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Spatial and Temporal Spread of Acute Viral Respiratory Infections in Young Children Living in High-Altitude Rural Communities: A Prospective Household-Based Study

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Abstract

Background—Few studies have described patterns of transmission of viral acute respiratory infections (ARI) in children in developing countries. We examined the spatial and temporal spread of viral ARI among young children in rural Peruvian highland communities. Previous work has described intense social interactions in those communities, which could influence the transmission of viral infections.

Methods—We enrolled and followed children <3 years of age for detection of ARI during the 2009–2011 respiratory seasons in a rural setting with relatively wide geographic dispersion of households and communities. Viruses detected included influenza, respiratory syncytial virus (RSV), human metapneumovirus (MPV), and parainfluenza 2 and 3 viruses (PIV2; PIV3). We used geospatial analyses to identify specific viral infection hot spots with high ARI incidence. We also explored the local spread of ARI from index cases using standard deviational ellipses.

Results—Geospatial analyses revealed hot spots of high ARI incidence around the index cases of influenza outbreaks and RSV outbreak in 2010. Although PIV3 in 2009 and PIV2 in 2010 showed

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Authors' contributions

MRG, KME, JVW, AIG, HV, CFL, and CGG conceived and designed the prospective household-based study. CGG and CBC implemented the GIS approach and analyzed the data. CBC and CGG jointly drafted the manuscript. All authors read and reviewed the final manuscript.

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distinct spatial hot spots, clustering was not in proximity to their respective index cases. No significant aggregation around index cases was noted for other viruses. Standard deviational ellipse analyses suggested that influenza B and RSV in 2010, and MPV in 2011 spread temporally in alignment with the major road network.

Conclusions—Despite the geographic dispersion of communities in this rural setting, we observed a rapid spread of viral ARI among young children. Influenza strains and RSV in 2010 had distinctive outbreaks arising from their index cases.

Keywords

acute viral respiratory illness; children; geographic information systems; GIS; Peru

Background

Acute respiratory infections (ARI) are a leading cause of morbidity and mortality among children in developing countries, with ninety-five percent of ARI-related deaths occurring in these regions ^{1–6}. However, measuring the ARI burden accurately can be difficult in low income countries ⁷ since conducting population-based studies poses geographic and logistic challenges. Few studies have characterized the burden of viral ARI among children living in high altitude settings, such as the Peruvian Andes. Our previous studies conducted in this region ^{6,8,9} reported an overall ARI incidence rate of 62 [95% CI: 59–65] per 100 child-years ⁸. The incidence rate of influenza ARI was 37 per 100 child-years, which is as high or higher than rates from other low and middle income countries ⁹, such as Bangladesh and Vietnam ^{7,10}.

Environmental factors can influence the risk of developing ARI. In certain high altitude regions, inclement weather may drive people indoors for longer periods of time ¹¹, increasing the length of the time individuals are exposed to indoor pollution ⁹ and/or social contacts with patients with ARI ^{12,13}. We have previously reported that in rural highland communities of the Peruvian Andes, social contacts that could facilitate the transmission of infections were very frequent and physical contacts appeared to be higher than in some other developing countries ¹⁴.

Little is known about the spatial and temporal pattern of overall ARI spread in rural highland communities in Peru, and the spread of specific laboratory-confirmed viral ARI in this or similar settings. The goal of this study was to identify spatial and temporal patterns of specific viral ARI spread, which could help inform the design and implementation of targeted preventative interventions.

Methods

Study area and population

San Marcos is located in the highlands of northern Peru in the Department of Cajamarca (Figure 1 Supplemental Digital Content) with elevations ranging from 1500 to 4000 meters above sea level ⁸. The climate in this equatorial highland region is typically dry and sunny with temperatures varying by altitude, ranging from 8 to 30 °C ⁶. The Winter season,

spanning June through August, is usually dry and cool while the Summer season, from December through March, is typically wet.

The population density in this region is approximately 40 persons/Km². The San Marcos population is mainly low income with a 2011 per capita per month income of U.S. \$92 (\$235 for Peru)¹⁵. San Marcos ranks low on the United Nations Development Program Human Development Index (HDI) with a 2011 score of 0.2523¹⁵, almost half the HDI score for Peru overall (0.4906); for comparison, the 2011 HDI score for the U.S. was 0.911. The proportion of households with electricity in San Marcos in 2011 was 54.1% (82.2% for Peru)¹⁵. In rural areas, such as San Marcos, there is limited access to healthcare services with both socioeconomic and geographic factors acting as barriers to accessing healthcare^{15–18}.

Data types and sources

ARI data—The current study is nested within the study of Respiratory Infections in Andean Peruvian Children (RESPIRA-PERU), a prospective household-based study conducted among children <3 years of age from May 2009 through September 2011 in San Marcos, Peru. Details of the study have been described elsewhere⁶. After informed consent was obtained, children <3 years of age, including newborns were enrolled and followed through weekly household visits. Additional newborns were enrolled throughout the study period to replace children leaving the study and to maintain a dynamic cohort of children under surveillance; baseline demographic and socioeconomic information was obtained at enrollment. Children were followed through weekly household-based surveillance for ARI until their 3rd birthday, withdrawal of consent, loss to follow-up, or study end, whichever came first. Each week, field workers visited the homes of each enrolled child and interviewed the parent/guardian about signs and symptoms of ARI from the previous week, using World Health Organization-Integrated Management of Childhood Illness (WHO-IMCI) guidelines¹⁹ to assess the children.

Nasal swabs were collected from children who had ARI symptoms within the previous week or at time of the visit for identification of respiratory viruses through RT-PCR^{6,8}. Target viruses included influenza A(H1N1)pdm09, A(H3N2) and B, respiratory syncytial virus (RSV), human metapneumovirus (MPV) and parainfluenza (PIV2 and PIV3). We excluded human rhinovirus and adenovirus ARI from this analysis because they had perennial activity²⁰ and because these viruses were often detected in asymptomatic children, making identification of index cases challenging. Viruses included in this study had pronounced seasonal distributions⁸.

Virus-specific incidence rates were calculated for children that were at risk at the beginning of each viral respiratory season. This analysis was restricted to children under surveillance at the beginning of each viral season, because children enrolled during the season may have already experienced a viral ARI prior to the onset of observation. For each calendar year and respiratory virus, we defined the beginning of the specific viral respiratory season as the first month of continuous viral activity (i.e. at least 2 consecutive months) with ≥4 positive tests for the respective virus. The season continued through the last month with ≥4 positive tests detected per month.

Geographic Information System (GIS) data—Data collected from the RESPIRA-PERU study also included the latitude and longitude of each study household. District and zonal boundary base map shape files for the study area were obtained from Estadística de la Calidad Educativa (<http://escale.minedu.gob.pe/mapas>). Satellite data for the study area were downloaded from the United States Geologic Survey (USGS) Earth Observer at <http://earthexplorer.usgs.gov/>. Geospatial data were projected into the WGS 1984 UTM Zone 17S coordinate system to more accurately represent the study area.

Meteorological conditions during viral respiratory seasons—Previous studies have described temperature, rainfall, and humidity with respect to ARI and recognize the importance of meteorological and environmental parameters^{21,22}. To assess the influence of temperature and rainfall, we compared average temperatures and rainfall among the corresponding viral respiratory seasons included in our study.

Spatial Statistical Analysis

Spatial associations of ARI incidence from eight different respiratory viruses were analyzed using ArcGIS 10.2.2 (ESRI, Redlands, CA). For each study viral ARI, Getis-Ord G_i^* ²³ hot spot analysis was used to determine whether high or low values of ARI incidences (by household) clustered spatially. These local spatial analyses identify not only whether clustering is present, but where clusters are spatially located^{23,24}. The nearest neighbor method was used to create a spatial weights matrix (SWM) of San Marcos, which represented the spatial geography of household locations (i.e. households containing a child enrolled in the study) in the hot spot analysis²⁵. In our spatial analysis, we did not exclude households with more than one young child enrolled in the study, as the median number of children <5 years/per household was one. A SWM was generated so that clustering could be assessed at a village level scale, where each household's rate and rates of the 15 nearest neighboring households were compared to the global mean rate of all the households in San Marcos. An advantage of using the nearest neighbor method, even when household densities were not uniform across a geography, was that it ensured each household had neighbors²⁶ and the hot spot analysis could identify where spatial clusters existed and which clusters were statistically significant ($p < 0.05$). Getis-Ord G_i^* hot spot results were adjusted for a false discovery rate to correct for multiple testing and spatial dependence^{27,28}.

To explore the spread of the infections from the hypothetical source of the viral epidemic, the index (first detected) case of each specific viral infection during individual respiratory seasons was mapped. For visual reference and scale only, a 3-km radius around each index case was also depicted. The decision to use 3-km was heuristically derived, based on village size dimensions in San Marcos and the knowledge of the community's assortative mixing structure¹⁴, where frequent contacts occurred within the household, village, and/or school.

To further characterize the spatio-temporal spread of viral infections, we calculated a standard deviational ellipse (SDE) for each specific viral detection per month. A SDE characterizes the directional distribution of detections and is a common way to measure the spread pattern for a set of observations²⁹. The SDE is calculated by using the standard deviation of x-coordinates and the y-coordinates from the mean center (geographic center of

a set of features) to create an elliptical polygon centered on the mean center of all the features. Thus, the SDE characterizes the distribution of the features and their orientation in space while illustrating the extent of the area affected ²⁹. To illustrate the virus-specific patterns of spread over time, we created a series of animations for each virus representing the number of cases by month for the virus season. When combined together in animation form, the series displays virus-specific spread over space and time. The animations play chronologically and end with a cumulative image of all of the virus counts for the entire season, then loop back to the first image to repeat the series (Animation: Supplemental Digital Content). The SDE and images for the animations were created in ArcGIS and integrated into GIMP 2.8 (<http://www.gimp.org/>).

RESULTS

Characteristics of Study Subjects

We identified eight distinct viral respiratory seasons, encompassing: PIV3 virus and influenza A(H1N1)pdm09 in 2009; influenza A(H3N2) and influenza B, RSV and PIV2 in 2010; and RSV and MPV in 2011. Other viruses were detected in 2009, however only PIV3 and A(H1N1)pdm09 had a pronounced viral season at study onset whereas the other viruses were already circulating within the community when surveillance started ⁸. Details for the specific viral respiratory seasons and the population at risk at the beginning of each season are shown in Table 1. The duration of the viral seasons during which risk was assessed ranged from two to five months. Age across the study period was relatively similar each year, indicating a new cohort of children enrolled each season and the dynamic nature of the underlying cohort study. The median number of children <5 years old per household was 1 (IQR 1, 2). During the 2009 viral season, incidence rates of influenza A(H1N1)pdm09 and PIV3 were 66.4 and 69.5 per 100 person-years, respectively. During 2010, incidence rates of influenza A(H3N2) and influenza B were 91.4 per 100 person-years and 68.9 per 100 person-years, respectively. The rate of RSV was 62.1 and 92.3 per 100 person-years in 2010 and 2011, respectively. The rate of PIV2 in the 2010 season was 33.2 per 100 person-years and MPV in 2011 was 52.3 per 100 person-years.

Geospatial patterns of virus-specific ARI incidence

Hot spots of higher rates and their proximity to the index case for each viral ARI are represented in Figure 2 (Supplemental Digital Content). For 2009, both influenza A(H1N1)pdm09 and PIV3 had hot spots indicating areas with higher rates. During 2010, influenza A(H3N2) and B, and RSV also had hot spots, although the A(H3N2) hot spot cluster did not reach statistical significance. During 2011, neither RSV nor MPV ARI had hot spots that were significantly higher than average RSV and MPV ARI rates for that season. No statistically significant aggregations of households with low viral-specific ARI rates (cold spots) were detected. The index case for each specific viral respiratory season was also identified and illustrated together with the 3-km radius area around each index case (Figure 2). During 2009, PIV3 hot spots were detected but the hot spot clusters were distal to the 3-km radius of the index case, whereas influenza A(H1N1)pdm09 had hot spots both within the 3-km radius of the index case and outside that radius. During 2010, influenza B

and RSV had hot spots contained within the 3-km radius of the index case. Neither RSV nor MPV had hot spots in the 2011 season.

Spatiotemporal Virus Spread by Month

To better characterize the trend and directionality of virus-specific ARI in each season, standard deviational ellipses (SDE) were created. A time series (animation; Supplemental Digital Content) was also incorporated, allowing one to appreciate how the viral infections spread over time (by month). The animations demonstrate viral spread in direction and orientation over the entire duration of the viral season.

The SDE spread pattern for influenza A(H1N1)pdm09 during 2009 was oriented in the southeast region of community, and remained in that region for its viral season of August and September. The SDE for influenza B in 2010 was initially oriented south along the major road network in August and September, then expanded by October with the distribution of cases including much of the study area. The SDE patterns for 2010 influenza A(H3N2) encompassed much of the area of the community from October to November, and near the end of the viral season in December, influenza A(H3N2) cases trended toward the southern region of the study area.

During 2009, PIV3 infections appeared to have a very widespread pattern. The SDEs representing the first two months in the PIV3 viral season (July and August) represented cases that were trending towards the central area of the community. By September and October PIV3 was geographically widespread despite having half as many cases compared to the other viral ARI. At the beginning of the 2010 PIV2 viral season in April, the SDE was centered within the center of the study communities. As the PIV2 viral season progressed to May and June, the SDE moved slightly southward as cases progressed. Like PIV3, PIV2 had almost half as many cases as the other viral ARI, but its geographic spread was not as broad as PIV3.

The 2010 RSV viral SDE patterns in April and May initially had an orientation in the southeast region of the study area surrounding the road network. During mid-viral season in June, RSV SDEs encompassed the community center and expanded thereafter incorporating a more widespread area of the community by the end of the viral season end in July and August. During 2011, RSV showed a wide geographic spread at the beginning of the viral season in April and May and continued to have a wide spread pattern through the viral season ending in July. In the same year, the SDE for the MPV viral season beginning in March trended near the central region of the community, and as the viral season progressed through April and May the virus spread and the SDE oriented along the road network in the southern region of the community. By June, the cumulative distribution of the virus was widespread across San Marcos.

Meteorologic conditions during and between viral respiratory seasons

We compared viral respiratory season and non-season mean temperatures and rainfall. On average, viral season months were slightly cooler with less rainfall than non-viral season months for all study viruses. For example, the RSV viral season in 2010 and 2011 was 1.0

°C and 1.2 °C cooler, respectively, compared the RSV viral off-season months. Rainfall during the 2010 and 2011 RSV viral seasons was also less (1.6 cms and 2.4 cms respectively) compared to the viral off-season. Additionally, we compared mean temperatures and rainfall among the corresponding viral respiratory seasons. We found all respiratory viral seasons in 2010 had slightly higher temperatures and slightly more rainfall than 2009 and 2011 viral respiratory seasons. The average temperature for the RSV season in 2010 was 1.1 °C warmer than the 2011 season. Regarding rainfall, there was 0.57 cms more rainfall in the 2010 RSV season compared to the 2011 season. The average temperature for the influenza season in 2010 (A(H3N2) and B) was 0.29 and 0.76 °C warmer respectively, than the influenza season in 2009 (A(H1N1)pdm09). There was between 0.46–1.86 cms more rainfall in the 2010 influenza season (A(H3N2) and B) than the 2009 influenza season (A(H1N1)pdm09). The 2009 PIV3 season was on average 0.67 °C cooler with 0.27 cms less rainfall in 2009 compared to 2010.

DISCUSSION

Using GIS statistics to characterize the spatial and temporal patterns of viral ARI spread among children age <3 years during three consecutive years in San Marcos-Peru, we identified clusters of children with high virus-specific rates for most study viruses. Influenza A(H1N1)pdm09, influenza B, RSV, PIV2 and PIV3 all exhibited spatial clustering. For several viruses, this clustering occurred in proximity to their respective virus index cases.

Interestingly, many viruses did not share the same hot spots and spatial distribution. Nevertheless, as respiratory viruses circulated during distinct respiratory seasons, and the underlying population at risk also changed over time, geographic patterns might be expected to differ. In addition, the circulating strains of specific viruses changed over time, which could also affect these patterns. Patterns in one year may affect patterns in subsequent years due to acquisition of immunity by some in the population. Viruses did not all share any general hot spot geography over the study period. However, for many viruses, the hot spots were located in proximity to their respective index cases. This suggested intense transmission may have been facilitated by the intense social mixing patterns previously described for this population¹⁴. Some study viruses did not show spatial clustering. One must keep in mind the nature of our incidence measurements and the Getis-Ord Gi* hot spot analysis when interpreting this observation. For example, RSV in 2011 had no significant hot spot clusters in contrast to RSV in 2010. However, RSV incidence rates were higher in 2011 than in 2010. Hot spot detection is most useful for detecting where values significantly differ from the mean. In our study, incidence rates capture more directly how fast susceptible children became sick with specific viruses. When a given study child shared very similar rates as other children across the study area, hot spots were unlikely to be detected. This can occur, as seen with RSV in 2011, when incidence rates were higher than in other seasons.

Specific antiviral immunity is important to consider when describing incidence rates during consecutive seasons. Children previously infected would have a specific antiviral immunity that could contribute to a different spatial pattern than immunologically naive children. Indeed, it is possible that older children could have partial immune protection due to prior infections. However, we did not consider immune protection as a significant contributing

factor in our study because the median age of children remained similar over the study period, reflecting a relatively new cohort of children during each season. In addition, immunity from previous exposures may be limited, as viral strains likely changed each year. Nevertheless, viral genotype information was not available for this study.

Several viruses had hot spots within the 3-km radius of their index cases. The referent 3-km radius was chosen as a scale to represent the village geography in San Marcos as well as the tight-knit assortative contact pattern of the study setting, where it is possible that transmission would radiate out from the index case and disproportionately affect nearby households. While there is no evidence that a 3-km distance encompasses San Marcos' assortative contact structure, this distance was used only as a referent to illustrate the potential contact space at a micro-geographic village scale. Inhabitants are likely to move and interact within and around the community beyond 3-km of their households, whereby transmission of ARI viruses would likely spread within the larger geography of the community and not necessarily affect households within 3-km any more than households beyond 3-km radius. Importantly, the 3-km radius distance was not a part of the hot spot spatial analysis, and aimed only to provide a referent of spread of viral infections in the geography near the index case.

Our study was conducted in a rural, widely dispersed community setting. Yet, we were able to demonstrate rapid spread of viral infections within the study communities. Influenza A(H1N1)pdm09 in 2009 and influenza B in 2010 had clear incidence hot spots near the index cases and became widespread during their seasons. This was similar for RSV in 2010, where hot spots were located near the index case, and subsequently cases were distributed across much of the study communities. Overall, it was surprising how rapidly influenza and RSV spread within the communities, despite the geographical dispersion of households and communities in this remote setting. In our examination of the directionality of the ARI spread, we noted that in spite of the rural setting and the difficult underlying geography, in 2010 both influenza B and RSV seemed to spread along the main road route from south to north, then radiate outward once the viruses were introduced into the more densely populated areas.

Given the observed rapid spread of viral infections, and the social contact patterns previously described for the study population, we consider that social distance measurements (e.g. staying at home while sick) may offer an opportunity to mitigate the transmission of infections. Social mixing, including physical contacts that could facilitate the transmission of infections was common in the study community, and contacts were similar during weekdays relative to the weekends when people usually attended local markets has also been reported¹⁴. Future studies would be needed to evaluate the feasibility and potential effectiveness of these interventions in the study setting. These potential interventions could complement but not replace recommendations for timely vaccination against respiratory pathogens.

Our study has several strengths and limitations. One strength is that it was conducted at the household level in a rural, high-altitude, low resource, dispersed low-population density setting, which provided a unique environment to investigate specific-viral ARI, and

represents a population that is typically excluded from traditional research. We used laboratory confirmation for specific viral infections to allow an accurate and detailed characterization of specific infections, and used GIS tools to determine spatial clustering of virus-specific ARI incidence, and to assess the directionality of the spread of infections. Several limitations must be acknowledged as well, including the study duration of only three consecutive years and the limited number of cases detected for some viral infections. In addition, our assessment was restricted to young children and did not consider older children or adults who are also infected by the study viruses and important in the transmission process¹⁴. We only concentrated on symptomatic ARI; however transmission from asymptomatic individuals could be possible²⁰. Although we noted some differences in average temperatures among viral respiratory seasons, more systematic analyses of meteorologic conditions were not conducted. Similarly, we did not include altitude in our estimations. Previous studies conducted in the same population have reported higher rates of influenza infection occurring between 2,322–2,641 meters above sea level compared with higher altitudes⁹. Similarly, higher rates of RSV were noted between 2,626–2,865 meters above sea level compared with higher altitudes³⁰. Larger subsequent studies would allow the exploration of urban/rural variation in viral transmission, the examination of the role of climatic and altitude parameters. Combining this environmental information with additional disease surveillance information would allow the development of predictive and transmission models that could be used to anticipate the occurrence or intensity of future viral outbreaks. Although our study was conducted in an area with relatively well-defined viral respiratory seasons, other areas may have different patterns of viral activity, for example year-round circulation of influenza viruses. Finally, direct extrapolation of our observations to other settings must be done with caution and considering the peculiarities of our study population.

In conclusion, geospatial analyses revealed significant aggregation of ARI incidence for several viral infections, notably influenza and RSV. This aggregation tended to occur in proximity to their respective index cases. This rapid geographic spread of viral ARI in this remote dispersed setting is likely an important contributor to child morbidity and mortality in the area. Because ARIs are the leading cause of morbidity and mortality among young children globally, understanding the spatial and temporal characteristics of ARI occurrences is important for developing sustainable and culturally appropriate means for lessening this burden among children around the world.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Characteristic	2009		2010				2011	
	Influenza A(H1N1)pdm09	PIV3	Influenza A(H3N2)	Influenza B	RSV	PIV2	RSV	MPV
Total number of children at risk at beginning of season	265	209	481	459	421	420	444	450
Median age (months) (IQR)	21 (13, 28)	21 (14, 28)	14 (5, 23)	16 (5, 23)	16 (8, 26)	16 (8, 26)	15 (9, 26)	14 (8, 25)
Female (%)	124 (48.4)	95 (45.5)	242 (50.3)	230 (50.1)	202 (48.0)	201 (47.9)	228 (51.4)	230 (51.1)
Total number of cases	21	32	73	54	74	25	93	68
Person-years	31.6	46.1	79.9	78.4	119.3	75.3	100.7	130.1
Rate (per 100 person- years)	66.4	69.5	91.4	68.9	62.1	33.2	92.3	52.3
Duration of respiratory season (months)	2	4	3	3	5	3	4	5