INQUIRY: The Journal of Health Care Organization, Provision, and Financing
Volume 56: 1–7

DOI: 10.1177/0046958019850731
journals.sagepub.com/home/inq
SAGE

Severe Acute Respiratory Infections With Influenza and Noninfluenza Respiratory Viruses: Yemen, 2011-2016

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Abstract

In 2010, Yemen started the surveillance for severe acute respiratory infections (SARIs) by establishing 2 sentinel sites in Sana'a and Aden city. This study aims to determine the proportions of influenza and noninfluenza viruses among SARI patients and to determine the severity of SARI and its associated factors. The data of SARI patients who were admitted to SARI surveillance sites at Al Johory hospital in Sana'a and Al Wahdah hospital in Aden city during the period 2011-2016 were analyzed. The proportions of positive influenza viruses (type A, B) and noninfluenza viruses (respiratory syncytial, adenovirus, human parainfluenza, and human metapneumovirus), intensive care unit (ICU) admission rate, and fatality rate among SARI patients were calculated. A total of 1811 of SARI patients were admitted during 2011-2016. Of those, 78% were <15 years old. A total of 89 (5%) patients had influenza viruses and 655 (36%) had noninfluenza viruses. The overall ICU admission rate was 40% and the case-fatality rate was 8%. Infection by influenza type (A, B) and mixed (adenovirus, human parainfluenza) was significantly associated with lower ICU admission. Age <15 years old, infection with influenza B, pre-existence of chronic diseases, and admission to Aden site were significantly associated with higher fatality rate among patients. In conclusion; SARI patients in Yemen had a high ICU admission and case-fatality rates. Influenza type B, chronic diseases, and admission to Aden site are associated with higher fatality rate. Expanding surveillance sites and panel of laboratory tests to involve other pathogens will help to provide accurate diagnosis for SARI etiology and give more comprehensive picture. Training staff for SARI case management will help to reduce severe outcomes.

Keywords

severe acute respiratory infection, severe outcome, influenza, noninfluenza, Yemen, Field Epidemiology Training Program

What do we already know about this topic?
The severe outcome of severe acute respiratory infection (SARI) is indicated by admission to intensive care unit and death.
How does your research contribute to the field?
This study provides insight into the role of influenza and noninfluenza respiratory viruses in severe outcome of SARI.
What are your research's implications toward theory, practice, or policy?
Public health authorities need to improve surveillance and implement control and intervention measures.

Introduction

Acute respiratory infections (ARIs) are a group of diseases that are caused by different microorganisms where viral etiologies are responsible for 80% of cases.[1] Influenza and noninfluenza viruses are responsible for significant annual morbidity and mortality across all age groups.[2] On average, influenza viruses infect 5% to 15% of the global population, resulting in 3 to 5 million cases of severe illness and between 260 000 and 650 000 deaths every year worldwide. The heaviest burden is among high-risk groups that include pregnant women,

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Received 15 May 2018; revised 16 December 2018; revised manuscript accepted 23 April 2019

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children under 59 months, the elderly, individuals with chronic medical conditions.[3] In 2015, it was estimated to cause 3.2 million hospital admissions and 59 600 hospital deaths in children below 5 years of age worldwide.[4,5]

Efforts were made to assess the role of noninfluenza viruses in morbidity and mortality of ARIs. Surveillance for hospitalized patients with severe acute respiratory infections (SARIs) is an important public health tool used to identify etiologies to understand the disease, track changes in circulating influenza viruses and as an alert mechanism for potential pandemic viruses[6] For that purpose, the Eastern Mediterranean Acute Respiratory Infection Surveillance (EMARIS) network was established in 2007 and initiated sentinel-site surveillance for SARI in Egypt, Jordan, and Oman. This was achieved through the collaboration of Ministries of Health, partnership with the Centers for Disease Control and Prevention (CDC), Naval Medical Research Unit No. 3 (NAMRU3), and the World Health Organization (WHO).[7]

Yemen joined EMARIS network in 2010 and established 2 surveillance sites for SARI in Sana'a and Aden. However, limited information about SARI, influenza, and noninfluenza respiratory viruses is available in Yemen. Few studies were carried out to describe the mortality after influenza epidemic,[8] estimate the proportion of influenza and noninfluenza viruses and mortality among SARI patients,[9] and to understand the clinical characteristics of SARI associated with most detected pathogens during 2014-2015.[10] Still, there is gap in the information related to the role of influenza and noninfluenza viruses in severe outcome of SARI and associated factors. This study aimed to determine the proportions of influenza and noninfluenza virus among SARI patients, and assess the severity of SARI and its associated factors in Yemen.

Methods

Study Design

This study is a retrospective descriptive study that was based on the analysis of the surveillance data of SARI patients who were admitted in the 2 sentinel sites from January 2011 to December 2016. Official and ethical approvals to analyze the data of SARI surveillance were obtained from Minister of Public Health and Population (MoPHP).

Description of SARI Surveillance

SARI surveillance started in Yemen in October 2010 by establishing 2 sentinel surveillance sites: one site at Al Jumhory General Tertiary Hospital located in Sana'a city (2 500 000 population) and another site at Al Wahdah Pediatric Tertiary Hospital located in Aden city (921 809 population).

The surveillance team at each hospital includes a surveillance focal point and medical doctor who are trained for collecting data and specimens from patients with SARI. The team screens all hospitalized patients with respiratory disease and select the patients who meet the case definition of WHO. The case definition includes any patient admitted for ARI, had a history of fever or measured fever of ≥38°C, cough within previous 10 days, and requiring hospitalization.[11] SARI investigation form with a unique ID for each patient is used for collecting data from adult patients or from parents in case of children.

Nasopharyngeal (NP) and oropharyngeal (OP) swabs are collected when the patients are being assessed for admission. The samples are transported at 4°C within 24 hours to National Central Public Health Laboratory (NCPH) along with the data collection and investigation forms. At NCPH the primers and probes provided by CDC are used for detecting influenza A and B viruses by real-time polymerase chain reaction (RT-PCR). Aliquots of the samples are kept at ™70°C and shipped to NAMRU3 in Cairo where the total nucleic acid (TNA) is extracted from 200 μL of each sample using MagMAX™ Pathogen RNA/DNA Kit with the MagMAX™ Express-96 Deep Well Magnetic Particle Processor (Applied Viosystems1). The TNA is analyzed by polymerase chain reaction (PCR) to identify viral deoxyribonucleic acid (DNA) for adenovirus (AdV) and real-time reverse transcription polymerase chain reaction (rtRT-PCR) to detect viral RNA for respiratory syncytial virus (RSV), human metapneumnovirus (hMPV), and human parainfluenza virus types 1–3 (hPIV1-3).[7] A copy of the investigation forms are sent to MoPHP where the data manager at SARI program enters the data electronically and sends them to NAMRU3. Feedback from NAMRU3 was received monthly by SARI program and then by sentinel sites.

Data Collection

We obtained a soft copy of the data from SARI program in Microsoft Excel format that included demographic characteristics, site name, date of admission, clinical data (symptoms such as fever of ≥38°C, cough onset within previous 10 days, wheezing, abnormal breath sound, nasal congestion, tachypnea, sputum production, hemoptysis chest pain, sore throat, and dyspnea), date of onset, chronic diseases (asthma, cardiac, chronic obstructive pulmonary disease, malnutrition and hepatic, neurologic, and renal diseases), intensive care unit (ICU) admission, specimens taken at admission (NP and OP swabs), lab results, and outcome.

Statistical Analysis

Data were analyzed using Epi info 7.2. Proportions of positive influenza and noninfluenza viruses, ICU admission, and fatality rate were calculated. Chi-square test was used to test the differences in ICU admission and case-fatality rates according to the relevant characteristics. Multivariate analyses of factors associated with ICU admission and fatal outcome among SARI patients were assessed by using binary

Table 1. Characteristics of SARI Patients and Proportion of Positive Respiratory Viruses Among SARI Patients in Yemen 2011-2016.

	SARI patients		Influenza A		Influenza B		RSV		AdV		hPIV1-3		hMPV		Mixed	
Characteristics	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Age																
<15	1413	78	49	3	12	1	258	18	98	7	132	9	8	1	112	8
≥15	398	22	18	5	10	3	21	5	11	3	5	1	4	1	6	2
			$P = .321$		$P = .007$		$P = .001$		$P = .002$		$P = .001$		$P = .340$		$P = .001$	
Gender																
Female	916	51	24	3	4	0.4	150	16	70	8	65	7	6	1	74	8
Male	895	49	43	5	18	2	129	14	39	4	72	8	6	1	44	5
			$P = .013$		$P = .002$		$P = .247$		$P = .003$		$P = .445$		$P = .967$		$P = .006$	
Site																
Aden	1084	60	36	3	9	1	176	16	63	6	103	10	2	0	64	6
Sana'a	727	40	31	4	13	2	103	14	46	6	34	5	10	1	54	7
			$P = .291$		$P = .068$		$P = .32$		$P = 0.65$		$P = .001$		$P = .002$		$P = .190$	
Chronic diseases																
Yes	411	23	17	4	9	2	36	14	25	6	25	6	4	1	18	4
No	1400	77	50	4	13	1	223	16	84	6	112	8	8	0.6	100	7
			$P = .592$		$P = .040$		$P = .251$		$P = .950$		$P = .191$		$P = .371$		$P = .045$	
Years																
2011	135	7	8	6	7	5	15	11	9	7	5	4	5	4	13	10
2012	211	12	3	1	5	2	40	19	15	7	3	1	1	0	25	12
2013	671	37	18	3	7	1	166	25	67	10	25	4	4	1	64	10
2014	392	22	23	6	0	0	46	12	18	5	104	30	2	1	16	4
2015[a]	40	2	4	10	2	5	12	30	0	0	0	0	0	0	0	0
2016[b]	362	20	11	3	1	0.3	0	0	0	0	0	0	0	0	0	0
			$P = .004$*		$P < .001$*		$P < .001$		$P < .001$*		$P < .001$*		$P < .005$*		$P = .0001$*	
Total	1811	100	67	4	22	1	279	15	109	6	137	8	12	0.6	118	7

Note. *An expected cell value <5. SARI = severe acute respiratory infections; RSV = respiratory syncytial virus; AdV = adenovirus; hPIV1-3 = human parainfluenza virus types 1–3; hMPV = human metapneumovirus.

[a]Less reporting.

[b]Samples were tested only for influenza viruses, due to starting of war and band against Yemen, samples not sent to NAMRU 3 and not tested for non-influenza viruses.

logistic regression. A P value of less than .05 was considered statistically significant.

Results

Patients' Characteristics

During 2011 to 2016, a total of 1811 SARI patients were tested for respiratory virus. About 78% of patients were <15 years old. Of those, 74% were admitted to Aden site, 47% were males, and 18% had chronic disease. A total of 398 (22%) patients were ≥15 years old. Of those, 11% were admitted to Aden site, 56% were males, and 39% had chronic diseases.

Of the total SARI patients, 1084 (60%) were admitted to Aden site (96% <15 years old, 49% males, and 21 had chronic disease) and 727 (40%) of patients were admitted to Sana'a site (51% < 15 years old, 51% males, and 75% had chronic disease). Table 1 shows the characteristics of SARI patients and the proportions of positive respiratory viruses in Yemen, 2011-2016.

Respiratory Viruses

Influenza viruses were detected in 89 (5%) of SARI patients, 76 (4%) influenza type A and 22 (1%) influenza type B. Influenza type A was significantly more common among males than females (5% vs 3%, $P = .013$). Influenza type B was significantly more common among patients ≥15 years old, among males and among patients with chronic diseases.

Noninfluenza viruses were detected in 655 (36%) of SARI patients: 279 (15%) RSV, 109 (6%) AdV, 137 (8%) hPIV1-3, 118 (7%) mixed (Ad and hPIV), and 12 (0.6%) human metapneumovirus (hMPV). All noninfluenza viruses were significantly more common among patients <15 years old except hMPV.

The detected respiratory viruses varied from year to year, with low number of reporting SARI cases and high proportion of positive viruses in 2015. Only influenza viruses were detected in 2016. Samples are not sent to NAMRU3 and not tested for noninfluenza viruses (Figure 1).

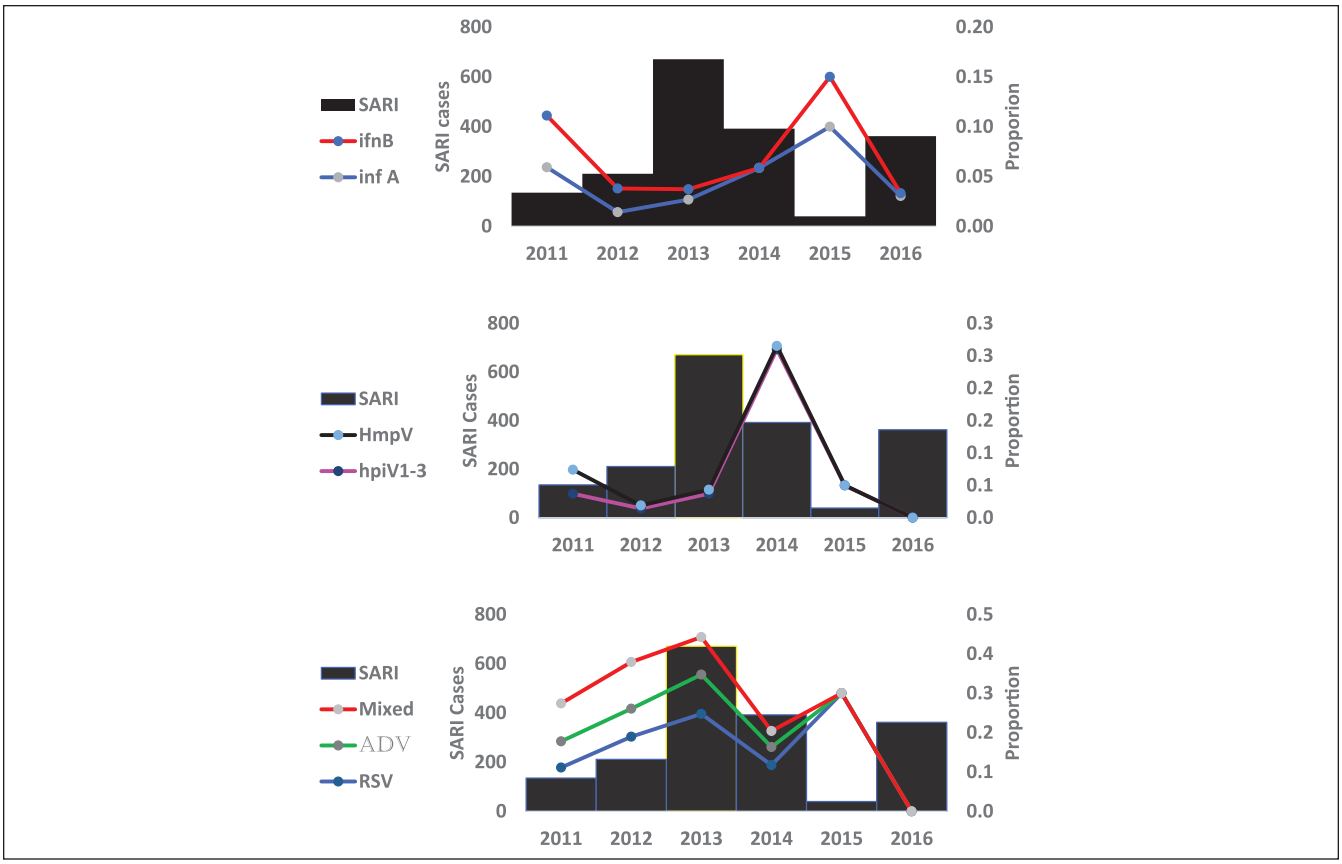

Figure 1. Proportion of positive respiratory viruses associated with SARI by years, 2011-2016, Yemen.
Note. SARI = severe acute respiratory infection; hMPV = human metapneumovirus; hPIV1-3 = human parainfluenza virus types 1–3; AdV = adenovirus; RSV = respiratory syncytial virus.

ICU Admission and Fatality Outcome

Table 2 shows the ICU admission and fatality according to patients' characteristics and respiratory viruses. A total of 731 (40%) patients were admitted to ICU. There was no significant difference in the rate of ICU admission according to demographic or clinical characteristic of SARI patients. Infection by influenza viruses was associated with lower rate ICU admission. Patients with positive influenza A or B were less likely to be admitted to ICU compared with patients not infected with these pathogens, 15% vs 41% and 9% vs 41%, respectively. Co-infection by mixed (Ad and hPIV) was associated with lower ICU admission. The SARI patient infected with both Ad and hPIV3 was less likely to experience ICU admission compared with patients not infected with the same pathogens (30% vs 41%).

The fatality rate was 8% among SARI patients. Higher fatality rate was seen among SARI patients <15 years old compared with patients ≥15 years old (9% vs 5%), among SARI patients who were admitted to Aden site compared with Sana'a site (10% vs 5%), among SARI patients who had chronic disease compared with patients without chronic diseases (13% vs 7% <.001) and among patients with positive influenza B compared with patients not infected with the same virus (23% vs 8%).

Multivariate Analysis of Factors Associated With Fatality

Table 3 shows factros associated with fatality by multivariate logistic regression; having a chronic disease, being infected with influenza B virus, and being admitted to Aden site were significantly associated with higher odds of fatality. Increased age was significantly associated with lower fatality. When categorized by age (Table 4), having a chronic disease, infection with influenza B virus, and admission to Aden site were significantly associated with higher odds of fatality among patients <15 years old only.

Discussion

Analysis of SARI surveillance data provides important insight into type of respiratory pathogens and severity of the disease outcome (ICU admission, fatality) associated with influenza and noninfluenza viruses. In this study, we analyzed the data for 1811 SARI patients. Of those, 78% were <15 years old, 60% were admitted to Aden site, 51% were females, and 23% had chronic diseases.

Almost three quarters of SARI cases were younger than 15 years old. This result was similar to previously reports in Yemen and Jordan.[10,12] About 50% of cases were males, a

Table 2. The ICU Admission and Fatality in Association to Patient's Characteristic and Respiratory Viruses, Yemen, 2011-2016.

	SARI N = 1811	ICU admission (N = 731)				Fatality (N = 145)			
	No.	No.	%	OR (95% CI)	*P*-value	No.	%	OR (95% CI)	*P*-value
Characteristics									
Age									
<15	1413	572	40	1.0 (0.8-1.2)	.64	126	9	1.9 (1.2-3.2)	.007
≥15	398	159	40	1.0		16	5	1.0	
Gender									
Male	895	360	40	0.9 (0.8-1.1)	.94	76	9	1.1 (0.8-1.6)	.45
Female	916	371	40	1.0		69	8	1.0	
Site									
Aden	1084	444	41	1.1 (0.9-1.3)	.52	110	10	2.2 (1.5-3.3)	<.001
Sana'a	727	287	40	1.0		35	5	1.0	
Chronic									
Yes	411	187	43	1.2 (0.9-1.4)	.16	53	13	2.1 (1.5-3.0)	<.001
No	1400	553	40	1.0		92	7	1.0	
Influenza viruses									
Type A									
+ve	67	10	14	0.2 (0.1-0.5)	<.001	3	5	0.5 (0.2-1.7)	.27
–ve	1744	721	41	1		142	8	1	
Type B									
+ve	22	2	9	0.1 (0.03-0.6)	.002	5	23	3.5 (1.2-9.5)	.01
–ve	1789	729	41	1		140	8	1	
Noninfluenza viruses									
RSV									
+ve	279	112	40	0.9 (0.7-1.3)	.93	25	9	1.2 (0.7-1.8)	.25
–ve	1532	619	44	1		120	8	1	
AdV									
+ve	109	44	40	1.0 (0.6-1.4)	1.0	10	9	1.2 (0.6-2.3)	.64
–ve	1702	687	40			135	8	1	
hMPV									
+ve	12	4	33	0.7 (0.2-2.4)	.62	1	8	1.0 (0.1-7.1)	.96
–ve	1799	727	40	1		144	8	1	
hPIV1-3									
+ve	137	58	42	1.0 (0.8-1.5)	.62	5	4	0.4 (0.1-1.0)	.71
–ve	1674	673	40	1		140	8	1	
Mixed (Ad and hPIV)									
+ve	118	35	30	0.6 (0.4-0.9)	.02	11	9	1.2 (0.6-2.3)	.586
–ve	1693	696	41	1		134	8	1	

Note. ICU = intensive care unit; SARI = severe acute respiratory infection; OR = odds ratio; CI = confidence interval; RSV = respiratory syncytial virus; AdV = adenovirus, hMPV = human metapneumovirus; hPIV1-3 = human parainfluenza virus types 1–3.

finding that is similar to what had been reported from Mediterranean region.[7]

The study showed a lower proportion of detected viruses among SARI patients (5% influenza and 36% noninfluenza viruses). This finding is similar to the finding of a previous study in Yemen,[9] which might suggest the presence of other pathogens such as bacteria or viruses associated with SARI. Expanding the panel of laboratory tests to involve other pathogens would provide accurate diagnosis for the etiology of SARI.

Table 3. Multivariate Logistic Regression for Factors Associated With SARI Fatal Outcome, Yemen, 2011-2016.

Factors	OR	95% CI	*P*-value
Chronic disease (yes vs no)	7.5	3.5-15.9	<.001
Influenza B (positive vs negative)	3.7	1.3-10.5	.015
Site (Aden vs Sana'a)	3.2	1.7-5.9	<.001
Age (y)	0.98	0.97-0.99	.004

Note. SARI = severe acute respiratory infections; OR = odds ratio; CI = confidence interval.

Table 4. Multivariate Logistic Regression for Factors Associated With SARI Fatal Outcome According to Age, Yemen, 2011-2016.

	Age < 15 y			Age ≥ 15 y		
Factors	OR	95% CI	*P*-value	OR	95% CI	*P*-value
Chronic disease (yes/no)	18.3	6.6-51.2	<.001	2.5	0.9-7.4	.086
Site (Aden vs Sana'a)	5.4	2.3-12.5	<.001	1.3	0.15-11.5	.797
Influenza B (positive vs negative)	6.8	1.9-23.7	.003	1.6	0.18-14.3	.663

Note. SARI = severe acute respiratory infection; OR = odds ratio; CI = confidence interval.

Noninfluenza viruses were more common than influenza viruses among SARI patients. This finding indicates the burden of noninfluenza viruses and comes with WHO Initiative of Battle against Respiratory Viruses, which highlighted the need for surveillance for noninfluenza viruses.[13]

Children were reported to have higher incidence of viral respiratory infection than adults.[14] Our result was consistent with this and showed significantly higher proportions of noninfluenza viruses (RS, AdV, hMPV, hPIV1-3: and mixed [Ad and hPIV]) among patients <15 years old. This finding had been reported in other EMARIS network countries including Oman, Jordan, and Egypt.[7,12,15]

However, RSV was found to be predominant in this study but it is less frequent than what had been reported in other studies.[16,17] This might be due to the difference in studied population. Our study involved children and adults, while previous studies focused on children <5 years old.

Influenza type A was less prevalent than that in other countries: 8% in Oman, 9% in Jordan, and 17% in Egypt.[12,15,18] This variation might be due to the differences in geography, etiological agents, or diagnostic methods. Furthermore, the limited number of surveillance sites in our study compared with the number of surveillance sites in other countries might be another explanation.

The severity as indicated by ICU admission was higher than that in Oman, Jordan, Lebanon, and Egypt.[7,12,15,19] The mortality was also higher than what had been reported by EMARIS network countries (3.5%) and Sub-Saharan Africa countries (2.8%).[7,20] This might be due to defect in SARI case management, or might be due to treatment delay, limited access, and inadequate surveillance sites in our study. Training staff on SARI case management will help to reduce severe outcomes. Furthermore, increasing surveillance sites will remove the access barrier and overcome the treatment delay.

Our results indicated that SARI patients with positive respiratory viruses (influenza A, influenza B, and mixed [Ad and hPIV3]) were less likely to be admitted to ICU compared with patients not infected with the same pathogens. This finding is in agreement with findings of a previous study conducted in EMARIS network countries.[7]

Infection with influenza B was associated with higher fatality outcome. Studies in Canada and the United States had attributed 22% to 44% of US pediatric influenza deaths to influenza B.[21,22] This might be due to the co-infection with other pathogens such as bacterial pneumonia, which contributes to the pathogenesis of fatal influenza B virus infection.[23,24] Similar to findings of a study in Egypt,[18] chronic diseases were found to be associated with fatality outcome.

This study had some limitations. Not all SARI cases were tested for viral respiratory pathogens and testing focused on a limited panel of viral respiratory pathogens. Other viral and bacterial etiologies might contributed to the severity of disease. Nevertheless, the current study provides a substantial amount of information about the influenza and noninfluenza viruses and severity of infections among hospitalized SARI patients in Yemen. Moreover, the influenza B virus positivity is very low. Therefore, one should be cautious when interpreting the association of influenza B virus positivity with fatality.

In conclusion, patients admitted with SARI in Yemen had a high ICU admission and case-fatality rates. Influenza type B, chronic diseases, and admission to Aden site were associated with higher fatality, mainly among patients <15 years old. Expanding the surveillance sites and panel of laboratory tests to involve other pathogens will help to provide accurate diagnosis for the etiology of SARI and will give more comprehensive picture. Training staff on SARI case management will help to reduce severe outcomes.

Acknowledgments

Authors would like to acknowledge the Eastern Mediterranean Public Health Network (EMPHNET) for their technical support. The support of Centers for Disease Control and Prevention (CDC), World Health Organization (WHO), and Training Programs in Epidemiology and Public Health Interventions Network (TEPHINET) is highly appreciated.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

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