Risk Factors for Hospitalization With Lower Respiratory Tract Infections in Children in Rural Alaska

WHAT'S KNOWN ON THIS SUBJECT: Rural Alaska children have high rates of hospitalization with lower respiratory tract infections from a variety of pathogens. Past studies of risk factors for respiratory syncytial virus infection associated medically high-risk status, household crowding, and infant feeding practices with hospitalization.

WHAT THIS STUDY ADDS: This study reveals the importance of medically high-risk status and infant feeding practices as important factors in respiratory hospitalization. In addition, we identified woodstove use and the absence of 2 or more sinks in household as risk factors for hospitalization.

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KEY WORDS

pneumonia, respiratory infectious diseases, case-control study, risk factors, Alaska Native

ABBREVIATIONS

hMPV—human metapneumovirus
hPIV—human parainfluenza virus
LRTI—lower respiratory tract infection
NPS—nasopharyngeal swab
OR—odds ratio
RSV—respiratory syncytial virus
RT-PCR—reverse transcriptase real-time polymerase chain reaction
RT-qPCR—reverse transcriptase real-time quantitative PCR
YKD—Yukon Kuskokwim Delta

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abstract

OBJECTIVE: Lower respiratory tract infections (LRTIs) are a major cause of morbidity for children worldwide and particularly for children from developing and indigenous populations. In this study, we evaluated risk factors for hospitalization with LRTI in a region in southwest Alaska.

METHODS: The study was conducted from October 1, 2006, to September 30, 2007, in the Yukon Kuskokwim Delta region of Alaska. Cases were recruited from children <3 years of age hospitalized with LRTI. Controls were recruited during visits to the surrounding communities in the region and matched posthoc to cases on the basis of subregion, season, and age. Parents were interviewed for potential risk factors, and medical records were reviewed. Participants had a nasopharyngeal swab sample taken for polymerase chain reaction (PCR) testing for a panel of respiratory viruses. Samples positive for respiratory syncytial virus, human metapneumovirus, or parainfluenza type 3 were quantitated by reverse transcriptase real-time quantitative PCR.

RESULTS: One hundred twenty-eight cases were matched to 186 controls. In a multivariable conditional logistic regression model, significantly ($P < .05$) increased risk of hospitalization was associated with medically high-risk status, having a woodstove in the house, being bottle fed, and vomiting after feeding; living in a house that had 2 or more rooms with sinks was a protective factor. Viral loads in hospitalized cases were significantly higher than those in controls, but a strict cutoff level was not observed.

CONCLUSIONS: Several risk factors for LRTI hospitalization were identified in this high risk population. Some factors are amenable to environmental and behavioral interventions. *Pediatrics* 2012;129:e1220–e1227

Lower respiratory tract infections (LRTIs) remain a major cause of morbidity and mortality worldwide, particularly for children.[1] Viruses important in LRTI hospitalization in infants include respiratory syncytial virus (RSV), influenza, human parainfluenza virus (hPIV),[2,3] and human metapneumovirus (hMPV).[4]

American Indian and Alaska Native children are disproportionately affected by LRTI.[5] From a study conducted in 1993–1996, the rates of infant RSV hospitalization in the Yukon-Kuskokwim Delta (YKD) region of western Alaska averaged 156/1000 infants and were among the highest ever reported.[6] Since that time, RSV rates have decreased, but LRTI hospitalizations remain at high levels.[7] In a previous study, we found the presence of high-risk medical conditions (prematurity, chronic lung disease, congenital heart disease) and household crowding associated with increased risk of RSV hospitalization, whereas breastfeeding lowered risk.[8]

During 2005 through 2007, we conducted a study to determine the etiology of all LRTI in YKD children <3 years of age. Using reverse transcriptase real-time polymerase chain reaction (RT-PCR) to identify a panel of viruses, this study revealed that RSV, hMPV, hPIV1-3, and influenza virus were associated with hospitalization for LRTI in children.[9] In this present article, we describe a case-control analysis nested in the overall study to evaluate risk factors for any LRTI hospitalization in cases compared with nonhospitalized control children. In addition, the viral loads of RSV, hMPV, and hPIV3 were compared in cases and controls.

METHODS

This study is a case-control evaluation nested in a larger study of LRTI conducted in the YKD region.[9] The area has a population of ~25 000 persons, 85% of whom are Alaska Native, primarily Yupik Eskimo. The residents live in the hub community of Bethel (2004 population 5888 persons) and 48 surrounding villages ranging from 50 to 1200 persons. Houses are typically small (34% have 1–2 rooms) and half lack complete plumbing facilities, defined as hot and cold piped water, a bathtub or shower, and a toilet.[10] Nearly all homes with running water also have a flush toilet.

The parent study was conducted from October 2005 to September 2007. All children <3 years of age hospitalized with an LRTI were eligible for enrollment as cases. Study nurses administered a questionnaire to consenting parents; topics included infant feeding, household crowding, household allergens, family history of allergy and asthma, water, and sanitation. In addition, the cases underwent a nasopharyngeal swab (NPS) to use for RT-PCR detection of a panel of viruses.

During the second year of the overall project (October 2006 through September 2007), study nurses recruited nonhospitalized control children during trips to YKD villages. Over the course of the year, nurses made trips to 29 villages throughout the region. When in the villages, nurses offered enrollment as controls to all children <3 years of age who had not been hospitalized with a respiratory diagnosis since October 2006 and who did not have an onset of respiratory symptoms within the last 3 days. Informed consent was obtained, and parents were administered the interview questionnaire. An NPS was collected from the control child for RT-PCR. The medical records of all participants were reviewed for recent respiratory illness encounters, influenza vaccination, and high-risk medical status. A child was considered medically high-risk if he/she had a history of prematurity (<35 weeks' gestation), congenital heart disease, or chronic lung disease.

The study was approved by the institutional review boards of the Alaska Area tribal health system and the Centers for Disease Control and Prevention, and by the YK Health Corporation, Alaska Native Tribal Health Consortium, and Southcentral Foundation.

Laboratory Methods

NPSs were tested by singleplex RT-PCR to detect RSV, hPIV 1/2/3, influenza A/B, and hMPV as previously described.[9] Additional viruses identified included adenovirus, rhinovirus, and coronavirus; these viruses were identified similarly in cases and controls and therefore were not considered primary pathogens producing LRTI hospitalizations for the subgroup analysis. All samples positive for RSV, hPIV3, or hMPV were tested a second time with a quantitative RT-PCR (RT-qPCR) assay. For the quantitative assays, the primer and probes sequences and reaction components were the same as for the original RT-PCR assays. The threshold cycles of the NPS were compared with a standard curve generated by amplification of known quantities of RNA for each virus. Results were expressed as copies/mL of original sample.

To prepare the RNA transcripts, High Fidelity Taq (Roche; Indianapolis, IN) was used to synthesize complementary DNA amplicons. Amplicons were cloned into vector pCR2.1-TOPO (Invitrogen; Carlsbad, CA). The plasmids were transformed into One Shot (Invitrogen) competent *Escherichia coli* and harvested. Tenfold serial dilutions of each transcript were added to the RT-q PCR reaction in duplicate except for the lowest 2 dilutions, which were added in triplicate.

Case/Control Matching

Only cases and controls from study year 2 (October 2006 through September 2007) were included in the case-control

study. For cases with multiple hospitalizations, the first hospitalization for which a case was enrolled was used for analysis. To account for age, subregion, and season, we employed a posthoc matching process. We tried to match each case with 2 controls from the same subregion, recruited during the same 3-month period (October through December, January through March, April through June, July through September), and of approximately the same age (within 2 months of age for cases <6 months of age, within 3 months of age for cases 6–23 months of age, within 4 months of age for older cases), but used only 1 control if a second could not be identified.

Statistical Analysis

Case- and control-subjects were compared by using conditional logistic regression to preserve the case-control matching. Conditional multivariate logistic regression models were created by using a backward stepwise selection process with re-entry. Variables were originally entered into the model if their bivariate significance level was <0.20. When correlation among variables (eg, bottle-feeding measures) made it impossible to fit all variables simultaneously, multiple models were run and the best fitting model selected. Subgroup analyses were performed with cases positive for RSV, hMPV, and hPIV pathogens and their matched controls. It was also performed on the combined subset of these cases and those for whom these pathogens could not be identified. The number of cases positive for influenza was too small for a separate analysis, but they are included in the combined subset. An analysis was also performed to determine interactions between identified risk factors and whether a known pathogen was identified in the case.

Viral loads were compared by using a Wilcoxon rank-sum test or a nonparametric test for trend. All P values reported are 2-sided, and $P < .05$ was considered statistically significant.

RESULTS

From October 1, 2006, to September 30, 2007, there were 352 hospitalizations with LRTI in YKD children <3 years of age. Two hundred eleven cases were recruited (60%), and 128 cases for whom matches were found were available for analysis (Fig 1). Cases recruited into the study did not differ from those not recruited in age, gender, subregion, or season.[9] Overall, an estimated 29% (555/1939) of children <3 years of age living in the region were recruited as controls during the study year. The cases and controls did not differ significantly in age, subregion, or season (Table 1). The cases who could not be matched to available controls were significantly younger than the matched cases (median age 6.2 months vs 10.0 months, $P = .006$) but did not differ significantly in the other factors listed.

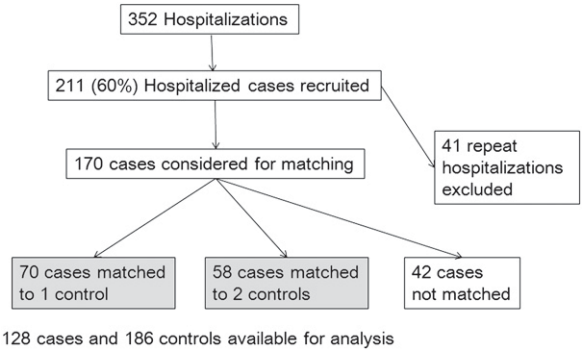

FIGURE 1
Schematic of recruitment of cases hospitalized with LRTI and matched controls, October 1, 2006, through September 30, 2007, YKD, Alaska.

Risk Factors

In the bivariate analysis, cases were significantly more likely than controls to be medically high-risk infants, have been born prematurely, have a family history of asthma or chronic coughing, and regularly choke during or vomit after feeding (Table 2). They were also more likely to be bottle-fed and receive a bottle at night. They were more likely to live in a house with 2 or more people per room and to live in a house where a woodstove was used, and they were less likely to live in a house with 2 or more rooms with sinks.

After selection for the multivariable conditional logistic model, the variables that remained were as follows: medically high-risk infant, regularly vomited after feeding, bottle-fed, and live in a house where a woodstove was used as risk factors. Living in a house with 2 or more rooms with sinks was a protective factor (Table 3).

Subgroup Analyses by Pathogen

The results of the analysis by subgroup are presented in Table 4. The table presents the results of the final multivariate model for each subgroup, as well as the bivariate results for each subgroup for those risk factors that remained in at least 1 final subgroup model. For all the subgroups except RSV (for which palivizumab was given to medically high-risk infants), status of the case as a medically high-risk infant was significantly associated with increased risk of hospitalization. Receiving a bottle at night was associated with significantly increased risk for hospitalization: with hMPV or with any or no identified viral pathogen. The presence of ≥6 people in the household was significantly associated

TABLE 1 Demographic Comparison of Case-Control Matching, YKD, Alaska, October 1, 2006, through September 30, 2007; Cases Were Hospitalized With LRTIs

		Cases (n = 128), n (%)	Controls (n = 186), n (%)
Boy		66 (52)	97 (52)
		P = .918	
Age, mo			
	<6	42 (33)	54 (29)
	6–11	30 (23)	43 (23)
	12–23	39 (30)	59 (32)
	24–35	17 (13)	30 (16)
		P = .848	
	Median	10.0 mo	11.4 mo
		P = .294	
Subregion			
	Bethel	10 (8)	10 (5)
	Bethel area	28 (22)	37 (20)
	South Coastal	25 (20)	38 (20)
	North Coastal	39 (30)	60 (32)
	Lower Yukon	12 (9)	21 (11)
	Upper River	14 (11)	20 (11)
		P = .942	
Season			
	Oct–Dec	34 (27)	50 (27)
	Jan–Mar	37 (29)	50 (27)
	Apr–Jun	39 (30)	56 (30)
	Jul–Sep	18 (14)	30 (16)
		P = .954	

TABLE 2 Case/Control Comparison; Potential Risk Factors, YKD, Alaska, October 1, 2006, through September 30, 2007

	Cases (n = 128), n (%)	Controls (n = 186), n (%)	Matched Analysis	
			Odds Ratio (95% CI)	P
Medically high-risk infant	43 (34)	21 (11)	4.53 (2.34, 8.77)	<.001[a]
Premature infant	23/127 (18)	15 (8)	2.44 (1.24, 4.79)	.010[a]
Boy	62 (48)	89 (48)	0.91 (0.56, 1.46)	.688
Family history of asthma	48/122 (39)	42/185 (23)	2.21 (1.28, 3.82)	.004[a]
Family history of chronic cough	22/122 (18)	16/185 (9)	2.26 (1.10, 4.64)	.027[a]
Family history of allergy	25/120 (21)	49/185 (26)	0.72 (0.40, 1.27)	.254
Received influenza vaccination this season	44 (34)	74 (40)	0.72 (0.39, 1.34)	.300
Regularly choke during feeding	32 (25)	14/184 (8)	4.12 (1.92, 8.84)	<.001[a]
Regularly vomit after feeding	28/126 (22)	20/183 (11)	2.75 (1.30, 5.83)	.008[a]
Regularly choke during or vomit after feeding	44 (34)	28/184 (15)	3.29 (1.72, 6.29)	<.001[a]
Ever breastfed	92/127 (72)	147 (79)	0.68 (0.39, 1.17)	.161
Ever breastfed by mother who used smokeless tobacco during that time	51/124 (41)	71/180 (39)	1.04 (0.64, 1.70)	.868
Ever breastfed by mother who did not use smokeless tobacco during that time	41/127 (32)	76 (41)	0.69 (0.42, 1.12)	.134
Currently bottle fed	107 (84)	128 (69)	2.52 (1.36, 4.66)	.003[a]
Given bottles at night	91/123 (74)	105/182 (58)	2.63 (1.46, 4.71)	.001[a]
Given a propped-up bottle	16 (13)	16 (9)	1.49 (0.70, 3.18)	.302
Given a bottle while lying down	40 (31)	59 (32)	1.08 (0.63, 1.86)	.782
≥6 people in household	88/127 (69)	123 (66)	1.14 (0.68, 1.91)	.630
≥4 children (≤15 y of age) in household	58/127 (46)	84 (45)	1.02 (0.64, 1.63)	.936
House has <4 rooms	50/127 (39)	157/185 (31)	1.45 (0.89, 2.35)	.132
≥2 people share bed with child	57/124 (46)	86 (46)	1.08 (0.66, 1.76)	.770
≥2 people/room	65/127 (51)	72/185 (39)	1.72 (1.04, 2.84)	.034[a]
≥1 smokers live in household	63 (49)	107 (58)	0.73 (0.47, 1.13)	.158
≥1 persons smoke inside house	3 (2)	1 (1)	4.37 (0.44, 43.1)	.206
Mother smoked during pregnancy	31/121 (26)	40/183 (22)	1.30 (0.75, 2.27)	.347
House has visible mold	70/120 (58)	97/182 (53)	1.21 (0.74, 1.97)	.455
Woodstove used for heating and/or cooking in house	60/125 (48)	69 (37)	1.82 (1.09, 3.02)	.021[a]
Pets in house	23/126 (18)	38 (20)	0.80 (0.44, 1.48)	.478
Running water in house	56/126 (44)	98 (53)	0.64 (0.37, 1.12)	.117
Sinks in 2 or more rooms	83/126 (66)	153/185 (83)	0.41 (0.23, 0.73)	.002[a]

95% CI, 95% confidence interval.
[a] $P < 0.05$.

with risk of hospitalization without an identified viral pathogen. Living in a home with <4 rooms was significantly associated with risk of hospitalization with hPIV. Woodstove use in the home was associated with increased risk of hospitalization without an identified viral pathogen. There was not a statistically significant difference between those with an identified viral pathogen and those without an identified viral pathogen in the odds ratio (OR) associated with any of these risk factors. However, for both ≥6 people in the household and presence of a woodstove in the home, the differences in the ORs between the 2 groups trended toward statistical significance (P = .062 and P = .098, respectively).

Viral Load Quantitation

NPSs with positive RT-qPCR results were significantly more common ($P < .001$) for cases (72/128, 56%) than for controls (24/186, 13%). Among participants positive for RSV or hMPV, cases had significantly ($P < .05$) higher viral loads than controls (Table 5). For all 3 viruses, there was considerable overlap of viral load between case and control participants (Fig 2). Exclusion of the PCR-positive controls did not substantially change the primary risk factor analysis (data not shown).

The viral load of RSV, hMPV, and hPIV3 did not vary significantly by age or between medically high-risk and other cases ($P > .05$).

DISCUSSION

In this study, we examined risk factors for LRTI hospitalization among children <3 years of age in a remote region of Southwest Alaska. This is the first study to examine risk factors for all LRTI hospitalizations in this region with high LRTI rates. We found increased risk associated with medically high-risk status, bottle-feeding, vomiting after feeding, and use of a woodstove in the home, and decreased risk associated with living in a house having sinks in 2 or more rooms. Some of these risk

TABLE 3 Results of Multivariate Conditional Logistic Regression, Hospitalized LRTI Cases Versus Nonhospitalized Controls, YKD, Alaska, October 1, 2006, through September 30, 2007

	OR (95% CI)	*P*
Medically high-risk infant	3.80 (1.80, 8.04)	<.001[a]
2 or more rooms with sinks in house	0.29 (0.14, 0.58)	<.001[a]
Woodstove used for cooking and/or heating in house	2.21 (1.20, 4.10)	.011[a]
Regularly vomit after feeding	2.95 (1.21, 7.20)	.018[a]
Currently bottle fed	2.28 (1.07, 4.85)	.032[a]

Likelihood ratio χ^2 = 46.7; df = 5; $P < .001$. 95% CI, 95% confidence interval.
[a] $P < 0.05$.

factors, bottle-feeding and medically high-risk, are similar to those documented for the RSV hospitalizations studied previously,[8] whereas woodstove use was a risk factor for LRTI in American Indian children in the southwest United States.[11] The previous finding that demonstrated the importance of in-home plumbing in preventing LRTI hospitalization[12] has been further refined to link 2 or more sinks in the home with a lower risk of hospitalization.

Prematurity and, more generally, medically high-risk status are widely recognized as risk factors for RSV,[13] hMPV,[14] and LRTI mortality in the first year after birth[15]; they are reflected in the recommendations for RSV prophylaxis.[16] Use of palivizumab has decreased the rate of RSV hospitalization in medically high-risk YKD children, and medically high-risk status is no longer a significant risk factor in the RSV subgroup.[17]

Woodstove use was a risk factor for hospitalization. Poor indoor air quality is an established risk factor for respiratory hospitalization worldwide.[1] Woodstove use has been documented as a risk factor in Native American populations in the southwest[11] but not previously in Alaska. Use of woodstoves for cooking and/or heating was common in both case (48%) and control (37%) households. Data from the 2000 census revealed 6.7% of YKD households reported using wood as the primary heating fuel, compared with 3.6% of other Alaska households, and 1.7% in the United States overall.[10] Woodstove use in our study may represent a supplemental heat source. There was a trend for woodstove use to be a stronger risk factor for hospitalization in children where a viral pathogen was not identified. This may indicate particulate's role in causing noninfectious respiratory problems such as asthma. Poor indoor air quality was associated with LRTI in the Baffin region with high rates of respiratory disease.[18]

TABLE 4 Case/Control Comparison by Identified Viral Pathogen; Bivariate and Multivariate Analyses, YKD, Alaska, October 1, 2006, through September 30, 2007

	RSV	hMPV	hPIV	Any Known[a]	Unknown[b]
No. of Cases	28	36	21	80	48
No. of Controls	40	48	31	114	72
Medically high-risk infant, OR (*P*)					
Multivariate results	NS[d]	11.1 (.049)[c]	10.8 (.028)[c]	3.90 (.003)[c]	3.50 (.043)[c]
Bivariate results	3.07 (.120)	10.5 (.027)[c]	4.46 (.027)[c]	4.79 (<.001)[c]	4.17 (.006)[c]
Given bottles at night, OR (*P*)					
Multivariate results	NS	2.28 (.034)[c]	NS	1.73 (.017)[c]	2.39 (.009)[c]
Bivariate results	1.24 (.551)	2.36 (.021)[c]	2.67 (.039)[c]	1.88 (.005)[c]	2.12 (.006)[c]
≥6 people in household, OR (*P*)					
Multivariate results	NS	NS	NS	NS	5.35 (.035)[c]
Bivariate results	1.09 (.864)	0.69 (.482)	0.88 (.835)	0.80 (.486)	2.43 (.076)
House has <4 rooms, OR (*P*)					
Multivariate results	NS	NS	15.5 (.020)[c]	NS	NS
Bivariate results	2.04 (.178)	0.90 (.820)	6.32 (.020)[c]	1.92 (.039)[c]	0.90 (.787)
Woodstove in home, OR (*P*)					
Multivariate results	NS	NS	NS	NS	6.23 (.009)[c]
Bivariate results	1.22 (.686)	1.61 (.351)	1.43 (.624)	1.32 (.391)	3.43 (.010)[c]
2 or more rooms with sinks in home, OR (*P*)					
Multivariate results	NS	NS	NS	NS	NS
Bivariate results	0.30 (.081)	0.58 (.350)	0.10 (.030)[c]	0.31 (.004)[c]	0.57 (.187)
Regularly vomit after feeding, OR (*P*)					
Multivariate results	NS	NS	NS	NS	NS
Bivariate results	2.56 (.448)	1.86 (.342)	NA	2.80 (.059)	2.70 (.064)
Currently bottle fed					
Multivariate results, OR (*P*)	NS	NS	NS	NS	NS
Bivariate results	1.71 (.447)	3.20 (.076)	1.59 (.471)	2.37 (.029)[c]	2.79 (.051)
χ^2 for multivariate model, (*P*)	NA	12.5 (.002)[c]	15.0 (<.001)[c]	19.0 (<.001)[c]	25.9 (<.001)[c]

This table includes results of the final multivariate model for each subgroup, as well as the bivariate results for each subgroup for those risk factors that remained in at least 1 final subgroup model or in the overall multivariate model.
[a] Any known includes any case positive for RSV, hMPV, hPIV, or influenza. Eleven cases were positive for more than 1 virus.
[b] Unknown refers to those negative for RSV, hMPV, hPIV, and influenza. Three of these were positive for *Streptococcus pneumoniae*.
[c] $P < 0.05$.
[d] NS, Term is non-significant in the final multivariate model for that subgroup.

TABLE 5 Viral Load Quantities of selected virus among cases and controls positive by RT-qPCR on NPS

	Median (copies/mL)			≥1 × 10^5 copies/mL		
	Case	Control	*P*	Case, *n* (%)	Control, *n* (%)	*P*
RSV	6.12 × 10^6 (n = 25)	1.05 × 10^5 (n = 7)	.013[a]	24/25 (96)	4/7 (57)	.025[a]
hMPV	1.90 × 10^5 (n = 32)	1.02 × 10^4 (n = 12)	.002[a]	17/32 (53)	0/12 (0)	.001[a]
hPIV3	3.61 × 10^6 (n = 17)	3.19 × 10^4 (n = 8)	.145	14/17 (82)	3/8 (38)	.061

[a] $P < 0.05$.

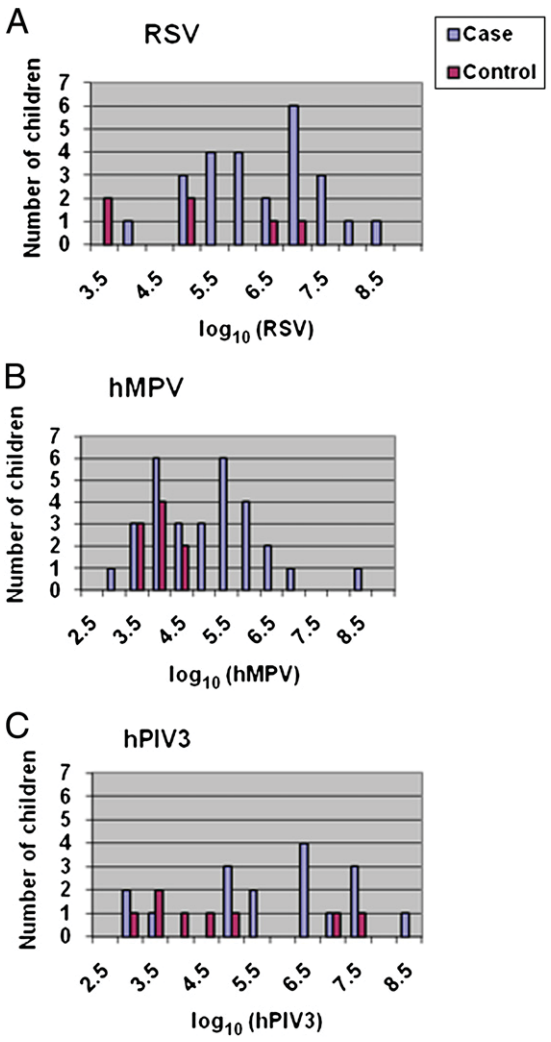

FIGURE 2
Viral load (copies/mL) of selected virus among cases and controls positive by RT-qPCR on NPS. A, RSV; B, hMPV; C, hPIV3.

In contrast to studies elsewhere,[19] specifically in indigenous populations,[20–22] neither smoking by a household member nor smoking by the mother during pregnancy was associated with increased hospitalization risk. Smoking is common (39%) among Alaska Native women,[23] but smoking in the house was reported rarely (1%). Our data match other reports from YKD where only 2% of newborns have household environmental tobacco exposure.[24] Because smoking is common, all children may be exposed to tobacco smoke, although educational efforts may have reduced smoking inside the home. An earlier YKD study revealed cotinine levels slightly above those of children from nonsmoking households in the contiguous United States.[25]

Use of a bottle for feeding and regularly vomiting after feeding were both risk factors for hospitalization. Our previous study of RSV hospitalization had revealed breastfeeding to be protective,[8] as have other studies.[20,21,26] Breastfeeding initiation remains common in this population with 92% of newborns initially breastfed, but with breastfeeding at 8 weeks of age declining to 76%.[24] Gastro-esophageal reflux, manifested by vomiting after feeding, with a risk of aspiration, has been noted in some children with RSV bronchiolitis.[27] The authors of a study among Canadian indigenous children suggested that difficulty swallowing, manifested by choking during feeding, may be a risk factor for LRTI.[28]

The presence of sinks in 2 or more rooms in the home was protective. This association supports the importance of access to adequate volumes of clean water in the prevention of infectious diseases,[1] particularly "water-washed diseases."[12,29] These studies suggest that increased access to running water in the home leads to increased hand-washing and possibly decreased transmission of disease. The former study revealed an increasing rate of pneumonia and RSV hospitalizations in children from YKD villages with a lower percentage of homes with running water. In our study, the effect of rooms with sinks was stronger than for "running water in home" where only a trend was seen. The measure of multiple rooms with sinks likely reflects the importance of ease of access to water for hand-washing.

Household crowding was previously identified as an independent risk factor for RSV hospitalization in this population[8] and has been shown in other arctic populations.[18,21] Two or more persons per room was associated with hospitalization in the bivariate analysis, but no overall effect of household crowding was seen in our multivariate analysis. Both larger household size (number of persons) and smaller numbers of rooms were statistically significant in subgroup analyses.

Few studies have been able to differentiate risk factors for hospitalization from multiple viral pathogens. Most have suffered from limited power to detect differences.[13,14] Here status as a medically high-risk infant was associated with increased risk of hospitalization in 4 of 5 subgroups, and the lack

of significance for RSV is explained by the successful use of palivizumab.[17] In addition, measures of household crowding were statistically associated with increased risk in some subgroups. The goal of our subgroup analysis was exploratory, looking for other possible avenues of prevention.

Thirteen percent of control subjects had samples positive by RT-PCR. Interpretation of positive RT-PCR results has been discussed widely.[30] We were able to show relatively higher levels in our hospitalized case-patients; however, considerable overlap occurred. Therefore, a quantitative PCR threshold to distinguish cases from controls could not be established. Presumably, the control children had been infected previously, but their infections did not result in hospitalization. Martin et al[31] found an increase in disease severity associated with higher levels of RSV and hMPV.

Our study has a number of limitations. Not all eligible cases were recruited, and we were not able to recruit matched controls for all the cases; these reduced the study's power. We attempted to eliminate known sources of bias by matching on region, time of year, and age, but cases who could not be matched tend to be younger than other cases.

Vaccination remains the primary means of prevention of many infectious diseases. Influenza vaccination of children is relatively common in this population as ~50% of children <3 years of age were vaccinated[9]; 31.8% of children 6 to 23 months of age nationwide received 1 or more doses of influenza vaccine during 2006–2007.[32] Development of vaccines against RSV[33] and hPIV[34] continues, but no new vaccines are anticipated in the near future.

Prophylaxis against RSV with human monoclonal antibody has been successful in preventing RSV hospitalization in medically high-risk infants for whom it is recommended[14] and been used in Alaska.[17] The Canadian Pediatric Society has suggested expanded use for Inuit infants of all gestational ages in remote communities.[35]

A primary goal of risk factor research is identification of prevention methods. In this study, we identified several risk factors that could be addressed by housing improvements including increasing the number of rural Alaska homes with adequate supplies of in-home running water, decreasing household crowding, and improving household ventilation. Efforts continue to improve water and sanitation services in Alaska, but funding and technical challenges remain; ~25% of rural homes still lack in-home running water.[36] Energy-efficient homes are proposed as a way to reduce heating costs and improve indoor air quality,[37] but sophisticated ventilation is also required.[38] Breastfeeding initiation rates are high, but more could be done to promote continued breastfeeding and educate parents about supplemental feeding as children grow.

CONCLUSIONS

In this study, we identified risk factors for LRTI hospitalization in a population with documented high rates of infection with many respiratory pathogens. A number of these risk factors related to infant feeding, sanitation, and indoor air quality suggest targets for intervention. We also confirmed the importance of LRTI in medically high-risk infants. Prevention of severe early respiratory infections in children is critical to long-term health and development, and improving the health of these children may provide direction for improving the health of children in other high-risk settings.

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