Children under five years of age in Senegal: A group highly exposed to respiratory viruses infections

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Abstract

Background: Acute respiratory infections (ARI) continue to be the leading cause of pediatric morbidity and mortality worldwide.

Objectives: The present study is a prospective analysis of the prevalence and diversity of respiratory viruses associated with acute RTIs in children under 5 years of age in Senegal, and their association with disease severity.

Patients/Methods: An active surveillance of ARI was conducted from March 2014 to December 2015 in three pediatric referral Healthcare departments of Dakar. 288 children with ARI were enrolled and respiratory specimens collected. A two-step multiplex real-time RT-PCR for the simultaneous testing of 16 different respiratory viruses was performed.

Results: 93 children required hospitalization. Viral etiologies were identified in 224 patients while 64 were negative for all tested viruses. Single viral infections accounted for 30.5% and co-infections for 46.9%. A total of 439 respiratory viruses were identified in all children. Among these, 154 (35.3%) were detected in hospitalized children. Adenoviruses with 44.4%, influenza viruses 36.5%, rhinoviruses (HRVs) 28.5%, enteroviruses 19.8% and respiratory syncytial virus (RSV) with 10.1% were the most detected. RSV infections were significantly more frequent in the first 6 months of life (p-value = 0.00213). RSV and HRV are mostly associated with bronchiolitis and bronchitis. Influenza detection is also the most related with pneumonia disease (47.6%).

Conclusion: This study investigated the role of 16 different respiratory viruses in children with ARI in this Senegal. Data clearly suggest that respiratory viruses are major contributors to childhood acute respiratory infections in Senegal.

Abbreviations: ARI: Acute respiratory infection; RTI: respiratory tract infection; RT-PCR: Reverse Transcription Polymerase Chain Reaction; RSV: respiratory syncytial virus; HRV: human rhinoviruses; ILI: Influenza-like Illness; HAdV: human adenovirus; HEV: human enterovirus; HMPV: human metapneumovirus; HCoV: human coronaviruses; PIV: parainfluenza virus; LRTI: lower respiratory tract infections; CRP: C-reactive protein; CBC: complete blood count; WHO: World Health Organization; MoH: Ministry of Health; IPD: Institut Pasteur de Dakar.

Background

Acute respiratory infections (ARI) continue to be the leading cause of pediatric morbidity and mortality worldwide [1,2]. In 2010, Nair and colleagues reported that 11.9 million and 3.0 million episodes of severe and very severe ARI respectively, contributed to childhood hospitalization [3]. Furthermore, 0.935 million deaths in 2013 were attributed to ARI [4]. In developing countries where pneumonia is responsible over 10–25% of all deaths among children under 5 years of age the situation is more alarming [5]. Within the etiology of ARIs, viruses play an important role and are the main cause of ARIs in children under the age of 5 [6]. Unfortunately, in some cases, they also become an important cause of death [7]. In Senegal, recent data collected in the framework of the sentinel surveillance of respiratory viruses have shown a variety of respiratory viruses circulating in the community [8]. The most common viruses associated with influenza-like illness (ILI) in patients were influenza viruses, adenoviruses (ADV’s), human rhinoviruses (HRVs), respiratory syncytial virus (RSV), enteroviruses (EVs), parainfluenza viruses (PIVs), human metapneumovirus (hMPV), and human coronaviruses (HCoVs) 229E, OC43, NL63, and HKU1. Studies focused on HRV and RSV, have revealed a high activity of both viruses in children under 5 in Senegal, especially during the rainy season [9,10]. Indeed, previous studies have well established that RSV is the leading cause of lower respiratory tract infections (LRTIs)

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in young children with 50% of children infected during their first year of life, and 100% having experienced at least one infection by 3 years of age [11]. Human rhinoviruses (HRV) were known as a frequent cause of upper respiratory tract infections (URTI). However, recently, HRV were found also to be associated with lower respiratory infections (LRTI), such as bronchiolitis [12], pneumonia, exacerbation of asthma or cystic fibrosis, [13,14] chronic obstructive pulmonary disease [15], and also hospitalization of children [16].

The present study is a prospective exploration of the prevalence and diversity of respiratory viruses associated with acute RTIs in children under 5 years of age, and their association with disease severity (clinical diagnostic).

Materials and methods

Samples and data collection

This prospective study was conducted from March 2014 to December 2015, and consisted of an active surveillance of ARI in three pediatric referral Healthcare departments of Dakar (Hôpital Aristide Ledantec, Hôpital Roi Baudoin and Hôpital Abass Ndao). A clinical team at each hospital was trained on the case definition identification and surveillance procedures; patients’ carers/tutors were asked for verbal consent to participate. The clinical team enrolled any patients presented at the hospital who met an ARI case definition. ARI was defined as any patient with sudden onset of one or more of the following symptoms and signs: rhinitis, cough, sore throat, wheeze, dyspnea associated or not with an axillary temperature of more than 38.5°C. A respiratory specimen (nasal and/or throat swab) was collected from each child up to 5 years of age and placed in 2-mL cryovials containing viral transport medium (Universal Transport Medium; COPAN Diagnostics Inc., Murrieta, CA) and immediately transported at 4°C to the laboratory. At the laboratory, the specimens were processed immediately for viral diagnostic. Aliquots of each sample were also stored at −80°C for additional analysis.

Data regarding hospitalized patients were collected from medical records, using a standardized report form that includes basic epidemiologic data and a description of the symptoms prior to presentation. For hospitalized children, an input record was routinely performed including a complete blood count (CBC), a C-reactive protein (CRP) and radiography in the case of pulmonary signs. Case reports were entered into an Epi Info database (Centers for Disease Control and Prevention, Atlanta, GA) and merged with laboratory data.

PCR assay for respiratory viruses diagnostic

Total Viral nucleic acid (RNA/DNA) was obtained from 140 μl of clinical specimen using a Viral Nucleic Acid Extraction kit (QIAGEN, Valencia, CA, USA) according to the manufacturer’s recommendation. RNA are eluted with 60μl nuclease-free water and stored at −80°C until use. A two-step multiplex real-time RT-PCR was performed with a Bio-Rad CFX-96 thermocycler (Bio-Rad Laboratories) as previously described [8] for the simultaneous testing for Influenza viruses (fluA and fluB), Human respiratory syncytial virus (RSV A and RSVB), Human adenoviruses (HAdV), Human metapneumovirus (HMPV), Human coronaviruses (229E, NL63, OC43), Human parainfluenza viruses (PIV1, -2, -3 and -4), Human rhinoviruses (HRV), Human enteroviruses (HEV) and Human bocaviruses (HBV).

Statistical analyses

The Fisher test or Chi-2 test was used for comparison of all patients according to viral results and clinical data in inpatients and outpatient’s groups. The logistic-regression model was used to examine association of virus detection with sex, age group and clinical data. A P value < 0.05 was considered statistically significant. The R software (R.3.0.1 version) was used to perform the statistical analyses.

Ethical management

This protocol was approved as less than minimal risk research by the Ministry of Health in its guidelines for influenza surveillance policy. The protocol and oral consent were determined as routine surveillance activity by the Senegalese National Ethics committee and the steering committee for IPD, WHO and Clinicians in compliance with all applicable National regulations governing the protection of human subjects. Data were collected anonymously in an objective of surveillance and applicable to a molecular epidemiology studies on the detected pathogen. The information provided to participants was an informal description of the study. Respiratory specimens were collected, only after informed consent was granted, verbally, to local health care workers by the parents or tutors of children. Oral consent was documented in the patient form with two questions about received information and about oral consent. For the surveillance activities, written consent is judged not necessary by the Senegalese national ethics committee, which has also previously approved the work of the National Influenza Center. Collections of non-sensitive data or an observation from normal care in which participants remain anonymous do not require ethics committee review. The patients included in this study were consulted the health care centers due to influenza-like symptoms; parents accept the sampling and the tests for respiratory viruses largely because they are free and safe.

Results

Demographic and clinical characteristics of children

From May 2014 to December 2015, nasopharyngeal swabs were collected from 288 children with ARI whose age varied from 0 up to 5 years (Table 1): 164 (56.9%) were from Roi Baudouin Hospital, 74 (25.7%) from Abass Ndao Hospital and 50 (17.4%) were from Aristide Ledantec Hospital. Of these children, 93 (32.3%) required hospitalization.

The ages of the children ranged from 3 days to 5 years, with a mean age of 25.5 months and a median age of 18 months. The male to female ratio was 1.54 (173 [60.8%] males and 112 [39.2%] females). Sex information was not available in 3 cases. The most common age group was infants with age > 24 months, 42% (121/288). Children of age group 12-24 months represented 23.3% (67/288), while children of age groups 0-6 and 6-12 months represented 16.3% (47/288) and 18.4% (53/288), respectively.

Regarding clinical symptoms the majority of children presented at admission suffered from fever (74.6%; 215/288), cough (62.1%; 179/288), and rhinorrhea (39.9%; 115/288). Dyspnea (21.2%; 61/288), sore throat (9.4%; 27/288) and tachypnea (9%; 26/288) were also reported. We also noted that dyspnea (73.8%, 45/61), tachypnea (84.6%; 22/26), pulmonary condensation (90%, 9/10) and weight loss (60%, 6/10) were closely linked to hospitalization.

Clinically, rhinitis (33%; 95/288), bronchitis (39.2%; 113/288), bronchiolitis (17.4%; 50/288), tonsillitis (14.6%; 42/288) and pneumonia (7.3%; 21/288) were the most common diagnostic. Otitis (4.2%; 12/288) and pharyngitis (3.1%; 9/288) were also found. Pneumonia (19/21; p < 0.0001), bronchiolitis (22/50; p < 0.001), acute bronchitis (26/113; p =
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Table 1. Demographic characteristics, symptoms and diagnosis.

| Inpatients (N=93) | Outpatients (N=195) | Total (N=288) | p Value |
|-----------------|-------------------|--------------|---------|
| Gender          |                   |              |         |
| Male            | 55(59.1)          | 118(61.5)    | 173(60.8)|         |
| Female          | 38(40.9)          | 74(38.5)     | 112(39.2)| 0.697   |

Group Age (months)

| [0-6] | [6-12] | [12-24] | 2+  |
|-------|--------|---------|-----|
| 28(2.5)| 17(18.3)| 23(24.8)| 33(35.5)|
| 27(13.9)| 36(16.6)| 44(22.2)| 88(45.4)|
| 47(19.4)| 53(15.5)| 67(23.0)| 121(42.2)|
| 0.3090 | 0.2800 | 0.3732 | 0.0578 |

Clinical signs

| Cough          | Dyspnea       | Sore throat  | Fever         | Tachypnea |
|----------------|---------------|--------------|---------------|-----------|
| 64(68.8)       | 45(48.4)      | 9(9.7)       | 73(78.5)      | 22(23.7)  |
| 115(59.0)      | 168(2)        | 18(9.2)      | 142(72.8)     | 4(2.1)   |
| 79(62.2)       | 61(21.2)      | 27(9.4)      | 215(74.7)     | 26(9.0)  |
| 0.1199 | 1.107e-08 | 0.903 | 0.3152 | 1.076-08 |

A total of 439 respiratory viruses were identified in all children. Of the 439 viruses detected in the children, adenovirus was the most common viral pathogen with 44.4% of the total number of detected viruses. This result is consistent with the data collected since

Discussion

This is the first study in Senegal that investigated the role of 16 different respiratory viruses in children with acute respiratory infections in Senegal. Interestingly, this study in line with previous reports suggests that acute respiratory infections are a major public health issue in children worldwide [2]. Therefore, these findings could be very useful for public health policies in our country and in the sub-Saharan region.

Indeed, we showed that 224 samples from the children with ARI out of 288 contained at least one of the targeted respiratory viruses. All targeted viruses have been detected in at least one patient.

The frequency of virus detection (77.8%) among the children with ARI in our study is high compared with those found in several other studies from other countries. For example, Kaplan, et al. [17], in a similar study conducted in Jordan detected at least one respiratory virus in 75.5% of the children, Kromoe, et al. [18], in Cameroon detected at least one respiratory virus in 65.4% of the children, Amer, et al. [19] in Saudi Arabia had a detection rate of 60.3%, Lee, et al. [20] in Taiwan 60.2%, Wertheim, et al. [21] 58.6% (in patients from Thailand, Vietnam and Indonesia), Lu, et al. [22] in China 55.8%, Giambarderini, et al. [23] in Brazil 55% or Khamis, et al. [24] in Oman with 50%. Even lower detection rates were observed in studies performed in Europe or the USA: Moe, et al. [25] in Norway (43%), Pierangelii, et al. [26] in Italy (42.7%) or Wansaula, et al. [27] in USA (43.3%). However, higher rates than ours were observed in a study conducted by Do, et al. [28] in children less than 2 years old in Vietnam (91%) and another one in Cyprus (85.8%) by Richter, et al. [29]. However, it should be noted that the technical approaches used could at least partly explain the discrepancies in viral detection rates: primarily in their sensitivity differences and secondly in the number of targeted viruses. Alternatively differences in rates of detection could be due to true geographical differences in overall burden, differences in study populations (outpatients or hospitalized patients), ARI case definition differences and to the studies sample collection periods.

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Patients and viral detection

Viral etiologies were identified in the vast majority (77.8%, 224/288) of patients while 64 (22.2%) were negative for all viruses tested. Single viral infections accounted for 30.5% (88/288) of cases and co-infections with more than two viruses were detected in 46.9% (135/288), mainly with the association of HAdV or influenza viruses (Table 2). In 56 samples (19.4%) more than two viruses were detected.

A total of 439 respiratory viruses were identified in all children. Among these, 254 (57.8%) were detected in hospitalized children. Adenoviruses (44.4%; 128/288), influenza viruses (37.3%; 108/288) and rhinoviruses (28.5%; 82/288) were the most frequently detected among the children (Table 3). We also detected human enteroviruses (HEV) in 57 children (19.8%) and human respiratory syncytial virus (RSV) in 29 children (10.1%). Other viruses have been detected below 5% rate: human bocavirus (4.5%; 13/288), parainfluenza viruses (3.1%; 9/288), human coronaviruses (2.4%; 7/288) and human metapneumoviruses (2.1%; 6/288). Regarding mono-infection criterion, rates are proportional to the virus whole detection rates. Indeed, adenoviruses are the most frequently detected in single infection with 31 cases (24.2%; 31/128) followed by influenza viruses (24.8%; 26/105), HRV (19.5%; 16/82) and HEV with 9 cases (15.8%; 9/57). RSV and HBoV are detected respectively three and two times in single infection. HRV mono-infections are associated to hospitalization in 92.3 % (12/13), a significantly higher percentage than other viruses (P < 0.01), followed by influenza virus (57.1%; 8/14). RSV infections occurred at a younger age than other viral infections, and were significantly more frequent in the first 6 months of life (Fisher exact test p-value = 0.0213). In contrast, none of the other viruses exhibited significant age group distribution differences.

Taking into account the clinical diagnosis and detected viruses, RSV and HRV are the most associated viruses with bronchiolitis disease (24.1 % and 15.8% respectively). HMPV detection was mostly associated with acute bronchitis (50 %) and HCoV with rhinitis (Table 3). These different associations were not statistically significant (P > 0.05). Any significant association (P > 0.05) was also observed between a virus detection and a clinical symptom.

No significance difference was observed in the distribution of the viral detection rate of the viruses according to the age group. However, we noticed a detection ratio of 1.8 viruses per patient in children less than 6 months, which represented a high ratio as compared to other groups.

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0.006) and tonsillitis (12/42; p < 0.001) were significantly associated with hospitalization. All cases of tracheitis (3), meningitis (2) and acute sinusitis (1) were also hospitalized.

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2012 from our sentinel surveillance of other respiratory viruses in Senegal [8]. Indeed we observed a strong activity of adenoviruses in Senegal throughout the year (data not shown). Adenoviruses were observed in the same proportions of complications regarding influenza virus’s infection and the prospect for transmission and infection are essential for better disease control. However, the current epidemiological data available in Senegal is insufficient to understand the real impact of this virus.

Virus infections are associated with a variety of upper respiratory tract manifestations such as rhinitis, pharyngitis, sinusitis, and conjunctivitis. Adenoviruses, for example, are known to cause acute pharyngitis and respiratory symptoms similar to those caused by other respiratory viruses such as influenza viruses. In addition, adenoviruses have been associated with more severe respiratory disease, such as bronchiolitis and pneumonia, particularly in young children.

Adenoviruses are also known to cause gastrointestinal illness, particularly in young children. In Senegal, adenoviruses were detected in 36.5% of patients, with a peak incidence in the summer months. Adenoviruses were detected more frequently in children under 5 years of age, with a higher detection rate in boys compared with girls. The detection rate of adenoviruses was higher in children with cough, fever, and respiratory distress.

Table 2. Viral co-detections in children less than 5 years old with acute respiratory infections in Senegal.

| Virus types | HAdV | PIV | FLU | HRV | HMPV | HBoV | HCoV | RSV | HEV |
|-------------|------|-----|-----|-----|------|------|------|-----|-----|
| N (%) | N (%) | N (%) | N (%) | N (%) | N (%) | N (%) | N (%) | N (%) | N (%) |
| Detection | 128(44.4) | 9(3.1) | 105(36.5) | 52(19.4) | 5(1.9) | 11(4.4) | 14(5.4) | 29(10.1) | 57(19.8) |
| Hospitalized | 43(33.6) | 4(44.4) | 30(36.6) | 2(23.1) | 2(23.1) | 2(23.1) | 2(23.1) | 57(19.8) | 20(19.8) |

Table 3. Clinical characteristic of acute respiratory infection and viral detection in children less than 5 years old in Senegal.

| Gender | Male | Female |
|--------|------|--------|
| Age groups/Viral detection | [0-6] months | [6-12] months | [12-24] months | <24 months | p-Value |
| Cough | 7(7.8) | 63(38.3) | 50(61.0) | 5(83.3) | 6(46.2) | 3(42.6) | 18(62.1) | 34(59.6) | 0.9759 |
| Dyspnea | 2(22.2) | 20(44.4) | 20(44.4) | 16(33.3) | 2(22.2) | 2(22.2) | 7(42.9) | 10(67.7) | 0.7553 |
| Sore throat | 1(11.1) | 11(10.2) | 14(17.1) | 0(0.0) | 1(11.1) | 1(11.1) | 1(6.7) | 6(41.3) | 0.2218 |
| Weight loss | 7(7.8) | 63(38.3) | 50(61.0) | 5(83.3) | 6(46.2) | 3(42.6) | 18(62.1) | 34(59.6) | 0.1241 |
| Fever | 3(33.3) | 80(47.1) | 59(72.0) | 8(33.3) | 11(84.6) | 3(42.7) | 24(82.8) | 42(73.7) | 0.3935 |
| Tachypnea | 1(11.1) | 10(9.3) | 5(5.1) | 0(0.0) | 0(0.0) | 0(0.0) | 4(13.8) | 5(8.8) | 0.1808 |
| Condensation pulmonary | 1(11.1) | 5(4.6) | 3(3.7) | 0(0.0) | 0(0.0) | 0(0.0) | 1(3.4) | 1(1.8) | 0.8985 |
| Rhinorrhea | 15(14.8) | 21(19.4) | 13(15.9) | 0(0.0) | 1(14.4) | 1(14.4) | 1(3.4) | 8(14.0) | 0.04677 |
| Weight | 10(10.5) | 10(10.5) | 10(10.5) | 10(10.5) | 10(10.5) | 10(10.5) | 10(10.5) | 10(10.5) | 10(10.5) |
| Condensation nasal | 10(10.5) | 10(10.5) | 10(10.5) | 10(10.5) | 10(10.5) | 10(10.5) | 10(10.5) | 10(10.5) | 10(10.5) |
| Diarrhea | 10(10.5) | 10(10.5) | 10(10.5) | 10(10.5) | 10(10.5) | 10(10.5) | 10(10.5) | 10(10.5) | 10(10.5) |
| Temperature | 10(10.5) | 10(10.5) | 10(10.5) | 10(10.5) | 10(10.5) | 10(10.5) | 10(10.5) | 10(10.5) | 10(10.5) | 0.04677 |

Investigations (epidemiology, circulating genotypes...) will help to assess the real importance of this virus in respiratory infection diseases.

Influenza viruses were detected in 36.5% of patients, while adenoviruses were detected in 36.5% of patients. The detection rate of adenoviruses was higher in children with cough, fever, and respiratory distress. The detection rate of adenoviruses was higher in children under 5 years of age, with a higher detection rate in boys compared with girls. The detection rate of adenoviruses was higher in children with cough, fever, and respiratory distress.

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of implementing seasonal influenza vaccination in this age group in Senegal becomes a real public health necessity.

Picornaviruses (Rhinovirus and Enterovirus) accounted for about 48.3% of viral infections in our population. This high circulation of picornaviruses in children was clearly reflected in the data collected after many years of surveillance of these viruses in people in Senegal [9]. Interestingly, in the present pediatric study about 59.7% of picornaviruses infection cases are related to lower respiratory tract infections (LRTIs) although these viruses are usually related to mild URTI. These results underline a need for picornaviruses investigation during viral diagnosis of respiratory tract diseases in light of recently published data regarding the association of rhinoviruses especially with severe respiratory tract infections in children [37-39], and in asthma exacerbations [16,40-42].

Regarding RSV, our results are lower than the rates reported in several other similar studies. Among many examples we can cite the studies carried out in other low and middle-income countries including Bangladesh [43], Kenya [44], Mozambique, South Africa [45] El Salvador [46], Costa Rica [47], in Jordan [17], in Vietnam [29] and Thailand [48]. Otherwise, the proportion in Senegal (10.1%) was similar to that reported in Cameroon [18], in Mozambique [49] or Nepal [50]. However, as shown in our study, it is globally well documented that RSV represents a substantial burden of acute respiratory tract illness particularly in the early years of life (especially in the first six months), leading to severe morbidity and hospitalization in very young children [43,51,52]. Therefore, in a World Health Organization (WHO) vaccine perspective against this virus, the importance of long-term molecular epidemiological surveys for early detection of prevalent strains and newly emerging genotypes cannot be over emphasized to foster better understanding of RSV infections in Senegal. In future study, for a better assessment of the RSV burden among children in Senegal focusing on pediatric hospitalized cases, data on disease outcome, atypical clinical presentations, and interpretation of viral respiratory tract infections in light of recently published data regarding the association of rhinoviruses especially with severe respiratory tract infections in children [37-39], and in asthma exacerbations [16,40-42].

The remaining viral etiologies were identified below 5%; bocaviruses 4.5%, parainfluenza with 3.1%, human coronaviruses 2.4% and human metapneumovirus with 2.1%. These low circulation rates are in line with those reported in many other similar studies [18,23,24,26,29].

Mixed infections were observed in approximately 46.9% of all samples, which is much higher than those previously reported rates ranging from 4.8% in Italy [27] to 29.5% in Cameroon [18]. EV, RSV, HBoV, and HCoV were found most frequently in co-infections. Even though this study did not allow for investigating a possible association between multiple infections and disease severity, literary data show that such a potential association is still controversial.

Our study did have several limitations. The first weakness is the small number of samples collected in this study. An increase number of samples, along with the participation of more hospital sites will be critical to complete the picture for both the targeted viruses and the clinical diagnoses in children with ARI in Senegal. It will also be interesting to extend the recruitment period of the study as it would make possible to assess the seasonality of the infections. The lack of matched control groups is another limitation of the study especially to appreciate the asymptomatic viral carriage which will help to investigate a clinical causal link. In future work, it will be critical to compare the bacterial and viral etiologies, and also to study the clinical value of virus/bacteria co-infections in children with ARI. The role of bacteria as a cause of LRTI or as cause of super infection is well known, especially in RSV and influenza virus infection [53]. Bacteria investigation is also important for antibiotic intervention strategies. However, bacteria diagnostic is not easy as lower airway secretions (like sputum) considered as the optimal specimen type for detecting bacterial (co-) infection, are often difficult to obtain from young children, and can only be readily obtained from intubated children.

Conclusion

In summary, our study provides novel insights into the epidemiology and clinical impact of respiratory viruses among children under 5 years old, the most vulnerable age group, in a low-income West African country, Senegal. It highlights a high diversity and prevalence of respiratory viruses circulating in this age group. It arises from these results a need for implementation of surveillance programs for respiratory viral infections in order to collect exhaustive data for crucial analyses (seasonality, targeted group ages, causal roles of viral pathogens and the risk factors that may correlate with more severe disease…) seeking to guide preventive public health measures.

Authors’ contributions

The work presented here was carried out in collaboration between all authors. ND, MN, CSB, and ON defined the research, analyzed and interpreted the data, and revised the manuscript; AF and AD1 performed and coordinated technical work; ND, AF, SFW and MNN wrote the draft and revisions of the paper; AD2, JBND, DB, YK and AS contributed in the samples and data collection. All authors contributed to, seen and approved the manuscript.

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Competing interests

The authors have no competing interests.

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