


Assessing the epidemiology and seasonality of influenza among children under two hospitalized in Amman, Jordan, 2010-2013

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Abstract

Background: The disease burden of influenza-associated hospitalizations among children in Jordan is not well established. We aimed to characterize hospitalizations attributed to influenza in a pediatric population.

Methods: We conducted a cross-sectional study from our viral surveillance cohort in children under 2 years hospitalized with acute respiratory symptoms and/or fever from March 2010 to March 2013. We collected demographic and clinical characteristics, and calculated the frequency of children who met the severe acute respiratory illness (SARI) criteria. Nasal specimens were tested using real-time reverse transcriptase polymerase chain reaction to detect influenza A, B, or C. Further subtyping for influenza A-positive isolates was conducted.

Results: Of the 3168 children enrolled in our study, 119 (4%) were influenza-positive. Influenza types and subtypes varied by season but were predominantly detected between December and February. Codetection of multiple respiratory pathogens was identified in 58% of children with the majority occurring among those <6 months. Bronchopneumonia and rule-out sepsis were the most common admission diagnoses, with influenza A accounting for over 2/3 of children with a rule-out sepsis admission status. One-third of children under 6 months compared to 3/4 of children 6-23 months met the SARI criteria.

Conclusions: Influenza was an important cause of acute respiratory illness in children under 2 years. Children <6 months had the highest burden of influenza-associated hospitalizations and were less likely to meet the SARI global surveillance case definition. Additional surveillance is needed in the Middle East to determine the true influenza burden on a global scale.

KEYWORDS

acute respiratory infections in MENA children, influenza in Jordanian children, influenza in the Middle East, influenza MENA region, influenza seasonality

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1 | BACKGROUND

Acute respiratory infections (ARI) are the leading cause of morbidity and mortality of children under 5 years outside the neonatal period.¹ The majority of ARIs are viral in origin, with influenza substantially contributing to outpatient and emergency department visits, hospitalizations, and even deaths in these children.¹ Influenza is a vaccine-preventable disease and impacts all age-groups, with the highest risk of influenza-related complications in children under 2 years, adults older than 65 years, pregnant women, and individuals with underlying medical conditions.² Worldwide, although influenza hospitalizations among the pediatric population are known to inflict a large burden, the exact number of global cases and hospitalizations attributed to influenza is not well described.^{1,3}

In 2008, a systematic review estimated the global incidence of influenza in children under 5 years to be 90 million cases, with approximately one million severe cases.¹ The uncertainties of global pediatric influenza-associated hospitalization burden estimates may be posited to the lack of standard worldwide reporting and testing.⁴ In response to the 2009 H1N1 pandemic and in an attempt to overcome the influenza surveillance gap, the World Health Organization (WHO) launched an initiative in 2011 to develop global standards for influenza surveillance, including a global case definition of severe influenza.⁵ The case definition was intended to capture hospitalizations related to influenza and is known as severe acute respiratory infection (SARI), defined as an acute respiratory illness with a measured temperature of $\geq 38^\circ$ Celsius and cough, with illness onset within the past 10 days, and hospitalization.⁵ Although a standardized approach for influenza surveillance has been developed, the epidemiology in many parts of the world, including the Middle East North Africa (MENA) region, remains unclear, especially among young children.^{1,3,4,6,7}

Since 2007, Jordan has participated in sentinel-site surveillance with the Eastern Mediterranean Acute Respiratory Infection Surveillance (EMARIS) network.⁸ One study conducted in Jordan identified that 9% of all patients who met the SARI case definition were influenza-positive, with 3% of influenza-associated deaths, of which all occurred among pediatric patients.⁴ Additional influenza research has been conducted in Jordan, but many of these studies have only included individuals who met the SARI case definition and have not solely focused on a pediatric population.⁴ Therefore, our study aimed to evaluate and describe the epidemiology, seasonality, and clinical characteristics of influenza-associated hospitalizations in Jordanian children under 2 years, who presented to a large government hospital with fever and/or respiratory symptoms over three full respiratory seasons.

2 | METHODS

2.1 | Study design

From March 13, 2010, to March 31, 2013, we conducted a prospective year-round viral surveillance study of children <2 years who

were hospitalized with acute respiratory symptoms and/or fever within 48-hours of hospitalization at Al-Bashir Hospital in Amman, Jordan.⁹ Enrollment occurred Sunday through Thursday and children with chemo-associated neutropenia and/or newborns never discharged from the hospital were excluded from the study (detailed inclusion/exclusion criteria are previously published).⁹ Written informed consent was obtained from parents or legal guardians prior to enrollment into our study.⁹ The study was approved by the Institutional Review Boards at the University of Jordan, the Jordan Ministry of Health, and Vanderbilt University.⁹

2.2 | Study site

During the study period, Al-Bashir Hospital had a total of 185 pediatric beds (120 pediatric and 65 neonatal intensive care unit) and 11 230 hospitalizations among children <2 years.^{7,9-11} Al-Bashir is one of three major government run hospitals that services the population of Amman (capital and largest city in Jordan [>2 million persons]), with over 60% of the pediatric care occurring at this hospital.^{7,9-11} As part of the government policy, all Jordanian children under 6 years are provided no-cost medical care, regardless of insurance status, at Al-Bashir Hospital.^{7,9-11}

2.3 | Data and specimen collection

After obtaining informed consent, trained research personnel collected nasal and throat swabs from all enrolled children.^{7,9-11} Parents/guardians were interviewed to obtain the child's demographic characteristics and medical and social histories using a standardized questionnaire.^{7,9-11} All interviews were conducted in Arabic using a standardized case report form and transcribed into English.^{7,9-11} After children were discharged, medical records were abstracted for the following: oxygen use, intensive care unit (ICU) stay, mechanical ventilation, length of stay in the hospital, and discharge status.¹⁰ Complete details on the methods of data collection are explained in a previous publication.¹⁰

We inputted and stored all data in a secure REDCap™ (Research Electronic Data Capture, Vanderbilt University, Nashville, TN, USA) database.^{9,12} Data quality checks were performed on a minimum of 10% of the charts, and data from all case report forms were verified after entry.^{7,9}

2.4 | Laboratory methods

Nasal and throat swabs were combined into transport medium (M4RT®, Remel), aliquoted into MagMAX™ Lysis/Binding Solution Concentrate (Life Technologies), snap-frozen, stored at -80°C , and shipped on dry ice to Nashville, TN, USA.^{7,9-11} Testing of original and lysis buffer aliquots was conducted through real-time reverse transcriptase polymerase chain reaction (RT-PCR) for eleven respiratory viruses: influenza A, B, and C; parainfluenza virus (PIV) 1, 2, and 3; human metapneumovirus (HMPV); respiratory syncytial virus (RSV);

human rhinovirus (HRV); adenovirus; and Middle East respiratory syndrome coronavirus (MERS-CoV).^{7,9-11} Influenza A was further subtyped as H1N1 or H3N2.

2.5 | SARI criteria/case definitions

We categorized children into two groups: (a) children who met SARI criteria and (b) children that did not meet SARI criteria. Qualifying characteristics were extracted from the interview-derived questionnaires and medical chart abstractions. The fever component of SARI was met if the child had one of the following: self-reported history of fever during current illness, temperature of $\geq 38^{\circ}$ Celsius recorded at admission, and/or an admission or discharge diagnosis of fever.¹⁰ Children were recorded to meet the cough component if it was self-reported as a symptom and/or was recorded as an admission or discharge diagnosis. Illness duration was captured on the standardized questionnaire, and the duration component of SARI was met if the child had illness duration of 10 days or less at enrollment.¹⁰

Intensive care unit stay included children who were transferred to the ICU during the admission or were admitted directly. Children were categorized as rule-out sepsis (ROS) if they had the admission diagnosis of "rule-out sepsis" or "febrile neonate".⁷

2.6 | Data analysis

Descriptive statistics are reported as frequency or median and interquartile range where appropriate. We used Pearson chi-square and Fisher's exact tests to compare categorical variables and two-sample *t* tests allowing for unequal variances for continuous variables. Seasonality and trends of influenza type and subtype are evaluated using an epidemiologic curve by the date of specimen collection. All analyses were conducted using statistical software Stata/IC 16.0 (StatCorp LLC).

3 | RESULTS

3.1 | Study population and demographics

From March 2010 to March 2013, we identified 3793 children eligible for enrollment; 618 (16%) children had parent/guardian refuse to study participation, three were deemed ineligible after enrollment due to being older than 2 years, and four children had a diagnosis of meningitis.⁷ Our final cohort included 3168 children, of which 119 (4%) were influenza-positive.

3.2 | Demographics and clinical characteristics

The most common symptoms reported were cough, fever, wheezing, and shortness of breath (SOB); children primarily had an admission

diagnosis of either bronchopneumonia or ROS (Table 1). Compared to influenza-negative children, influenza-positive children were older and more likely to present with fever. Overall, influenza-positive children were less likely to be administered oxygen, but had a higher proportion of death, but these were not statistically significant (Table 1). Of those children who died, two had influenza A H3N2 and one had influenza A H1N1pdm09. Interestingly, two of the children had a serious comorbid condition, osteogenesis imperfecta. Of note, only six children were reported to have influenza vaccination and none were influenza-positive.

3.3 | Codetection with other viruses

Among influenza-positive children, 58% had additional co-pathogens detected. Children with influenza codetection with other respiratory viruses were more likely to be male compared to children with influenza detection alone (Table 1). Whereas children with only influenza detection were more likely to present with fever, they were less likely to have SOB. Interestingly, no children with influenza detection alone had an admitting diagnosis of bronchiolitis (Table 1).

3.4 | Influenza types and seasonality

Throughout our study, influenza types and subtypes varied by season; however, the majority of influenza-positive cases were detected in the months of December through February (Figure 1). The majority of the cases were influenza A (H1N1pdm09 =35; H3N2 =32; unable to subtype =4), followed by influenza B (n =28), influenza C (n =19), and influenza A/B (n =1). From December 2011 to January 2012, influenza A H3N2 was the most frequently identified subtype among children. During the following influenza season (December 2012-March 2013), influenza A H1N1pdm09 was the predominant subtype detected, followed by influenza B. In February 2011 and 2012, other respiratory viruses peaked as influenza cases declined (Figure 1).

3.5 | Clinical presentation, codetection, and admission diagnosis stratified by age

We stratified influenza-positive children into three age-groups: under 6 months; 6-11 months; and 12-23 months. Compared to the 6-11 months age-group, children under 6 months with influenza were more likely to have a history of breastfeeding, but less likely to be premature and had higher birthweight (Table 2). In addition, they were less likely to present with SOB and wheezing and had longer hospital stay. Compared to the 12-23 months of age-group, children under 6 months with influenza were more likely to be male and less likely to have an underlying medical condition and present with vomiting. When compared to both other age-groups, the under 6 months children were less likely to have fever, cough, and meet the

TABLE 1 Demographic and clinical characteristics of Jordanian children hospitalized with ARI over three respiratory seasons

| Characteristics | Influenza Positive (n = 119) | Influenza Negative ^a (n = 3049) | P-value | Influenza, Only (n = 50) | Influenza Codetection (n = 69) | P-value |
|---|------------------------------|--|--------------------|--------------------------|--------------------------------|-----------------------------|
| Age, months (median [IQR]) | 5.4 [1.8-12.5] | 3.5 [1.6-8.4] | .003 | 6.6 (1.6-15.2) | 5.5 (1.9-11.9) | .308 |
| Sex, male | 71 (60.0) | 1841 (60.4) | .875 | 24 (48.0) | 47 (68.1) | .027 |
| Cesarean section | 36 (30.3) | 857 (28.1) | .610 | 12 (24.0) | 24 (34.8) | .206 |
| Premature, <37 wks | 16 (13.5) | 434 (14.2) | .809 | 5 (10.0) | 11 (15.9) | .348 |
| Birthweight, kg (median [IQR]) | 3 (2.7-3.5) | 3 (2.5-3.5) | .617 | 3.0 (2.5-3.5) | 3.0 (2.7-3.5) | .485 |
| Underlying medical condition | 20 (16.8) | 355 (11.6) | .087 | 9 (18.0) | 11 (15.9) | .767 |
| Breastfeeding Hx. | 96 (80.7) | 2565 (84.1) | .313 | 40 (80.0) | 56 (81.2) | .874 |
| No. days reported sick (median [IQR]) | 3.0 (2.0-7.0) | 3.0 (2.0-4.0) | .965 | 3.0 (2.0-7.0) | 3.0 (2.0-5.0) | .101 |
| No. of household members (median [IQR]) | 6.0 (4.0-7.0) | 5.0 (4.0-7.0) | .316 | 6.0 (4.0-7.0) | 6.0 (5.0-7.0) | .538 |
| Smoke exposure, nargila, or cigarette | 91 (76.5) | 2334 (76.6) | .984 | 40 (80.0) | 51 (73.9) | .440 |
| Influenza vaccine | 0 (0.0) | 6 (0.2) | .369 ^b | 0 (0.0) | 0 (0.0) | - |
| Met SARI criteria | 63 (52.9) | 1198 ^c (39.3) | .003 | 28 (56.0) | 35 (50.7) | .569 |
| Symptoms | | | | | | |
| Fever | 86 (72.3) | 1676 (55.0) | <.001 | 42 (84.0) | 44 (63.8) | .015 |
| Cough | 90 (75.6) | 2276 (74.7) | .809 | 34 (68.0) | 56 (81.2) | .099 |
| Congestion | 0 (0.0) | 26 (0.9) | .623 ^b | 0 (0.0) | 0 (0.0) | - |
| Runny nose | 2 (1.7) | 51 (1.7) | 1.000 ^b | 2 (4.0) | 0 (0.0) | .174 ^b |
| Vomiting | 12 (10.1) | 510 (16.7) | .055 | 5 (10.0) | 7 (10.1) | .979 ^b |
| Diarrhea | 14 (11.8) | 303 (9.9) | .515 | 7 (14.0) | 7 (10) | .519 |
| Apnea | 0 (0.0) | 10 (0.3) | .531 ^b | 0 (0.0) | 0 (0.0) | - |
| Shortness of breath | 63 (52.9) | 1769 (58.0) | .271 | 18 (36.0) | 45 (65.2) | .002 |
| Wheezing | 65 (54.6) | 1692 (55.5) | .851 | 24 (48.0) | 41 (59.4) | .217 |
| Seizures/ab. movement | 4 (3.4) | 121 (4.0) | 1.000 ^b | 1 (2.0) | 3 (4.4) | .638 ^b |
| Admitting diagnosis | | | | | | |
| Bronchiolitis | 14 (11.8) | 533 (17.5) | .106 | 0 (0.0) | 14 (20.3) | <.001^b |
| Bronchopneumonia | 48 (40.3) | 972 (31.9) | .053 | 23 (46.0) | 25 (36.2) | .284 |
| Pneumonia | 13 (10.9) | 381 (12.5) | .610 | 3 (6.00) | 10 (14.5) | .233 ^b |
| Febrile seizure | 3 (2.5) | 80 (2.6) | 1.000 ^b | 1 (2.0) | 2 (2.9) | 1.000 ^b |
| Rule-out sepsis | 31 (26.1) | 881 (28.9) | .501 | 16 (32.0) | 15 (21.7) | .208 |
| Severity | | | | | | |
| Length of stay, days (median [IQR]) | 5.0 (3.0-7.0) | 5.0 (3.0-6.5) | .155 | 5.0 (3.0-6.0) | 5.0 (3.0-7.0) | .895 |
| Admission to ICU | 10 (8.4) | 274 (9.0) | .827 | 3 (6.0) | 7 (10.1) | .517 ^b |
| Admin. oxygen | 30 (25.2) | 983 ^d (32.2) | .092 | 9 (18.0) | 21 (30.4) | .123 |
| Mechanical ventilation | 1 (0.8) | 110 ^e (3.7) | .128 ^b | 1 (2.0) | 0 (0.0) | .420 ^b |
| Died | 3 (2.5) | 28 ^e (0.4) | .111 ^b | 1 (2.0) | 2 (2.90) | 1.000 ^b |

Note: Data are n (%), unless otherwise specified. P-values were calculated using Pearson chi-square test for categorical variables and independent samples t test for continuous variables.

Abbreviations: Ab., abnormal; Admin., administration; ARI, acute respiratory infection; Hx., history; Kg, kilogram; No., number; SARI, severe acute respiratory infection (ie, defined as fever, cough, and symptom onset in past 10 d).

Bold values are statistically significant <.05.

^aIncludes children who were virus negative.

^bFisher's exact test.

^cn = 3045.

^dn = 3018.

^en = 3017.

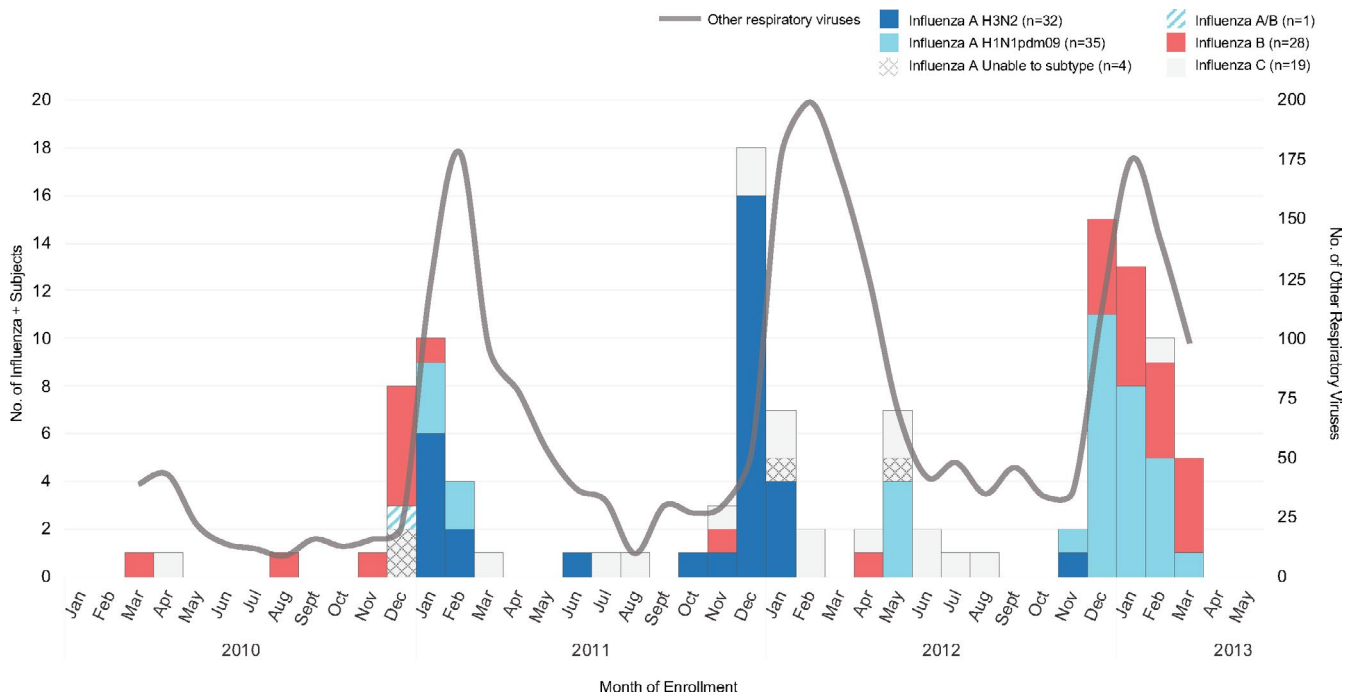


FIGURE 1 Seasonality of Influenza-Positive Children compared to Other Respiratory Viruses Detected from March 2010 to March 2013, stratified by type/subtype

SARI case definition (Table 2). In addition, all three mortalities were in children under 6 months.

Of the influenza-positive children with multiple respiratory pathogens detected, 24% had greater than one co-pathogen, with the majority of codetection occurring among children under 6 months (66%) (Figure 2A). Respiratory syncytial virus was the co-pathogen detected in 14% of influenza-positive children with no differences between age-groups. Overall, influenza A and B were more commonly detected in children under 6 months, while influenza C was equally detected in children under 6 months and 6-11 months (Figure 2B). Bronchiolitis and ROS were the most common admission diagnoses given to children under 6 months compared to children 6 months and older (Figure 2C), with influenza A accounting for >70% of all children with an ROS admission status (Figure 3). In comparison, influenza type was moderately similar among those children with a bronchiolitis admitting diagnosis.

4 | DISCUSSION

Our 3-year prospective viral surveillance study of 3168 Jordanian children identified influenza in 4% of all total acute respiratory hospitalizations, and even higher during winter months. One-half of the influenza-associated hospitalizations were among children younger than 6 months, and influenza A was the most common subtype identified. Our findings suggest that influenza is a common respiratory pathogen impacting young children throughout the winter season in Jordan, and these children are not routinely vaccinated against influenza, further placing an emphasis on the importance of surveillance and prevention measures, such as annual vaccination.

Influenza A/H1N1pdm09 and H3N2 were the most predominant subtypes throughout the study period, with influenza B primarily co-circulating in the 2012-2013 winter season. The subtypes we identified circulating over the 3 years are consistent with other population-based surveillance studies in the MENA region and Northern Hemisphere.^{4,13-15} In a 6-year sentinel surveillance study in Jordan of all ages, influenza A H3N2 predominately circulated in 2011-2012 and H1N1pdm09 was more common in 2012-2013.⁴ Similarly, in a systematic review from 2010-2016, 61.9% of cases in the MENA region were attributed to influenza A H1N1pdm09, with a primary peak from Jordan regularly occurring in January.¹⁴ However, these studies evaluated cases who met the SARI criteria and categorized pediatric cases into age-groups that do not provide sufficient epidemiological information on children under 2 years. Therefore, pediatric studies focusing on influenza burden are important for education campaigns and uptake of annual influenza vaccination.⁴ This information can help provide information to inform MENA initiatives targeted toward children.

In our study, fever was an important clinical criterion with influenza-positive children, particularly in children 6-23 months. Specifically, fever seems to be a unique component of the presentation to children who only had influenza detected. While cough was another common presenting symptom, it was much less common in children under 6 months was significantly more commonly detected in children with codetection. Moreover, the combination of fever and cough together was rarely seen in these young children. Therefore, our results imply that fever may be a useful clinical metric to determine which pediatric patients should be tested for influenza, especially during winter months when influenza circulation is more likely. Cough may be a less useful indicator, and when it is a required

TABLE 2 Demographic and clinical characteristics of influenza-positive Jordanian children hospitalized over three respiratory seasons, stratified by age-group

| Characteristics | Age-Group | | | | |
|--|-----------------------------|------------------|--------------------|-------------------|-------------------------|
| | <6 mo ^a (n = 62) | 6-11 mo (n = 24) | P-value | 12-23 mo (n = 33) | P-value |
| Sex, male | 42 (67.7) | 17 (70.8) | .782 | 12 (36.4) | .003 |
| Cesarean section | 20 (32.3) | 7 (29.2) | .782 | 9 (27.3) | .615 |
| Premature, <37 wks | 5 (8.1) | 6 (25.0) | .035 | 5 (15.2) | .284 |
| Birthweight, kg (median [IQR]) | 3.1 (2.7-3.5) | 2.8 (2.1-3.3) | .044 | 3.2 (2.8-3.5) | .676 |
| Underlying medical condition | 7 (11.3) | 3 (12.5) | 1.000 ^b | 10 (30.3) | .021 |
| Breastfeeding Hx. | 54 (87.1) | 16 (66.7) | .029 | 26 (78.8) | .290 |
| No. days reported sick (median [IQR]) | 2.0 (1.0-5.0) | 3.0 (1.5-6.0) | .651 | 4.0 (2.0-7.0) | .151 |
| No. of household members (median [IQR]) | 5.0 (4.0-7.0) | 5.0 (4.5-6.5) | .646 | 6.0 (5.0-7.0) | .214 |
| Smoke exposure, nargila or cigarette | 51 (82.3) | 17 (70.8) | .243 | 23 (69.7) | .160 |
| Met SARI criteria | 20 (32.3) | 18 (75.0) | <.001 | 25 (75.8) | <.001 |
| Influenza, codetection | 38 (61.3) | 14 (58.3) | .801 | 17 (51.5) | .358 |
| Symptoms | | | | | |
| Fever | 37 (59.7) | 20 (83.3) | .037 | 29 (87.9) | .004 |
| Cough | 39 (62.9) | 22 (91.7) | .008 | 29 (87.9) | .010 |
| Fever & cough | 17 (27.4) | 18 (75.0) | <.001 | 25 (75.8) | <.001 |
| Runny nose | 1 (1.6) | 0 (0) | 1.000 ^b | 1 (3.0) | 1.000 ^b |
| Vomiting | 2 (3.2) | 3 (12.5) | .130 ^b | 7 (21.2) | .008^b |
| Diarrhea | 8 (12.9) | 1 (4.2) | .434 ^b | 5 (15.2) | .762 |
| Shortness of breath | 27 (43.6) | 17 (70.8) | .023 | 19 (57.6) | .193 |
| Wheezing | 26 (41.9) | 20 (83.3) | .001 | 19 (57.6) | .146 |
| Seizures/abnormal movement | 0 (0) | 2 (8.3) | .076 ^b | 2 (6.1) | .118 |
| Severity | | | | | |
| Length of stay, days (median [IQR]) | 5.0 (3.0-8.0) | 4.0 (2.5-5.0) | .002 | 5.0 (3.0-6.0) | .171 |
| Admission to ICU | 8 (12.9) | 0 (0) | .099 ^b | 2 (6.1) | .486 |
| Administered oxygen during hospitalization | 18 (29.0) | 6 (25.0) | .708 | 6 (18.2) | .247 |
| Mechanical ventilation | 1 (1.6) | 0 (0) | 1.000 ^b | 0 (0) | 1.000 ^b |
| Died | 3 (4.8) | 0 (0) | .557 | 0 (0) | .549 |

Note: Data are n (%), unless otherwise specified. P-values were calculated using Pearson chi-square test for categorical variables and independent samples t test for continuous variables.

Abbreviations: Ab., abnormal; Admin., administration; Kg, kilogram; No., number; SARI, severe acute respiratory infection (ie, defined as fever, cough, and symptom onset in past 10 d). Bold values are statistically significant <.05.

^aDenotes referent group for pairwise comparisons.

^bFisher's exact test.

criterion to test for influenza, it may actually lead to an underestimation, particularly in young infants. In a comparable study from the United States in children that enrolled 160 children under 5 years with influenza who were hospitalized for fever or acute respiratory symptoms, fever and cough were common presenting symptoms.³ However, both cough and fever plus cough were also less common in children younger than 6 months. Rhinorrhea was much more common in this study (83% compared to 1.7% in our study) but this could be attributed to the wider age range enrolled in this study. In another similar study from China in 480 children with influenza who were <15 years old and hospitalized for ARI, fever was a common presenting symptom in children under 24 months but was less common in

younger infants.¹⁶ Therefore, the inclusion of fever or cough for viral surveillance is important but both should not be required for surveillance studies that are trying to estimate the exact influenza burden to avoid underestimation of influenza in young children.

Several prior epidemiological studies in this region have focused on children with SARI, which may also result in a misestimation of the true burden of influenza in the pediatric population given the specific case definition that requires both fever and cough. This is supported by results from our study where approximately half of influenza cases met SARI case definitions, and only one-fifth of influenza cases in the <6-month group met SARI case definitions. In other reports in the region, influenza surveillance studies often use

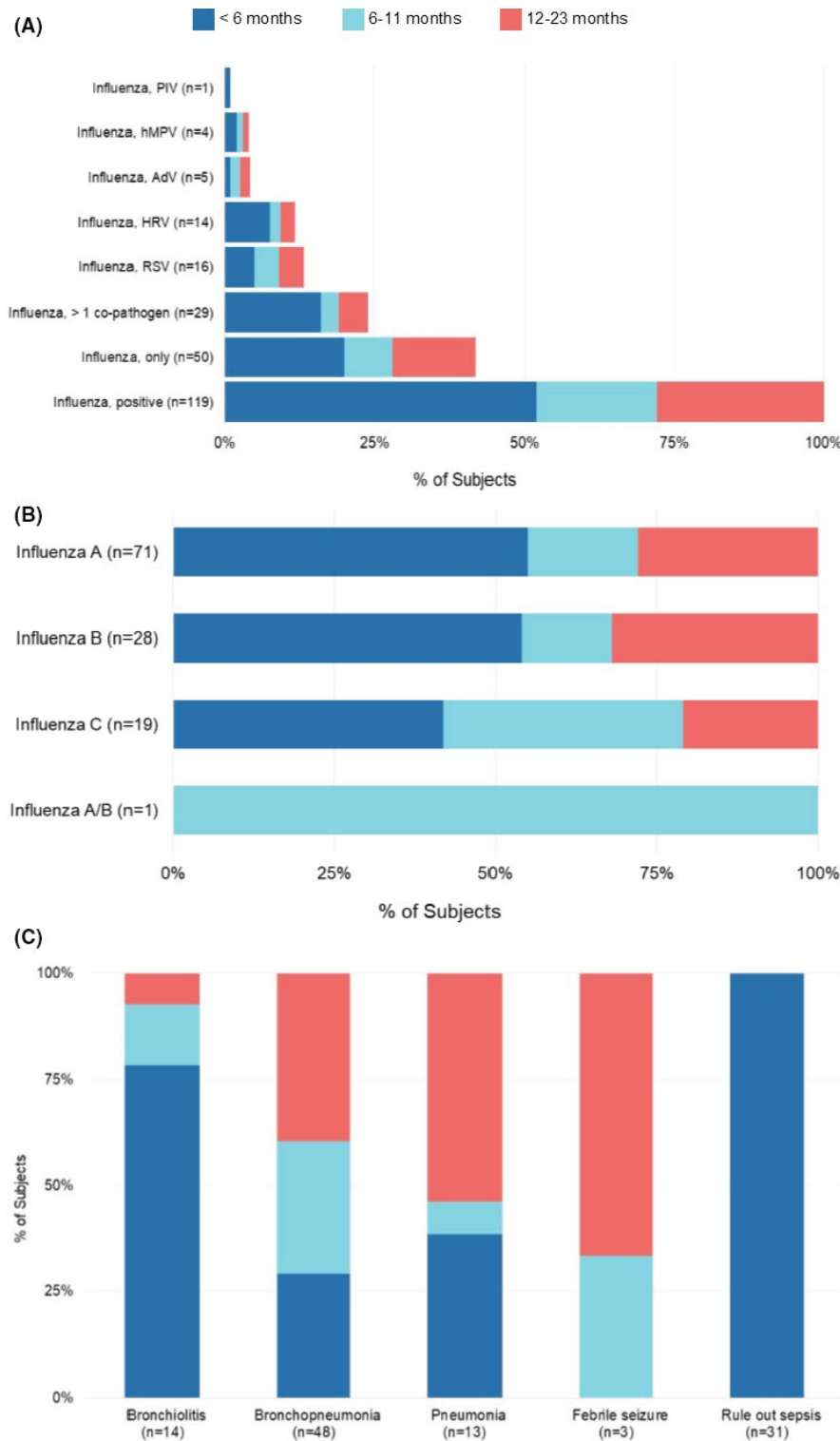


FIGURE 2 Proportion of Single and Codetection of Influenza (A), Type of Influenza (B), and Admitting Diagnosis (C) of Hospitalized Jordanian Children, by Age-Group

the SARI case definition, include adults as well as children, and do not identify clinical characteristics of infection in influenza-positive children.^{4,8,15,17-19} Therefore, caution should be used when using SARI for enrollment criteria and estimating the true burden of influenza disease.

A high index of suspicion must also be maintained for influenza infection as infants may present differently compared to older children and adults. In our study, many infants eventually diagnosed with

influenza were admitted with a rule-out sepsis diagnosis. A study of admission diagnoses in 401 children under 16 years who were hospitalized for influenza in Finland also showed that suspected sepsis was a common admission diagnosis in children <6 months.²⁰ Similar to our study, the previously discussed US study reported bronchiolitis, pneumonia, and fever/suspected sepsis as some of the most common diagnoses; however, this study only recorded discharge rather than our study which recorded admission diagnoses.³

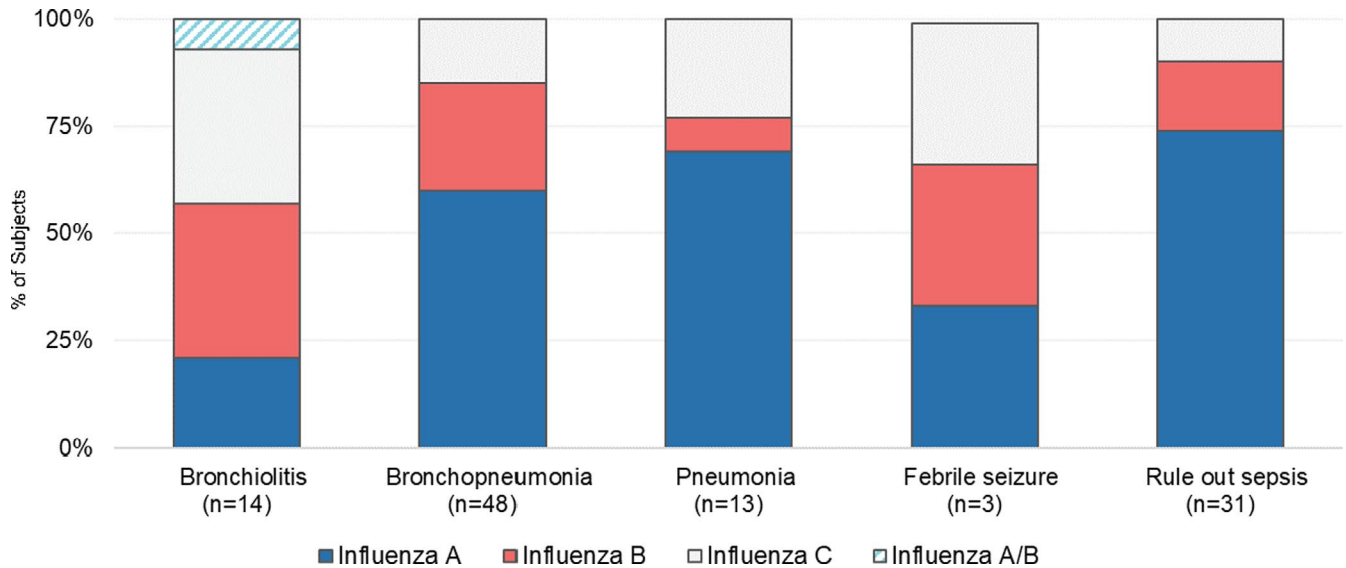


FIGURE 3 Admitting Diagnosis of Hospitalized Jordanian Children with Influenza, by Influenza Type

Importantly, children under 6 months who were influenza-positive were the only children who died and had a longer length of stay than other age-groups, highlighting the risks of severe disease in the younger pediatric population. Further studies may be needed to determine the importance of influenza in this population, especially considering that few studies have been conducted in this region and treatment for influenza virus infection is available and early diagnosis and treatment improves outcomes.

A major strength of our study was that we conducted a prospective 3-year viral surveillance study in children <2 years in a major government hospital in Jordan. All specimens from enrolled children were tested via RT-qPCR for viral detection, which is more sensitive than detection methods used in previous studies. Also, since research personnel enrolling children were different than the clinical providers hospitalizing the patients, differential surveillance bias was reduced. Although we have many strengths, we do have some notable limitations. First, our surveillance efforts were restricted to Al Bashir Hospital in Amman, Jordan. The hospital services families of low and middle income and is not the only government hospital in Jordan. Therefore, our results are not generalizable to all children under 2 years in Jordan. Additionally, our study allowed for re-enrollment of children from season to season; therefore, there may be children who were captured in our surveillance more than once. Finally, our study enrolled children only 5 days per week, thus indicating our results may be an underestimation of the true influenza burden in Amman, Jordan.

In conclusion, the burden of influenza requiring hospitalization among children in Amman, Jordan, was highest in those younger than 6 months, with influenza A being the most predominant type circulating annually. Our results suggest that using SARI criteria may exclude cases of influenza illness that can nonetheless be quite severe in patients under 2 years of age. Modifying the SARI surveillance definition to include either fever or cough for young children who present with different clinical symptoms may impact the annual

influenza rates, which in turn can assist with implementation of prevention strategies on a global scale. Maternal vaccination and targeting influenza vaccination in children older than 6 months may help reduce burden of influenza in the region.

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CONFLICT OF INTEREST

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AUTHOR CONTRIBUTIONS

Stephanie L Rolsma: Writing-original draft (lead); Writing-review & editing (lead). **Danielle A Rankin:** Formal analysis (lead); Writing-original draft (lead); Writing-review & editing (lead). **Zaid Haddadin:** Writing-review & editing (equal). **Lubna Hamdan:** Writing-review & editing (equal). **Herdi K Rahman:** Formal analysis (equal); Writing-review & editing (equal). **Samir Faouri:** Conceptualization (equal); Methodology (equal); Supervision (equal); Writing-review & editing (equal). **Asem Shehabi:** Investigation (equal); Methodology (equal); Supervision (equal); Writing-review & editing (equal). **John Williams:**

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