial Markets Foundation for Children [project grant 2010-005]. DW is supported by scholarships from the Thoracic Society of Australia and New Zealand/Allen and Hanbury’s, Queensland Children’s Medical Research Institute and NHMRC [1039688]. AC and HSV are supported by NHMRC practitioner fellowships [1058213 and 1024175]. The views expressed in this publication are those of the authors and do not reflect the views of the NHMRC.
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### TABLES

#### Table 1: Baseline demographic and clinical characteristics of study participants

<table>
<thead>
<tr>
<th></th>
<th>PBB followed-up (N=106)</th>
<th>PBB total (N=161)</th>
<th>Controls (N=25)</th>
<th>P-value$^1$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, M:F</td>
<td>74:32</td>
<td>106:55</td>
<td>12:13</td>
<td>0.085</td>
</tr>
<tr>
<td>Age - Mo</td>
<td>23 (14, 53)</td>
<td>22 (13, 50)</td>
<td>44 (7, 97)</td>
<td>0.061</td>
</tr>
<tr>
<td>Prior pneumonia – X-ray confirmed$^2$</td>
<td>24 (23%)</td>
<td>35 (22%)</td>
<td>2 (8%)</td>
<td>0.109</td>
</tr>
<tr>
<td>Household tobacco smoke exposure</td>
<td>36 (34%)</td>
<td>55 (34%)</td>
<td>6 (24%)</td>
<td>0.662</td>
</tr>
<tr>
<td>Aboriginal or Torres Strait Islander</td>
<td>3 (3%)</td>
<td>10 (6%)</td>
<td>0</td>
<td>0.363</td>
</tr>
<tr>
<td>Current cough</td>
<td>89 (84%)</td>
<td>134 (83%)</td>
<td>2 (8%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Length of current cough – wks, median (IQR)</td>
<td>26 (7, 52)</td>
<td>26 (6, 52)</td>
<td>0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Current antibiotics</td>
<td>16 (15%)</td>
<td>19 (12%)</td>
<td>1/15 (7%)</td>
<td>0.695</td>
</tr>
<tr>
<td>&gt;5 doctor visits past yr for cough</td>
<td>95 (90%)</td>
<td>140 (87%)</td>
<td>3/15 (20%)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Abbreviations: PBB followed-up = Subset of patients with PBB who completed 2-year follow-up;

PBB total = all patients with PBB irrespective of whether 2-year follow-up was completed.

$^1$ Comparison of ‘PBB total’ to controls; $^2$ Parent-reported
Table 2: Uni- and multi-variate analysis of risk factors for bronchiectasis (BE) in children with PBB

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Group 1 BE present (N=13)</th>
<th>Group 2 BE absent (N=148)</th>
<th>Odds ratio (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Univariate analysis</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex, M:F</td>
<td>8:5</td>
<td>98:50</td>
<td>0.816 (0.25, 2.63)</td>
<td>0.733</td>
</tr>
<tr>
<td>Recruitment age – mths, median (IQR)</td>
<td>29 (10, 45)</td>
<td>22 (13, 50)</td>
<td>0.99 (0.97, 1.01)</td>
<td>0.521</td>
</tr>
<tr>
<td>Prior pneumonia</td>
<td>3 (23%)</td>
<td>32 (22%)</td>
<td>1.09 (0.28, 4.19)</td>
<td>0.903</td>
</tr>
<tr>
<td>Recurrent PBB (&gt;3 ep/year)¹</td>
<td>11 (85%)</td>
<td>56 (38%)</td>
<td>9.04 (1.93, 42.27)</td>
<td>0.005</td>
</tr>
<tr>
<td>Household tobacco smoke exposure</td>
<td>3 (23%)</td>
<td>52 (35%)</td>
<td>0.55 (0.14, 2.08)</td>
<td>0.377</td>
</tr>
<tr>
<td>Maternal smoking in pregnancy</td>
<td>3 (23%)</td>
<td>18/85 (21%)</td>
<td>1.40 (0.34, 5.81)</td>
<td>0.647</td>
</tr>
<tr>
<td>Aboriginal or Torres Strait Islander</td>
<td>1 (8%)</td>
<td>9 (6%)</td>
<td>1.29 (0.15, 11.03)</td>
<td>0.818</td>
</tr>
<tr>
<td>No. children in household, median (IQR)</td>
<td>3 (2, 4)</td>
<td>2 (2, 3)</td>
<td>1.28 (0.91, 1.80)</td>
<td>0.156</td>
</tr>
<tr>
<td>≥2 siblings</td>
<td>8 (62%)</td>
<td>47 (32%)</td>
<td>3.44 (1.07, 11.08)</td>
<td>0.039</td>
</tr>
<tr>
<td>≥1 sibling</td>
<td>13 (100%)</td>
<td>123 (83%)</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Childcare attendance, ever</td>
<td>8/9 (89%)</td>
<td>71/82 (87%)</td>
<td>1.24 (0.14, 10.90)</td>
<td>0.847</td>
</tr>
<tr>
<td>BAL organism</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adenovirus positive (on PCR)²</td>
<td>3/12 (25%)</td>
<td>26/138 (19%)</td>
<td>1.44 (0.36, 5.68)</td>
<td>0.606</td>
</tr>
<tr>
<td>H. influenzae</td>
<td>11 (85%)</td>
<td>72 (49%)</td>
<td>5.81 (1.24, 27.10)</td>
<td>0.025</td>
</tr>
<tr>
<td>M. catarrhalis</td>
<td>4 (31%)</td>
<td>43 (29%)</td>
<td>1.09 (0.32, 3.71)</td>
<td>0.896</td>
</tr>
<tr>
<td>S. pneumoniae</td>
<td>3 (23%)</td>
<td>41 (28%)</td>
<td>0.78 (0.21, 2.99)</td>
<td>0.720</td>
</tr>
</tbody>
</table>
S. aureus | 1 (8%) | 12 (8%) | 0.94 (0.11, 7.90) | 0.958

Multivariate analysis

H. influenzae | 7.60 (1.53, 37.79) | **0.013**
≥2 siblings | 3.53 (0.98, 12.70) | 0.054
Recurrent PBB (>3 ep/year) | 11.48 (2.33, 56.50) | **0.003**

1 As determined at 1-year time-point in study. 7 children had not reached the 1-year time-point, for the purposes of the multi-variate analysis these children were assumed to have non-recurrent PBB.

2 As compared to previously published rate of 4% (adenovirus positivity) in BAL samples of control children. 

3 Beta-lactamase positive strains of H.influenzae were found in 17 of 83 (20.5%) of all isolates. Of these, 3 occurred in children from group 1 (27%) and 14 from group 2 (19%). Odds ratio=2.87, 95%CI 0.70, 11.67; p for difference between groups 0.143.
Table 3: Survival analysis – PBB to bronchiectasis (Months) (n=161)

<table>
<thead>
<tr>
<th></th>
<th>HR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Univariable</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>H. influenzae</em></td>
<td>5.81 (1.28 – 26.37)</td>
<td>0.022</td>
</tr>
<tr>
<td>≥2 siblings</td>
<td>3.18 (1.04 – 9.73)</td>
<td>0.042</td>
</tr>
<tr>
<td>Recurrent PBB (&gt;3 episodes/yr)</td>
<td>7.65 (1.67 – 34.92)</td>
<td>0.009</td>
</tr>
<tr>
<td><strong>Multivariable</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>H. influenzae</em></td>
<td>7.55 (1.66 – 34.28)</td>
<td>0.009</td>
</tr>
<tr>
<td>Recurrent PBB (&gt;3 episodes/yr)</td>
<td>9.77 (2.13 – 44.80)</td>
<td>0.003</td>
</tr>
</tbody>
</table>

1 Lower airway infection with *H. influenzae* defined as ≥10^4 cfu/ml growth on BAL fluid culture
FIGURE LEGENDS

Figure 1: CONSORT diagram
Recruited to ‘cough study’ (n = 343)

Excluded (n = 182)
• Did not meet PBB criteria

Included (n = 161)
‘PBB total’

Excluded (n = 55)
• Withdrew (n = 13)
• Incomplete cough diaries (n = 42)

Included (n = 106)
‘PBB followed-up’