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Etiology and Seasonality of Viral Respiratory Infections in Rural Honduran Children

Elizabeth P. Schlaudecker, MD, MPH¹, Joan P. Heck², Elizabeth T. MacIntyre, BA³, Ruben Martinez, MD⁴, Caitlin N. Dodd, MS⁵, Monica M. McNeal, MS¹, Mary A. Staat, MD, MPH¹, Jeffery E. Heck, MD⁶, and Mark C. Steinhoff, MD

¹Division of Infectious Diseases, Global Health Center, Cincinnati Children's Hospital and Medical Center, Cincinnati, OH, USA

²Harvard University, Cambridge, MA, USA

³Weill Cornell Medical College of Cornell University, New York, NY, USA

⁴Shoulder to Shoulder, Santa Lucia, Intibucá, Honduras

⁵Global Health Center, Cincinnati Children's Hospital and Medical Center, Cincinnati, OH, USA

⁶Department of Family Medicine, University of North Carolina, Asheville, NC, USA

Abstract

Background—Limited data are available in Honduras describing the etiology and seasonality of respiratory infections, especially in rural outpatient settings. Better data may lead to improved therapeutic and preventative strategies. The goal of our study was to determine the viral etiology and seasonality of acute respiratory infections in a rural Honduran population of children.

Methods—Prospective clinic surveillance was conducted to identify children <5 years of age presenting with respiratory symptoms <5 days duration. We obtained data on age, sex, medical history, breastfeeding history, symptoms, risk factors, house hold setting, temperature, respiratory rate, and chest exam findings. To assess the association between specific viruses and weather, regional meteorological data were collected. Nasopharyngeal samples were tested for 16 respiratory viruses using a multiplex PCR panel.

Results—From February 2010 through June 2011, 345 children <5 years of age were enrolled; 17%, 23%, 30%, and 31% were <6, 6–11, 12–23, and 24–60 months old, respectively. Including all clinics in the region, 44.5% of patients <5 years of age with documented respiratory diagnoses were enrolled. At least one virus was identified in 75.4% children, of which 7.5% were co-infections; 13.3% were positive for parainfluenza, 11.9% for influenza, 8.1% for human metapneumovirus (hMPV), and 7.5% for respiratory syncytial virus (RSV). Rainfall correlated with parainfluenza ($p = 0.0001$), influenza ($p = 0.0001$), hMPV ($p = 0.0182$), and RSV ($p = 0.0001$).

Corresponding author (reprints available): Elizabeth P. Schlaudecker, M.D., M.P.H., 3333 Burnet Avenue, MLC 7017, Cincinnati Children's Hospital Medical Center, Cincinnati, OH 45229, USA, Phone: 513-803-5187, Fax: 513-636-8055, Elizabeth.Schlaudecker@cchmc.org.

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Conclusions—These results suggest that the spectrum of viruses in ill rural Honduran children is similar to that in North and Central America, though the seasonality is typical of some tropical regions.

Keywords

viral respiratory infections; influenza; seasonality; Honduras; child

INTRODUCTION

Acute respiratory infections (ARIs), including pneumonia, are the leading cause of death among children under five years of age in several regions with limited resources^{1,2}. Recent data from the World Health Organization (WHO) suggest that 18% of global deaths in children under five are due to pneumonia alone^{1,2}. Throughout the world, the etiologies of ARIs and pneumonia are largely unknown. It is estimated that 18% to 65% of global pediatric patients admitted to the hospital for ARIs and pneumonia are infected with viruses^{3–7}. Even with the best diagnostic techniques, 25% to 33% of pneumonia cases do not have a clear etiology⁸.

In the United States, up to 9% of all infants younger than 6 months of age are hospitalized or seen in a clinic or emergency department secondary to influenza during some influenza seasons⁹. The burden of influenza is unknown in most resource-poor countries¹⁰, but some data from the tropics and subtropics demonstrate incidence and hospitalization rates for influenza that exceed those reported for temperate regions^{11–15}. The seasonality of influenza virus in the tropics is variable¹⁶, with studies demonstrating year round disease^{10,17} or one or two clear annual peaks^{18–23}. Several sites in sub-Saharan Africa, Latin America, and Asia have recently added influenza surveillance programs^{24–26}; but new technologies, including RT-PCR (reverse transcription-polymerase chain reaction) for virus detection, are often unavailable in these settings.

Honduras is a resource-limited country in Central America with a population of approximately 7.5 million people and gross national income per capita of US\$1869.8²⁷. The under-five mortality rate per 1000 births is 42.6, and acute respiratory infections are the leading cause of death in this age group²⁸. Only two studies have examined the viral etiology of respiratory illness in Honduras^{29,30}, and both of these studies were localized to urban regions and did not include surveillance in rural areas.

Because mortality rates for acute respiratory infections in resource-limited countries far exceed those of economically developed countries^{25,31,32}, information about burden of these pathogens in the resource-limited countries is crucial for the development of effective prevention, surveillance, and treatment strategies. The objective of our study is to describe the etiologic agents, seasonality, and clinical characteristics of viral respiratory infections in rural Honduran children less than five years of age.

MATERIALS AND METHODS

Study Design

Prospective clinic surveillance was conducted to describe the spectrum of viral etiologies of acute respiratory infections in a rural outpatient Honduran population of children less than five years of age.

Surveillance Sites

We conducted surveillance in two villages, Santa Lucia and Magdalena, located in Intibucá, one of the poorest of the 18 departments of Honduras. Santa Lucia is located in a remote, mountainous region at 13° N and 88° W. The average monthly temperature ranges from 17° to 22° Celsius, and the rainy season extends from May through October with peaks in June and September. Santa Lucia is located approximately five kilometers from the El Salvador border, and Magdalena is approximately three kilometers north of Santa Lucia. The capital of Intibucá, La Esperanza, is approximately three hours by car from each town. The mountainous terrain and limited transportation hinder access to care for Hondurans in this region. Pneumococcal vaccines were recently introduced in Honduras and were not available to participants at the time of the study³³. Influenza vaccine was introduced in 2003 in Honduras³⁴ and is intermittently available to pregnant women in this region.

Surveillance was conducted at the Clinica Hombro a Hombro in Santa Lucia and Centro de Salud in Magdalena. The two clinics provide primary medical care, health education, and community resources for more than twenty thousand rural Hondurans. Both clinics are operated by Shoulder to Shoulder and Hombro a Hombro, two partnering, private, non-profit, non-governmental organizations (NGOs) formed in the United States and Honduras, respectively. No other access to primary care is available in this region of Honduras.

Subjects

All children less than 5 years of age who presented at the two clinics from February 2010 through June 2011 and met the study criteria were eligible for enrollment. Children were eligible for recruitment if they presented with an acute respiratory illness defined as a maternal report of illness, with any one respiratory symptom including runny nose, nasal congestion, cough, difficulty swallowing or difficulty breathing, occurring more than 7 days after a previous illness. For children greater than 1 year of age, fever was defined as a temperature > 37.8 degrees Celsius. This definition of respiratory illness with fever was modified for infants and young children from the Centers for Disease Control and Prevention (CDC) definition of influenza-like illness. Patients were excluded if they were 5 years of age, previously enrolled within 7 days, or symptomatic for greater than 5 days. All other children less than 5 years of age seen in the clinics were recorded in the clinics' computer database to determine our capture rate within the community. Weekly queries identified all children seen in the clinics less than 5 years of age.

Study Procedures

If the child was eligible for the study and the parent agreed to participate, informed consent from the parent or guardian of the child was obtained. Following informed consent, there were four parts to data collection: a parent questionnaire, nasopharyngeal sampling, physician's exam, and data abstraction from the child's medical record by study personnel.

All demographic, clinical, and laboratory data were entered into a study computer database by study personnel. These data included parent questionnaire responses, clinical exam findings recorded by the physician, medical history recorded from the clinical chart, and multiplex PCR results when available. Denominator data were obtained from the clinic database, identifying all patient encounters in children less than 5 years with respiratory code diagnoses. Clinic staff manually enter clinical data from all patient encounters in the clinic databases on a daily basis. Meteorological data were obtained from the nearest weather station located at the airport in Santa Rosa de Copán, approximately 190 kilometers from Santa Lucia.

Laboratory Procedures

Two flexible nasopharyngeal nylon flocked swabs (FLOQSwabs™, Copan Diagnostics, Murrieta, California, USA) were used for specimen collection for each participant. The distance between the participant's nares and ear lobe was measured to estimate the maximum depth of insertion, and the swabs were gently inserted towards the pharynx until resistance was felt and then rotated three times to obtain epithelial cells from the nasopharynx. Swabs were placed in universal transport medium (UTM). The UTM specimens were then separated into aliquots and stored in the laboratory freezer (−80 degrees Celsius). Specimens were shipped bimonthly by air on dry ice to Cincinnati Children's Hospital Medical Center.

Specimens were tested for respiratory viruses using the commercially available respiratory viral panel (RVP ID-Tag™, Luminex Diagnostics, Austin, Texas, USA), a multiplex nucleic acid amplification test. This assay can detect 16 different viruses and subtypes from a single respiratory specimen, including: parainfluenza 1, 2, 3, 4, influenza A, influenza B, human metapneumovirus (hMPV), respiratory syncytial virus (RSV), enterovirus/rhinovirus, adenovirus, and coronavirus. This method has a reported sensitivity of 97.8% and a specificity of 96.4% for detection of any respiratory virus^{14,35,36}, and is a Federal Drug Administration certified diagnostic test.

Statistical analysis

The viral agents, demographic characteristics, and clinical characteristics of viral respiratory infections were described using Chi Square and Fisher's Exact tests. We defined a fever as an axillary temperature > 37.8 degrees Celsius¹⁴, and we used the World Health Organization's Integrated Management of Childhood Illness guidelines²⁹ to define fast breathing in children less than 12 months old (< 50 breaths per minute) or 12 months of age and older (< 40 breaths per minute). The monthly distribution of respiratory viral infections and rainfall were graphed, and the relationship was assessed by correlation coefficient (R^2). We used Poisson regression to model the number of influenza positives as a function of rainfall.

Ethical Considerations

The protocol was approved by the Institutional Review Board (IRB) of both Cincinnati Children's Hospital Medical Center and the Hospital Regional del Occidente in Santa Rosa de Copan, Honduras.

RESULTS

From February 15, 2010 to June 14, 2011, 355 children were eligible for enrollment and 345 children (97.2%) were enrolled. Ten children (2.8%) refused enrollment. During this time period, the Clinica Hombro a Hombro and the Centro de Salud had 3298 patient encounters for children less than 5 years of age documented in the computerized clinic database. According to diagnostic codes assigned by the Honduran physicians, 776 of these children had respiratory symptoms during their clinic visits. Including both clinics, 44.5% of patients less than 5 years of age with documented respiratory diagnoses were enrolled in the study.

Demographic Characteristics

Of the 345 participants, 158 (45.8%) were female, and the average age of the children enrolled was 19 months (range 18 days – 58 months) (see Table, Supplemental Digital Content 1, <http://links.lww.com/INF/B254>). Fifty-nine (17.1%) were less than 6 months of age, 78 (22.6%) were 6–11 months of age, 102 (29.6%) were 12–23 months of age, and 106 (30.7%) were 24–59 months of age. Most children (84.3%) were born at home. Very few

children slept in the room where food was prepared (5.5%), but 95.7% of subjects lived in homes where wood was used to prepare food. Of all participants, 14.8% were exposed to cigarette smoke at home. More than half of the subjects (53.3%) have at least one family member working in the United States. Children with family in the United States were more likely to have influenza, and children without family in the United States were more likely to have hMPV.

Clinical Characteristics

Overall, the most common symptoms reported by parents were cough (88.1%), fever (78.6%), and runny nose (78.8%) (see Table, Supplemental Digital Content 2, <http://links.lww.com/INF/B255>). Parents reported shortness of breath in 67.5% of children. The mean temperature recorded at the clinic was 37.1° Celsius, and 19.5% of children had a fever at the time of recruitment. Of the 269 children (78%) with an oxygen saturation measured, 49 (18.2%) had an oxygen saturation less than 92%. Of children less than 12 months old, 17.5% had a respiratory rate at or above 50 breaths per minute, while 20.2% of children 12 months of age or older had a respiratory rate at or above 40 breaths per minute. Per clinical chart abstraction, no participants required transfer or hospitalization.

The mean temperature recorded for children with RSV was significantly higher than the mean for parainfluenza ($p=0.0179$). Children with parainfluenza also had a significantly lower rate of fever compared to children with other viruses, both by chart review ($p=0.0164$) and parent history ($p<0.001$).

The most common physical exam findings documented by the physician were rhinorrhea (62.6%), followed by wheezing (25.8%), and pharyngitis (23.2%) (see Table, Supplemental Digital Content 3, <http://links.lww.com/INF/B256>). Children with hMPV and RSV were more likely to have rhinorrhea than children with parainfluenza or influenza ($p<0.001$). Presence of wheezing was similar between viruses ($p=0.538$). Otitis media was documented by physicians in 3.8% of participants.

Viral Agents Identified

At least one virus was detected in 75.4% of children. Coinfections were identified in 26 children (7.5%). Enterovirus/rhinovirus was most commonly identified in 33.4% of children. Parainfluenza was identified in 46 children (13.3%); 8 (2.3%) were type 1, 24 (7.0%) were type 3, and 14 (4.1%) were type 4. Influenza was identified in 41 children (11.9%); 21 (6.1%) were influenza A, H3; 12 (3.5%) were influenza A, non-H3; and 8 (2.3%) were influenza B. Human metapneumovirus was identified in 28 children (8.1%). RSV was seen in 26 (7.5%) children; 10 (2.9%) were RSV A and 16 (4.6%) were RSV B. Eight specimens (2.3%) yielded adenovirus.

Seasonality (Figure 1)

Parainfluenza peaked in June 2010 and 2011 and was present nine out of 12 months. Influenza peaked in the months of August and September 2010. Influenza rose from 1.8% of isolates in February through June to 25.7% of isolates in July through October. No cases of influenza were identified from February 2010 through May 2010 and November 2010 through March 2011. Influenza B was present in April 2011 through June 2011. Influenza was present seven out of 12 months (June 2010 through October 2010, April 2011 through June 2011). Human metapneumovirus peaked in February 2010 and was present nine out of 12 months. RSV peaked in September 2010 and was present seven out of 12 months.

Rainfall data obtained from Santa Rosa de Copán revealed an increase in rainfall from May to September 2010, as well as an increase beginning in May 2011. The number of influenza

cases detected monthly demonstrated a positive correlation with monthly rainfall ($R^2 = 0.334$, $p=0.0151$). Using Poisson regression, measured rainfall was significantly correlated with circulating influenza ($p = 0.0001$), parainfluenza ($p = 0.0001$), hMPV ($p= 0.0182$), and RSV ($p = 0.0001$).

DISCUSSION

To our knowledge, these are the first data describing the etiology of acute respiratory infections in rural Honduras.

Clinical and Demographic Characteristics

The most common symptoms reported by the parents were cough, fever, and runny nose. The most common clinical findings reported by the physician were rhinorrhea, wheezing, and pharyngitis. These findings were much more common than difficulty breathing and retractions, suggesting that subjects had more upper respiratory symptoms and were not severely ill. Though all parents reported a recent fever at the time of recruitment, the average temperature of all participants with viruses recorded at the clinic was less than 37.8 degrees Celsius. Only 19.5% of participants had a fever greater than 37.8 degrees Celsius at the time of enrollment. None of the participants required hospitalization, affirming the likelihood of mild respiratory illness. Several factors may explain this finding. Hondurans in this region have had access to primary care since the introduction of the Shoulder to Shoulder health care system in 1990. Because of this availability of care, we speculate that some severe illness is prevented by early medical care. Further studies are needed to analyze the receipt of antibiotics in this population and its relationship to improved outcomes in viral infections. Additionally, we may have failed to capture severely ill children taken directly to the hospital in La Esperanza without initial triage in the outpatient clinics.

Etiology of Acute Respiratory Infections

This study identified a fairly large proportion of respiratory disease caused by parainfluenza (13.3%). Previous studies in Honduras²⁹ and Brazil²² have identified RSV as the most frequent viral agent identified in hospitalized children with respiratory symptoms. This elevated proportion of parainfluenza may be attributable to the outpatient surveillance setting or limited testing capabilities prior to the availability of respiratory multiplex PCR. Reyes et al. tested for parainfluenza using immunofluorescence techniques and failed to identify any cases among hospitalized Honduran and El Salvadoran children²⁹. To fully describe the patterns, further studies and extended surveillance are necessary to determine the relative frequency of influenza, parainfluenza, human metapneumovirus, and RSV over several years.

Influenza was the next most prevalent virus throughout the year (11.9%). This high rate of disease cannot be attributed to the 2009–2010 pandemic H1N1 influenza epidemic, because only a small proportion (2.3%) of the influenza A isolates identified were not H3. When the pandemic H1N1 influenza epidemic spread to Honduras in the spring of 2009, the WHO and the Honduran government provided monovalent H1N1 vaccine in populous areas. Though the vaccine did not reach rural Intibucá, the availability of the vaccine in La Esperanza and other nearby urban regions may have limited spread of the virus prior to study initiation in February 2010.

Reyes et al. investigated children hospitalized in Honduras and El Salvador in 1991–1992, and they detected influenza by immunofluorescence in 29 of 135 (21%) nasopharyngeal samples²⁹. Twenty (69%) of the 29 influenza virus cases occurred during the first three months of life, and influenza and RSV cases peaked at the end of the rainy season. A recent

study by Laguna-Torres et al. analyzed etiologic agents associated with influenza-like illness in five participating hospitals or health centers in large urban areas in El Salvador, Honduras, and Nicaragua³⁰. Out of 427 samples tested in Honduras, 66 (15%) were positive for influenza A or B, 37 (9%) for adenovirus, 29 (7%) for parainfluenza, 15 (4%) for RSV, and 1 for hMPV. Our study similarly selected for influenza-like illness in children, possibly increasing the number of children identified with influenza in both studies.

The low prevalence of hMPV in the urban study by Laguna-Torres et al. contrasts with our findings³⁰. We identified hMPV in over 8% of our nasopharyngeal samples, surpassing RSV and adenovirus. Previous studies have failed to identify hMPV due to limited diagnostic techniques, so future studies may further define the prevalence of this virus.

RSV was the most common pathogen detected by Laguna-Torres et al. in children less than five years of age in all three countries³⁰. It is associated with high prevalence, hospitalization, and mortality rates²². However, we detected RSV in 7.5% of nasopharyngeal samples in our study. This finding may reflect the relatively low severity of illness in children identified in our study, as well as the utilization of outpatient clinic data only.

Adenovirus was present in much smaller numbers. It tended to occur in small clusters that can be attributed to the closed nature of this rural community. The individuals in this community have limited access to large cities in Honduras and other surroundings areas. The presence of different viruses may vary year to year based on exposure to outside communities.

Seasonality

Measured rainfall was significantly correlated with circulating influenza, parainfluenza, hMPV, and RSV. These results demonstrated a clear peak of influenza, hMPV, and RSV in the months of July through October, coinciding with the rainy season in this region of Honduras. Parainfluenza peaked in May and June at the onset of the rainy season. Previous research in Brazil has shown that influenza circulation coincides with the rainy season³⁷, but further research is needed to understand if these environmental conditions affect circulation of other respiratory viruses.

This influenza seasonality in rural Intibucá differs from that of urban Honduras, where influenza circulates throughout the year with two clear peaks³⁸. This urban pattern is consistent with data from other tropical countries but may vary year to year²⁰. This pattern may also be explained by travelers between urban settings around the globe³⁹, and the remote setting of Intibucá may influence the local prevalence and seasonality of influenza virus. Further data are needed to assess the current use of the Northern Hemisphere vaccine in Honduras³⁴ as the influenza peak in July and August occurred before Northern Hemisphere vaccines were available.

The statistical correlation between respiratory viruses and rainfall may be due to several factors, including increased crowding with increased transmission of respiratory viruses⁴⁰. Some have speculated that the seasonality of influenza is mediated by vitamin D levels⁴¹, but limited data are available about vitamin D levels by season at high latitudes in Latin American countries to establish a relationship between influenza seasonality and vitamin D. A recent study in older Mayan adults showed lower vitamin D levels in elderly adults⁴², but we are not aware of published studies of seasonal vitamin D level variation in Honduran children. Further research is needed to confirm these findings and to assess the relationship between vitamin D levels and seasonality of respiratory infection.

There were several limitations to this study. Even though the Clinica Hombro a Hombro and Centro de Salud serve a large catchment area for ill child care, we did not confirm that we sampled all children with respiratory disease. Some ill children may have been unable to travel to the clinic due to severity of illness, and some families may not have sought care for their children if the illness was mild. Our denominator data from the computerized clinic database were obtained retrospectively using diagnostic codes, so the data were limited by physician coding and lack of diagnostic specificity. It is likely that patients with other respiratory symptoms were included in the denominator data, limiting the utility of these data.

This study was also limited by the lack of a healthy comparison group. We collected data for 17 months, making it difficult to fully characterize details of local seasonality of individual virus species. The nearest available weather data were not local, so correlations between viruses and rainfall may not be exact. Our sample size limited our ability to do more detailed analyses examining differences in clinical and demographic features of children with different respiratory viruses.

While epidemiological data are available from industrialized nations, minimal etiologic information is available for respiratory disease in other parts of the world. These unique rural results suggest that the spectrum of viruses in rural Honduran children is similar to that found in North America, though the circulation of viruses coinciding with the rainy season is more typical of previous findings in several tropical regions. Data from this study will guide further research into prevention and treatment of acute viral respiratory diseases, including improved therapeutic options and prevention with immunization.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1. Respiratory viruses by month (%) and mean monthly rainfall (mm)

The peaks in influenza and other respiratory viruses coincided with the rainfall peak from June through September.