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ORIGINAL RESEARCH

Prospective community programme versus parent-driven care to prevent respiratory morbidity in children following hospitalisation with severe bronchiolitis or pneumonia

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ABSTRACT

Background Hospitalisation with severe lower respiratory tract infection (LRTI) in early childhood is associated with ongoing respiratory symptoms and possible later development of bronchiectasis. We aimed to reduce this intermediate respiratory morbidity with a community intervention programme at time of discharge.

Methods This randomised, controlled, single-blind trial enrolled children aged <2 years hospitalised for severe LRTI to 'intervention' or 'control'. Intervention was three monthly community clinics treating wet cough with prolonged antibiotics referring non-responders. All other health issues were addressed, and health resilience behaviours were encouraged, with referrals for housing or smoking concerns. Controls followed the usual pathway of parent-initiated healthcare access. After 24 months, all children were assessed by a paediatrician blinded to randomisation for primary outcomes of wet cough, abnormal examination (crackles or clubbing) or chest X-ray Brasfield score ≤22.

Findings 400 children (203 intervention, 197 control) were enrolled in 2011–2012; mean age 6.9 months, 230 boys, 87% Maori/Pasifika ethnicity and 83% from the most deprived quintile. Final assessment of 321/400 (80.3%) showed no differences in presence of wet cough (33.9% intervention, 36.5% controls, relative risk (RR) 0.93, 95% CI 0.69 to 1.25), abnormal examination (21.7% intervention, 23.9% controls, RR 0.92, 95% CI 0.61 to 1.38) or Brasfield score ≤22 (32.4% intervention, 37.9% control, RR 0.85, 95% CI 0.63 to 1.17). Twelve (all intervention) were diagnosed with bronchiectasis within this timeframe.

Interpretation We have identified children at high risk of ongoing respiratory disease following hospital admission with severe LRTI in whom this intervention programme did not change outcomes over 2 years.

Trial registration number ACTRN12610001095055.

Key messages

What is the key question?
► Can ongoing respiratory symptoms after hospital admission for a severe lower respiratory tract infection in a young child be prevented with a community-based intervention programme?

What is the bottom line?
► Despite regular community clinic review with treatment of respiratory symptoms, encouragement of health-resilient behaviours and referrals for environmental concerns, there was no difference between intervention and control children in the high prevalence of respiratory morbidity 2 years after the index admission.

Why read on?
► This study has identified children at high risk of ongoing respiratory morbidity with the potential to develop bronchiectasis who need close monitoring after hospitalisation and new strategies to prevent long-term disease.

INTRODUCTION

The prevalence of chronic suppurative lung disease (CSLD), which includes protracted bacterial bronchitis and bronchiectasis, unrelated to cystic fibrosis (CF), has increased over the last decade.[1 2] It is particularly high in vulnerable populations, even in affluent countries.[3] Pneumonia at an early age has been described as a sentinel event in 28%–42% of adult populations with bronchiectasis,[4] with 60%–80% also reporting a wet cough since childhood.[5]

Indigenous children who developed bronchiectasis in a cohort study involving Australia, New Zealand and Alaska, USA had a median of four lower respiratory tract infections (LRTIs) including a median of two requiring hospitalisation in the first year of life.[3] Hospitalised pneumonia was associated with children having 2.9–5.5 times higher odds for ongoing respiratory symptoms over the next 2–5 years.[6 7] Children with lung parenchymal densities on chest X-ray (CXR) were at higher risk of developing irreversible disease[8 9] and such focal changes also predicted treatment failure for pneumonia in a WHO study involving >1000 children.[10]

New Zealand (NZ) has high rates of both early respiratory infection requiring hospitalisation and later end-stage disease.[11 12] This is particularly so in South Auckland where 13% of the NZ paediatric population reside, with 61% of births of Māori and/or Pasifika ethnicities, and 58% living in the most socioeconomic deprived quintile in NZ.[13] Annual admissions for bronchiolitis <1 year of age were 111.3/1000 and for pneumonia 0–14 years of age 5.6/1000 in South Auckland, which were 47%–49% greater than the national rates over a 4-year period.[13] Hospitalisations for bronchiectasis nationwide have increased by 30% between 2000 and 2013, and deaths per year have doubled for all ages.[14]

In a previous study, we prospectively assessed 94 children at a time of stable health 1 year posthospitalisation with severe LRTI when aged <2 years.[15] Over two-thirds had a history of chronic wet cough, wet cough or crackles on examination and/or an abnormal CXR. In addition, 56% and 51% had required further primary and hospital care, respectively, for respiratory infection.[15]

Our hypothesis was that reducing this ongoing respiratory morbidity would prevent later development of CSLD.[3 16] We adopted the model of care recommended for CF with regular assessments to address evolving health issues, including treatment for ongoing respiratory disease and encouragement of health resilient behaviours (immunisations, dental care, nutrition and reduced smoke exposure).[17] The aims were to reduce the prevalence of ongoing respiratory symptoms in a high-risk population after hospitalisation for severe LRTI aged <2 years when randomised to this 'intervention' programme compared with a 'control' group receiving usual parent-directed care. The primary outcomes were: (1) wet cough in clinic, (2) crackles or clubbing on examination and/or (3) Brasfield[18] score ≤22 on CXR when assessed 2 years postdischarge at a time of health stability.

METHODOLOGY
Study design and setting
This was a randomised, controlled, single-blind study enrolling 400 children in a 1:1 ratio at time of admission with severe LRTI to an 'intervention' programme versuss 'control' in South Auckland (paediatric population aged 0–14 years 15 500) from March 2011 to September 2012.

Caregivers provided written, informed consent prior to enrolment. The trial has Australian and New Zealand Clinical Trials Registry registration, and the protocol is available https://www.middlemoretrials.nz/document-centre

Participants
Children <2 years of age hospitalised with severe LRTI (pneumonia or bronchiolitis) that included *any* of the following admission ≥5 days, admission to intensive care unit, oxygen therapy >36 hours or consolidation on CXR. Exclusion criteria were: ≥2 previous LRTI admissions, prematurity <32 weeks' gestation, diagnosis of chronic lung disease or other chronic condition. Demographics, medical and family history and admission details were collected at enrolment.

Intervention programme
Follow-up was 1 month postdischarge, then a minimum of 3 monthly visits at one of four community clinics with general practitioner review until final follow-up at 24 months. A questionnaire and standard assessment were completed at each visit (online supplementary material). Training for all investigators on respiratory assessments standardised interpretation.

Respiratory interventions: (1) 7 days of oral antibiotics (amoxicillin, amoxicillin clavulanic, cefaclor or erythromycin depending on tolerance) were given with prolonged wet cough on history, wet cough present in clinic or crackles on examination. At 1-month follow-up, a further 14 days of antibiotics were given if symptoms persisted or recurred, with a further 1-month review and a repeat of 14 days of antibiotics and referral to paediatric clinic for non-resolution or recurrence. If resolution occurred at either visit, routine follow-up at 3 months was organised. Further infections were treated using the same pathway. (2) Wheeze was assessed and managed according to 'Guidelines for Asthma 1–15 years' and 'Cough and Wheeze Guidelines in <1 year olds', Paediatric Society of New Zealand (www.paediatrics.org.nz/files/guidelines/asthmaendorsed). (3) If admission CXR had focal abnormalities, a repeat CXR was performed 4 months postdischarge. If focal abnormalities remained, 14 days of oral antibiotics were given. If there was no resolution at 6 weeks, a referral was made to the paediatric clinic.

Other interventions: dental, ear, skin and general examinations were carried out at each review and identified issues treated according to the local hospital guidelines (www.Starship.org.nz/for-health-professionals/Starship-clinical-guidelines). Growth was recorded with caregivers receiving nutritional advice. Iron and vitamin D levels were measured at the first visit and treated if deficient. Immunisation status was ascertained via the National Immunisation Register (www.health.govt.nz/our-work/preventative-health-wellness/immunisation) with 'catch-up' immunisations if required.

Environmental interventions: (1) smoke exposure was recorded by self-report with smoking cessation programmes offered. (2) Housing was assessed by home visit with referrals for housing initiative programmes (insulation, repair and government housing). These were repeated with each change of residential address during the 2-year period.

The community clinics could access general paediatric (secondary care) and respiratory advice (tertiary care) by telephone. Referral to paediatric clinic was for any of the following indications: persisting respiratory symptoms over three visits; ≥3 prescriptions of antibiotics for respiratory illness; persistent focal changes on CXR; two further hospitalisations for LRTI; four further hospitalisations for any reason; and diagnostic difficulties and/or other unresolved problems. Referral to respiratory clinic was for: persistent wet cough; crackles and/or wheeze despite treatment; clinical aspiration syndrome; persistent or recurrent stridor; a first degree relative with bronchiectasis; and/or persistent focal CXR abnormality.

Control programme
The control group received the usual practice of care with discharge to their primary health provider and parent-driven health engagement as needed. Families were contacted 6 monthly to confirm address and willingness to continue participation.

Outcomes
The final outcome visit for all was undertaken 24 months after the index admission at a time of parent-determined health stability by one of two investigators blinded to randomisation and history. The primary outcomes were: (1) wet cough present (the original protocol noted this as 'moist cough in clinic' but 'wet cough' is the term now in common use), (2) abnormal examination (clubbing and/or crackles) and/or (3) CXR Brasfield score of ≤22/25 (25/25 is normal with points deducted for abnormalities).[18] Secondary outcomes were: other respiratory

parameters (readmission with LRTI, presence of wheeze, asthma diagnosis and any CXR abnormality); presence of skin infections, ear disease or dental caries; and immunisations completed and on time. Bronchiectasis if diagnosed through usual clinical pathways was recorded. At this review, the investigators were asked to assess the child's respiratory state as (1) normal, (2) suspicious for CSLD, (3) asthma or wheeze or (4) upper airway or tracheomalacia abnormality. All CXRs done at final visit were reported by a paediatric radiologist blinded to clinical information using the WHO definition of alveolar consolidation[19] and the Brasfield score.[18] The control group also had a home visit to conduct a housing assessment. The study team attempted to review families until 3 months beyond their final outcome date.

Randomisation

An independent statistician used a computer-generated, permuted block design of six to generate randomisation sequences placed in sealed opaque envelopes and opened sequentially.

Sample size and analysis

The intention was to enrol 400 children assuming 80% retention at 24 months. Based on the pilot study, assuming 40% of controls would have chronic respiratory outcomes present, there was 98% power to detect a 50% reduction at the 5% level of significance and 80% power to detect a 38% reduction. An intention-to-treat analysis was planned on all completed cases that had baseline and final outcome visit data. The demographic variables were presented as counts and proportions for categorical variables and mean with SD or median with IQR for the continuous variables depending on distribution of the data. The intervention effect for the outcomes was measured by producing the relative risk (RR) with 95% CIs, which was chosen over OR as the latter tends to overestimate the effect size when the events are not rare. So, for example, an RR of 0.93% means that the risk is 7% lower in the intervention group.[20] χ^2 or Fisher's exact test was used to examine for associations. P values less than 5% was deemed as significant.

Role of funding source

This was a government 'Investment Signal' sponsored project that required the intervention use existing community and hospital resources so it could be rolled out to other communities without substantial additional costs. Sponsors had no role in study design, data interruption or manuscript preparation.

RESULTS

In the study period, 3100 children aged <2 years were admitted for LRTIs in South Auckland with 960 (31%) meeting the 'severity' inclusion criteria. Of these, 400 were enrolled (mean age 6.9 months, SD 6.1 months, 230 boys), 203 to intervention and 197 to control with 560 excluded (264 declined, 51 not approached and 245 had chronic conditions/comorbidities). Of those enrolled 229/400 (57%) had pneumonia (mean age 10.8 months, SD 6.2) and 171/400 (43%) had bronchiolitis (mean age 4.1 months, SD 3.1). Fifty-five per cent were of Pacifica ethnicity, 32% Māori, 9% European and 3% other with 83% living in the most socioeconomically deprived quintile areas. Baseline demographics (table 1) show the groups were similar but more children in the intervention group required admission for 5 days and had more than one virus isolated in the index event.

Primary outcomes

A percentage of 80.3 attended the final outcome clinic 2 years after enrolment (165/203 (81.3%) intervention and 156/197 (79.2%)

Table 1 Summary of patients' characteristics by group

Characteristics	Intervention n=203	Control n=197
Age (months)		
Mean (SD)	8.4 (6.3)	7.4 (5.9)
Median (IQR)	7 (2.8–12.6)	6.6 (2.3–10.8)
Pneumonia, n (%)	123 (60.6)	106 (53.8)
Bronchiolitis, n (%)	80 (39.4)	91 (46.2)
Gender, n (%)		
Male	108 (53.2)	122 (61.9)
Female	95 (46.8)	75 (38.1)
Ethnicity, n (%)		
Pasifika	136 (67)	111 (56.4)
Māori	43 (21.2)	60 (30.5)
European	16 (7.9)	21 (10.7)
Other	8 (3.9)	5 (2.5)
Weight on arrival at hospital (ED) (kg)		
Mean (SD)	8.35 (2.6)	8.14 (2.8)
Median (IQR)	8.64 (6.2–10.1)	8.5 (5.6–10.2)
Weight at enrolment (Z-score)		
Mean (SD)	0.91 (1.02)	0.96 (1.02)
Median (IQR)	0.93 (0.32–1.55)	0.96 (0.36–1.57)
Duration of admission (in days)		
Mean (SD)	4.1 (2.8)	3.9 (3.5)
Median (IQR)	3 (2–5)	3 (2–4)
Admitted ≥5 days, n (%)	12 (5.9)	3 (1.5)
Oxygen ≥36 hours, n (%)	54 (26.6)	63 (31.9)
Admitted to ITU/CPAP, n (%)	17 (8.4)	26 (13.2)
June/July/August (winter months)	122 (60.1)	118 (59.9)
Positive PCR* on nasopharyngeal aspirate, n (%)	186 (91.6)	190 (96.4)
More than one virus, n (%)	87 (42.8)	63 (32)
RSV, n (%)	106 (52.2)	107 (54.3)
Positive bacterial culture, n (%)	7 (3.5)	8 (4.1)
Previous admission with respiratory illness (presentation to EC), n (%)	79 (38.9)	63 (31.9)
Overcrowding index		
Mean (SD)	0.56 (0.26)	0.57 (0.33)
Median (IQR)	0.50 (0.33–0.71)	0.50 (0.33 to 0.67)
Number of children in household, n (%)		
1	25 (12.3)	26 (13.2)
2	45 (22.2)	50 (25.4)
3	46 (22.7)	48 (24.4)
4	32 (15.8)	29 (14.7)
≥5	55 (27.1)	44 (22.3)
Number of children under 5 years in household, n (%)		
1	58 (28.6)	60 (30.5)
2	84 (41.4)	83 (42.1)
3	41 (20.2)	38 (19.3)

Continued

Table 1 Continued

Characteristics	Intervention n=203	Control n=197
≥4	18 (8.9)	16 (8.1)
Breastfeeding, n (%)	176 (86.7)	176 (89.3)
Pregnancy smoke exposure, n (%)	63 (31)	62 (31.5)
Household smoke exposure, n (%)	113 (55.9)	117 (59.7)
Immunisations, n (%)		
Yes	141 (69.5)	135 (68.5)
Too young	24 (11.8)	33 (16.8)
IF no, due for next immunisations/nil	36 (17.7)	27 (13.7)
Family history asthma (first degree), n (%)	132 (65)	130 (66)
NZ dep index		
Mean (SD)	8.9 (1.9)	9.2 (1.5)
Median (IQR)	10 (9–10)	10 (9–10)

*Automated multiplex PCR using AusDiagnostics Resp 12 Panel, which detects respiratory syncytial virus, influenza, parainfluenza types 1–2, adenovirus and picornavirus (detecting both rhinovirus and enterovirus).[36]

CPAP, continous positive airway pressure; ED, emergency department; ITU, intensive care unit; NZ dep, New Zealand deprivation score; RSV, respiratory syncytial virus.

control) with a total of 321 completing the clinical outcomes and 295 completing the radiological outcome (figure 1). In total, there were 113 (35.2%) children with wet cough present but no difference between groups (33.9% intervention, 36.5% control, RR 0.93, 95% CI 0.69 to 1.25). There were 73 (22.7%) children who had an abnormal examination with crackles and/or clubbing, again with no difference between groups (21.7% intervention, 23.9% control, RR 0.92, 95% CI 0.61 to 1.38). There were no difference in the baseline characteristics between those
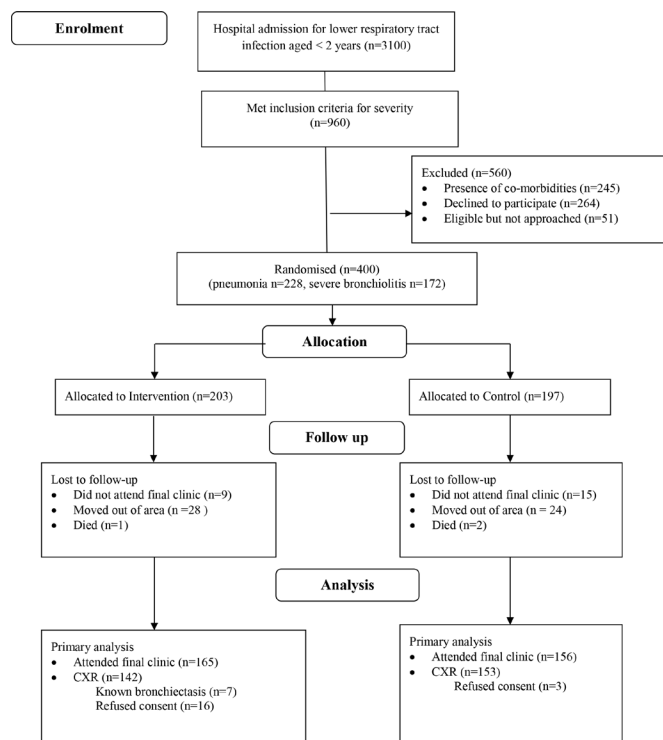

Figure 1 CONSORT diagram for trial. CONSORT, Consolidated Standards of Reporting Trials; CXR, chest X-ray.

completing the study and those lost to follow-up (table 1, online supplementary material).

In the intervention group, 142/165 (85.5%) children had an outcome CXR with 30 families refusing consent; 16 did not want further CXRs and 7 were already known to have developed bronchiectasis. Three of 156 in the control group refused consent. There were 104/295 (35.4%) with a Brasfield score of ≤22/25 at final visit; 46 intervention and 58 control with no significant difference (RR 0.85, 95% CI 0.63 to 1.17). In the intervention group, 24 (16.8%) had focal changes, 67 (47.2%) were abnormal (bronchial wall thickening, hyperinflation and/or hilar adenopathy) and 29 (20.4%) had normal CXRs. In addition, 12 (6%) were known to have bronchiectasis on chest CT scans. Of the control group, 25 (16.5%) had focal changes, 62 (40.5%) were abnormal and 32 (20.9%) had normal CXRs, with a single CXR uninterpretable. The numbers with none, one, two or all three abnormal outcomes at final visit is given in table 2.

Secondary outcomes

Table 3 documents the secondary outcomes with no difference between the two groups for any parameter listed but with high levels of comorbidities found. Eleven (6.7%) and 7 (4.5%) were noted to have increased work of breathing (tracheal tug, subcostal or costal recession) (RR 1.49 95% CI 0.59 to 3.73), 44 (26%) and 40 (25.6%) had chest deformity (predominantly Harrisons sulcus) (RR 1.04, 95% CI 0.72 to 1.5) in the intervention and control groups, respectively. Of the 295 who also had outcome CXRs, 24 (16.9%) and 25 (16.3%) had focal changes in the intervention and control groups, respectively (RR 1.03, 95% CI 0.62 to 1.73). In the intervention group by the final outcome visit, 12 (6%) were known to have bronchiectasis.

Adherence to protocol

Table 4 documents adherence showing routine community clinic attendance for the intervention group ranged from 195/203 (96.1%) at the first follow-up to 105/203 (51.7%) in the penultimate clinic, with 165/203 (81.3%) attending the final outcome clinic. Fifty-two parents quit smoking. With regards to housing, 414 assessments were conducted and 221 (54%) qualified for assistance but only 41 consented and were referred for housing improvements.

Over the 2-year period in the study, the intervention group had a total of 1311 oral antibiotic courses for any reason (mean 7.9, range 0–28), while the control group through health practitioner and emergency presentations had a total of 1093 oral antibiotic courses (mean 7, range 0–34). Only 15 children had no antibiotics over this time. The groups also had similar numbers of emergency department presentations (239 intervention, 278 control) and hospital admissions for any reason (118 intervention, 113 controls).

Final respiratory assessment

The considered respiratory diagnoses given by the 'blinded' investigators at the final clinic were 112 (34.9%) normal (61 intervention, 51 control), 203 (63.2%) asthma/wheeze (103 intervention, 100 controls) and 34 (10.65) CSLD suspicious (20 intervention, 14 controls), with 28 (8.7%) thought to have both.

DISCUSSION

This first prospective study using a community intervention programme instituted at time of hospital discharge for severe LRTI in young children did not show a reduction in the prevalence of respiratory symptoms when compared with usual

Table 2 Primary outcomes at final clinic

Parameter	Total (n=321) (n (%))	Intervention (n=165) (n (%))	Control (n=156) (n (%))	RR (95% CI)
Wet cough present	113 (35.2)	56 (33.9)	57 (36.5)	0.93 (0.69 to 1.25)
Crackles/clubbing	73 (22.7)	36 (21.7)	37 (23.9)	0.92 (0.61 to 1.38)
	Total	**Intervention**	**Control**	
The denominator for the following results reflects those that had an exit CXR	(n=295, 91.6%)	(n=142, 85.5%)	(n=153 to 98%)	
CXR score ≤22/25	104 (35.4)	46 (32.4)	58 (37.9)	0.85 (0.63 to 1.17)
CXR focal change	49 (17)	24 (16.9)	25 (16.3)	1.03 (0.62 to 1.73)
Number with normal/abnormal outcomes				
Normal	142/321 (44.2)	77/165 (46.7)	65/156 (41.7)	1.12 (0.87 to 1.43)
One or more abnormal outcome	175/321 (54.5)	88/165 (53.3)	91/156 (58.3)	
Two or more abnormal outcomes	78/321 (24.3)	40/165 (24.2)	42/156 (26.9)	
Three abnormal outcomes	30/295 (10.2)	14/142 (9.9)	20/153 (13.1)	

CXR, chest X-ray; RR, relative risk.

parent-driven care. After 2 years, high levels of respiratory morbidity remained in both groups with two-thirds having one or more of the primary outcomes present. Focal changes on the final CXR were also common, occurring in 17%. In addition, high levels of non-respiratory disease were present with between 17% and 44% also having otitis media, skin conditions and/or dental disease. However, there were no significant differences in any of these health parameters between the two groups. What ultimately was of concern was the number diagnosed with bronchiectasis on chest CT scan in the intervention group (n=12) compared with controls (n=0) in this short timeframe. These children were referred for a diagnostic scan likely because of their repeated assessments.

Table 3 Healthy Lungs Study: secondary outcomes

Parameter	Total n=321	Intervention n=165	Control n=156	RR (95% CI)
Respiratory				
Wet cough >8 weeks or >4 weeks on two occasions	52 (16.2%)	27 (16.4%)	25 (16%)	1.02 (0.62 to 1.68)
Increased work of breathing	18 (5.6%)	11 (6.7%)	7 (4.5%)	1.49 (0.59 to 3.73)
Chest deformity	84 (26.2%)	44 (26.7%)	40 (25.6%)	1.04 (0.72 to 1.50)
Doctor diagnosed asthma by final visit	87 (27.1%)	40 (24.2%)	47 (30.1%)	0.80 (0.56 to 1.15)
Wheeze on examination	45 (14%)	23 (13.9%)	22 (14.1%)	0.99 (0.57 to 1.70)
Bronchiectasis by study end*	12 (3.7%)	12 (7.3%)	0 (0%)	22.8 (1.36 to 382)
Other parameters				
Eczema and/or skin infections present	139 (43.3%)	77 (46.7%)	62 (39.7%)	1.17 (0.92 to 1.51)
Otitis media present	76 (23.7%)	39 (23.6%)	37 (23.7%)	0.99 (0.67 to 1.48)
Dental disease	54 (16.8%)	29 (17.8%)	25 (16%)	1.10 (0.67 to 1.79)
Immunisation recorded	316/321 (98.4%)	163 (98.8%)	153 (98.1%)	1.01 (0.98, 1.04)
Completed and on time†	195/316 (61.7%)	96/163 (58.9%)	101/153 (66%)	0.89 (0.75 to 1.06)
Healthcare use				
Number of oral antibiotic courses for all indications	2404/321	1311/165	1093/156	
Mean (range)		7.9 (0–28)	7.1 (0–34)	
Per child per annum		4	3.5	
All readmissions to hospital	231/321	118 in 63 children	113 in 57 children	
Mean (range)		0.72 (0–7)	0.72 (0–8)	
Per child per annum		0.36	0.36	
Readmissions to hospital with LRI	190/321	100 in 53 individuals	90 in 40 individuals	
Mean (range)		0.61 (0–6)	0.58 (0–8)	
Per child per annum		0.3	0.29	

*Determine by referral through usual clinical pathways as a chest CT scan was not an outcome measure.
†As measured by the New Zealand immunisation programme (www.health.govt.nz/our-work/preventative-health- wellness/immunisation). If an immunisation was given greater than 1 month after the recommended age, it was considered 'delayed'. In total, 119 had delayed immunisation (67 intervention, 52 control) and 5 (2 intervention, 3 control) had no immunisations.
LRI, lower respiratory infection; RR, relative risk.

Table 4 Healthy Lungs Study: protocol adherence

Protocol assessments	Intervention (n=203)
Clinic follow-up, n (%)	
Clinic one attended	195 (96·1)
≥4 more clinics attended*	165 (81·3)
Respiratory, n (%)	
Wet cough in clinic	290 (79·3) oral antibiotics prescribed in 161 children
Wheeze	86 (42·4) trials inhaled salbutamol via spacer
	30 (14·8) trial inhaled fluticasone via spacer
Follow-up CXR	136 (67) requested as per protocol
	102/136 (75) undertaken by family
Smoking, n (%)	
Number of assessments	203 (100)
Number with parents who smoke	90 (44·3)
Consent to referral for smoke cessation	88/90 (97·8)
Housing	
Total assessments done in number of families	414 in 192 families
Qualified for retrofitting insulation in those assessed	221/414 (54%)
Consented to referral	41/221 (18·6%)
Immunisations, n (%)	
Number with any immunisation	163 (80·3)
Number delayed at 5 months† and caught up in clinic visits	61 (30)
Referrals, n (%)	
To paediatric clinic	90 (27·6) visits in 56 children
To respiratory clinic	22 (10·8) children

*Eight community clinics were scheduled 3 monthly per child in intervention programme; this would represent 50% adherence to clinic visits.
†The New Zealand Immunisation programme over this timeframe recommends diphtheria/pertussis/tetanus vaccination at 6 weeks, 3 months and 5 months of age. 'Delay' is determined here as at least 1 month later than recommended age.

So why did the intervention not reduce the ongoing respiratory morbidity? Unbalanced randomisation did not seem to be at fault when reviewing baseline characteristics between groups. We also do not believe that missing data or poor adherence impacted the outcomes. We achieved the planned 80% retention with similar numbers (19% intervention and 21% control children) unable to be assessed at the final outcome. The percentage of children that had abnormal outcomes in the group attending all routine clinics (25% of the total) were similar to the intervention group overall (wet cough: 34.7%–33.9%, abnormal examination: 16.3%–21.7%, abnormal CXR: 31.4%–32.4%, respectively). The development of CSLD occurs with a combination of infection, inflammation, airway obstruction and reduced mucus clearance.[21] [22] However, our intervention only targeted possible infection; we did not use any anti-inflammatory medication (unless treating asthma) and did not formally teach airway clearance techniques. Also many infections may have been of viral origin. It also proved difficult to substantially alter their environment. Insulation has been shown to reduce respiratory disease in children.[23] These families moved a mean of four times with repeated housing assessments undertaken but only 41

(9.3%) of those eligible for assistance agreed to referral, reportedly because of concern regarding landlord reaction. Furthermore, no housing intervention was completed within our 2-year study timeframe. Similarly, while smoking cessation programmes were taken up by parent/s in the intervention group, the children were still exposed to secondhand smoke at home from other family members. It also may have been too late to change their disease trajectory because of established in utero developments or genetically programmed host response to early infection. We now know that much of the adult respiratory disease arises from early events during the period of rapid growth.[24] [25] Lung structural development starts in utero with restriction a risk factor for lower lung function in infancy and throughout childhood.[26] There was also a high prevalence (31.2%) of antenatal smoke exposure in this population. Nicotine readily crosses the placenta causing DNA damage and decreases bronchiole-alveolar attachments leading to smaller lungs with fewer alveoli and a low capillary density.[27] [28] In addition, recent studies have suggested both innate and adaptive immune dysfunction may contribute to bronchiectasis development.[29] Reduced alveolar macrophage phagocytosis of apoptotic cells,[30] poor clearance of certain bacteria[31] and impaired antibody response[32] have all been described. Finally, when reviewed by study end, the intervention programme may not have been different enough from parent-driven care as further healthcare utilisation with antibiotics, emergency department presentation and hospital admission were also high in controls.

There were two major limitations to this study. The first was attempting a CF model of care in a socioeconomically deprived community without the necessary CF resources: no physiotherapist, social worker, dietician in clinics and no CF association pastoral care. The second was not to include chest CT scans as a main outcome of the study. Low radiation dose chest CT scans and fast acquisition (reducing the need of general anaesthesia in young children) was in evolution at the time of protocol development. We also had not appreciated that a number would rapidly progress to bronchiectasis within this time frame and were concerned about exposing many preschool children to radiation and general anaesthesia. Furthermore, it was not financially feasible within this 'Investment Signal' project funding constraints. Instead, our outcomes were set to determine if we could reduce the intermediate respiratory morbidity between an early respiratory event and the later potential evolution of CSLD. Ultimately to end of 2016, a total of 18 (14 intervention, 4 controls) have been diagnosed with bronchiectasis. This means, at a minimum, 7% of the intervention group have bronchiectasis, raising concern not only about others still unrecognised in both groups (especially controls) but in all the 960 originally meeting the severity enrolment criteria for this study.

We believe that regular review led to early referral and diagnosis of bronchiectasis but, using current paediatric pneumonia guidelines, few would have scheduled follow-up after discharge.[33] [34] Our findings would suggest that *all* of these children in a high risk setting need assiduous follow-up with early referral for low dose chest CT scan when symptoms persist. 'How does bronchiectasis develop and continue' was the top research priority of adult patients with bronchiectasis[35] and following these children further may identify the pathway to bronchiectasis development.

In conclusion, while this intervention programme did not reduce the presence of respiratory morbidity 2 years after hospitalisation with severe bronchiolitis or pneumonia in early childhood, it did reveal significant ear, skin and lung disease, with high rates of bronchiectasis incidentally diagnosed. This group of children are correctly identified to be at very high risk of

continued respiratory disease and their poor long-term respiratory outcomes may be allayed if we were able to reduce this ongoing respiratory morbidity.

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