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Indigenous Children From Three Countries With Non-Cystic Fibrosis Chronic Suppurative Lung Disease/Bronchiectasis

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Summary. Objective: Indigenous children in developed countries are at increased risk of chronic suppurative lung disease (CSLD), including bronchiectasis. We evaluated sociodemographic and medical factors in indigenous children with CSLD/bronchiectasis from Australia, United States (US), and New Zealand (NZ). Methods: Indigenous children aged 0.5–8 years with CSLD/bronchiectasis were enrolled from specialist clinics in Australia (n = 97), Alaska (n = 41), and NZ (n = 42) during 2004–2009, and followed for 1–5 years. Research staff administered standardized parent interviews, reviewed medical histories and performed physical examinations at enrollment. Results: Study children in all three countries had poor housing and sociodemographic circumstances at enrollment. Except for increased household crowding, most poverty indices in study participants were similar to those reported for their respective local indigenous populations. However, compared to their local indigenous populations, study children were more often born prematurely and had both an increased frequency and earlier onset of acute lower respiratory infections (ALRIs). Most (95%) study participants had prior ALRI hospitalizations and 77% reported a chronic cough in the past year. Significant differences (wheeze, ear disease and plumbed water) between countries were present. Discussion: Indigenous children with CSLD/bronchiectasis from three developed countries experience significant disparities in poverty indices in common with their respective indigenous population; however, household crowding, prematurity and early ALRIs were more common in study children than their local indigenous population. Addressing equity, especially by preventing

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prematurity and ALRIs, should reduce risk of CSLD/bronchiectasis in indigenous children.
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INTRODUCTION

Bronchiectasis, is thought to be relatively rare in developed countries[1]; however, indigenous children in developed countries and children in developing countries remain at high risk.[2–5] Bronchiectasis unrelated to cystic fibrosis (CF) is common among indigenous children from remote communities in Australia's Northern Territory (NT; 14.7/1,000 children aged <15 years),[6] Alaska's Yukon Kuskokwim (YK) Delta (14–20/1,000 births)[4] and in Maori (0.7/1,000) and Pacific Island children (1.6/1,000) children aged <15 years in New Zealand (NZ).[7] In contrast, the estimated bronchiectasis prevalence rate in the United States (US) is 4.2/100,000 in 18–34-year olds[8] and in NZ the national incidence of bronchiectasis for children aged <15 years is 3.7/100,000 per year.[7]

The diagnosis of bronchiectasis is usually established radiologically by chest high-resolution computerized tomography (HRCT) scans. However, many children living in remote, isolated communities do not have access to HRCT scanners. Furthermore, because children's peripheral pulmonary airways are significantly smaller than the adjacent blood vessels, adult-derived radiographic diagnostic criteria for bronchiectasis may under-estimate this disorder in the pediatric age group.[9] It was also well recognized in the pre-antibiotic era that young children with a persistent ''wet cough'' following pneumonia and recurrent acute lower respiratory infections (ALRIs) could progress from having no radiographic evidence of bronchiectasis to an established radiographic diagnosis in a matter of months to years.[10] Taken together, this led some clinicians recently to introduce the term chronic suppurative lung disease (CSLD) to describe a diagnosis where there are clinical symptoms and signs of bronchiectasis without a current HRCT-confirmed diagnosis.[11] In light of this development we too have adopted the term CSLD to describe participants in our study who fulfill these diagnostic criteria.

In these indigenous populations, CSLD/bronchiectasis is associated with childhood pneumonia and other ALRIs.[11–13] ALRIs occur at extremely high rates in these regional populations, and are associated with crowded living conditions,[14] poverty, lack of running water,[15,16] exposure to indoor air pollutants,[17] and poor maternal education. While the risk factors identified above are common in these indigenous communities, it is not known if they are more common still in children who develop CSLD/bronchiectasis.

No studies have used a common methodology to collect data on risk factors for CSLD/bronchiectasis. Hence, differences in patient characteristics across countries may reflect bias and non-standardized data collection. We enrolled indigenous children with CSLD/bronchiectasis from Australia, Alaska US, and NZ in a multicenter bronchiectasis study. Our study's first aim was to use standardized data collection to evaluate similarities and differences in the sociodemographic features and medical histories of children with CSLD/bronchiectasis at enrollment. Our second aim was to compare these demographic and medical factors in the participants with their respective regional indigenous population and country of origin.

ABBREVIATIONS:

AI/AN	American Indian/Alaska Native
ALRI	acute lower respiratory infection
CSLD	chronic suppurative lung disease
CF	cystic fibrosis
FEV_1	forced expiratory volume in 1 sec
HRCT	high resolution computerized tomography
IRB	institutional review board
LBW	low birth weight
NT	Northern Territory
NZ	New Zealand
RSV	respiratory syncytial virus
US	United States
YK	Yukon Kuskokwim

MATERIALS AND METHODS

Study Population

Indigenous children (Australian Aboriginal and Torres Strait Islander, Alaska Native (AN, NZ Māori,

and Pacific Islander) with CSLD/bronchiectasis were enrolled after informed consent in the Multicentre Bronchiectasis Study in Australia (central [arid] and northern [tropical] parts of the NT), US (Alaska's YK Delta region in the arctic), and NZ (the city of Auckland in a temperate climate), respectively, during 2004–2009 and followed prospectively for 1–5 years. Eligible children were recruited as they presented to their regional pulmonary clinics. The study has two components: (i) *observational study* (2004–2008): Australian and Alaskan children (aged 6 months to 8 years) with HRCT-confirmed bronchiectasis[2,18] or chronic (>3 months) daily wet (productive) cough were enrolled in a prospective cohort study (participants received standard tests and clinical care for CSLD/bronchiectasis and were followed for 1–5 years; Fig. 1); (ii) *interventional study* (2008–2011): Australian and NZ children (aged 12 months to 8 years) were enrolled in placebo controlled study examining efficacy of azithromycin in children with CSLD/bronchiectasis (Fig. 1).[19] In both studies, children were excluded if they had an underlying cause of bronchiectasis (primary ciliary dyskinesia, immunodeficiency, CF, etc.), current treatment for cancer or diabetes, or a central nervous system or neuromuscular disorder, which affected respiratory function. Baseline data (collected at enrollment) from both studies are presented.

Approval

Each local institutional review board (IRB) and indigenous ethics committees in Australia, Alaska US, and NZ approved the study (see Acknowledgements Section).

Procedures/Data Collection

All sites used the same standardized data collection forms. On the first visit research staff interviewed the parent/guardian to obtain a sociodemographic and medical history. Medical records were reviewed for past medical history, including respiratory illnesses. The attending pulmonologist performed a physical examination, obtained height and weight measurements (normalized for age z-scores), and assigned a respiratory diagnosis. Data were entered locally into a password-protected study database, on a secure website. An Australian-based data manager conducted regular data checks and queries to ensure data completeness and accuracy. Investigators and research nurses met regularly to discuss data collection issues and study progress.

ALRI episodes prior to enrollment were defined as a new diagnosis of pneumonia, bronchiolitis, bronchitis, or respiratory illnesses. This included any of the following: increased cough, shortness of breath/dyspnea, increased sputum volume or color intensity, new chest examination findings, new chest radiograph changes, deterioration in (forced expiratory volume in 1 sec) FEV_1 by >10%, or hemoptysis. All clinic visits for a respiratory infection within 2 weeks were counted as the same ALRI episode. Over-crowded housing was calculated as persons in house/(rooms in house—1) >2 to match the Canadian Crowding Index of >2 persons per bedroom in the house.[20]

Clinical Care

All sites provided optimal known standard of care including: antibiotic therapy for exacerbations, suppressive antibiotics for selected patients, chest clearance techniques, asthma therapy, parental smoking cessation advice, immunizations, nutritional support, and management of exacerbating factors (e.g., gastro-esophageal reflux disease and dysphagia).

Statistical Analysis

Analyses of the characteristics and clinical results were performed for each site for the baseline data, with comparisons made between sites. Some continuous data were collapsed into categorical groups (e.g., age, z-scores). Categorical data were analyzed using the Chi-squared tests and Fisher's exact test (two-tailed), as appropriate. Continuous data were analyzed using the Wilcoxon rank-sum test and Kruskal–Wallis test, as appropriate. Statistical significance was set at $P < 0.05$. Statistical software package SPSS (v18 and v19) was utilized to conduct the statistical analysis. In addition, EpiInfo (v3.5.3) was utilized to calculate z-scores. Children were classified as stunted or underweight if their enrollment "height-for-age" or "weight-for-age" z-scores were more than 2 standard deviations (SDs) below the corresponding population means.

RESULTS

Demographics

During the study period, 182 children with CSLD/bronchiectasis were invited to participate, and 180 (57% boys) were recruited (response rate 99%; Table 1). The median age at recruitment was 3.2 years (range: 0.5–9.0). NZ children (who only participated in the Intervention study which required HRCT-confirmed bronchiectasis) were significantly older than Australian or Alaskan children. The diagnosis at enrollment was chronic cough +/− radiographic pulmonary infiltrate in 85 (47%), and bronchiectasis in 95 (53%) children.

Household Demographics

As study participants came from diverse geographic settings and climates, there were significant differences

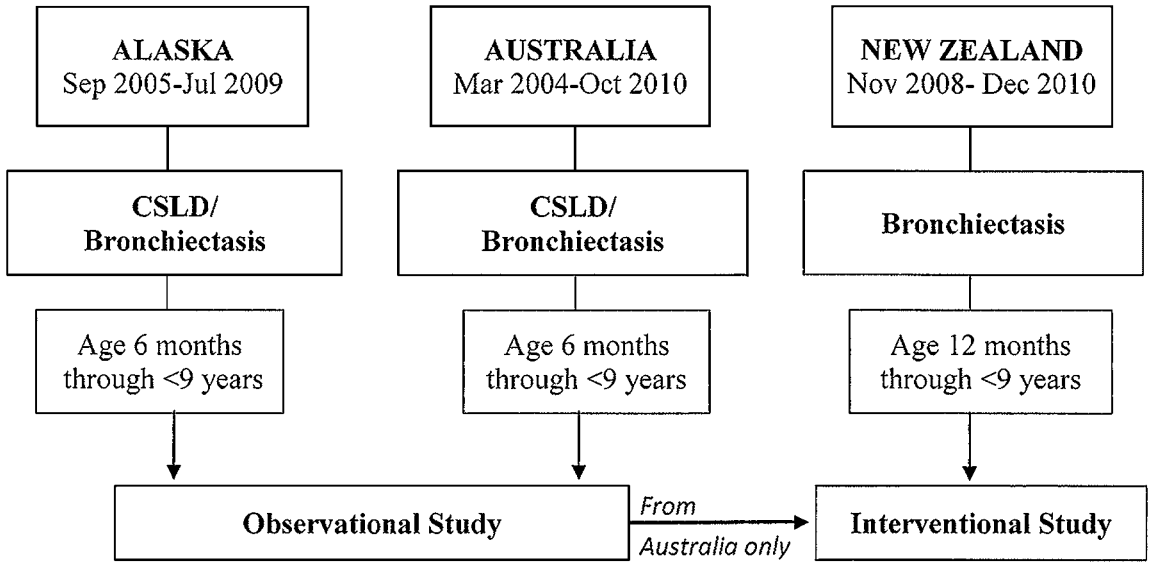

Fig. 1. Flow chart showing timeline of enrollment and study period of indigenous children from Australia, Alaska United States, and New Zealand with chronic suppurative lung disease (CSLD) or bronchiectasis enrolled in the Bronchiectasis Observational and Interventional Studies.

among groups for wood burning in the house (highest in Alaska), absence of refrigerator (most common in Australia) and absence of flush toilet (most common in Alaska). However, significant household crowding was evident in all groups. Using the Canadian Crowding Index,[20,21] 71% of households were overcrowded. Overcrowding was highest in Australia and lowest in NZ (Table 1).

Smoke Exposure

Tobacco exposure during pregnancy and in the household was high in all groups, but significantly lower in NZ than in Australia and Alaska (Table 1).

Parent Education

Although most female primary caregivers (90%) had some high school education, the high school completion rate was low in all groups and significantly different among groups (highest in Alaska and lowest in Australia). Attainment of a bachelor degree was rare for caregivers in all groups; no caregivers in Australia or Alaska attained a bachelor degree (Table 1).

Past Medical History

Birth Weight

Birth weights in full-term infants were significantly different among groups (highest in NZ and lowest in Australia) (Table 1). A high proportion of the study children (30%) were born <36 weeks gestation with no significant difference between groups, and few children (5%) were diagnosed with neonatal chronic lung disease.

Nutritional Status

At study enrollment, there was a statistically significant difference between the groups in nutritional status with more Australian children having low weight-for-age z-scores (18% classified as underweight) compared to the Alaskan and NZ groups (Table 1).

Feeding

While breastfeeding was common, the proportion of children who breastfed was significantly different between the groups (highest in Australia and lowest in NZ) (Table 1). Most children (65%) breast or bottle fed lying down at least sometimes. Also, 47% of the total group reported propping the bottle during feeds, but for most it was an occasional event. During feeding, 24% of children would "regularly choke;" and choking was more commonly reported for Alaskan (46%) than Australian (13%) or NZ (18%) children.

Past History of Respiratory Infections

By enrollment, 91% had recorded a previous hospitalized ALRI and 100% had prior ALRIs (total of 2,299 ALRIs, median 10 per child, range 1–43; Table 2). Participants were relatively young at the time of their first ALRI (median 3.7 months), and experienced a median of four ALRIs and two hospitalized ALRIs in the first year of life. One-third of all ALRI episodes

TABLE 1— Demographic Features for Study Household by Location of Indigenous Children From Australia, Alaska United States, and New Zealand With Chronic Suppurative Lung Disease or Bronchiectasis at Enrollment Into the Bronchiectasis Observational or Interventional studies, 2004—2010

Demographic characteristic	Australia (N = 97)	Alaska, US (N = 41)	New Zealand (N = 42)	Total (N = 180)	Difference between sites (*P*-value)
Demographics					
Median age at enrollment (years, range)	3.0 (0.8–8.9)	2.8 (0.5–7.9)	5.4 (1.8–9.0)	3.2 (0.5–9.0)	<0.001
Male (n, %)	55/97 (56.7)	22/41 (53.7)	25/42 (59.5)	102/180 (56.7)	0.865
Household demographics					
Median occupants per room (range)	2.7 (0.8–18.5) (n = 89, 91.8%)	2.0 (1.0–9.0) (n = 41, 100%)	1.5 (0.6–3.5) (n = 42, 100%)	2.3 (0.6–18.5) (n = 172, 95.6%)	<0.001
Overcrowding >1 person/room (n, %)	87/89 (97.8)	38/41 (92.7)	37/42 (88.1)	162/172 (94.2)	0.079
Overcrowding (n, %)[a]	75/89 (84.3)	27/41 (65.9)	21/42 (50.0)	123/172 (71.5)	<0.001
Absence of running water (n, %)	5/95 (5.3)	18/41 (43.9)	0/42 (0.0)	23/178 (12.9)	<0.001
Absence of flush toilet (n, %)	7/94 (7.4)	17/41 (41.5)	0/42 (0.0)	24/177 (13.6)	<0.001
Wood burning in house (n, %)	22/94 (23.4)	19/40 (47.5)	2/42 (4.8)	43/176 (24.4)	<0.001
Absence of refrigerator in house (n, %)	27/91 (29.7)	1/11 (9.1)	0/40 (0.0)	28/142 (19.7)	<0.001
Mostly cook with an open fire (n, %)	8/95 (8.4)	1/39 (2.6)	0/42 (0.0)	9/176 (5.1)	0.106
Smoke exposure					
Median # of smokers in household (range)	2.0 (0.0–17.0) (n = 82, 84.5%)	0.0 (0.0–3.0) (n = 30, 73.2%)	1.0 (0.0–8.0) (n = 14, 33.3%)	1.0 (0.0–17.0) (n = 126, 70.0%)	<0.001
Mother used tobacco in pregnancy (n, %)[b]	53/90 (58.9)	35/40 (87.5)	10/42 (23.8)	98/172 (57.0)	<0.001
Education: female caregiver					
Completed high school (n, %)	12/87 (14.3)	33/41 (80.5)	21/39 (53.8)	66/164 (40.2)	<0.001
Bachelor's degree (n, %)	0/21 (0.0)	0/19 (0.0)	3/13 (23.1)	3/53 (5.7)	0.012
Education: male caregiver					
Completed high school (n, %)	9/44 (20.5)	25/35 (71.4)	12/27 (44.4)	46/106 (43.4)	<0.001
Bachelor's degree (n, %)	0/16 (0.0)	0/15 (0.0)	0/6 (0.0)	0/37 (0.0)	n/a
Birth status					
Premature (n, %)	33/89 (37.1)	7/30 (23.3)	9/42 (21.4)	49/161 (30.4)	0.124
Median full-term birthweight (g, range)	3170 (2240–4615) (n = 55/56, 98.2%)	3500 (2790–4770) (n = 22/23, 95.7%)	3745 (213–6630) (30/33, 90.9)	3500 (2130–6630) (107/112, 95.5%)	0.046
Full-term low birth weight[c] (n, %)	9/55 (16.4)	0/22 (0)	2/30 (6.7)	11/107 (10.3)	0.082
Total low birth weight [c] (n, %)	34/91 (37.4)	4/28 (12.5)	9/39 (23.1)	47/162 (29.0)	0.018
Mechanical ventilation required (n, %)	15/91 (16.5)	2/37 (5.4)	3/39 (7.7)	20/167 (12.0)	0.178
Chronic lung disease (n, %)	7/90 (7.8)	0/35 (0.0)	1/39 (2.6)	8/164 (4.9)	0.232
Breast and bottle feeding					
Child was breastfed (n, %)	79/91 (86.8)	26/41 (63.4)	31/42 (73.8)	136/174 (78.2)	0.008
Child used a bottle (n, %)	47/89 (52.8)	36/40 (90.0)	34/42 (81.0)	117/171 (68.4)	<0.001
Child fed laying down (n, %)	36/46 (78.3)	22/36 (61.1)	16/32 (50.0)	74/114 (64.9)	0.031
Bottle was propped (n, %)	24/43 (55.8)	10/31 (32.3)	11/23 (47.8)	45/97 (46.4)	0.132
Choked regularly	7/56 (12.5)	17/37 (45.9)	6/33 (18.2)	30/126 (23.8)	0.053
Nutritional status					
Height-for-age z-scores (n, %)					
>2 SD below the norm	12/87 (13.8)	1/33 (3.0)	0/42 (0.0)	13/162 (8.0)	0.003
≤2 SD from the norm	73/87 (83.9)	32/33 (97.0)	37/42 (88.1)	142/162 (87.7)	
>2 SD above the norm	2/87 (2.3)	0/33 (0.0)	5/42 (11.9)	7/162 (4.3)	
Weight-for-age z-scores (n, %)					
>2 SD below the norm	17/94 (18.1)	0/38 (0.0)	0/42 (0.0)	17/174 (9.8)	0.001
≤2 SD from the norm	77/94 (81.9)	36/38 (94.7)	31/42 (73.8)	144/174 (82.8)	
>2 SD above the norm	0/94 (0.0)	2/38 (5.3)	11/42 (26.2)	13/174 (7.5)	

[a]Calculated as (adult + children in house/(rooms in house—1) to match the Canadian Crowding Index of >2 persons people per bedroom in the house.
[b]Mothers were considered to be tobacco users if they reported to either chew or smoke tobacco.
[c]Birth weight <2,500 g.

TABLE 2— Baseline Respiratory History by Location of Indigenous Children from Australia, Alaska United States, and New Zealand With Chronic Suppurative Lung Disease/Bronchiectasis at Enrollment Into the Bronchiectasis Observational or Interventional Studies, 2004–2010

Respiratory characteristic	Australia (n = 97)	Alaska, United States (n = 41)	New Zealand (n = 42)	Total (n = 180)	Global *P*-value (excl. missing data)
Respiratory episodes: (medical records)	# (%)	# (%)	# (%)	# (%)	
Total acute lower respiratory infections (ALRI) (n, %)	933 (100.0)	695 (100.0)	971 (100.0)	2299 (100.00)	
Median # ALRI (range)	9 (1–29)	15 (1.43)	13.5 (3–39)	10 (1–43)	<0.001
Median # hospitalized ALRI (range)	3 (0–12)	3 (0–13)	6 (0–17)	3 (0–17)	<0.001
Proportion with at least one non-hospitalized ALRI (n, %)	94/97 (96.9)	38/41 (92.7)	41/42 (97.6)	173/180 (96.1)	0.513
Proportion with at least one hospitalized ALRI (n, %)	85/97 (87.6)	39/41 (95.1)	39/42 (92.9)	163/180 (90.6)	0.341
Median # ALRIs in first year of life (range)	4 (1–11)	5 (1–12)	4 (1–12)	4 (1–12)	0.046
Median # hospitalized ALRIs in first year of life (range)	2 (0–6)	2 (0–9)	2 (0–10)	2 (0–10)	0.114
Median age in months at first ALRI episode (range)	3.7 (0–46.9)	2.4 (0–9.9)	5.9 (0.9–50.7)	3.7 (0–50.7)	<0.001
Median age in months at first hospitalized	4.4 (0–61.9)	3.9 (0–16.1)	7.1 (0.9–53.1)	5.0 (0–61.9)	0.048
ALRI episode (range)	(n = 85, 100%)	(n = 39, 100%)	(n = 39, 100%)	(n = 163, 100%)	
Pneumonia episodes: (medical record)					
Total pneumonia episodes (n, %)	321/933 (34.4)	302/695 (43.5)	94/971 (14.0)	717/2299 (31.2)	<0.001
Median # pneumonias (range)	2 (0–14)	7 (1–20)	2 (0–6)	3 (0–20)	<0.001
Median # pneumonias in first year of life (range)	1 (0–6)	2 (0–8)	1 (0–2)	1 (0–8)	<0.001
Proportion of pneumonia episodes that were hospitalized	133/321 (41.4)	118/302 (39.1)	73/94 (77.7)	324/717 (45.2)	<0.001
Median age in months at first pneumonia episode (range)	6.1 (0–42.8)	4.0 (0.9–19.6)	10.8 (1.5–53.1)	6.1 (0.0–53.1)	<0.001
	(n = 82, 100%)	(n = 40, 100%)	(n = 37, 100%)	(n = 159, 100%)	
Cough					
Current cough (past 2 weeks)[a] (n, %)	58/97 (59.8)	38/41 (92.7%)	21/42 (50.0)	117/180 (65.0)	<0.001
Cough in past 12 months[a] (n, %)	67/93 (72.0)	40/41 (97.6)	32/42 (76.2)	139/176 (79.0)	0.003
Productive cough past 12 months[a] (n, %)	33/62 (53.2)	31/40 (77.5)	24/30 (80.0)	88/132 (66.7)	0.008
Cough in past 12 months caused minimal disruption[a] (n, %)	22/60 (36.7)	8/40 (20.0)	4/30 (13.3)	34/130 (26.2)	0.034
Cough in past 12 months has disrupted sleep[a] (n, %)	30/60 (50.0)	28/40 (70.0)	22/30 (73.3)	80/130 (61.5)	0.042
Cough in past 12 months has disrupted sports[a] (n, %)	10/60 (16.7)	7/40 (17.5)	8/30 (26.7)	25/130 (19.2)	0.497
Cough in past 12 months has disrupted school[a] (n, %)	3/60 (5.0)	4/40 (10.0)	7/30 (23.3)	14/130 (10.8)	0.030
Wheezing					
Wheeze in past 12 months (n, %)[a]	30/94 (31.9)	37/41 (90.2)	24/42 (57.1)	91/177 (51.4)	<0.001
Troublesome wheezing at least once per week (n, %)[a]	8/28 (28.6)	6/36 (16.7)	9/23 (39.1)	23/87 (26.4)	0.154
Recurrent wheezing illness[b] (n, %)	17/95 (17.9)	28/36 (77.8)	11/40 (27.5)	56/171 (32.7)	<0.001
Age in months at first wheeze (median, range)	5.0 (0.0–36.0)	3.5 (1.0–13.0)	6.0 (1.0–12.0)	4.0 (0.0–36.0)	0.332
	(n = 11, 64.7%)	(n = 22, 61.1%)	(n = 10, 90.9%)	(n = 43, 76.8%)	
Dyspnoea					
Breathing difficulties in previous 12 months (n, %)[a]	28/95 (29.5)	23/10 (57.5)	11/42 (26.2)	62/177 (35.0)	0.003
Non-respiratory conditions in the past 12 months					
Previously diagnosed with otitis media (OM) (n, %)	89/94 (94.7)	34/38 (89.5)	31/39 (79.5)	154/171 (90.1)	0.037
Total # of OM with perforation (n, %)	42/80 (52.5)	16/23 (69.6)	27/30 (90.0)	85/133 (63.9)	0.001
Median # times antibiotics prescribed for OM (range)	5 (1–40)	10 (1–.34)	2.5 (0–19)	5 (0–40)	<0.001
	(n = 67, 69.1%)	(n = 25, 61.0%)	26 (61.9%)	(n = 118, 65.6)	
Previously diagnosed with gastroenteritis (n, %)	48/94 (51.1)	1/36 (2.8)	9/39 (23.1)	58/169 (34.3)	<0.001
Median # of hospitalized gastroenteritis episodes (range)	1 (1–4)	— (n = 0, 0.0%)	1 (1–2)	1 (1–4) (n = 53, 29.4%)	0.126
	(n = 44, 45.4%)		(n = 9, 21.4%)		
Previously diagnosed with urinary tract infection (n, %)	20/95 (21.1)	8/35 (22.9)	2/40 (5.0)	30/170 (17.6)	0.057
Current regular medications					
Child takes any medication on a regular basis (n, %)	53/96 (55.2)	27/30 (90.0)	14/39 (35.9)	94/165 (57.0)	<0.001
Antibiotics (n, %)	46/97 (47.4)	3/41 (7.3)	0/42 (0.0)	49/180 (27.2)	<0.001

(*Continued*)

TABLE 2—(*Continued*)

Respiratory characteristic	Australia (n = 97)	Alaska, United States (n = 41)	New Zealand (n = 42)	Total (n = 180)	Global *P*-value (excl. missing data)
Bronchodilators (n, %)	4/97 (4.1)	18/41 (43.9)	12/42 (28.6)	34/180 (18.9)	<0.001
Corticosteroids oral/inhaler (n, %)	6/97 (6.2)	19/41 (46.3)	13/42 (31.0)	38/180 (21.1)	<0.001
Physical exam					
Audible wheeze (n, %)	7/95 (7.4)	16/39 (41.0)	7/42 (16.7)	30/176 (17.0)	<0.001
Clubbing (n, %)	9/95 (9.5)	2/39 (5.1)	19/42 (45.2)	30/176 (17.0)	<0.001
Auscultory crackles (n, %)	30/95 (31.6)	16/39 (41.0)	13/42 (31.0)	59/176 (33.5)	0.565
Chest wall deformity (n, %)	13/95 (13.7)	7/39 (17.9)	24/42 (57.1)	44/176 (25.0)	<0.001
Retractions (n, %)	1/95 (1.1)	3/39 (7.7)	3/42 (7.1)	7/176 (4.0)	0.098
Productive cough on exam (n, %)	47/94 (50.0)	30/40 (75.0)	22/42 (52.4)	99/176 (56.3)	0.013
Normal results for ear pathology (n, %)	11/91 (12.1)	27/36 (75.0)	28/39 (71.8)	66/166 (39.8)	<0.001
OM with effusion (n, %)	58/91 (63.7)	3/36 (8.3)	2/39 (5.1)	63/166 (38.0)	<0.001
Suppurative OM (n, %)	12/91 (13.2)	1/36 (2.8)	2/39 (5.1)	15/166 (9.0)	0.138
OM with dry perforation (n, %)	8/91 (8.8)	3/36 (8.3)	3/39 (7.7)	14/166 (8.4)	1.00

[a]Based on parent-reported data at first interview.
[b]Recurrent wheeze defined as three or more wheezing episodes in the last 12 months based on the medical record review.

resulted in hospitalization. One-third of ALRIs had been diagnosed as pneumonia (45% resulting in hospitalization), and there was a median of 3 (range 1–20) pneumonia episodes per subject prior to enrollment.

Cough and Wheeze

Almost two-thirds (65%) of children had a current (daily) cough at enrollment (Table 2), and 79% had experienced a chronic cough in the past 12 months, especially the Alaskan children (98%). Most children (67%) had a ''wet or productive'' cough, and in most, the cough impacted on other activities (sleep, sport, or school). Alaskan children (90%) were more likely to have reported wheeze, compared to Australian children (32%) and NZ children (51%). Likewise, Alaskan children (78%) were most likely to have had recurrent wheezing and difficulty breathing in the previous 12 months.

Past History Other Conditions

The most common non-respiratory illnesses before enrollment were otitis media (OM) and gastroenteritis which were most common among Australian children (Table 2).

First Clinical Assessment

One-third of study children had crackles on chest auscultation at their first examination, and 56% had a wet or productive cough (Table 2). Several significantly different examination findings were reported between groups. Over 40% of Alaskan children had audible wheeze, compared with 7% of Australian and 17% of NZ children. Over half of NZ children had a chest wall deformity compared with 14% and 18% of Australians and Alaskans, respectively. Clubbing was present in nearly half of the NZ children, compared with 10% of Australian and 5% of Alaskan children. Only 12% of Australians had a normal ear examination, compared with three-fourths of Alaskan and NZ subjects (Table 2).

Comparison of Children With HRCT-Confirmed Bronchiectasis and Other CSLD Children

Many Australian and Alaskan study children lived in remote communities without access to HRCT scanning facilities. Most (91%) of NZ children, 54% of Australian children, and only 12% of Alaska children had HRCT-confirmed bronchiectasis at enrollment; the other children had CSLD (i.e., symptoms suggestive of bronchiectasis without a HRCT-confirmed diagnosis; E-Table 1). Children with HRCT-confirmed bronchiectasis were similar to those without HRCT confirmation, except that they were significantly older (4.0 vs. 2.7 years,

$P = 0.001$), were more likely to be taking regular antibiotics (69% vs. 30%, $P < 0.001$), and to have digital clubbing (26% vs. 7%, $P = 0.001$) on initial examination.

Comparison of Study Children With Respective Regions and Countries

We compared demographic characteristics and known risk factors in the study children from Australia, Alaska, and NZ with those of their respective local indigenous regional populations and their country's indigenous and general population (Table 3), and found interesting similarities and disparities across the three countries. In all study settings, exposure to environmental risk factors for ALRIs (e.g., education, lack of running water) among the study children was much higher than in their country's general population. Other than overcrowding in Australia and Alaska, these were however similar to that recorded for their local indigenous regional population. In contrast, the biological risk factors of premature birth and hospitalized ALRI occurred substantially more often in study children than in their local indigenous regional population.

DISCUSSION

This is the first study that uses standardized methodology to evaluate possible risk factors for CSLD/bronchiectasis in indigenous children from Australia, NZ, and Alaska US and compares these factors to their local indigenous and their national populations. Within these indigenous study cohorts from three developed countries there were some unique country-specific environmental factors (e.g., lack of running water in Alaskan children, lack of refrigerators in Australian children), comorbidities (e.g., low birth weight (LBW) and malnutrition in Australian indigenous children) and clinical features (wheezing in AN children). Not surprisingly, all study cohorts experienced significant disparities in poverty indices. Except for household crowding, most poverty indices in study children were similar to expected in their regional indigenous populations, but study children experienced an increased frequency of ALRI and prevalence of preterm birth compared with their respective regional indigenous population.

Study children from all three countries experienced a common pathway of early and recurrent pneumonia with subsequent development of CSLD/bronchiectasis.[22] All cohorts experienced an early onset age of ALRIs (median 3.7 months), a high proportion (90%) of hospitalization for ALRIs, and a high number of pneumonia episodes (median 3) beginning in the first year of life. ALRIs, especially pneumonia, are major predictors of CSLD/bronchiectasis.[4,22,23] Indigenous children from Alaska, US,[12] Australia,[24] and NZ[25] experience hospitalization rates for ALRI or pneumonia that are at least three times higher than their non-indigenous counterparts. Among all indigenous children from Australia and Alaska, the ALRI attack rate is much higher in poor, remote populations. Australian indigenous children from the NT have one of the highest annual rates (up to 7%) of radiographically confirmed pneumonia.[26] Similarly, the rate of ALRI hospitalizations of American Indian/Alaska Native (AI/AN) infants[27] is twice that of the general US infant population[28]; however, among AI/AN children, Alaskan YK Delta infants experience the highest ALRI hospitalization rates, sevenfold higher than for the general US population.[13] Indigenous children also have an increased frequency of repeated hospitalizations for pneumonia,[2] and in all three countries, recurrent pneumonia has been linked with development of bronchiectasis.[2,23,29]

Indigenous study children, especially from Australia, demonstrate evidence of inequities in general health including LBW (<2,500 g), prematurity and ear disease. LBW was more common among Australian study children than their Alaskan or NZ counterparts. The LBW rate for indigenous children from the NT (where most Australian study children reside) is 14.3% which is more than twice the rate for all Australian infants,[30] while similar disparities occur for prematurity (Table 3).[31] AN and non-native Alaskan infants have similar rates of LBW, but AN infants have a higher rate of prematurity.[32] LBW and prematurity are major risk factors for ALRI (including bronchiolitis)[33] and bronchiectasis.[34]

Inequities in environmental factors are also marked. More than 92% of Alaskan study children lived in households with >1 person per room compared with 6% of US general population (Table 3).[35] Similar inequities in overcrowding are observed using Canadian Crowding index for Australia and NZ households (Table 3).[20,21] In Australia, housing characteristics for the cohort is representative of remote communities where there are five to seven people per room.[36] Nearly half of Alaska participant households lacked running water, compared with 0.6% of US households (Table 3).[15] Lack of in-home running water is common in AN homes in the YK Delta (Table 3) and associated with higher rates of ALRI and respiratory syncytial virus (RSV) hospitalization, and invasive pneumococcal disease.[14–16] Alternatively, while most Australian study homes were plumbed for water, functional household appliances, such as refrigerators (28%), were frequently unavailable. In a study of Aboriginal houses, only 6% had functional appliances for food preparation and storage space, exacerbating food insecurity.[37] Also, Alaskan (48%) and Australian households (23%)

TABLE 3— Demographic Characteristics and Known Risk Factors for Respiratory Infection in Indigenous Bronchiectasis Study Children From Australia, Alaska United States, and New Zealand, Compared With Their Respective Indigenous Populations and General Populations, 2004–2010

Demographic characteristics	Study	Australia local indigenous population	National population
Household	%	%	%
Overcrowding[a]	84.3	58[b]	2.6[21]
Caregiver education			
High school graduate	12.4 (Female)	31[c 42]	83[c 42]
Bachelor's degree	0.0	3.6 (Remote)[43]	25[43]
Risk factors			
Breast feeding	86.8	84.1 (Urban)[44] 98 (Remote)[44]	88[45]
Tobacco exposure in utero	58.9	35.4[44]	51 (Indigenous)[43] 15 (Non-indigenous)
Smoke exposure (any)	84.5	98[46]	65 (Indigenous)[43] 32 (General)[21]
Premature	37.1	14[31]	14 (Indigenous)[31] 8 (General)[31]
Low birth weight (<2,500 g)	37.4	13[31]	13.1 (Indigenous)[47]
Proportion with hospitalized acute lower respiratory infection (ALRI)	87.6	49.2[34]	6.1 (General)[47] 4[14]
Age in months at first hospitalized pneumonia (median)	6.1 months	15 months[26]	N/A

Demographic Characteristics	Study	United States local indigenous population	National population
Household			
Overcrowding (>1 person/room)	92.7	39[17]	5.8[48]
No running water (%)	43.9	47[d 17]	0.6[g 35]
Wood burning in house	47.5	37[d 17]	1.7[g 35]
Educational attainment			
High school graduate (female)	80.5	80 (Both sexes)[e 49]	85.6[f 50]
Bachelor's degree	0.0	13[e 49]	27.3[f 50]
Risk factors			
Breast feeding	63.4	79[17]	77.1[51]
Tobacco exposure in utero	87.5	43.4[52]	12.8[51]
Smoke exposure (any)	73.2	58[17]	12.2 (National)[53] 9.6% (Alaska)[32]
Premature	23.3	12.8[32]	8.2 (National)[53]
Low birth weight (<2,500 g)	12.5	5.9[32]	5.7% (Alaska)[32]
Hospitalized ALRI (%)	95.1	41.2 per 1,000 (Alaska Native)[h 13]	13.8 per 1,000[h 13]

Demographic characteristics	Study	New Zealand indigenous population	National population
Household			
Overcrowding[a]	50.0	23 (Maori)[i 20] 43 (Pacific)[i 20]	10[i 20]
Caregiver education			
High school graduate	50 (female)	52.0 (Pacific)[j 54] 65.4 (Maori)[j 54]	75[j 54]
Bachelor's degree	7 (female)	8.3 (Pacific)[j]	22[j 54]
Risk factors			
Breast feeding	73.8	58 (Maori)[k55] 53 (Pacific)[k55]	65[k 55]
Tobacco exposure (any)	33.3	59.3 (Maori)[l 55] 48.1% (Pacific)[l 55]	35.3[l 55]
Premature	21.4	6.6 (Maori)[55] 5.6 (Pacific)[55]	6[55]
Low birth weight (<2,500 g)	23.1	6.8 (Maori)[55] 5.6% (Pacific)[55]	5.6[55]
Hospitalized ALRI	92.9	6.7/1,000 (Maori)[m 56] 14.0/1,000 (Pacific)[m 56]	5.0 per 1,000[m 56]

[a]Defined by Canadian Crowding Index. http://www.abs.gov.au/ausstats/abs@.nsf/0/F4302CEC55D5B8EECA2574390014A785?opendocument.[21]
[b] http://www.abs.gov.au/ausstats/abs@.nsf/Lookup/4725.0Chapter830Apr%202011.
[c]Australian Bureau of Statistics. March 2011: Year 12 Attainment. Young adults 20–24 years old. http://www.abs.gov.au/AUSSTATS/abs@.nsf/Lookup/4102.0Main+Features40Mar+2011.[42]
[d]Households of control children from Yukon Kuskokwim Delta.[17]
[e]2008 Educational attainment for American Indians and Alaska Native 25 years and older.[49]
[f]Educational Attainment 2006–2010 U.S. population 25 years and older http://factfinder2.census.gov/faces/tableservices/jsf/pages/productview.xhtml?pid=ACS_10_5YR_S1501&prodType=table.[50]
[g]US Census Summary 2000 http://www.census.gov/prod/2002pubs/c2kprof00-us.pdf.
[h]Average annual lower respiratory infection hospitalization rate for children <5 years old.
[i]Defined by Canadian Crowding Index http://www.socialreport.msd.govt.nz/economic-standard-living/household-crowding.html.[20,21]
[j]Educational attainment, New Zealand adult population http://socialreport.msd.govt.nz/knowledge-skills/educational-attainment-adult-population.html.[54]
[k]Exclusive breastfeeding at 6 weeks, 2007. National Breastfeeding Advisory Committee of New Zealand.
[l]Children 0–14 years living in house with smoker.[55]
[m]Data limited to pneumonia. Average annual pneumonia hospitalization rate.

frequently burned wood in the house for heat, in contrast with US general population households (<2%; Table 3). Household wood burning has been associated with increased risk of ALRI's among Navajo children[38] and ALRI hospitalizations among AN children.[17]

Recurrent wheezing illness (77%), wheezing in the past 12 months (90%), and audible wheeze on chest examination (41%) were more common in Alaskan children than in other study children. Alaskan YK Delta children experience very high annual rates (156 per 1,000 infants) of hospitalization associated with RSV,[39] and there is a high prevalence of wheezing (45%) among YK children up to 5 years following RSV hospitalization.[40] The highest recorded RSV hospitalization rate is also from the far north, in Canadian Inuit children.[41] The higher rates of wheezing in the Alaskan cohort may reflect the high rates of post-viral childhood wheezing in the YK child population.

This study's limitations include: (a) possibility of inadequate representation. However, in Australia and Alaska, the clinics where children were recruited are the health facilities where these indigenous children access health care, and in NZ, they are the referral health service for children with CSLD/bronchiectasis. Therefore, with high enrollment response rate (99%) and sequential enrollment of children during pulmonary clinic visits, we feel we have captured a high proportion of eligible children with severe CSLD. (b) Observation bias may be present as different research team members collected data and interview questions were not validated in each setting. By using standardized data collection forms and structured interview questions we sought to minimize this type of error. Investigators agreed beforehand on clinical assessment issues (e.g., definitions of bronchiectasis and ALRIs). (c) Information about medical history was obtained retrospectively and therefore was subject to coding and interpretive uncertainties. (d) NZ study children were older than other study children possibly because they required a diagnosis of HRCT-confirmed bronchiectasis. HRCT-confirmed bronchiectasis was an artificial determinant as it was highly dependent on access to HRCT scanning facilities which varied between the three groups Therefore rates and characteristics of children with HRCT-confirmed bronchiectasis cannot be compared across these populations. Since this study was not a case–control study of risk factors, the determination of which risk factors are independently determinative remains speculative. (e) Lastly, due to lack of available data, we could not statistically compare our study cohorts to their respective indigenous population's data in Table 3.

In conclusion, indigenous children from three developed countries with CSLD/bronchiectasis exhibit unique local environmental risk factors, clinical features, and co-morbidities. Compared with the other two countries, Australian children were more likely to be LBW and to have a high rate of suppurative middle ear disease, while Alaskan children experienced a high prevalence of wheezing and were less likely to have access to plumbed water. In common with their respective local indigenous populations, all groups experienced significant disparities in poverty indices; however, household crowding, prematurity, and a high frequency and early onset of ALRIs were more common in study children than their local indigenous population and appear particularly associated with development of bronchiectasis. Persistence of social and environmental risk factors for transmission of respiratory pathogens contributes to this continuing health inequity in indigenous children. Addressing these general and specific equity issues is imperative to reducing the burden of CSLD/bronchiectasis and chronic respiratory morbidity.

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