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Short communication

Exceptional influenza morbidity in summer season of 2017 in Israel may predict the vaccine efficiency in the coming winter

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ABSTRACT

Influenza infections are the leading cause of respiratory viral infections worldwide, and are mostly common in the winter season. The seasonal influenza vaccine is currently the most effective preventive modality against influenza infection. Immediately following each winter season the World Health Organization (WHO) announces the vaccine composition for the following winter. Unexpectedly, during the summer of 2017, in Israel, we observed in hospitalized patients, an exceptionally high numbers of Influenza positive cases. The majority of the influenza B infections were caused by influenza B/Yamagata lineage, which did not circulate in Israel in the previous winter, and most of the influenza A infections were caused by influenza A/H3N2, a strain similar to the strain that circulated in Israel in the previous winter. We therefore predict that these two viruses will circulate in the coming winter of 2017/18 and that the trivalent vaccine, which includes antigenically different viruses will be inefficient.

1. Introduction

Influenza is a contagious virus that results in acute respiratory disease. Influenza infections occur mostly in the fall and winter seasons. In Israel, influenza virus infections usually starts around November, peaks around January and continues until the end of March, causing significant mortality and morbidity each year [1,2].

Influenza infection in the summer is a very rare event that was not observed in Israel in the last years (except for the 2009 A/H1N1 pandemic infection). The lack of infectivity in the summer may be due to the high temperature or low humidity, however, the role of environmental conditions in the transmission of influenza viruses are not completely understood [3].

Influenza infections are caused primarily by influenza A and influenza B viruses. Two antigenically distinct influenza B virus lineages, B/Yamagata and B/Victoria, are currently circulating around the world [4,5]. In the winter season of 2015/16, the B/Victoria strain was dominant [6], while in the winter season of 2016/17 only few cases of influenza B virus infections were noticed in Israel, most of which belong to the B/Yamagata lineage. The dominant influenza A strain in the 2016/17 winter season was influenza A/H3N2 that belongs to the 3C.2a clade. This subtype of influenza acquired mutations resulting in genetic divergent virus, different from the one included in the vaccine, and thus the given vaccine was inefficient [7–9].

2. Methods and results

We initiated this research due to exceptionally high number of patients hospitalized during 2017 summer season with Influenza like illness (ILI) symptoms (Fig. 1A). Most of these hospitalized patients had an underlying chronic disease. Analysis of the patient's age showed that most of the patients were above 60 years old (Fig. 1B). The patients live in different geographic regions in Israel and were unrelated to each other. In order to identify the responsible viral agent; total viral nucleic acid was extracted using NucliSENS easyMAG (BioMerieux, France). Using qPCR or qRT-PCR, samples were tested for the presence of the following respiratory viruses: adenovirus, Respiratory Syncytial Virus (RSV), influenza viruses (A, B, and A(H1N1)pdm09), parainfluenza virus 3 and human Metapneumovirus (hMPV) [10]. Surprisingly, we found an exceptionally high number of influenza A

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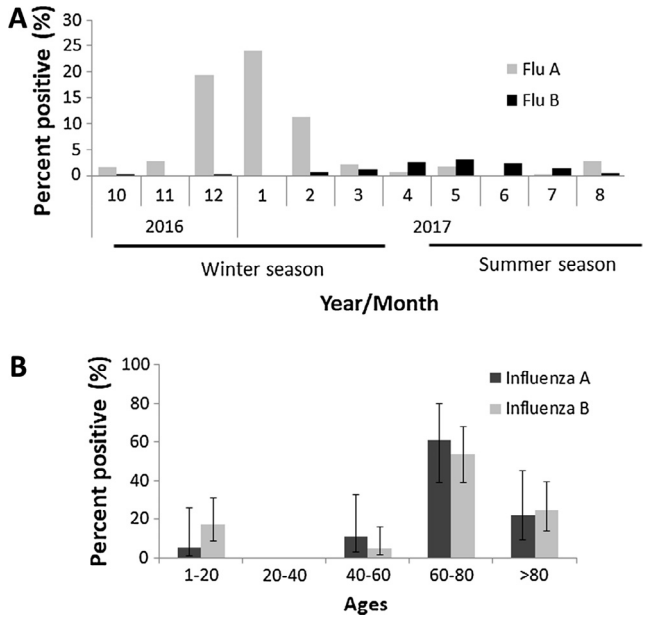

Fig. 1. Positive influenza A and influenza B cases from winter 2016 – summer 2017 and age distribution of the summer 2017 patients. (A) Monthly distribution of the percent of positive hospitalized patients with ILI symptoms infected with influenza A or influenza B. (B) Figure presents all summer positive influenza A and influenza B cases distribution divided to age groups.

and influenza B positive cases in the summer season of 2017 (64), of which, 70% were infected with influenza B and 30% with influenza A (Fig. 1A).

To identify the influenza A or influenza B virus strains, all influenza positive samples were subjected to an in-house laboratory developed assay using Taqman real-time reverse transcription-PCR (qRT-PCR) chemistry as previously described [5,11]. We determined that all influenza A virus (except for 3 cases of A/H1N1pdm) infections were due to A/H3N2, a virus that circulate in the country in the previous winter. As for influenza B, most the infections were due to B/Yamagata virus (95% of all influenza B positive cases), while in the previous year almost no influenza B infections were observed in Israel.

We also performed phylogenetic analysis using RT-PCR amplification for the HA gene of influenza A [11] and influenza B [5]. The PCR products were sequenced using the ABI PRISM Dye Deoxy Terminator cycle sequencing kit (Applied Biosystems, Foster City, CA). Phylogenetic trees were prepared by nearest neighbor joining analysis, using Clustal X with 1000 bootstraps, and trees were visualized using TreeView or NJ plot software. Sequences were placed in either GISAID or Gene Bank.

As can be seen in Fig. 2A, all the tested influenza A samples (marked in blue) belong to the 3C.2a clade and were similar to the common sub-clades circulated in 2016/17 winter season. These sub-clades are genetically different from the A/Hong-Kong/4801/2014 vaccine strain (marked in red) and resemble more the A/Singapore/INFIMH-16-0019/2016 vaccine strain (marked in red and a blue box), which was recently recommended to be included in the southern hemisphere vaccination [11].

Most of the tested influenza B-positive viruses belong to the B/Yamagata clade 3 while only few belonged to the B/Victoria clade 1A (marked in blue in Fig. 2B). The current influenza B strain, which present in the trivalent vaccine is B/Brisbane/60/2008, marked in red which belong to the B/Victoria lineage. Interestingly, the WHO recently announced that the B/Phuket/3073/2013, which belong to B/Yamagata lineage would replace the previous vaccine strain in the trivalent vaccine given in the southern hemisphere [12].

The institutional review board (IRB) of the Sheba Medical Center (Helsinki Number 1967-15-SMC) approved the research.

3. Discussion

Influenza virus infections which occur mostly in the winter season are a major cause of morbidity and mortality around the world [1]. Influenza infections during the summer are very rare. Here we report an unusual number of influenza virus infections during the summer period. All patients, but one, did not leave Israel around the time of the infection (so that they were not infected abroad), and all patient had no known relation to each other (same place of habitat, same place of work, etc.) which indicates it was not a local outbreak.

We evaluate influenza infection since the summer of 2011 and found that the percent of positive influenza cases during the summer was around 2% and some of these patients were abroad around the time of the infection. In contrast, this year the percent of positive cases was around 4% which was clearly separated from the winter season, with a clear peak in May that ended in August. Throughout this summer season, only one patient was abroad around the time of the infection.

Exceptional summer influenza morbidity suggests for a low immunity against the viruses, which allows the spread of the virus out of its typical season. Such low immunity might be due to the emergence of a new virus, like the A(H1N1)pdm09 virus reported in Israel in summer 2009 [13]. Another cause for influenza summer morbidity may be due to a mismatch between the circulating virus and the influenza strains present in the vaccine. Similar phenomena was observed in the winter season of 2015/16 in which the vaccine strain in the trivalent vaccine was the B/Yamagata while the dominant circulating strain was B/Victoria [14,15].

The Influenza virus undergoes rapid and significant changes that prevent the generation of a long-lasting protective immunity [16,17]. The yearly vaccine includes 3–4 influenza virus strains, which are selected annually based on the circulating influenza viruses, is the primary preventive strategy against the influenza viruses. The trivalent 2017/2018 vaccine include the A/Michigan/45/2015 A(H1N1)pdm09-like virus, A/Hong Kong/4801/2014 (H3N2)-like virus, and B/Brisbane/60/2008-like virus (B/Victoria lineage). The quadrivalent vaccine contains an additional B virus B/Phuket/3073/2013-like virus (B/Yamagata lineage) [18]. Here we show that two viruses caused the unusual infection in the summer: A/H3N2 and the B/Yamagata viruses; unfortunately, these viruses differ from those planned to be in the vaccine. Interestingly, in Taiwan a similar phenomenon was reported with influenza A/H3N2 in the same season [19].

At the end of September 2017, WHO announced the recommended composition of the trivalent vaccine for the 2018 southern hemisphere influenza season [12,20]. In this vaccine, the influenza A/H3N2 strain is A/Singapore/INFIMH-16-0019/2016 that belongs to clade 3C.2a1 and the influenza B is B/Phuket/3073/2013, which belong to the B/Yamagata lineage. Both viruses are similar to the strains circulated in Israel during the summer of 2017. We thus predict that the planned vaccine for the northern hemisphere will be inefficient and that the vaccine given in the southern hemisphere is actually more suitable to protect from for the current circulating influenza strains. Indeed, in the beginning of the winter season in Israel B/Yamagata was detected.