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Acute Viral Respiratory Illnesses in Andean Children: a Household-Based Cohort Study

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Abstract

Background—Few community studies have measured the incidence, severity, and etiology of acute respiratory illness (ARI) among children living at high-altitude in remote rural settings.

Methods—We conducted active, household-based ARI surveillance among children aged <3 years in rural highland communities of San Marcos, Cajamarca, Peru from May 2009 through September 2011 (RESPIRA-PERU study). ARI (defined by fever or cough) were considered lower respiratory tract infections (LRTI) if tachypnea, wheezing, grunting, stridor, or retractions were present. Nasal swabs collected during ARI episodes were tested for respiratory viruses by real-time reverse-transcriptase polymerase chain reaction. ARI incidence was calculated using Poisson regression.

Results—During 755.1 child-years of observation among 892 children in 58 communities, 4,475 ARI were observed, yielding an adjusted incidence of 6.2 ARI/child-year (95% CI 5.9 – 6.5). Families sought medical care for 24% of ARI, 4% were classified as LRTI, and 1% led to hospitalization. Two of five deaths among cohort children were attributed to ARI. One or more respiratory virus was detected in 67% of 3957 samples collected. Virus-specific incidence rates per 100 child-years were: rhinovirus, 236; adenovirus, 73; parainfluenza virus, 46; influenza, 37; respiratory syncytial virus, 30; and human metapneumovirus, 17. Respiratory syncytial virus, metapneumovirus, and parainfluenza virus 1-3 comprised a disproportionate share of LRTI compared to other etiologies.

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Conclusions—In this high-altitude rural setting with low population density, ARI in young children were common, frequently severe, and associated with a number of different respiratory viruses. Effective strategies for prevention and control of these infections are needed.

Keywords

influenza; respiratory syncytial virus; human metapneumovirus; acute respiratory infection; Peru

INTRODUCTION

Acute respiratory illness (ARI) is a leading cause of child morbidity and mortality worldwide. Acute lower respiratory tract infections caused 1.3 million deaths among children <5 years of age in 2011, mostly from low-income countries.¹⁻³ However, measuring ARI burden in developing nations is often complicated by limited access to health care and the logistical challenges of conducting population-based surveillance in remote locations,⁴⁻¹⁰ creating a paucity of longitudinal, population-based studies from which incidence rates can be directly calculated.

Respiratory viruses are common causes of ARI, including severe lower respiratory tract infections and pneumonia.^{5-9,11-13} Recent household-based studies of viral ARI among children in developing countries report rates ranging from 1.2 to 2.4 ARI/child-year, with pneumonia rates of 12 to 50 per 100 child-years.^{6,8,9} Several studies have examined the contribution of respiratory viruses to ARI in developing nations,¹³⁻¹⁶ but most are health center-based, relying on passive surveillance and lacking clearly-defined population denominators for calculating incidence rates. There is a particular lack of data regarding incidence and etiology of ARI in rural, high-altitude, low population-density areas, despite higher morbidity and mortality of ARI in such areas.¹⁷ We therefore conducted a prospective, household-based cohort study to calculate ARI incidence and identify ARI-associated viruses among infants and young children in rural highland communities of Peru.

MATERIALS AND METHODS

Study population

The study of Respiratory Infections in Andean Peruvian children (RESPIRA PERU) was conducted in San Marcos Province, department of Cajamarca, in the northern highlands of Peru.¹⁸ Altitude in San Marcos ranges from 1,500 to 4,000 meters; population density is approximately 40 persons/km². A detailed description of the study cohort has previously been published.¹⁸ Briefly, families with children <3 years of age (including newborns) residing within the study communities were eligible for inclusion if they anticipated maintaining residence in the area for at least one year.

Enrollment and follow-up

After obtaining approvals from each community, trained field workers conducted a census to enumerate eligible families, and households with potentially eligible children were invited to participate. After obtaining signed informed consent, field workers collected baseline demographic and socioeconomic information from participating households. Children aged

<3 years, including newborns, were enrolled March 23, 2009 through August 8, 2011 with the aim of maintaining a dynamic cohort of approximately 500 children under observation at any given time. After the initial enrollment, newborns identified in the study area were enrolled to replace children leaving the cohort. Active household-based ARI surveillance was conducted from May 1, 2009 through September 30, 2011. Once enrolled, children were followed until their third birthday, withdrawal of consent, loss to follow-up, death, or end of the study (September 30, 2011), whichever came first.

Household visits

Field workers were recruited locally and trained by the investigators on data and sample collection, and on the recognition of respiratory signs and symptoms through workshops and reviews of educational material prepared by the Pan American Health Organization for training in the Integrated Management of Childhood Illness (IMCI)-WHO protocol. They visited the home of each enrolled child weekly and interviewed the parent or guardian about signs/symptoms of ARI over the preceding week, recording the date of onset, duration, and specific symptoms. If two or more consecutive visits were missed, during the next visit data were collected the fourteen days preceding this visit, but no further. Person-time preceding this 14 days was not considered under observation. At each household visit, field workers assessed children experiencing cough or fever on the household visit day or day prior for the presence of general WHO danger signs (inability to drink or breastfeed, persistent vomiting, convulsions, lethargy, or unresponsiveness) or signs of lower respiratory tract infection (LRTI) including: tachypnea, audible wheezing, intercostal and subcostal retractions, grunting, nasal flaring, stridor, or cyanosis.¹⁹⁻²² Tachypnea was defined as having two respiratory rate (breaths per minute) measurements >60 for infants <2 months of age, >50 for infants 2-11 months of age, and >40 for children 1-2 years of age. The study employed a physician to provide care to children participating in the study; field workers notified the study physician or study nurse by cell phone of children with WHO danger signs or signs of LRTI to arrange a household visit or coordinate referral to the healthcare center.

ARI and LRTI definitions

ARI was defined as the presence of either cough or fever.²² Because infants with influenza and other respiratory viruses can often present with fever in the absence of other respiratory symptoms,^{23,24} fever was included as an independent indicator. An ARI episode encompassed the period from the date of symptom onset to the last day of ARI symptoms that was followed by at least seven days without cough or fever. LRTI was defined by the presence of signs of LRTI described above or one or more of the WHO-IMCI danger signs. This study definition of LRTI was chosen to separate routine, “cold-like” upper respiratory infections from more clinically severe illness and is comparable to the WHO-IMCI designation “pneumonia”.

Collection and handling of nasal samples

Field workers collected nasal swabs (NS) for each ARI episode at the first weekly visit following onset of symptoms. NS were not collected in consecutive weeks, unless manifestations of LRTI developed. Field workers handled NS samples using collection and transport procedures previously described.^{23,24} In brief, one cotton-tipped swab was placed

into each nostril sequentially and rotated beneath the turbinates to collect epithelial cells and absorb secretions. The swab was placed into a tube with Remel M4RT® (Thermo Fisher Scientific Remel Products, Lenexa, Kansas, USA) viral transport medium and delivered in envelopes with cold packs to the local research laboratory in San Marcos within eight hours of collection. Two 800 µL aliquots were preserved as original samples and three 200 µL aliquots were preserved in cryovials with 300 µL lysis buffer (MagNA Pure LC Lysis/Binding Buffer, Roche Diagnostics®, Pleasanton, California, USA or MagMAX Lysis/Binding Solution, Life Technologies®, Carlsbad, California, USA). All vials were stored at -70° C. Samples were shipped on dry ice in batches to Vanderbilt University for detection of the following respiratory viruses using real-time multiplex RT-PCR as previously described:²⁴⁻²⁸ influenza viruses (A, B, and C); respiratory syncytial virus (RSV); human metapneumovirus (MPV); parainfluenza viruses 1-3 (PIV); human rhinovirus (HRV); and adenovirus (AdV).

Data handling

Supervisors reviewed study forms for data completeness at the end of each day, assured prompt delivery of samples to the laboratory, and performed audits of a random subset of households to confirm accuracy of the data collected.

Statistical analyses

Crude incidence was calculated as the number of ARI events observed divided by cumulative person-time under observation and at-risk. Children were not considered under observation during surveillance gaps of >14 days or when lost to follow-up. A minimum of seven asymptomatic days were required between separate ARI episodes; if a child developed ARI symptoms within seven days of his last ARI symptoms they were considered an extension of a single ARI. Therefore, following the symptom onset day children were not considered at risk for a new ARI during the ARI episode or during the first seven days after resolution of ARI symptoms. For calculating LRTI incidence, we conservatively assumed that ARI for which no physical assessment was performed (ARI not observed by the study team) were not LRTI. This was based on our observation that the duration of ARI observed by the study team were longer (median 7 days) than unobserved ARI (median 2 days) and therefore less likely to have lower respiratory tract involvement. Because recurrent events were allowed (i.e. children could contribute more than one ARI episode), it was necessary to account for correlation at the level of the individual child. We therefore used a mixed effects Poisson regression model to adjust for clustering at the level of the individual child; because this model did not converge for influenza incidence, the influenza estimate was calculated using zero-inflated negative binomial regression, accounting for clustering at the level of the individual child. All statistical analyses were performed using Stata 12.1 (StataCorp).

Human subjects review

The study protocol was approved by the Vanderbilt Institutional Review Board and by the Ethics Committee of the Instituto de Investigacion Nutricional.

RESULTS

Characteristics of study population

In total, 892 children from 810 households in 58 communities were enrolled. Thirty percent of cohort children had previously been enrolled in the Integrated Home-based Intervention Package (IHIP) trial in the same area;²⁹ among IHIP trial families the refusal rate for enrollment was 32.5%.¹⁸ Refusal rate among non-IHIP families was not recorded and no demographic or other data was collected for households refusing enrollment. A detailed description of enrolled households and children has been published previously¹⁸ and a summary is available online (Supplemental Digital Content 1). Median household size was 5; most (86%) heads of households were laborers, primarily in agriculture. Most homes were crowded, with 2 or fewer rooms used for sleeping and 97% of enrolled children sharing a bed with another household member. In 93% of households, wood was used for cooking and in 63% meals were prepared over an open (non-vented) fireplace. Median age at enrollment was 4.6 months, 48% of enrolled children were female, and median length of time in the study was 14.5 months. The majority of children (94%) were enrolled in government-provided health insurance.

Retention in the study was high; 79% of enrolled children remained in the study until either study end (51%) or until reaching three years of age (28%). Follow-up in the remaining children ended because of consent withdrawal (14%), loss to follow-up (6%) or death (1%). Among the five deaths occurring during the study, two were ARI-related, based on clinical history. Both children progressed from onset of symptoms to death over the course of two days and neither was seen by the study team or hospitalized during the course of the terminal illness.

ARI incidence, severity, and seasonality

There were 4,475 ARI episodes during 755.1 observed child-years at risk, giving a crude incidence rate of 5.9 (95% CI 5.8-6.1) ARI/child-year. Adjusted incidence, accounting for multiple ARIs within each individual, was 6.2 (95% CI 5.9-6.5). The highest rates were in children three to eleven months of age (7.9 to 8.1 ARI/child-year) with a gradual decrease in incidence with increasing age (see Figure, Supplemental Digital Content 2).

Field workers directly witnessed and assessed severity for 2,450 ARI episodes (55%); LRTI was documented in 189 cases (7.7 % of assessed ARI, 4.2% of all ARI episodes). Incidence of LRTI was 25 per 100 child-years (95% CI 21 – 30). LRTI were most frequent among children 12-14 months of age (see figure, Supplemental Digital Content 2). Tachypnea was the most frequent indicator of LRTI (63% of LRTI cases), followed by stridor (21%), wheezing (15%), retractions (11%), and nasal flaring (9%). WHO-IMCI indicators of severe pneumonia, stridor or subcostal retractions, were present in 54 (29%) of the 189 LRTI, corresponding to annual incidence of severe pneumonia of 7.2 (95% CI 5.3 – 9.8) per 100 child-years.

ARI incidence was higher in late fall, winter, and spring (May – December, range: 5.4-7.3 ARI/child-year), compared to the summer and early fall (January – April, range: 3.5-4.3 ARI/child-year); the proportion of LRTI was also higher during the late fall to early spring

months (see figure, Supplemental Digital Content 2). Because winter months were over-represented in the study we conducted separate analyses of two complete calendar years: May 1, 2009 – April 30, 2011 and October 1, 2009 to September 30, 2011; these periods had annual estimates of 6.3 (95% CI 6.0 – 6.6) and 5.8 (95% CI 5.5 – 6.1) ARI/child-year, respectively.

ARI etiology

Nasal swab specimens were obtained for 3,957 (88%) of 4,475 ARI, including 174 (92%) of 189 LRTI. Viruses were detected in 67% of all samples; multiple viruses were detected in 14%. Influenza virus, RSV, MPV, and PIV 1-3 were each detected in 3-9% of samples, while HRV and AdV were detected in 44% and 15%, respectively. When present as the only virus detected, RSV, MPV and PIV were disproportionately detected in LRTI (see figure, Supplemental Digital Content 3). Of the 545 specimens with multiple viruses detected, 86% contained HRV, 61% AdV, 23% PIV, 17% RSV, 13% influenza, and 8% MPV. Forty two (24%) of the 174 specimens associated with LRTI yielded >1 virus; HRV was detected in 81% of these samples, AdV in 45%, PIV in 33%, RSV in 24%, MPV in 12%, and influenza in 12%. The odds of having LRTI was 1.71-fold greater (95% CI 1.16 – 2.50) when >1 respiratory virus was detected, vs. detection of only one virus.

Incidence and seasonality of respiratory viruses

Among individual viruses, HRV incidence was by far the highest, with an adjusted rate of 236 ARI per 100 child-years, (2.4 ARI/child-year). Incidence rates of AdV, influenza, PIV 1-3, RSV, and MPV ranged from 17 to 73 ARI per 100 child-years (**Table 1**). RSV, MPV, and influenza viruses were detected seasonally in winter or spring, HRV and AdV circulated year-round, and PIV was detected sporadically (see figure, Supplemental Digital Content 4).

Clinical features

The median ARI duration was 5 days (IQR 2-8); fever, cough, and rhinorrhea were the most common symptoms. Fever was most frequently associated with MPV (89%) and influenza (88%). Cough was most frequently associated with RSV (98%), MPV (95%), PIV 1-3 (90%), and influenza (88%). Care was sought at the health center for 24% of ARI episodes and 1% led to hospitalization; the proportion seeking care was highest for influenza (41%) and RSV (41%, **Table 2**). The odds of seeking care among ARI from which only one study virus was detected varied by virus; compared to HRV as a reference, odds ratios for seeking care were: AdV 1.4, PIV 2.5, MPV 2.8, influenza 3.1, and RSV 3.2 ($p < 0.001$ for the group comparison, data not shown). Roughly 16% (N=704) of the 4,475 ARI were defined by fever in the absence of respiratory symptoms (cough, rhinorrhea, or ear pain). ARI defined by cough in the absence of fever, rhinorrhea, or ear pain comprised 4.7% of all ARI (N=212). Respiratory viruses were detected in 36% (95% CI 32 – 40%) of “fever-only” and 52% (95% CI 45 – 60%) of “cough-only” ARI for which NS samples were collected (specific viruses associated with each ARI type are reported as Supplemental Digital Content 5).

DISCUSSION

The incidence of 6.2 ARI/child-year observed in this study is higher than that reported in some,³⁰⁻³² but not all³³ of several landmark household studies from North America, but direct comparisons are hampered by variability in ARI definition among studies. Because we wished to detect several respiratory virus infections, our study used a sensitive ARI definition (fever or cough) and an intensive surveillance strategy (weekly household visits with daily reporting of symptoms). We included fever as an independent ARI criterion because respiratory viral infections often present with fever in the absence of respiratory symptoms in infants.^{23,24} ARI defined by fever in the absence of upper respiratory symptoms (cough, rhinorrhea, or ear pain) comprised 16% of ARI in our study; excluding these ARI would reduce the adjusted incidence estimate to 5.4 (95% CI 5.1 – 5.6).

To our knowledge, ours is the first household study of acute viral respiratory infections conducted in a high altitude and low population density setting. Our study is similar in scope and design to that of Homaira et al in Dhaka, Bangladesh⁸, which reported a lower overall rate of ARI (1.25/child-year) and a higher rate of LRTI (52/100 child years), but these differences are partly due to differences in study design. We defined ARI by parental report of symptoms while in the Dhaka study, children observed to have symptoms at the time of a household visit were referred to the clinic, and only children presenting to the clinic could be diagnosed with ARI. The Dhaka study also likely selected for more severe ARI, which may be of longer duration and therefore more likely to be observed during a household visit; unobserved ARI in our study were markedly shorter (median duration 2 days, IQR 2-4) than observed ARI (those symptomatic at the time of a household visit; median 7 days, IQR 5-11). In addition, children in the Dhaka study were younger (age <2 years) and thus more susceptible to severe infection. Limiting our analysis to the same age group yielded an incidence of 30 (95% CI 25 – 37) LRTI/100 child years. Using a similar panel of viruses, we detected at least one virus in 67% of ARI specimens and 79% of LRTI specimens—almost exactly the same proportions observed in Dhaka.⁸ In both studies the detection of multiple viruses, RSV, or MPV was more often associated with lower respiratory tract disease, while HRV, AdV, and influenza alone represented a similar proportion of upper and lower respiratory tract infection. PIV was associated with LRTI in our study but not theirs. Our study also observed a much higher incidence of HRV (236/100 vs. 17/100 child-years); reasons for this marked difference are not readily apparent, since the same HRV detection assay was used in both studies.²⁵ Our detection of HRV in approximately 40% of samples is consistent with results of other etiologic studies.^{9,16,34}

One might expect differences in ARI frequency or viral etiology between Dhaka and the Peruvian Andes, given the differences in climate, altitude, and population density between the two locations. Whereas high population density may favor viral transmission in Dhaka, colder ambient temperatures (resulting in enhanced survival of viruses on fomites), lower humidity, and household air pollution may favor transmission in the Peruvian Andes.³⁵

The current analysis from the RESPIRA PERU study has important strengths. First, it is one of very few large prospective household studies of ARI in rural, high-altitude, low-population-density settings. Second, it combined rigorous active surveillance with sensitive

molecular detection of multiple viruses. The daily parental record of ARI symptoms allowed comparisons among ARI associated with several viruses. Furthermore, active household-based surveillance and collection of NS samples from a high proportion of all ARI episodes provides a sensitive assessment of all viruses associated with symptomatic ARI in this community, not just those severe enough to result in presentation at a health center. This last point is underscored by the observation that influenza, RSV and MPV accounted for a lower proportion of ARI in this study than in recent health center-based studies of viral pneumonia,^{13,34,36-38} while the proportion of RSV associated with LRTI in our study is comparable to that observed in other household studies.^{5,8}

Our study also has several limitations. LRTI or severe pneumonia was detected only when a child had signs of LRTI or severe infection at the time of a household visit. Thus, some LRTI and severe infections were missed, including the two deaths due to ARI that were not observed during household surveillance. Our study therefore provides conservative estimates of the occurrence of LRTI and severe pneumonia, yet even these conservative estimates indicate a substantial burden of disease among Andean children. Another limitation is recall bias; mothers may not be able to recall with accuracy respiratory signs and symptoms that developed more than 3 or 4 days prior to the visit, especially if mild.³⁹⁻⁴¹ Although having more than 1 household visit per week would have been useful, that option was deemed logistically unfeasible for our project. As discussed above, our highly sensitive ARI definition (fever or cough) may have resulted in non-infectious and/or non-respiratory causes of fever or cough to be counted as ARI. Finally, although we tested for a large panel of respiratory viruses we did not attempt to identify all viruses (such as coronaviruses), bacteria, or mycoplasma that may have been responsible for ARI symptoms. In addition, detection of viral nucleic acid in a nasal swab sample is not a certain indicator that the virus detected is responsible for the ARI symptoms observed; in recent Kenyan studies of viral ARI, only influenza, RSV, and MPV were more frequently detected among ARI cases than among asymptomatic controls, with detection of HRV in as many as 45% of control samples.^{9,42} Similar evaluations of asymptomatic Andean children will be important in understanding the relationship between viral carriage and disease.

CONCLUSION

Incidence of ARI and LRTI in young Andean children living at high altitude in a remote, low population-density, rural setting are among the highest reported from children in temperate and tropical, developed and underdeveloped regions of the world. Development and implementation of effective strategies for prevention and control of ARI in these remote rural settings is needed.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Adjusted incidence per 100 person-years

Virus	Incidence (95% CI)			
	All ages	0 - 5 months	6 - 11 months	12 - 35 months
Human rhinovirus	236 (221 - 252)	266 (234 - 303)	313 (280 - 351)	206 (190 - 224)
Adenovirus	73 (65 - 82)	27 (19 - 38)	99 (78 - 125)	81 (71 - 93)
Parainfluenza 1-3	46 (41 - 51)	41 (31 - 53)	54 (43 - 68)	45 (39 - 51)
Influenza	37 (31 - 43)	35 (26 - 48)	44 (34 - 57)	31 (27 - 37)
Respiratory syncytial virus	30 (26 - 34)	34 (25 - 47)	34 (25 - 45)	28 (23 - 33)
Human metapneumovirus	17 (14 - 20)	12 (8 - 20)	27 (19 - 37)	16 (13 - 20)
Any one of the above viruses	360 (340 - 380)	365 (327 - 409)	472 (430 - 518)	328 (306 - 352)

Table 2

Symptoms associated with the detection of each virus in isolation (as the only virus detected in the nasal swab specimen)

Virus	N	Fever	Cough	Poor appetite	Malaise	Rhinorrhea	Sought health care[*]
All ARI	4575	71%	75%	35%	41%	75%	24%
Influenza	187	88%	88%	49%	61%	90%	41%
Respiratory syncytial virus	131	77%	98%	50%	55%	94%	41%
Human metapneumovirus	87	89%	95%	53%	59%	90%	38%
Parainfluenza virus 1-3	218	80%	90%	46%	56%	87%	36%
Human rhinovirus	1260	62%	82%	30%	35%	84%	18%
Adenovirus	220	74%	72%	41%	46%	72%	25%
> 1 virus detected	545	68%	86%	39%	44%	89%	25%
No virus detected	1309	76%	63%	35%	42%	59%	24%

* The child was brought to the local health center or study physician for evaluation or, rarely, the study physician or nurse was called to evaluate the child if signs of lower respiratory tract infection or danger signs were noted at the time of a household visit