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Epidemiology of severe cases of influenza and other acute respiratory infections in the Eastern Mediterranean Region, July 2016 to June 2018

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ABSTRACT

Background: Influenza surveillance systems in the Eastern Mediterranean Region have been strengthened in the past few years and 16 of the 19 countries in the Region with functional influenza surveillance systems report their influenza data to the EMFLU Network. This study aimed to investigate the epidemiology of circulating influenza viruses, causing SARI, and reported to the EMFLU during July 2016 to June 2018.
Methods: Data included in this study were collected by 15 countries of the Region from 110 SARI sentinel surveillance sites over two influenza seasons.
Results: A total of 40,917 cases of SARI were included in the study. Most cases [20,551 (50.2%)] were less than 5 years of age. Influenza virus was detected in 3995 patients, 2849 (11.8%) were influenza A and 1146 (4.8%) were influenza B. Influenza A(H1N1)pdm09 was the predominant circulating subtype with 1666 cases (58.5%). Other than influenza, respiratory syncytial virus was the most common respiratory infection circulating, with 277 cases (35.9%).
Conclusion: Influenza viruses cause a high number of severe respiratory infections in EMR. It is crucial for the countries to continue improving their influenza surveillance capacity in order detect any unusual influenza activity or new strain that may cause a pandemic.

Introduction

Influenza is an important national, regional and global public health concern because it causes year-round severe morbidity and mortality [1]. Cases can require hospitalization and require admission to the intensive care unit [2,3]. The unpredictable, continuous and rapid mutational potential of influenza viruses poses a serious threat to global health security with a possibility of pandemics at any time [4]. The zoonotic strains of influenza such as influenza A(H5N1) first detected in humans in 1997 in Hong Kong and then reported widespread globally since 2003, A(H7N9) reported in humans since 2013 in China and A(H9N2) reported for decades to be circulating in poultry and recently reported in humans, are strong evidence of these mutational capabilities; [5–8]. Therefore,

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influenza surveillance is essential to monitor and rapidly detect the circulation of different influenza viruses and the emergence of genetic changes in these viruses in humans and animals [9]. Information from influenza surveillance is also important in order to identify circulating strains to be included in the biannual vaccine strain selection to ascertain the needs for each region globally [10]. Nevertheless, surveillance systems have limitations such as lack of consensus on case definition, non-systematic sampling methods, scarcity of information on the circulating influenza viruses, and inconsistent and delayed reporting of cases [11].

The influenza surveillance systems in the World Health Organization's (WHO) Eastern Mediterranean Region have been strengthened since 2006 through collaboration with the Influenza Division of the Centers for Disease Control and Prevention (CDC-Atlanta) [12], support of the Pandemic Influenza Preparedness (PIP) Framework for influenza viruses sharing, and other benefits adopted by the World Health Assembly in May 2011 to improve global pandemic influenza preparedness and response. Implementation of PIP Framework activities started in the Region in 2014 [13]. Currently, seven countries of the Region—Afghanistan, Egypt, Jordan, Lebanon, Morocco, Sudan and Yemen—benefit from the Partnership Contribution (PIP-PC) to enhance their capacities in the areas of influenza laboratories and surveillance. Also, the establishment of the Eastern Mediterranean Acute Respiratory Infections Network in 2007 has played a crucial role in intensifying the influenza surveillance and response programme in the Region [14].

Most of the 22 countries of the Eastern Mediterranean Region are located in the northern hemisphere [15] where the influenza season usually starts between September and November and ends between March and May. They are distributed in four influenza transmission zones: Northern Africa, Eastern Africa, Western Asia and South Asia [16].

Up to June 2018, 19 of the 22 countries of the Eastern Mediterranean Region had already established functioning epidemiological surveillance for influenza-like illness (ILI) and/or severe acute respiratory infections (SARI). Sixteen of the 19 countries regularly and consistently report their influenza data from their sentinel surveillance sites to the Eastern Mediterranean Flu (EMFLU) Network: Afghanistan, Bahrain, Egypt, Islamic Republic of Iran, Jordan, Kuwait, Lebanon, Morocco, Palestine, Oman, Pakistan, Qatar, Saudi Arabia, Sudan, Syrian Arab Republic and Yemen. The EMFLU Network is a web-based surveillance platform used to enter real-time influenza data at the country level, which provides useful information on trends and estimates of influenza and helps detect any abnormal patterns of circulating influenza viruses in the Region. The platform was established by the WHO Regional Office for the Eastern Mediterranean and launched officially in May 2016. The EMFLU Network focuses mainly on collecting data on SARI and influenza-like illness from sentinel surveillance sites according to a specific case definition.

In this study, we examined the epidemiology of circulating influenza strains in cases of SARI in the Region that were reported to the EMFLU Network during the period 01 July 2016 to 30 June 2018.

Materials and methods

Surveillance site

Data included in this study were collected by 15 countries of the Eastern Mediterranean Region, which shared their data on influenza viruses and 6 out of these 15 countries shared also their data on other respiratory infections with the EMFLU Network. The data were collected from 110 SARI sentinel surveillance sites in the 15 countries. Data from one country were excluded during data analysis because the country reports aggregated numbers of enrolled cases and numbers of SARI-positive cases without providing information on demographic characteristics (age group or sex) or types/subtypes of influenza viruses.

Study population

All individuals included in this study presented with signs and symptoms of SARI to the sentinel sites in their countries, were hospitalized and reported as SARI cases at the sentinel sites and to the EMFLU Network. The WHO case definition for SARI, modified in January 2014, was used [15]. A case was defined as an acute respiratory infection with all the following features: history of fever or measured fever of $\geq$38 °C, cough, onset within the last 10 days, and requires hospitalization.

Study duration

Two consecutive years were included during the period 01 July 2016 to 30 June 2018.

Laboratory methods

All SARI cases tested for viruses that are reported by the countries to the EMFLU Network are laboratory-confirmed using real-time polymerase chain reaction techniques.

Data analysis

The collected data was revised, tabulated and introduced to a PC on Excel file (Microsoft Office). Data cleaning and checking for quality of data entry was performed. The demographic characteristics were stratified by age and sex and compared for flu positive and negative using the chi-squared test. A P-value less than 0.05 was considered statistically significant. Exploratory data analysis was carried out by epidemiological week and year against the number of SARI cases over the study period to show the influenza peaks and seasonal variations, the virus types and subtypes, and the distribution of cases of respiratory infection other than influenza.

Results

During the period between epidemiological week 26/2016 and 26/2018, a total of 40,917 cases of SARI fulfilling the SARI case definition were uploaded on the EMFLU Network and included in the study from 15 countries in the Eastern Mediterranean Region, after excluding the data from one country. Of these, 17,868 (43.8%) were female and 22,920 (56.2%) were male; in 129 cases, the sex was not given. Most cases, 20,551 (50.2%), were less than 5 years with 17,551 (42.9%) cases less than 2 years (Table 1).

The number of suspected SARI cases that were tested for laboratory confirmation in the 15 countries of the Region was 24,211 (59.2%). Influenza virus was detected in 3995 cases giving a proportion of 16.5%, of which 2849 (11.8%) were influenza A positive and 1146 (4.8%) were influenza B positive. Male sex represented 2128 (53.3%) of SARI cases that tested positive for influenza viruses, and the age group 16–50 years represented 1365 (34.4%) (Fig. 1a). All age groups are reported throughout the two years period of the study (Fig. 1b).

During the study period, the reported influenza cases included influenza A(H1N1)pdm09 as the predominant circulating subtype with 1666 cases (58.5%), followed by influenza A(H3N2) with 671 cases (23.6%), influenza A(H5N1) with 1 case (0.04%) and 511 influenza A cases (17.9%) that were not-subtyped (Table 2); while 1146 cases of influenza B were reported during the same period in the Eastern Mediterranean Region.

Table 1
Demographic characteristics of cases of severe acute respiratory infection (SARI) reported to the EMFLU Network from epidemiological weeks 26/2016 to 26/2018.

Characteristic	Total enrolled SARI cases No.	Total tested SARI cases		Not tested SARI cases No. (%)	P-value
		Positive cases[a] No. (%)	Negative cases No. (%)		
Sex					
Female	17,868	2190 (12.3)	8536 (47.8)	7142 (39.9)	
Male	22,920	2577 (11.2)	10,865 (47.4)	9478 (41.4)	0.015548
Not given	129	4 (3.1)	39 (30.2)	86 (66.7)	
Age group (years)					
<2	17,551	970 (5.5)	5833 (33.3)	10,748 (61.2)	
3–5	3016	308 (10.2)	1372 (45.5)	1336 (44.3)	
6–15	2619	360 (13.8)	1439 (54.9)	820 (31.3)	
16–50	8054	1522 (18.9)	5046 (62.6)	1486 (18.5)	<0.00001
51–65	4641	783 (16.9)	2757 (59.4)	1101 (23.7)	
>65	4855	780 (16.1)	2860 (58.9)	1215 (25.0)	
Not given	181	48 (26.5)	133 (73.5)	0 (0.0)	
Subtotal		4771	19,440		
Total	40,917	24,211		16,706	

[a] Positive for any type of virus, influenza or other respiratory diseases. Positivity rate = 11.7% (4771/40,917 × 100).

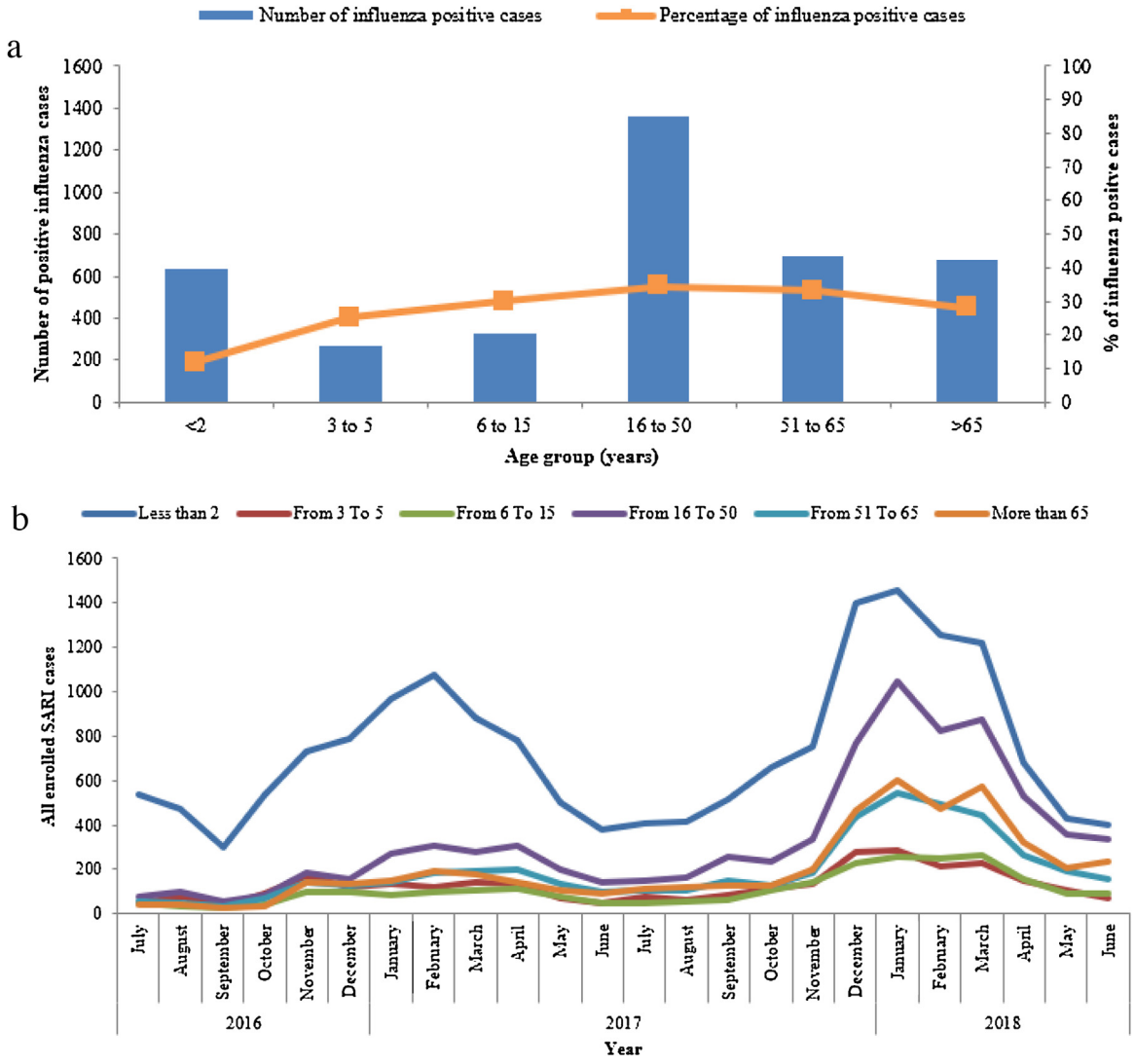

Fig. 1. (a) Number and percentage of influenza positive cases reported to EMFLU Network, by age group, epidemiological weeks 26/2016-26/2018. (b) Number of all SARI cases reported to EMFLU Network, by age group, distributed from epidemiological weeks 26/2016 to epidemiological week 26/2018.

The distribution of SARI cases by epidemiological week and year is presented in (Fig. 2a and b). Influenza infection in SARI cases reported during the study period peaked in epidemiological week 46/2016 (in November 2016) during the influenza season 2016/17. Influenza B was predominantly circulating with 344 cases during the same season 2016/17., While, the peak was in epidemiological week 3/2018 (in January 2018) during the influenza season 2017/18. Influenza A(H1N1)pdm09 was

Table 2
Distribution of influenza virus types and subtypes reported to the EMFLU Network in influenza seasons 2016/17 and 2017/18.

Season	Total enrolled cases	Total tested cases	Positive influenza cases	Influenza A				Influenza B	Positive cases (%)
				A (H1N1)pdm09	A(H3N2)	A(H5N1)	A (not-subtyped)		
2016/17	15,180	7951	1082	240	286	1	211	344	13.6
2017/18	25,737	16,260	2913	1426	385	0	300	802	17.9
Total	40,917	24,211	3995	1666	671	1	511	1146	16.5

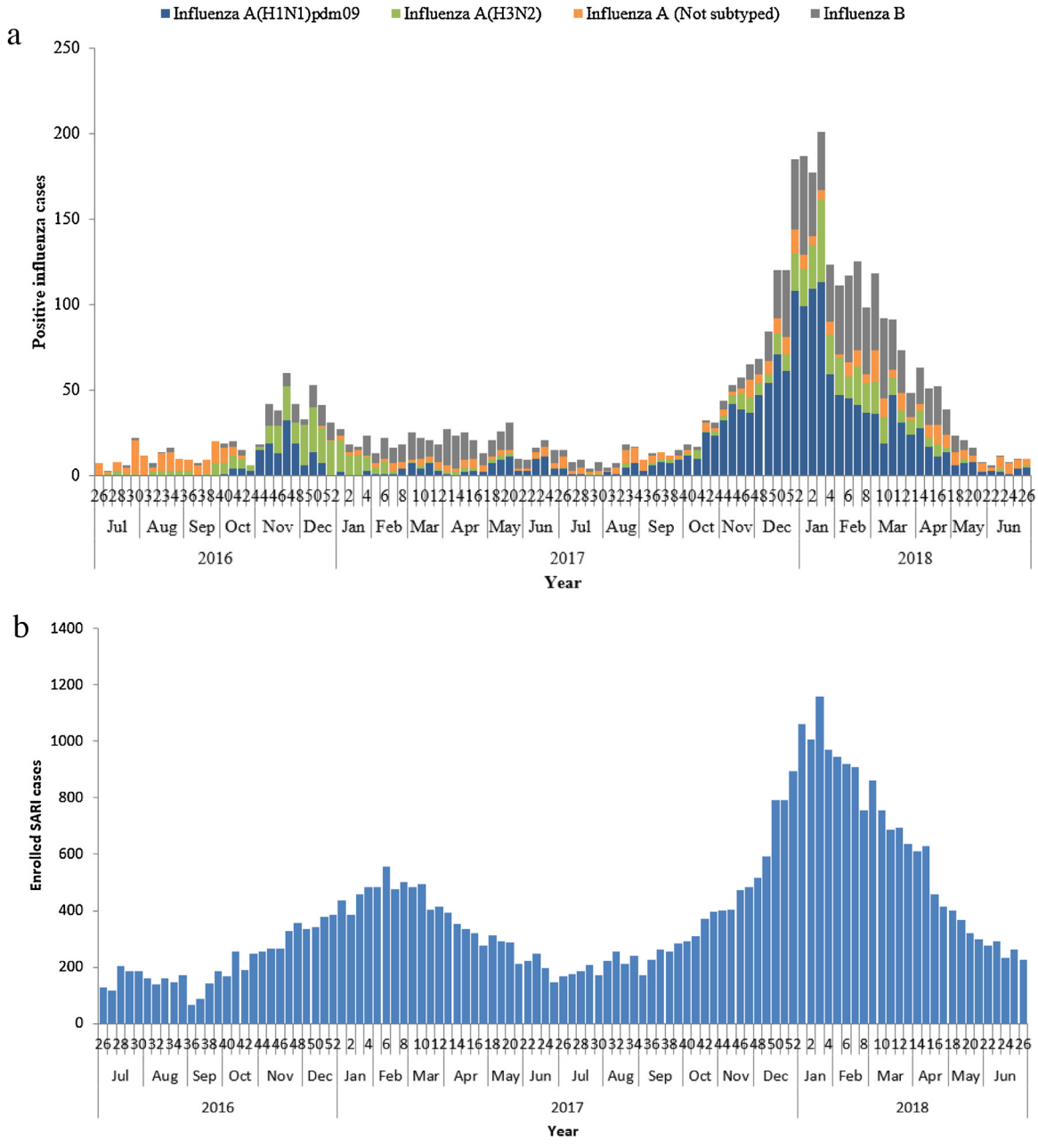

Fig. 2. (a) Distribution of influenza positive cases reported to EMFLU Network by subtype each year, epidemiological weeks 26/2016-26/2018. (b) Distribution of enrolled SARI cases reported to EMFLU Network by each year, epidemiological weeks 26/2016-26/2018.

predominantly circulating with 1426 cases during this season 2017/18.

The SARI cases reported to EMFLU Network during the study period were not exclusively influenza viruses; other respiratory infections such as adenovirus, human metapneumovirus, human parainfluenza viruses, respiratory syncytial virus (Fig. 3), mixed infections and other respiratory infections, including Middle East respiratory syndrome, are also reported to the regional platform by 6 countries of the Region.

A total of 772 positive cases of respiratory infections other than influenza viruses were reported 6 countries in the Region to the EMFLU Network during the period from epidemiological week 26/2016 to epidemiological week 26/2018. Respiratory syncytial virus was the most common circulating non-influenza respira-

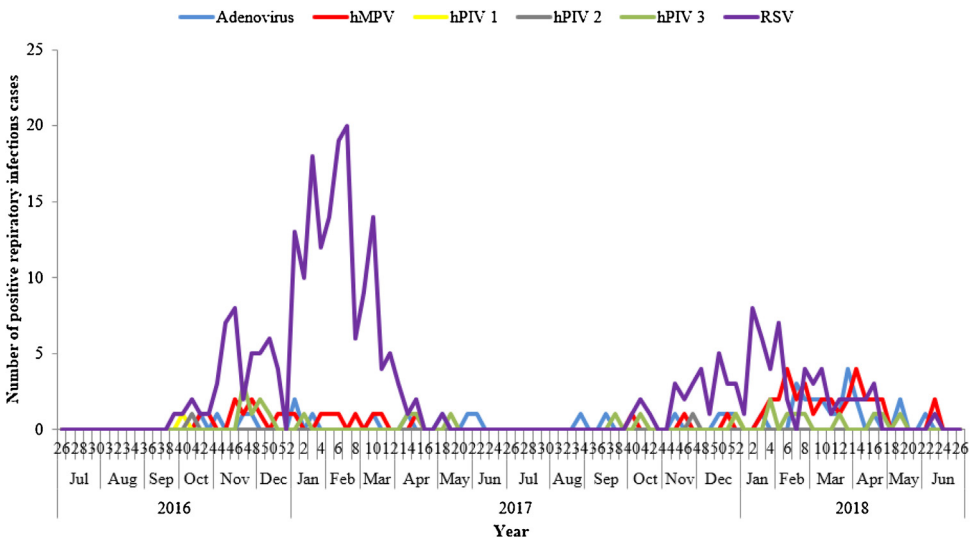

Fig. 3. Distribution of positive respiratory infection cases reported to EMFLU Network, by type, epidemiological weeks 26/2016-26/2018 (hMPV: human metapneumovirus, hPIV: human parainfluenza virus, RSV: respiratory syncytial virus).

tory infection reported in the Region with 277 cases (35.9%), with the highest peak reported in epidemiological week 7/2017. This was followed by 266 (34.5%) cases of "other" infections, which includes Middle East respiratory syndrome cases and other respiratory viruses not registered on EMFLU Network by name. "Mixed" infections (co-infections) came next with 107 cases (13.9%), the highest number of co-infections reported was in males with 61 cases (57%) and in age group less than 2 years old with 40 cases (37.4%); and then human metapneumovirus with 55 cases (7.1%), followed by adenovirus with 40 cases (5.2%), and finally human parainfluenza viruses, including three serotypes (hPIV 1, hPIV 2 and hPIV 3) with 27 cases (3.5%). Three positive SARI cases were reported to the EMFLU Network during the study period under "unspecified" viruses.

SARI data reported to EMFLU Network during the study period came from 15 countries in three of the four influenza transmission zones, Northern Africa, Western Asia and South Asia; only the Eastern Africa transmission zone did not report SARI cases to the regional platform.

During the study period, in the Northern Africa influenza transmission zone, influenza A virus was the predominant virus at the beginning of the influenza season 2016/17, with 174 cases influenza A(H3N2), 2 cases influenza A(H1N1)pdm09, 1 case influenza A(H5N1) and 3 cases not-subtyped influenza A; while influenza B became the predominant virus at the end of the same season with 182 reported cases. In the influenza season 2017/18, influenza A was the predominant circulating virus with 164 cases influenza A(H1N1)pdm09 and 111 cases influenza A(H3N2) (Fig. 4a).

In the South Asia influenza transmission zone, influenza A virus was the predominant circulating influenza viruses in season 2016/17 with 123 cases not-subtyped influenza A, 23 cases influenza A(H3N2) and 3 cases influenza A(H1N1)pdm09 and. During the season 2017/18, influenza A virus was also predominant with 219 cases influenza A(H1N1)pdm09 and 186 cases influenza A(H3N2) (Fig. 4b).

In the Western Asia influenza transmission zone, influenza A virus was the predominant circulating influenza viruses in season 2016/17 with 252 cases influenza A(H1N1)pdm09, 116 cases not-subtyped influenza A and 93 cases influenza A(H3N2). During the season 2017/18, influenza A virus was also predominant with 1026 cases influenza A(H1N1)pdm09, 269 cases influenza A not-subtyped and 84 influenza A(H3N2) cases (Fig. 4c).

Discussion

Preparedness for prevention and control of influenza outbreaks, as well as unpredictable pandemics, starts with a clear understanding of the seasonality of influenza viruses. Furthermore, identification of circulating influenza viruses helps vaccine manufacturers to determine the composition of the seasonal influenza vaccine; in addition to characterizing the influenza seasonality in the region helping to define when the vaccination can be implemented to prevent the occurrence of major influenza outbreaks. The epidemiology of influenza is not well characterized in the Eastern Mediterranean Region. Although the number of research papers published from the Region has increased considerably in the past decade [17], still many gaps remain and some questions are still unanswered.

This is the first study in the Eastern Mediterranean Region to focus on SARI using data reported by countries to the regional platform, EMFLU Network. We analysed influenza surveillance data in the Region from July 2016 to June 2018. From our analysis, it is clear that influenza viruses circulate in the Region throughout the year, which is consistent with previous studies [13]. Influenza peaks were observed during the winter, December to March, which is similar to other northern hemisphere countries [17].

The predominance of influenza viruses varied from one season to another; influenza B was the predominant type circulating in the influenza season 2016/17, while influenza A(H1N1)pdm09 was the predominant circulating virus in the influenza season 2017/18. Moreover, the influenza A subtypes varied by time; influenza A(H3N2) circulated predominantly in influenza season 2016/17, whereas influenza A(H1N1)pdm09 was predominant in the influenza season 2017/18. The trends in influenza viruses observed in our study are similar to those described in a previous study in the Region [18].

According to our study findings, the incidence of influenza virus infection was highest in children less than 5 years, which is consistent with findings from other studies conducted in different regions [19]. Children are more susceptible to influenza viruses; therefore, they have a higher incidence of severe cases of influenza than other age groups [20]. Nevertheless, it is possible that the vigilant care of parents of their children may be the reason for the higher number of children less than 5 years reported at the SARI sentinel sites in the Region. In addition, adults can usually take over-the-counter

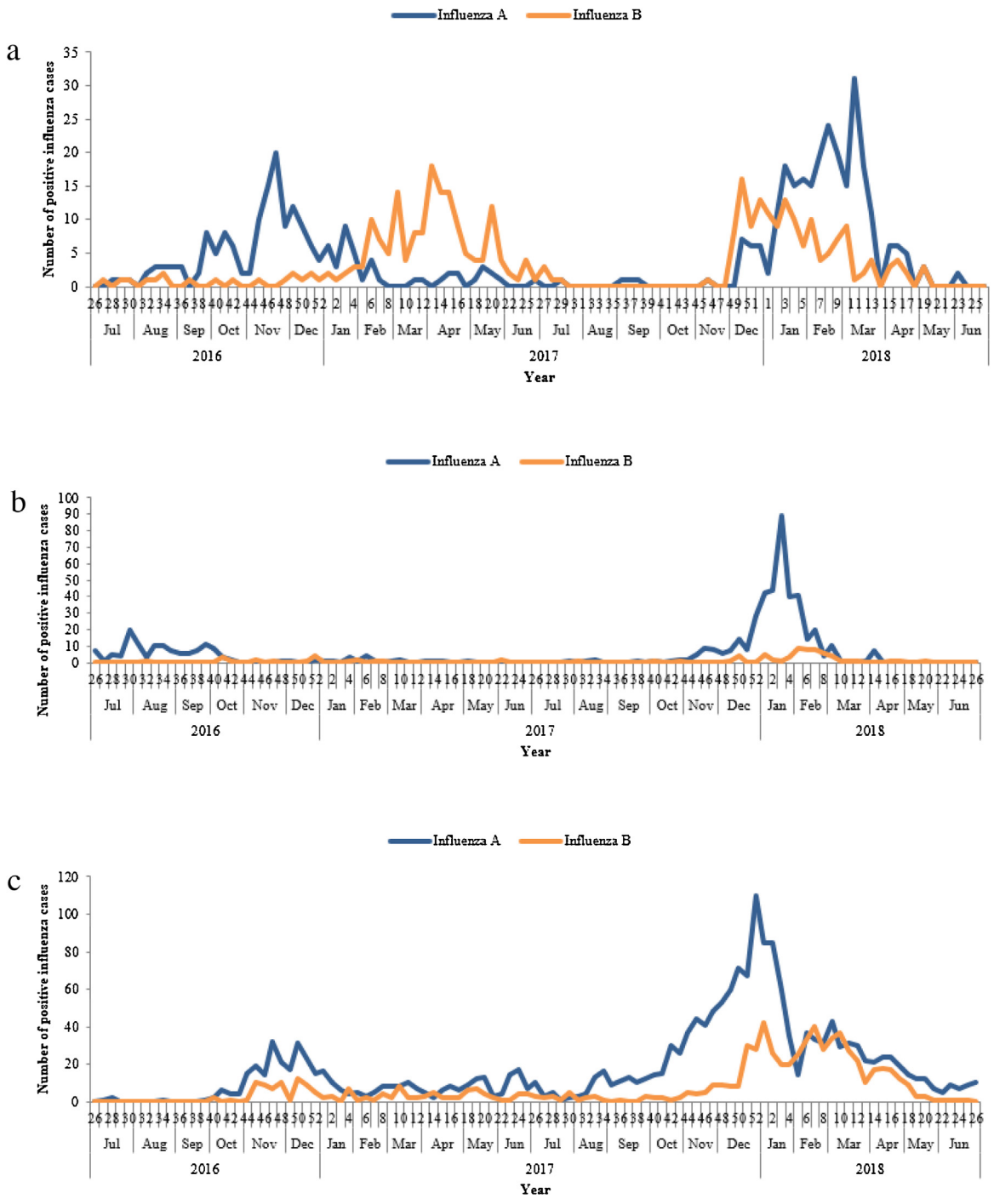

Fig. 4. (a) Distribution of cases of influenza A and B in the Northern Africa influenza transmission zone in epidemiological weeks 26/2016-26/2018 by virus type. (b) Distribution of cases of influenza A and B in the South Asia influenza transmission zone in epidemiological weeks 26/2016-26/2018. (c) Distribution of cases of influenza A and B in the Western Asia influenza transmission zone in epidemiological weeks 26/2016-26/2018.

medicines instead of seeking medical advice at healthcare facilities, which is not the case with young children.

There were many lessons learnt from the development of EMFLU Network in the EMR. These lessons include, but not merely: the confidence and trust built between the Ministries of Health/ Public Health in the Region and the WHO EMRO, in terms of data sharing for influenza and other acute respiratory infections, through the high level of confidentiality that the website offers and the full authority and power of each county over its own data reported to EMFLU Network. Each country has its own situation and conditions while implementing the SARI surveillance, these conditions should be respected while supporting the country to build its surveillance capacities.

These lessons and the requirements collected from countries at the EMR, shaped our vision while developing the second version of EMFLU Network, that will be officially launched in 2019. EMFLU version two will include new features as follows: a monitoring dashboard to monitor and track different activities, the progress of data entry and detect any abnormal influenza trend or activity. An offline use of the platform and automatic synchro-

nization once connected helping the users to upload their data even during the absence of internet connection. As well, a new mobile application will be developed to facilitate the data entry at any place.

Our study had some limitations. Up to June 2018, 16 out of the 22 countries of the Region had started reporting their SARI data to the EMFLU Network. After excluding data from one reporting country, the data analysed covered only 15 countries and did not include data from seven countries of the Region. In addition, no data were available from one of the four influenza transmission zones in the Region, the Eastern Africa transmission zone; thus, our findings are not fully representative of all influenza zones in the Region. Finally, some of the sentinel sites in the Region included in our study were not strictly following the same ideal criteria for choosing SARI sentinel sites, for example, some sites were pediatric hospitals, and this may explain the high number of enrolled SARI cases reported to EMFLU Network within the age group less than 2-year-old. Therefore, the age group and other demographic analyses should be interpreted with caution due to possible biases.

Conclusion

The current study shows that influenza viruses cause a notable number of severe respiratory infections throughout the year in the Eastern Mediterranean Region, although the strains of the virus vary from one country to another and over time. Influenza peaks in the Region are observed during winter months, consistent with results from other studies in northern hemisphere countries. Calculating the burden caused by influenza viruses in the Region requires further studies to be conducted. It is important for countries of the Region to continue their efforts to enhance their influenza surveillance capacities in order to be able to rapidly detect any unusual influenza activity or new strain that may cause a pandemic.

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Competing interests

None declared.

Ethical approval

The case-patient and aggregated data lists reported to EMFLU Network are anonymous, thus neither informed consent nor approval from an institutional review board was required.

Author contributions

All authors contributed equally to the manuscript.

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