


RESEARCH ARTICLE

Clinical spectrum, risk factors, and outcomes of children with laboratory-confirmed influenza infection managed in a single tertiary hospital: A 6-year retrospective cohort study

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Abstract

Background: Influenza is a highly contagious disease that causes severe illness each year. Data in the United Arab Emirates are scarce.

Objectives: To study the seasonality, morbidity, mortality rate, and comorbidities associated with confirmed influenza infection in a tertiary hospital in Al-Ain city, UAE.

Methods: Retrospective study, from 2012 to 2017, of the electronic medical records in Tawam hospital, of children up to 15 years of age with laboratory-confirmed influenza infection.

Results: There were 1392 children, with the highest number in 2017 ($n = 461$, 33%). The incidence peaked between October and March. The infection was more common between 1 and 11 years of age ($n = 948$, 68%). The overall prevalence of influenza A ($n = 1144$, 82%) was higher than influenza B ($n = 276$, 19.8%). One-third of the patients required admission. The commonest underlying comorbidity was asthma ($n = 170$, 12%). The two commonest complications were pneumonia ($n = 165$, 12%) and acute otitis media ($n = 82$, 6%).

Conclusion: Our findings serve as a benchmark for comparison with reports from other countries and need to be considered when reviewing the national vaccination program.

KEYWORDS

children, epidemiological study, hospitalization, influenza, respiratory tract infections, United Arab Emirates

Abbreviations: ARDS, acute respiratory distress syndrome; ARI, acute respiratory infections; RT-PCR, reverse transcriptase polymerase chain reaction (RT-PCR); UAE, United Arab Emirates.

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1 | INTRODUCTION

Acute respiratory infections (ARIs) are major contributors to morbidity and mortality worldwide. Influenza, a vaccine-preventable disease, is a significant cause of ARI, affecting annually 5% to 10% of the population globally and causing morbidity and mortality, especially in high-

risk groups such as children.¹ It causes approximately one million influenza-associated hospitalizations among children younger than 5 years of age and 500 000 deaths among all age groups.^{2,3}

Different strains of influenza exist and include type A, B, and C. Type A and B can cause outbreaks and epidemics in humans; accordingly, circulating strains of both types are incorporated in seasonal influenza vaccines.^{4,5} Human influenza infection is most commonly caused by type A virus, which is the only type known to cause pandemics.^{6,7} Transmission of the influenza virus occur through the respiratory droplets, and it tends to increase during the winter season in countries with temperate climates, often severely impacting healthcare services.¹

Symptoms of influenza infection include fever, sore throat, nasal discharge, headache, myalgia, cough, vomiting, and diarrhea.⁸ Complications are not uncommon and remain a public health concern. They include pneumonia, acute respiratory failure, acute respiratory distress syndrome (ARDS), otitis media, febrile seizure, encephalitis/encephalopathy, myositis, rhabdomyolysis, myocarditis, renal failure, multi-organ failure, and can lead to death.⁹⁻¹²

The wide spectrum of the clinical presentation¹³ with ill-defined signs and symptoms often leads to empirical management without respiratory sampling. Such practice makes it difficult to estimate the true burden of influenza.¹⁴ Quantifying the latter is required to reveal the pattern of illness severity and guide public health policies. It is also needed to justify the seasonal influenza vaccination,⁹ which remains the key preventive intervention for influenza-related hospitalizations and deaths, and assess its impact.¹⁵

Seasonal influenza vaccine was started in the United Arab Emirates in 2006 for high-risk healthcare professionals and people with chronic illnesses. Since 2012, elderly (>65 years) were added to the high-risk groups, and in 2015, all community members were encouraged (but not mandated) to receive the vaccine including infants >6 months. The

trivalent seasonal vaccine contains influenza A(H1N1), A(H3N2), and influenza B strain (Colorado), while the tetravalent vaccine has, in addition, the Phuket strain (an additional B strain). In our center, a trivalent vaccine was given to all children >6 months of age, while children with certain comorbidities received the tetravalent vaccine. Those comorbidities include: Chronic lung diseases, asthma, congenital heart disease, and patients on immunosuppressant medications.

The existing literature on influenza infection among the pediatric population in the United Arab Emirates is scarce.¹⁶ Thus, we conducted this study to estimate the demographic, clinical features, laboratory findings, and the outcomes of children with confirmed influenza virus infection who presented to a tertiary hospital in Al Ain City in the United Arab Emirates over a 6-year period, and the relationship to their seasonal influenza vaccination status.

2 | MATERIAL AND METHODS

2.1 | Setting

This retrospective observational cohort study was conducted over a 6-year period (2012-2017) in Tawam hospital, a large 461-bed tertiary regional teaching hospital in Al Ain city and one of the busiest pediatric services in the UAE. The catchment area includes over 767 000 persons (latest 2016 census), of whom 165 330 (21.5%) are under 15 years of age.

2.2 | Case definition

Children under 15 years of age who presented to the hospital during the study period and found to be infected with influenza A and

TABLE 1 Demographic data of 1392 children with proven Influenza infection. Results expressed as numbers and percentage

	All patients 1392 (100)	Influenza A 1144 (82)	Influenza B 248 (18)	OR (95% CI) ^a	P value
Sex				1.08 (0.81, 1.44)	.58
Males	798 (57)	652 (57)	146 (59)		
Females	594 (43)	492 (43)	102 (41)		
Age				1.83 (1.40, 2.38)	<.001
<1 month	38 (3)	38 (3)	0 (0)		
2-12 months	343 (25)	301 (26)	42 (17)		
1-10 years	948 (68)	758 (66)	190 (77)		
11-15 years	83 (4)	47 (4)	16 (6)		
Prior seasonal Influenza vaccination	142 (10)	121 (11)	21 (8)	0.78 (0.45, 1.28)	.32
Number of healthcare visits before admission				4.4 (1.4, 22.3)	.006
0	62 (4)	59 (5)	3 (1.2)		
1	1033 (74)	832 (73)	201 (81)		
≥2	297 (21)	253 (22)	44 (18)		
Admitted to hospital	467 (34)	421 (37)	46 (18)	0.39 (0.27, 0.55)	<.001

Abbreviations: CI, confidence intervals; OR, odds ratio.

^aChi-squared or Fisher exact test.

B viruses were identified from the electronic medical records, based on the International Classification of Diseases, Ninth Revision (ICD-9) codes until 2015, and ICD-10 codes (J09-J18) thereafter. Their viral diagnosis was also always confirmed by matching the laboratory data.

2.3 | Data collected

We collected, from the electronic medical records, the demographic and clinical data of all children fulfilling the case definition. These included age, gender, clinical presentation, admission diagnosis, radio-

FIGURE 1 Yearly distribution of children with influenza infection, and their immunization status, managed solely in emergency room (ER) or admitted to hospital

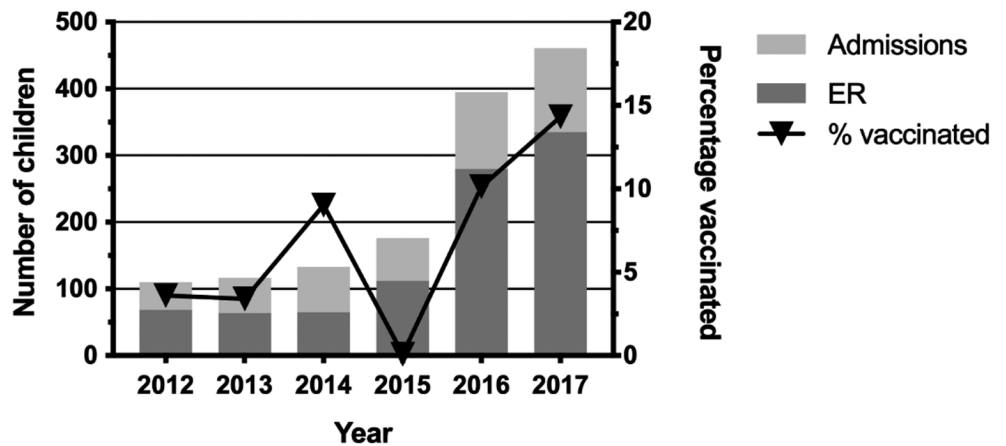


FIGURE 2 Annual pattern of influenza isolates in 1392 children between 2012 and 2017, and percentage of infected children admitted to hospital

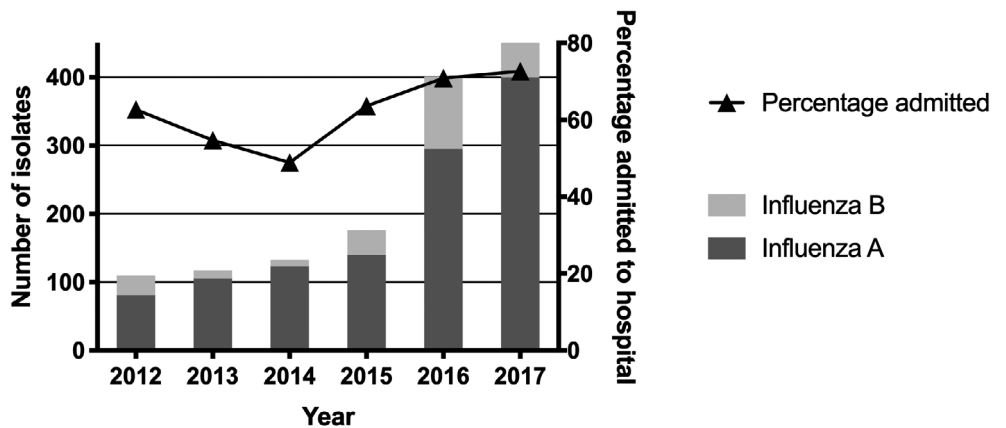
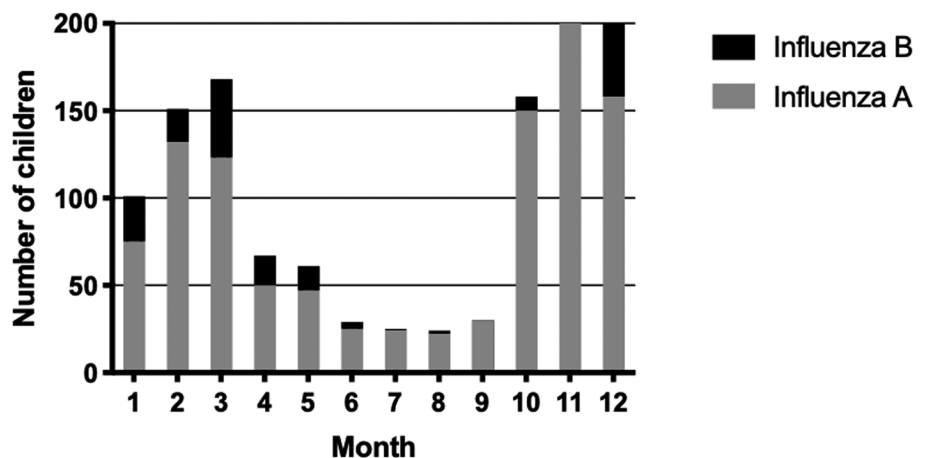


FIGURE 3 Seasonality of influenza isolates in 1392 children between 2012 and 2017



logical findings, underlying medical conditions, interventions, complications. The children's vaccination status was obtained from the medical record and by parental report. The participants were classified into four age groups: less than 1 month (newborn), 2 to 12 months (infant), 1 to 10 years (child), and 10 to 15 years (adolescent).

2.4 | Laboratory

During the study period, all children presenting to the hospital with febrile respiratory infections underwent aspiration of nasopharyngeal secretions as required by the infection control department. We collected nasopharyngeal aspirates using swabs with a synthetic tip and a plastic shaft that were immediately placed in a universal transport medium (UTM) as per the manufacturer's instructions. Specimens were rapidly transported to the laboratory on ice or cold packs in an appropriate triple bag packaging, where they were

stored refrigerated at 4°C to 6°C. An infected patient was defined as having a positive result for the rapid immunofluorescent antigen detection test for influenza A and B viruses (Sofia Influenza A + B FIA immunofluorescence, Quidel Corporation, San Diego, California). The sensitivity and specificity of the test are, respectively, 97% and 95% for influenza A, and for influenza B 90% and 97%. Since 2017, the results were also confirmed by reverse transcriptase polymerase chain reaction (RT-PCR) analysis (Seegene, Seoul, South Korea). The PCR sensitivity is 100 copies/reaction and its specificity is 100%. Tawam hospital laboratory is accredited by the College of American Pathologists.

2.5 | Definitions

Inpatient hospitalization was defined as a hospital admission resulting in an overnight stay.

TABLE 2 Seasonal influenza vaccination status of 1392 children with proven influenza infection: demographics, complications, and outcomes

	Vaccinated 142 (10%)	Unvaccinated 1250 (90%)	OR (95% CI) ^a	P value	Adjusted OR (95% ci) ^b	P value
Sex	86 (60)	712 (57)	1.16 (0.82, 1.45)	.41	NA	NA
Age			2.22 (1.65, 3.0)	<.001	NA	NA
< 1 month	0 (0)	38 (3)				
2-12 months	10 (7)	333 (27)				
1-10 years	121 (85)	827 (66)				
11-15 years	10 (7)	53 (4)				
Infection with			0.78 (0.48, 1.27)	.32	NA	NA
Influenza A	121 (85)	1023 (82)				
Influenza B	21 (15)	227 (18)				
Acute respiratory distress syndrome	5 (3.5)	43 (3)	1.02 (0.31, 2.64)	.96	0.51 (0.18, 1.38)	.18
Bacterial pneumonia	22 (15)	143 (11)	1.41 (0.83, 2.33)	.15	0.82 (0.48, 1.40)	.47
Acute otitis media	3 (2)	79 (6)	0.32 (0.06, 0.99)	.04	0.41 (0.12, 1.33)	.13
Croup	0 (0)	9 (0.7)	0 (0, 3.75)	.31	NC	NC
Carditis	0 (0)	4 (0.3)	0 (0, 8.49)	.49	NC	NC
Toxic shock syndrome	0 (0)	2 (0.1)	0 (0, 16.98)	.63	NC	NC
Myositis	0 (0)	7 (0.5)	0 (0, 4.83)	.37	NC	NC
Acute kidney insufficiency	1 (0.7)	19 (1.5)	0.46 (0.01, 2.93)	.43	0.21 (0.03, 1.69)	.14
Multiorgan failure	1 (0.7)	18 (1.4)	0.48 (0.01, 3.12)	.47	0.24 (0.03, 1.92)	.18
Encephalitis	1 (0.7)	4 (0.3)	2.21 (0.04, 22.5)	.46	2.41 (0.24, 24.36)	.45
Febrile convulsions	0 (0)	20 (1.6)	0 (0, 1.67)	.13	NC	NC
Admitted to hospital	55 (39)	412 (33)	1.28 (0.88, 1.86)	.16	0.97 (0.63, 1.50)	.92
Required intensive care	16 (11)	100 (8)	1.46 (0.77, 2.58)	.18	0.83 (0.44, 1.56)	.56
Length of stay in hospital			1.27 (0.87, 1.85)	.18	0.88 (0.65, 1.18)	.41
<1 week	36 (25)	261 (21)				
>1 week	19 (13)	153 (12)				
Death	2 (1.4)	20 (1.6)	0.87 (0.09, 3.67)	.86	0.46 (0.10, 2.12)	.32

Note: Results expressed as numbers and percentage.

Abbreviations: CI, confidence intervals; NA, not applicable; NC, could not be calculated; OR, odds ratio.

^aChi-squared or Fisher exact test.

^bMultivariate logistic regression adjusting for virus type, gender, age, year of admission, coinfections, vaccination status, and presence of comorbidity.

TABLE 3 Coinfections with respiratory pathogens in 1392 children with proven influenza infection

	All patients 1392 (100%)	Influenza A 1144 (82%)	Influenza B 248 (18%)	OR (95% CI) ^a	P value	Adjusted OR (95% CI) ^b	P value
Coinfection				0.38 (0.19, 0.70)	.001	0.61 (0.32, 1.16)	.13
None	1245 (89)	1009 (88)	236 (95)				
One pathogen	133 (10)	121 (10)	12 (5)				
RSV	85 (6)	82 (7)	3 (1)				
Adenovirus	21 (2)	15 (1)	6 (2)				
Parainfluenza	27 (2)	24 (2)	3 (1)				
Two pathogens	14 (1)	14 (1)	0 (0)				
RSV and adenovirus	8 (0.5)	8 (10.7)	0 (0)				
RSV and parainfluenza	2 (0.1)	2 (0.2)	0 (0)				
Adenovirus and parainfluenza	4 (0.3)	4 (0.3)	0 (0)				

Note: Results expressed as numbers and percentage.

Abbreviations: CI, confidence intervals; OR, odds ratio.

^aChi-squared or Fisher exact test.

^bMultivariate logistic regression adjusting for virus type, gender, age, year of admission, coinfections, vaccination status, and presence of comorbidity.

TABLE 4 Comorbidities in 1392 children with proven influenza infection. Results expressed as numbers and percentage

	All patients 1392 (100%)	Influenza A 1144 (82%)	Influenza B 248 (18%)	OR (95% CI) ^a	P value
Prematurity	65 (5)	62 (5)	3 (1)	0.21 (0.04, 0.66)	.004
Respiratory	208 (15)	182 (13)	26 (2)	0.62 (0.38, 0.96)	.0001
Asthma	170 (12)	145 (13)	25 (10)		
Cystic fibrosis	3 (0.2)	3 (0.2)	0 (0)		
Chronic lung disease	9 (0.6)	8 (0.7)	1 (0.4)		
Primary ciliary dyskinesia	1 (0.1)	1 (0.1)	0 (0)		
Tracheostomy	25 (1.8)	25 (2.2)	0 (0)		
Cardiac	31 (2)	28 (2.4)	3 (1)	0.48 (0.09, 1.6)	.2
Neurologic	51 (4)	50 (4)	1 (0.4)	0.08 (0.002, 0.5)	.002
Genetic or metabolic	107 (8)	99 (9)	8 (3)	0.35 (0.14, 0.73)	.003
Immunocompromised	35 (2.5)	29 (2.5)	6 (2.4)	0.95 (0.32, 2.37)	.9

Abbreviations: CI, confidence intervals; OR, odds ratio.

^aChi-squared or Fisher exact test.

Emergency department visit was defined as an unscheduled ambulatory visit to the emergency department without overnight stay.

Acute otitis media (AOM) was defined as a visually abnormal tympanic membrane suggesting an effusion in the middle ear cavity concomitant with one or more of the following symptoms: fever ($\geq 38^{\circ}\text{C}$), earache, irritability, diarrhea, vomiting, acute otorrhea not caused by external otitis media.

Pneumonia was defined by the presence of focality of signs on chest examination (crepitations, decreased air entry, bronchial breathing) with the presence of infiltrates on chest X-ray.

Pediatric ARDS was defined as per the consensus recommendations from the Pediatric Acute Lung Injury Consensus Conference.¹⁷

Deaths only include those that had occurred in hospital.

A child was defined as immunized if, after the age of 6 months, he/she had received one or more doses of a licensed seasonal influenza vaccine within 1 year of their presentation.

2.6 | Statistical analyses

Statistical analysis was performed using the Stata statistical package version 15 (StataCorp, Texas). Categorical variables were expressed as numbers with percentages and were compared using the Chi-square or Fisher's exact test where appropriate. For all the studied variables, their relationship with the virus type as well as with the children's vaccination status was analyzed in a univariate model using the odds ratio (OR), with 95% confidence intervals (CI) and also the adjusted ORs with 95% CI using a multivariate regression logistic model to adjust for virus type, gender, age, year of admission, coinfections, vaccination status, and presence of comorbidity. To analyze trends in the prevalence of complications and outcomes with increasing number of coinfecting pathogens, or increasing age, we also calculated the odds of these outcomes their P value with the Chi-squared test for trend. A significant trend existed when the odds of each outcome varied

TABLE 5 Treatment modalities for 1392 children with proven influenza infection

	All patients 1392 (100%)	Influenza A 1144 (82%)	Influenza B 248 (18%)	OR (95% CI) ^a	P value	Adjusted OR (95% CI) ^b	P value
Required intensive care	116 (8)	111 (10)	5 (2)	0.19 (0.06, 0.46)	<.001	0.30 (0.12, 0.79)	.06
Oxygen therapy	192 (14)	187 (16)	5 (2)	0.10 (0.03, 0.25)	<.001	0.15 (0.06, 0.39)	<.001
High-frequency ventilation	11 (0.8)	11 (0.9)	0 (0)	0 (0, 1.6)	.12	1 (NA)	NA
Mechanical ventilation	109 (7)	108 (9)	1 (0.4)	0.03 (0.001, 0.2)	<.001	0.06 (0.009, 0.46)	.007
Oseltamivir administration	1010 (73)	845 (73)	165 (66)	0.70 (0.52, 0.95)	.02	0.76 (0.61, 0.95)	.016
Within 48 hours	731 (52)	603 (52)	128 (51)				
Later administration	279 (20)	242 (21)	37 (15)				
Antibiotherapy	513 (37)	439 (38)	74 (30)	0.68 (0.50, 0.93)	.01	0.84 (0.61, 1.15)	.27

Note: Results expressed as numbers and percentage.

Abbreviations: CI, confidence intervals; NA, not applicable; OR, odds ratio.

^aChi-squared or Fisher exact test.

^bMultivariate logistic regression adjusting for virus type, gender, age, year of admission, coinfections, vaccination status and presence of comorbidity.

TABLE 6 Complications in 1392 children with proven Influenza infection

	All patients 1392 (100%)	Influenza A 1144 (82%)	Influenza B 248 (18%)	OR (95% CI) ^a	P value	Adjusted OR (95% CI) ^b	P value
Acute respiratory distress syndrome	48 (3)	47 (4)	1 (0.4)	0.09 (0.002, 0.56)	.003	0.15 (0.02, 1.5)	.06
Bacterial pneumonia	165 (12)	143 (12)	22 (9)	0.7 (0.4, 1.1)	.11	0.91 (0.55, 1.51)	.73
Acute otitis media	82 (6)	62 (5)	20 (8)	1.5 (0.85, 2.63)	.10	1.47 (0.86, 2.52)	.15
Croup	9 (0.6)	8 (0.7)	1 (0.4)	0.57 (0.01, 4.32)	.59	0.50 (0.06, 4.11)	.52
Carditis	4 (0.3)	3 (0.3)	1 (0.4)	1.54 (0.03, 19.2)	.70	3.90 (0.36, 41.5)	.26
Toxic shock syndrome	2 (0.1)	1 (0.09)	1 (0.4)	4.62 (0.06, 363.5)	.23	10.99 (0.58, 206.45)	.11
Myositis	7 (0.5)	5 (0.4)	2 (0.8)	1.85 (0.17, 11.4)	.45	1.68 (0.31, 9.1)	.54
Acute kidney insufficiency	20 (1.4)	20 (1.8)	0 (0)	0 (0, 0.87)	.03	NC	NC
Multiorgan failure	19 (1.4)	19 (1.7)	0 (0)	0 (0, 0.92)	.04	NC	NC
Encephalitis	5 (0.3)	5 (100)	0 (0)	0 (0, 3.54)	.29	NC	NC
Febrile convulsions	20 (1.4)	17 (1.5)	3 (1.2)	0.81 (0.15, 2.83)	.74	0.93 (0.26, 3.26)	.91

Note: Results expressed as numbers and percentage.

Abbreviations: CI, confidence intervals; NC, could not be calculated; OR, odds ratio.

^aChi-squared or Fisher exact test.

^bMultivariate logistic regression adjusting for virus type, gender, age, year of admission, coinfections, vaccination status and presence of comorbidity.

significantly with the number of coinfecting pathogens, or with age. For all calculations, a *P* value <.05 was considered to be statistically significant.

3 | RESULTS

3.1 | Demographics

Between January 2012 and December 2017, a total of 1392 hospital encounters occurred with children infected with the influenza virus, of which 925 (66.5%) were managed in the emergency department (ED) then discharged home, while 467 (33.5%) required admission (Table 1 and Figure 1). Males comprised 800 (57.3%) of the cases. The

age group with the highest prevalence was between 1 and 10 years. Fever was the most common presenting symptom, occurring in 698 children (50.2%). Influenza A was significantly more prevalent than type B in the younger age groups, but there was no difference between the sexes. There was no significant difference in prior vaccination status between the two types of infection. Admission to hospital was significantly more often required for children infected with influenza A than B (Table 1).

3.2 | Isolates

Across the 6-year study period, the most common isolate was influenza A (Table 1 and Figure 2), and this pattern was maintained in the

TABLE 7 Coinfections and disease severity in 1392 children with proven influenza infection

	Number of coinfecting pathogens			P value ^a
	0 n = 1245	1 n = 133	2 n = 14	
Acute respiratory distress syndrome	33 (2.6) [0.02]	14 (10.5) [0.11]	1 (7.1) [0.07]	<.001
Toxic shock syndrome	1 (0.08) [0.001]	1 (0.7) [0.007]	0 (0) [0]	.12
Encephalitis	3 (0.2) [0.002]	2 (1.5) [0.015]	0 (0) [0]	.06
Carditis	1 (0.08) [0.001]	3 (2.2) [0.02]	0 (0) [0]	.003
Renal insufficiency	13 (1.0) [0.01]	7 (5.2) [0.05]	0 (0) [0]	.002
Multiorgan failure	12 (0.9) [0.01]	7 (5.2) [0.05]	0 (0) [0]	.001
Intensive care admission	73 (5.8) [0.06]	37 (27.8) [0.38]	6 (42.8) [0.75]	<.001
Oxygen therapy	119 (9.5) [0.10]	64 (48.1) [0.92]	9 (64.3) [1.8]	<.001
High-frequency ventilation	5 (0.4) [0.004]	6 (4.5) [0.04]	0 (0) [0]	<.001
Mechanical ventilation	67 (5.4) [0.05]	36 (27.1) [0.37]	6 (42.8) [0.75]	<.001
Death from any cause	13 (1.0) [0.01]	8 (6.0) [0.06]	1 (7.1) [0.07]	<.001
Death from Influenza infection	9 (0.7) [0.007]	3 (2.2) [0.02]	1 (7.1) [0.07]	.05

Note: Results expressed as numbers (percentage) and odds of outcome.

^aChi-squared test for trend: a significant trend exists when the odds of each outcome increase with increasing number of coinfecting pathogens.

seasonality analysis (Figure 3). There was no association between the prevalence of infection with influenza A and the vaccination status (Table 2). Coinfections with at least another viral respiratory pathogen occurred in 11% of the children, 10% of whom were coinfecting with two pathogens (Table 3). Coinfections were significantly more prevalent in children infected with influenza A than B.

3.3 | Seasonality and time trends

The yearly distribution (Figures 1 and 2) showed a progressive increase in the incidence of influenza infections from 2012 to 2017. The seasonality (Figure 3) showed an increased prevalence from October to March.

3.4 | Vaccination status

Only 142 children (10%) had received prior seasonal influenza vaccine (Table 1). The progressively increasing prevalence of influenza infection over the study period seemed to mirror the modest but progressive rise from 4% to 14% in the proportion of vaccinated children (Figure 1).

3.5 | Comorbidities

The majority of children with influenza had no underlying comorbidities (n = 898, 64%). The remaining had underlying medical conditions (Table 4), of which asthma was the commonest (12%). Prematurity, underlying respiratory, neurologic, or genetic comorbidities were more prevalent in children infected with influenza A

than B, but that difference was not significant in the multivariate regression model (Table 4).

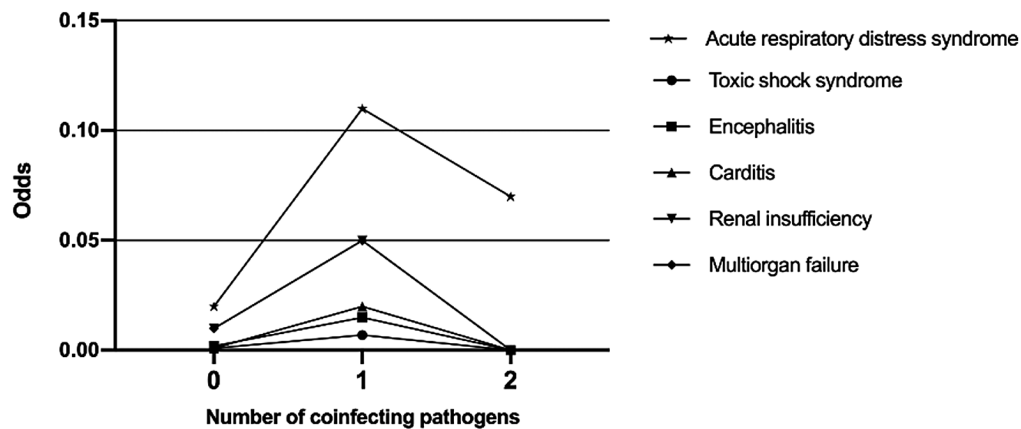
3.6 | Management

Oxygen therapy and mechanical ventilation were more often required in influenza A than influenza B infections (Table 5). Of all the cases, Oseltamivir was administered to 731 children (52%) in the first 48 hours of presentation, and antibiotics to 513 (37%), of whom 247 had either pneumonia or otitis media and the others much less frequent conditions such as tonsillitis, sinusitis, or multiorgan failure. Oseltamivir in combination with antibiotics was administered more often with influenza A than B infection, but without a significant difference in the logistic regression model. Admission to the pediatric intensive care unit (PICU) was necessary for 116 children (8%), with 120 (7.8%) requiring mechanical ventilation or high-frequency ventilation.

3.7 | Complications

Bacterial pneumonia was diagnosed in 165 children (12%) and another 82 (6%) had AOM. Although ARDS, acute renal insufficiency, and multiorgan failure were more common with influenza A than B, this did not reach statistical significance in the multivariate regression model ($P < .05$) (Table 6). The prevalence of ARDS, carditis, acute renal insufficiency, and multiorgan failure showed a significant trend with the increasing number of coinfecting pathogens (Table 7 and Figure 4). However, the rate of complications did not differ significantly between age groups and showed no trend (Table 8 and Figure 5).

Complications



Outcomes

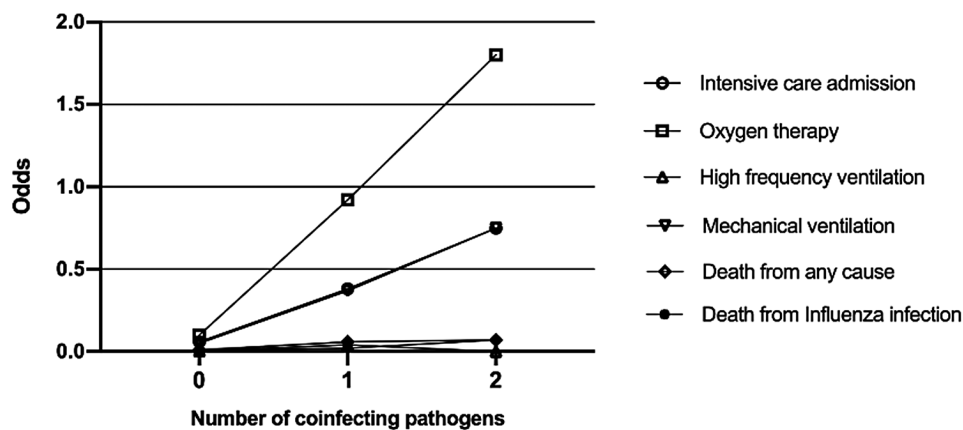


FIGURE 4 Complications and outcomes by number of coinfecting pathogens

3.8 | Outcomes

There was no difference in hospital admissions between the vaccination status (Table 2). Neither the need for oxygen therapy, admission to intensive care unit, mechanical or high-frequency ventilation, nor death rate from influenza infection or death from any cause showed a significant trend with increasing number of coinfecting pathogens (Table 7, Figure 4). The prevalence of admission to hospital, oxygen therapy, admission to intensive care unit, need for mechanical or high-frequency ventilation, or death from any cause showed a significant trend with increasing age (Table 8, Figure 5).

In-hospital death of any cause occurred in 22 children (1.6%), all infected with influenza A ($P = .02$), but there was no difference between vaccinated children (1.4%) and the others (1.6%) (Tables 2 and 9). Death directly attributed to influenza infection occurred in 13 children (0.9%).

Of the cases that required admission, 63% stayed in the hospital for less than a week and 37% stayed for more than a week, and there was no difference between vaccinated children and the others (Table 2).

4 | DISCUSSION

In this 6-year study of 1392 children with laboratory-confirmed influenza, the infection was more common between 1 and 11 years of age, similar to studies from England and United States.^{12,14} The most common symptoms were fever, cough and runny nose, consistent with previous studies.¹ One-third required hospital admission. The peak season was from October to March, similar to other studies in USA.⁴ The overall prevalence of influenza A was higher than influenza B. The commonest underlying comorbidity was asthma, and the two commonest complications were pneumonia and AOM. Influenza can

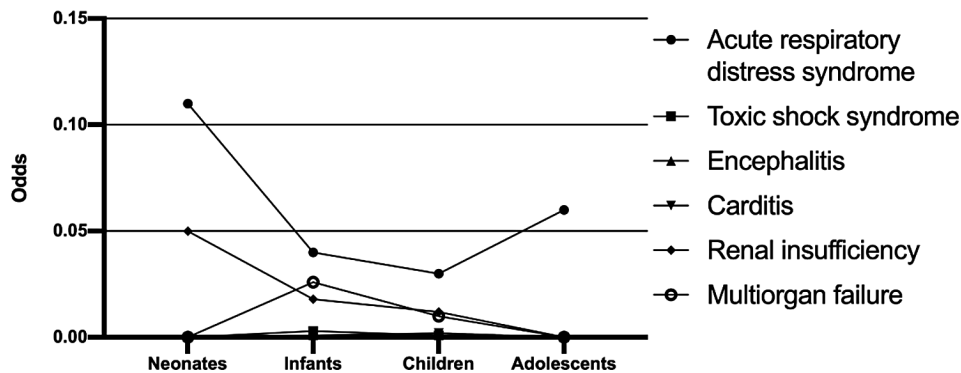
TABLE 8 Complications and outcomes by age in 1392 children with proven Influenza infection

	Age group				P value ^a
	Neonates n = 38	Infants n = 343	Children n = 948	Adolescents n = 63	
Admission to hospital	32 (84.2) [5.3]	152 (44.3) [0.8]	266 (28.0) [0.39]	17 (26.9) [0.37]	<.001
Acute respiratory distress syndrome	4 (10.5) [0.11]	15 (4.4) [0.04]	25 (2.6) [0.03]	4 (6.3) [0.06]	.08
Toxic shock syndrome	0 (0) [0]	1 (0.3) [0.003]	1 (0.11) [0.001]	0 (0) [0]	.77
Encephalitis	0 (0) [0]	3 (0.9) [0.009]	2 (0.2) [0.002]	0 (0) [0]	.18
Carditis	0 (0) [0]	2 (0.6) [0.006]	2 (0.2) [0.002]	0 (0) [0]	.39
Renal insufficiency	2 (5.2) [0.05]	6 (1.7) [0.018]	12 (1.3) [0.012]	0 (0) [0]	.057
Multiorgan failure	0 (0) [0]	9 (2.6) [0.026]	10 (1.0) [0.01]	0 (0) [0]	.09
Intensive care admission	12 (31.6) [0.46]	36 (10.5) [0.11]	62 (6.5) [0.07]	6 (9.5) [0.10]	<.001
Oxygen therapy	28 (73.7) [2.8]	63 (18.4) [0.22]	94 (9.9) [0.11]	7 (11.11) [0.12]	<.001
High-frequency ventilation	2 (5.2) [0.05]	6 (1.7) [0.017]	3 (0.3) [0.003]	0 (0) [0]	<.001
Mechanical ventilation	17 (44.7) [0.80]	35 (10.2) [0.11]	51 (5.4) [0.05]	6 (9.5) [0.04]	<.001
Death from any cause	2 (5.2) [0.05]	7 (2.0) [0.02]	13 (1.4) [0.014]	0 (0) [0]	.04
Death from Influenza infection	1 (2.6) [0.03]	3 (0.9) [0.008]	9 (0.9) [0.009]	0 (0) [0]	.42

Note: Results expressed as numbers (percentage) and [odds of outcome].

^aChi-squared test for trend: a significant trend exists when the odds of each outcome increase with increasing age).

Complications



Outcomes

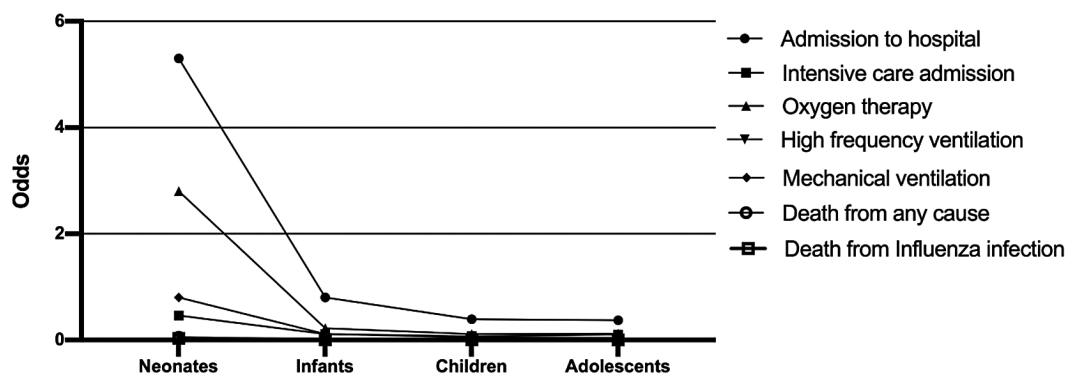


FIGURE 5 Complications and outcomes by age

TABLE 9 Complications and outcomes by vaccination status and age in 1392 children with proven Influenza infection

	Neonates n = 38 (0 vaccinated, 0%)	Age group			P value ^a
		Infants n = 343 (10 vaccinated, 3%)	Children n = 948 (121 vaccinated, 13%)	Adolescents n = 63 (10 vaccinated, 16%)	
Admission to hospital	NA	1.26 (0.28, 5.60)	1.55 (1.0, 2.36)	3.41 (0.65, 17.33)	.009
Acute respiratory distress syndrome	0 (0, NA)	6.15 (0.57, 35.15)	0.58 (0.06, 2.43)	1.85 (0.03, 25.9)	.74
Toxic shock syndrome	NA	NA	NA	NA	.67
Encephalitis	NA	0 (0, 46.43)	6.8 (0.08, 540.9)	NA	.23
Carditis	NA	0 (0, 69.5)	0 (0, 13.19)	NA	.55
Renal insufficiency	NA	7.2 (0.13, 74.9)	0 (0, 2.17)	NA	.54
Multiorgan failure	NA	0 (0, 14.7)	0.75 (0.017, 5.55)	NA	.64
Intensive care admission	NA	2.19 (0.21, 11.6)	1.34 (0.59, 2.76)	7.14 (0.76, 61.7)	.04
Oxygen therapy	NA	1.11 (0.11, 5.78)	1.72 (0.93, 3.05)	5.25 (0.61, 37.6)	.01
High-frequency ventilation	NA	7.28 (0.13, 74.9)	0 (0, 8.8)	NA	.59
Mechanical ventilation	NA	0.97 (0.02, 7.43)	0.90 (0.31, 2.19)	7.14 (0.76, 61.7)	.44
Death from any cause	NA	6.0 (0.12, 58.4)	0.56 (0.013, 3.9)	NA	.94
Death from Influenza infection	NA	0 (0, 46.4)	0 (0, 2.90)	NA	.23

Note: Results expressed OR of outcome (95% CI).

Abbreviations: NA, could not be calculated; OR, odds ratio.

^aChi-squared test.

still cause severe disease in young children, even in those without underlying medical risk factors.

The OR of influenza infection by sex was not statistically significant, contrary to other studies where the greater humoral and cell-mediated immune responses of females to viral antigens were postulated to be beneficial against infectious diseases.¹⁸ Bronchial asthma was the most commonly associated underlying risk factor accounting for 12% of all admissions, confirming previous studies emphasizing the burden of influenza on asthmatic children.¹⁰ We also found a large number of patients (8%) with underlying inborn errors of metabolism, which can be attributed to the fact that our center is the regional referral center for metabolic diseases in the country.

A previously unreported aspect is the need for intensive care in children hospitalized with influenza. In our study, 8% of admitted children required PICU admission, most frequently due to respiratory failure and the need for mechanical ventilation. The majority of these children were having underlying medical conditions such as chronic lung disease, congenital heart disease, or immunosuppressive disorders. Although this result is comparable to reports from other countries, such as Malaysia and Spain, where the ICU admission rates were 9.1% and 10% respectively,^{19,20} it was considerably lower than other countries, such as the United States where it was as high as 20% to 26%.²¹ This might be attributed to the comorbid conditions that increase the risk of ICU admission. The high mortality rate in the reports from the United States is very likely attributed to the H1N1 pandemic.¹⁴

In our study, the rates of serious complications in children were similar to other studies.¹⁴ Bacterial pneumonia was the most common complication accounting for 12% of cases, followed by AOM in 8% of the patients. The prevalence of other complications, such as acute kidney injury, febrile convulsion, croup, myositis, carditis, encephalitis, toxic

shock syndrome, and multiorgan failure, was consistent with previous reports from the region.²¹ The majority of admitted patients stayed in hospital less than 7 days, similarly to other regional studies.²² The death rate (3%) in this cohort was also consistent with previous reports.

We found that only 10% of the studied children with proven influenza infection were vaccinated. This is perhaps due to the fact that, during the study period, influenza vaccine in the United Arab Emirates was only recommended, but not mandated, for children with comorbidities such as bronchial asthma, cystic fibrosis, or inborn errors of metabolism. The vaccine used during that period was the trivalent vaccine that included the following strains H1N1, H3N2, and Colorado (influenza B strain).

There are some limitations to this study. As it was a single tertiary center retrospective descriptive study limited to children presenting to the ED or hospitalized, the results should be interpreted with caution, and the findings may not be generalized to other settings. In addition, we did not have accurate data on individual seasonal influenza vaccination history for many children, as some were only available from verbal reports from the parents, neither did we know if the influenza vaccination was provided in the current season or much earlier. Furthermore, molecular epidemiology to delineate the subtype and genetics analysis of the isolated viruses could not be performed. Finally, detailed healthcare cost analysis was not performed to give quantitative costs of the disease burden.

A strength of the study is that, with viral testing being mandated for all hospitalized children with respiratory symptoms during the study period, it includes only laboratory-proven influenza infection. Confounding was reduced by excluding other causes of ARIs, and the ascertainment of cases was most likely complete with little or no under-reporting.

Although the reasons for the observed significant increase in influenza infections during later years are most likely multifactorial,

the need to vaccinate all children with the seasonal influenza vaccine is clear.

5 | CONCLUSION

Despite the widespread availability of influenza vaccines and antivirals, the global burden of influenza-related disease remains high. As no similar studies had been previously performed in the region, our findings serve as a benchmark for regional comparison. Influenza infection remains a major problem for all children, and not exclusively for those with underlying risk factors. We therefore recommend incorporating the influenza vaccine into our national vaccination program. Health education programs should also strongly encourage all parents to immunize their children against influenza.

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CONFLICT OF INTEREST

All the authors have no conflict of interest to declare.

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Writing—Review and Editing: Alya AlAli, Najla AlKuwaiti, Salwa AlKaabi, Hassib Narchi.

All authors have read and approved the final version of the manuscript.

Alya AlAli had full access to all of the data in this study and takes complete responsibility for the integrity of the data and the accuracy of the data analysis.

TRANSPARENCY STATEMENT

Alya AlAli affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important

aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

DATA AVAILABILITY STATEMENT

The authors confirm that the data supporting the findings of this study are available within the article and/or its supplementary materials. All the data would be made available by the author upon a reasonable request.

ETHICS STATEMENT

Ethical approval was obtained from the institution Human Research Ethics Committee. Informed consent was waived as it was a retrospective electronic medical chart review; the collected data were anonymized with all patients' identifiers removed.

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