Morbidity burden, seasonality and factors associated with the human respiratory syncytial virus, human parainfluenza virus, and human adenovirus infections in Kenya

Therese Umuhoza¹,*, Julius Oyugi¹, James D. Mancuso², Anwar Ahmed², Wallace D. Bulimo³

¹ Institute of Tropical and Infectious Diseases, University of Nairobi
² Department of Preventive Medicine and Biostatistics, Uniformed Services University of the Health Sciences, Bethesda, MD, USA
³ Centre for Virus Research, Kenya Medical Research Institute, Nairobi, Kenya

Background: Human respiratory syncytial viruses (HRSV), human parainfluenza viruses (HPIV), and human adenoviruses (HAdVs) cause a substantial morbidity burden globally. The objective was to estimate morbidity burden, assess seasonality, and determine factors associated with these respiratory viruses in Kenya.

Methods: The data were obtained from Kenyan sites included in the Köppen-Geiger climate classification system. We defined the proportion of morbidity burden by descriptive analysis and visualized time-series data for January 2007–December 2013. Logistic regression was used to identify factors associated with infection outcomes.

Results: The morbidity burden for HRSV was 3.1%, HPIV 5.3% and HAdVs 3.3%. Infants were more likely to be infected than other age groups. HRSV exhibited seasonality with high occurrence in January–March (odds ratio [OR] = 2.73) and April–June (OR = 3.01). Hot land surface temperature (>240 °C) was associated with HRSV infections (OR = 2.75), as was warmer air temperature (19–22.9 °C) (OR = 1.68), compared with land surface temperature(<30) and cooler air temperature (<19 °C) respectively. Moderate rainfall (150–200 mm) areas had greater odds of HRSV infection (OR = 1.32) than low rainfall (<150 mm).

Conclusion: HRSV, HPIV and HAdVs contributed to morbidity burden, and infants were significantly affected. HRSV had a clear seasonal pattern and were associated with climate parameters, unlike HPIV and HAdVs.

HRSV has 2 main types, A and B, which occur either independently or co-circulate with a slight predominance of type A. However, clinically, infection with either of the 2 types does not present differently (Hirsh et al., 2014). Other respiratory viruses that cause ILI include human parainfluenza viruses (HPIV) and human adenoviruses (HAdVs) (Lim et al., 2017). HPIV has 4 major types, namely HPIV-1, HPIV-2, HPIV-3 and HPIV-4 (Henrickson, 2003), with a predominant occurrence of types HPIV-3, HPIV-1 and HPIV-2. Although the HPIV-4 type is less common, there is evidence that it can cause both the mild and severe respiratory illnesses described for the HPIV 1-3 types (Vachon et al., 2006; Villaran et al., 2014). HAdVs constitute 7 known species that vary from HAdV-A–G and cause a range of syndromes, including pneumonia.

Amongst the HAdVs, Species B (serotypes 3 and 7), C (serotypes 1, 2, and 5) and E (serotype 4) viruses cause ILI (Schmitz et al., 1983). HAdV-B3 occurs most frequently amongst HAdVs serotypes.

Abbreviations: HRSV, Human respiratory syncytial virus; HAdV, Human adenovirus; HPIV, Human parainfluenza virus; ILI, Influenza-like illness.

* Corresponding author: Therese Umuhoza, Institute of Tropical and Infectious Diseases, University of Nairobi, P.O. Box 19676 -00200, Nairobi, Kenya
E-mail address: umuhozatddy@gmail.com (T. Umuhoza).

https://doi.org/10.1016/j.ijregi.2021.10.001
Received 29 July 2021; Received in revised form 30 September 2021; Accepted 1 October 2021
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Understanding the seasonality of acute viral respiratory tract illnesses is important for timely preventive and treatment interventions (Janet et al., 2018). In temperate climates, most acute viral respiratory illnesses show distinct seasonality, with peaks during the winter months (Paynter, 2015). However, this seasonal variation is less evident in the tropics due to diminished fluctuations in meteorological parameters (Li et al., 2019). HRSV seasonality varies significantly within geographical regions and across time (Mullins et al., 2003). HRV infections are mostly reported during winter in temperate regions and are also associated with the rainy season in tropical countries (van der Sande et al., 2004). Nevertheless, epidemics of HRV are also observed during the dry season in areas located south of the equator (Shek and Lee, 2003). The epidemic duration of HRV is approximately 5 months in both temperate and tropical regions (Sandell et al., 2016).

The epidemics of HPIV last for slightly longer (6 months) and occur in the spring or early summer months (Li et al., 2019). Differences in seasonality are observed for HPIV types in the temperate zones. HPIV-3 epidemic peaks occur in spring (Fry et al., 2006), whereas HPIV-1 and HPIV-2 circulation occur periodically in early winter in the temperate regions (Murphy et al., 1980). The reported prevalence of HPIV-4 is low; hence the seasonality of HPIV-4 is not well defined. In contrast, HPIVs occur throughout the year in the tropics. It has been described in autumn mainly for the HPIV-1 subtype; HPIV-3 and HPIV-2 peaked in spring.

The seasonality of the HAdVs is different; the infections occur throughout the year, with peaks observed in late winter, spring or early summer in temperate climates (Chen et al., 2016). Similarly, in tropical climates, HAdV infections were detected throughout the year with peaks of different amplitudes, without a clear seasonality (Faden et al., 2011).

Factors influencing the occurrence of HRV, HPIV and HAdVs are similar. The 3 viruses are transmitted directly through human contact or indirectly through fomites (Rutter et al., 2018). The common demographic factors associated with the 3 viruses have been reported in various studies and include age, sex and preexisting health conditions (Simoes, 2003). Additionally, host attributes and behaviors, comprising household overcrowding, daycare attendance, birth during the seasonal peak of infection, lower parental education level, inadequate hygiene, and lower breastfeeding rates, have been suggested to affect the distribution of these viruses (Sommer et al., 2011). Furthermore, environmental factors such as humidity, temperature, precipitation and airflows have been suggested to influence occurrence substantially (Pica and Bouvier, 2012). This study sought to estimate morbidity burden, assess seasonality, and determine factors associated with HRSV, HPIV and HAdVs infections in Kenya between 2007 and 2013.

Methodology

Study regions

Kenya is the 47th largest country in the world with a population of 48 million and a landmass of 580 367 km² characterized by variable geographical features and diverse climate (Kenya Population 2019). The climate varies from warm to cool across the different geographic regions of the country. Figure 1 shows the current Kenyan Köppen-Geiger climate classification map at a 1-km resolution (Beck et al., 2018), combined with the Kenya regional boundaries and ILI surveillance sites generated by qGIS 3.8.1-Zanzibar. The western region of the country has an equatorial tropical climate and some temperate savanna areas. This region experiences rainfall throughout the year, with the heaviest rain in April and a temperature range of 14-36 °C. The Rift Valley region has different climates ranging from the hot desert or arid region in the north to the tropical savanna and cooler temperate areas in the south. The average monthly rainfall ranges from 20 mm in July to 200 mm in April, and temperature varies from 20 °C to 40 °C. In the northeast part of the country, the climate is characterized by the warmest desert and arid areas that become cooler toward the center, followed by the oscillation of arid and tropical savanna climates in the coastal region. The average temperature range on the coast is 22-30 °C, with annual rainfall varying between 20 mm to 300 mm (Ayugi et al., 2016). ILI surveillance sites presented in this study are geographically distributed in each regional climate, except in the warm desert, characterized by low population density, which was not accessible due to security concerns. Eight surveillance sites were used to represent the target population in these different climatic zones.

Source of the data

In this study, the primary dataset was participants presenting with ILI, recruited by the Kenya Medical Research Institute’s (KEMRI) influenza and other respiratory virus surveillance program from 2007 to 2013. Participants were enrolled based on the World Health Organization case definition for ILI (World Health Organization 2015). Briefly,
any individual presenting at the selected outpatient departments with (1) fever $>$38°C (oral or equivalent), (2) cough/sore throat, and (3) onset of illness within the previous 10 days was eligible for participation. The nasopharyngeal specimens and demographic data from consenting participants were submitted to the surveillance program that had received prior approval from the KEMRI Science and Ethics Research Unit under protocol numbers SSC#981.

The surveillance program assigned each hospital site a health care provider who collected patient specimens and demographic data on a weekly basis. The residence of each patient, including the village and the estate, was recorded along with other demographic information (age, gender, and occupation). The collected nasopharyngeal specimens were tested for influenza and other respiratory viruses, including HRSV, HPIV, and HADVs, using a series of assays. These assays included polymerase chain reaction, viral culture in the appropriate cell lines, and immunofluorescence using appropriate virus-specific antisera. Data management and retrieval of the ILI dataset was performed using a program-specific Microsoft Access database.

Supplementary datasets comprised spatial coordinates of each surveillance site, monthly mean land temperature, air temperature, rainfall and regional Köppen-Geiger climate classification (1980-2016) (Beck et al., 2018). The spatial coordinates of each surveillance site were sourced via Earth Pro (7.3 Google LLC). Monthly mean land temperature data was derived from measurements of the Earth Observing System Moderate Resolution Imaging Spectroradiometer instrument aboard the Terra (EOS AM-1) spacecraft (Wan et al., 2002). The rainfall data were obtained from the African Rainfall Climatology dataset with data derived from satellite cold clouds (Novella and Thiaw, 2013). Air temperature data were produced from several sources, including but not limited to the Global Historical Climatology Network Monthly (Willmott and Matsuura, 2001).

### Data analysis

The ILI dataset was reviewed to ascertain participants’ characteristics and error checking completed. We performed a descriptive analysis to determine the morbidity burden of infection caused by HRSV, HPIV and HADVs. In this analysis, the morbidity burden was defined and expressed as a proportion of laboratory-confirmed positive cases for HRSV, HPIV and HADVs per the total number of ILI cases recorded by the surveillance program (World Health Organization et al., 2015). In addition, we obtained estimates for each specific virus by participants’ demographic characteristics and by the surveillance sites over the study period.

The seasonal pattern of HRSV, HPIV and HADVs infections were recorded as the monthly total number of cases for the study period of January 2007 to December 2013. To increase the signal to noise ratio, we visualized by line plot the total number of each specific respiratory virus per annual quartile. We applied Fourier transformation to the time series data to describe monthly trends and showed if any steady seasonal patterns of HRSV, HPIV and HADVs were present. Initially, a fast Fourier transformation was performed to identify the magnitude and phases of

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### Table 1

Demographic characteristics of study participants by respiratory viruses.

| Variable/Outcome Overall | Total Population | HRSV Positive | HRSV Negative | HPIV Positive | HPIV Negative | HPIV Chi-square | HPAV Positive | HPAV Negative | HPAV Chi-square |
|--------------------------|-----------------|--------------|--------------|--------------|--------------|----------------|--------------|--------------|----------------|
| Gender                   |                 |              |              |              |              |                |              |              |                |
| Male                     | 17261           | n (%)        | n (%)        | P-value      | n (%)        | n (%)          | P-value      | n (%)        | n (%)          |
| Female                   | 8263(48)        | 249(3)       | 801(97)      | 0.429        | 452(5)       | 781(114)       | 0.002        | 581(3)       | 1668(97)       |
| Age                      |                 |              |              |              |              |                |              |              |                |
| <1 year                  | 9650(56)        | 351(4)       | 929(96)      | <0.001       | 32(3)        | 32(97)         | <0.001       | 32(4)        | 32(96)         |
| 2 to 4 years             | 6135(39)        | 166(3)       | 597(97)      | <0.001       | 32(5)        | 581(97)        | <0.001       | 175(3)       | 596(97)        |
| 5 to 18 years            | 1163(7)         | 20(2)        | 114(98)      | <0.001       | 16(2)        | 111(97)        | <0.001       | 14(1)        | 114(99)        |
| 19-49 years              | 300(2)          | 10(2)        | 298(98)      | <0.001       | 3(2)         | 294(98)        | <0.001       | 10(3)        | 299(99)        |
| 50+ years                | 9(0.5)          | 0(0)         | 9(100)       | <0.001       | 0(0)         | 9(100)         | <0.001       | 0(0)         | 9(100)         |
| Occupation               |                 |              |              |              |              |                |              |              |                |
| Rural                    | 16932(98)       | 532(3)       | 164(9)       | 0.023        | 8(0.4)       | 7(97)          | 0.012        | 574(3)       | 635(98)        |
| Sick contact             |                 |              |              |              |              |                |              |              |                |
| Yes                      | 6001(35)        | 174(3)       | 582(97)      | 0.213        | 36(5)        | 569(95)        | 0.362        | 589(3)       | 589(97)        |
| No attend school         | 11245(65)       | 365(3)       | 1080(98)     | <0.001       | 41(5)        | 1063(95)       | <0.001       | 389(3)       | 1085(97)       |
| Location                 |                 |              |              |              |              |                |              |              |                |
| Rural                    | 319(2)          | 7(2)         | 312(98)      | 0.335        | 9(0.5)       | 299(94)        | 0.458        | 354(3)       | 354(99)        |
| Year                     |                 |              |              |              |              |                |              |              |                |
| 2007                     | 2925(17)        | 22(1)        | 290(99)      | <0.001       | 13(5)        | 284(97)        | <0.001       | 133(5)       | 272(95)        |
| 2008                     | 3052(18)        | 103(4)       | 294(96)      | <0.001       | 100(5)       | 286(94)        | <0.001       | 101(3)       | 295(97)        |
| 2009                     | 3806(22)        | 86(2)        | 372(98)      | <0.001       | 123(3)       | 368(97)        | <0.001       | 131(3)       | 367(97)        |
| 2010                     | 3027(17)        | 116(4)       | 291(96)      | <0.001       | 188(6)       | 289(94)        | <0.001       | 102(3)       | 292(95)        |
| 2011                     | 2289(13)        | 140(6)       | 214(99)      | <0.001       | 110(8)       | 215(91)        | <0.001       | 44(2)        | 224(98)        |
| 2012                     | 1338(8)         | 53(4)        | 128(96)      | <0.001       | 110(8)       | 122(98)        | <0.001       | 52(4)        | 128(96)        |
| 2013                     | 824(5)          | 19(2)        | 805(98)      | <0.001       | 96(2)        | 728(88)        | <0.001       | 18(2)        | 806(98)        |
Table 2
Factors associated with the respiratory syncytial virus, human parainfluenza, and adenoviruses.

| Variable/Outcome | HRSV | P-Value | Adjusted OR | Adjusted P-Value |
|------------------|------|--------|------------|-----------------|
|                  | Crude OR | 95% CI | Crude OR | 95% CI |
| Age              | <0.001 | Ref | 0.73 (0.61-0.88) | 0.001 |
| ≤ 1 year         |        |      | 0.75 (0.62-0.91) | 0.003 |
| 2 to 4 year      |        |      | 0.91 (0.79-1.05) | 0.235 |
| 5 to ≤ 18 year   |        |      | 0.46 (0.29-0.73) | 0.001 |
| 19-49 year       |        |      | 0.46 (0.29-0.73) | 0.001 |
| 50+ year         |        |      | NA         | NA |
| Oct-Dec (Q4)     | <0.001 | Ref | 3.10 (2.32-4.14) | <0.001 |
| Jan-March (Q1)   | <0.001 | 2.73 (2.00-3.73) | 0.83 (0.68-1.02) | 0.091 |
| Apr-Jun (Q2)     | <0.001 | 3.01 (2.23-4.07) | 1.07 (0.90-1.27) | 0.432 |
| Jul-Sept (Q3)    | <0.001 | 0.77 (0.63-1.52) | 0.71 (0.58-0.97) | 0.001 |
| LTM LST: Cooler (<30°C) | <0.001 | Ref | 1.05 (0.75-1.45) | <0.001 |
| LTM LST: Warmer (30-39.9°C) | <0.001 | 0.93 (0.75-1.15) | 0.90 (0.78-1.05) | 0.098 |
| LTM LST: Hot (≥40°C) | <0.001 | 2.75 (1.79-4.24) | 1.02 (0.85-1.23) | 0.775 |
| LTM MMAT: Cooler (<19°C) | <0.001 | Ref | 1.06 (0.75-1.49) | <0.001 |
| LTM MMAT: Warmer (19-22.9°C) | <0.001 | 1.68 (1.03-2.70) | 1.06 (0.73-1.52) | 0.028 |
| LTM MMAT: Hot (≥23°C) | <0.001 | 2.59 (1.58-4.23) | 2.25 (1.48-3.43) | <0.001 |
| LTM rainfall: Low (<150mm) | <0.001 | Ref | 1.09 (0.89-1.31) | <0.001 |
| LTM rainfall: Moderate (150-200mm) | <0.001 | 1.32 (1.05-1.66) | 1.06 (0.76-1.47) | 0.627 |
| LTM rainfall: Heavy (>200mm) | <0.001 | 1.67 (1.25-2.22) | 1.60 (1.21-2.13) | <0.001 |
Figure 2. The monthly trend of HRSV, HPIV and HAdVs infections during the study period

*Monthly trend of Influenza-like illness (ILI) by HRSV, HPIV and HAdVs, Kenya (2007-2013). Human respiratory syncytial virus (HRSV), human parainfluenza virus (HPIV), and human adenoviruses (HAdVs). The inverse discrete Fourier transform (IDFT) represents the monthly periodicity trend for every 12 months cycle. Blue dots denote the observed seasonal peak of HRSV around April–May.

The overall morbidity burden of ILI caused by HRSV was 3.1% (2.8%–3.3%; 95% CI). HPIV and HAdVs represented 5.3% (5.0%–5.6%; 95% CI) and 3.3% (3.1%–3.6%; 95% CI), respectively. Amongst the HPIV types, HPIV-3 was the most dominant (38.6%), followed by HPIV-1 (34.1%) and HPIV-2 (10.4%). The proportion of multiple HPIVs infections was 16.8%.

The proportions of ILI caused by HRSV, HPIV and HAdVs varied by demographics. HRSV infection differed significantly across the age categories (P<0.001), as did HPIV and HAdVs. Further, differences were observed in the proportions of HRSV (P = 0.023), HPIV (P = 0.001), and HAdVs (P = 0.012) among occupation categories. There was a significant difference in the proportion of participants who attended school (P<0.001) for HRSV, HPIV and HAdVs infections compared with non-school attending participants. The proportion of disease caused by the 3 respiratory viruses varied significantly across surveillance sites and throughout the years of the surveillance period. HRSV, HPIV and HAdVs occurred at all surveillance sites with varying distribution of infections. HRSV infections were most commonly found in Malindi (5%), Port-Reitz (4%) and Kisii (4%). Other surveillance sites had lower proportions of HRSV infection. The proportions of HPIV infections were the highest in Malindi, Port-Reitz, Kisii, Kericho and Isiolo. The proportion of HAdVs infections were highest in Malindi (5%), New-Nyanza (4%) and Mbagathi (4%), compared with Port-Reitz, Kisii and Kericho.

The ILI participants presented with various clinical symptoms (S1 figure 1). Fever (100%), cough (98%), runny nose (87%) and nasal stuffiness (53%) were the most common symptoms. Many clinical characteristics, including malaise, vomiting, fatigue, difficulty in breathing, diarrhea, headache, sore throat, retro-orbital pain, sputum production, abdominal pain, joint pain, muscle aches, bleeding, and neurological signs, were reported in <35% of participants. These symptoms varied by HRSV, HPIV and HAdVs infection type. After adjusting for age, none of the clinical characteristics, except for fever and cough, were significantly associated with a specific respiratory virus outcome among the participants.
HRSV, HPIV and HAdVs circulated throughout the 7 years of surveillance (2007-2013), roughly following a quarterly pattern (S2 Figure 2). There were 3 major spikes of HRSV activity in the years 2008, 2010 and 2011. HRSV had a defined seasonal peak appearing around April–May every year of the surveillance period (Figure 2). Fourier series analysis revealed no clear pattern in the seasonal trends for HPIV and HAdVs cases. HPIV was the most prevalent respiratory virus, with spikes occurring irregularly every year during the surveillance period. In contrast, major erratic spikes were observed for HAdVs in 2007, followed by 2009; the number of cases then decreased progressively toward 2013.

Demographic factors, season, and climate had significant associations with the occurrence of HRSV, HPIV and HAdVs (Table 2). Infants had higher proportions of all 3 viruses than other age groups. In addition, HRSV was 2.73 times more likely to occur in Jan–Mar (Q1) and 3.01 times in Apr-Jun (Q2) than in Oct-Dec (Q4). Hot land surface temperature (≥40 °C) favored HRSV infections more than cooler land surface temperature (<30 °C) (OR: 2.75). HRSV infections also had higher odds (OR: 1.68) of occurring in warmer (19-22.9 °C) than cooler air temperatures (<19 °C), and during moderate (150-200 mm) compared with low rainfall (<150 mm) (OR = 1.32). There were no associations between season and climatic conditions for either HPIV or HAdVs infections. Higher land surface temperature (≥40 °C) as opposed to cooler land surface temperature (<30 °C) was associated with HAdVs infections (OR = 2.25).

Discussion

In this study, we identified that HRSV, HPIV and HAdVs contributed substantially to the morbidity burden of ILI at all hospitals in the influenza and other respiratory viruses surveillance program network across Kenya. The record of multiple infections of HPIV subtypes suggested a co-circulation and/or co-morbidity with other respiratory viruses. However, co-infections of the 3 viruses were outside the scope of this study. HRSV exhibited seasonality, occurring more frequently in January through June, whereas HPIV and HAdVs exhibited no seasonality. Hot land surface temperature, warmer air temperature, and increased monthly rainfall were also associated with HRSV infections; no associations were seen between temperature or rainfall with either HPIV or HAdVs.

The proportion of HRSV, HPIV and HAdVs infections was greater in sites in the coastal tropical savanna (Malindi and Port-Reitz) and the western tropical forest (Kisii and Kericho) climatic regions. Indeed, climatic factors are an important driver for viral respiratory infection dynamics (Weber et al., 2001). The increasing number of HRSV cases from January to June with a peak around April–May coincided with the rainy season in Kenya, and moderate rainfall (150-200 mm) showed a positive effect on the occurrence of HRSV. This observation concurs with various studies in the tropics that recognized similar trends and further associated viral respiratory infections with rainfall (Murray et al., 2012).

Other climate parameters that were suitable for HRSV circulation included warm air temperature (19-22.9 °C) and hot land surface temperature (≥40 °C). Temperature is a known meteorological predictor of respiratory syncytial virus infections; several studies have reported an association of monthly average temperature with respiratory syncytial virus Infections in the tropics (Rodriguez-Martinez et al., 2015). In contrast, HPIV and HAdVs exhibited no seasonality for either respiratory virus. This finding supports previous studies, which have also shown clear seasonal patterns for HRSV, but not for HPIV and HAdVs (Li et al., 2019).

This study had several limitations. Whereas influenza as a major cause of IILI burden was not included here because it has been reported previously (Umuhouza et al., 2020), the morbidity burden of other viruses causing IILI was not examined. Further, possible co-infections between HRSV, HPIV or HAdVs and other viruses were not examined. In addition, this study likely overestimated the prevalence of the 3 respiratory viruses in the underlying population at risk since all participants had symptoms of IILI at the time of enrollment. As 91% of study participants were aged <5 years, the associations seen in this study may have had insufficient power to assess associations in other age groups. Finally, other unmeasured environmental or temporal confounding factors may have influenced the associations seen in this study. Notwithstanding these weaknesses, this study has considerable strengths, including the large sample size, long study period, broad geographic region covering the entire country, reliable data source from a robust surveillance network, and application of a pre-defined protocol and stratified analysis.

Conclusion

Our findings indicate that HRSV, HPIV and HAdVs cause a substantial proportion of IILI morbidity burden in Kenya. The age category of infants had a higher proportion of these 3 respiratory viruses. HRSV has a steady seasonal pattern, with cases increasing early in the year and peaking around April–May coincidental with the rainy season. Hot land surface temperature, warmer air temperature, and moderate rainfall were associated with increased HRSV infection. In contrast, HPIV and HAdVs were not seasonal and were not associated with climate parameters. mmcl.docx

Conflicts of interest

The authors declare that they have no financial or personal relationships which may have an inappropriate influence on conducting this study.

Acknowledgements

The authors acknowledge the support of the Kenya Medical Research Institute (KEMRI) for scientific and ethical review support. We also acknowledge the Organization of Women in Science for Developing countries (OWSD), Swedish International Development Cooperation Agency (SIDA), and Institute of Tropical and Infectious Diseases at the University of Nairobi (UNITID) for logistical and administrative support.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1177/0009922810392775.

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