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Review

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2012-2015

ABSTRACT Information on the prevalence of influenza, circulating virus subtypes and seasonality is essential for selecting strains for annual vaccines and for planning immunization programmes. Data were obtained from the 13 sentinel surveillance sites throughout Egypt during 2012–2015. Laboratory-confirmed influenza was found in 13% of cases of influenza-like illness (ILI) and 18% of cases of severe acute respiratory infection (SARI); positivity for influenza was similar in cases of ILI and SARI in patients up to 15 years of age but increased for SARI and decreased for ILI in people aged ≥ 15 years. The most commonly observed influenza

virus subtypes were B followed by A/H3 in ILI cases, and A/H1N1 followed by B in SARI cases. The seasonality of influenza in ILI cases was November–February, and that in SARI cases was November–March, peaking in January.

Égypte : positivité et sous-types circulants du virus de la grippe parmi les cas de syndrome de type grippal et d'infection respiratoire aiguë sévère, 2012-2015

RÉSUMÉ Les informations sur la prévalence de la grippe, les sous-types circulants du virus et la saisonnalité sont essentielles pour la sélection des souches destinées aux vaccins annuels, ainsi que pour la planification des programmes de vaccination. Les données sont issues des 13 sites sentinelles de surveillance à travers l'Égypte pour la période 2012-2015. La présence de la grippe a été confirmée en laboratoire pour 13 % des cas de syndrome de type grippal (STG) et 18 % des cas d'infection respiratoire aigüe sévère (IRAS) ; chez les personnes dont l'âge est inférieur ou égal à 15 ans, le taux de positivité pour la grippe était semblable pour les cas de STG et d'IRAS. Cependant, il augmentait pour les IRAS et diminuait pour le STG chez les personnes de 15 ans et plus. Les sous-types du virus de la grippe les plus fréquemment identifiés étaient le virus B suivi du A/H3 pour les cas de STG, et le virus A/H1N1 suivi du B pour les cas d'IRAS. La saisonnalité de la grippe s'étendait de novembre à février pour les cas de STG, et de novembre à mars, avec un pic en janvier, pour les cas d'IRAS.

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Introduction

Influenza is an acute viral respiratory infection causing morbidity and mortality worldwide with serious public health implications (1). Although influenza causes self-limiting infection and most people recover quickly, pregnant women, the very young, the elderly and chronically ill people are at high risk of severe complications such as pneumonia (2). Globally, seasonal influenza kills 250 000–500 000 people annually (3). Seasonal influenza viruses continually circulate causing annual epidemics, mainly during winter months in temperate climates (4). In temperate regions of the northern and southern hemispheres, influenza activity has been well described showing that annual winter epidemics are associated with excess deaths from influenza and pneumonia (1). However, limited data are available in tropical and developing countries on

influenza epidemiology, circulating influenza virus types and seasonality.

As influenza is a vaccine-preventable disease, improved understanding of the geographic circulation of the virus, risk factors for severe infection and associated disease burden is essential for the development of prevention and control strategies. Information on the circulating virus subtypes and the demographic distribution of laboratory-confirmed cases is crucial for selecting vaccine strains, cost–effective reallocation of resources and selecting target groups for vaccination and antiviral medication. In countries with tropical or subtropical climates, the seasonality of influenza is unclear; activity may be observed all year round. These varying patterns of seasonality complicate optimal timing of vaccination and the recommended composition of influenza virus vaccines.

Egypt is a lower middle-income country in Africa with a population of about 90 million. It has a tropical to temperate climate. The Ministry of Health and Population established a sentinel-based surveillance system for influenza and influenza-like illness (ILI) in 1999. Since 2006, after the emergence of avian influenza A (H5N1) virus infection in humans in the country, the influenza surveillance system has been further strengthened in close collaboration with the World Health Organization (WHO) and the Centers for Disease Control and Prevention (CDC) in the United States of America through establishing a surveillance system for severe acute respiratory infection (SARI) in selected hospitals. The goals of influenza surveillance in Egypt are: to improve understanding of the epidemiology and seasonality of influenza virus infection; monitor the circulation of the influenza virus strains; contribute to global influenza surveillance and vaccine strain selection by submitting virus strains to the WHO Global Influenza Surveillance and Response System; and contribute to the development of influenza prevention and control strategy. The surveillance system in Egypt collects data on mild infections caused by influenza (ILI) from the outpatient clinics as well as on severe infections in patients hospitalized with acute respiratory infections (SARI).

In this report, we present surveillance data on frequency, seasonality and distribution of circulating influenza virus strains in Egypt from 2012 to 2015 from the 13 sentinel sites across the country. We also describe the proportion of influenza-positive infections in patients visiting outpatient clinics and among those hospitalized with severe infections, the demographic characteristics of patients and the circulating influenza subtypes in mild and severe cases, and identify groups at high risk for severe disease and death.

Methods

Setting and case sampling

Influenza surveillance is conducted in Egypt through 13 sentinel surveillance sites distributed

throughout the country. Of these sites, five hospitals (Mahala, Shipin El-Kom, Abassia Fever Hospital, Abassia Chest Hospital and Damiette Chest Hospital) are registered sentinel sites for SARI patients only, while five sites, El-Gabarty polyclinic and the outpatient clinics of Helwan, Embaba, Zagazig and Damietta fever hospitals, collect data on ILI cases only. Additionally, three more sites collect data for both ILI and SARI cases: Alexandria, Aswan and Minya fever hospitals.

At the eight sentinel sites for ILI, the first two ILI cases meeting the WHO case definition and seen from Saturday to Thursday were selected systematically for sampling and enrolment, however, at the 8 sentinel sites for selecting SARI cases a cluster random sampling technique was used for enrolment and sampling. We used the WHO case definition for SARI for enrolment. Thus, all cases enrolled in the influenza surveillance system from 2012 to 2015 and meeting the WHO case definitions for ILI and SARI (5) were analysed for the purpose of this study.

Laboratory methods

Both oropharyngeal and nasopharyngeal swabs were collected from all ILI and SARI patients enrolled in the surveillance system. The swabs were placed in a single cryovial with transport medium and immediately refrigerated at 2–8 °C. If transport was postponed, specimens were immediately placed in a nitrogen tank at –80 °C. Samples were tested by real-time reverse transcription polymerase chain reaction (rtRT-PCR) for influenza A and B viruses using the standard WHO and CDC protocol (6). All specimens positive for influenza A virus were further subtyped for H1, H3, H5 and pH1N1 using specific primers from the CDC at the Central Public Health Laboratory, which is also a national influenza centre of the WHO Global Influenza Surveillance and Response System. A subset of both positive and negative samples was further tested at the US Naval Medical Research Unit No. 3 (NAMRU-3) in Cairo, a WHO regional laboratory for quality assurance.

Data analysis

A standard surveillance form was used for collecting surveillance data from all patients who were sampled. Data were manually checked for accuracy, cleaned and analysed in MSExcel, and Epi-Info 7. The demographics of mild cases (ILI) were compared with those of severe cases (SARI) using appropriate statistical tests; time series were plotted and the odds of mild and severe influenza laboratory-confirmed cases were modelled by variables such as age (

In order to calculate the influenza threshold, a baseline (average epidemic curve) was set, representing the usual level of disease activity, which varies over time during the disease season and the off-season. The average epidemic curve was estimated from a time series of 3 years, centred on the median week of peak transmission for those years, aligning or shifting the real curve. A moving average of 4 weeks of the aligned 5-year data, accounting for a set of 20

weeks, gave the baseline at 1 week, and was used to make up the moving average (baseline influenza activity), while the alert threshold is above the average weekly values by 1.645 standard deviations, which defines the 90% confidence interval of the mean in order to detect any unusually severe season.

Ethical considerations

As these data were obtained from the influenza sentinel surveillance system and the use of such data is part of the national surveillance activities, the study did not require formal ethical review.

Results

Demographic characteristics

During the 4 years 2012–2015, from a total of 18 171 (13%) samples collected from ILI, 2367 were laboratory-confirmed for influenza (Table 1). The median age of the ILI cases was 5 years (range 1 month–92 years), while for infection caused by other laboratory-confirmed influenza virus subtypes, the median age was 7 years (range 1 month–80 years). Males accounted for 56.2% (1324) of all ILI cases tested for influenza virus. The highest proportion of laboratory-confirmed ILI cases was found in the age group 5 –

Among the 11 114 SARI cases enrolled in the influenza surveillance during 2012–2015 (Table 1), a total of 1851 (17%) samples were positive for influenza virus. The median age of all those enrolled was 39 years (range 1 month–95 years). The median age was 40 years (range 1 month–94 years) among those who tested positive for influenza virus. Among the influenza-positive cases, males accounted for 47.5% (879/1851). Most of the influenza-positive SARI cases were found in the age group 15 –

Risk factors

The positivity for influenza virus was similar in people up to 15 years of age with ILI and also in those with SARI but positivity increased in SARI cases and decreased in ILI cases in people aged ≥ 15 years (Figure 1). Influenza positivity among SARI cases was more likely to result in prolonged hospitalization (Table 2) and also more likely among people aged ≥ 15 years, pregnant women and people with chronic medical conditions such as diabetes, asthma, chronic lung disease, heart disease, kidney and liver or metabolic disorders, people with weakened immune systems and morbidly obese people. The highest mortality rate from influenza-associated SARI (Table 3) was seen in the age group > 15 years (OR 3.25; 95% CI: 1.10–13.44) and was significantly associated with the influenza A virus subtype (OR 3.54; 95% CI: 1.32–11.88). The proportion of influenza-associated SARI cases that required ventilation or admission to intensive care units

was around 21%.

Circulating patterns of influenza virus subtypes and seasonality

During the period 2012–2015, different influenza virus subtypes were seen to have been predominant during different periods. Influenza A/H3N2 was the predominant circulating virus subtype among patients presenting with mild influenza-like illness in the outpatient clinics during 2012–2013 and 2013–2014 (Figure 2A) while during 2014–2015, the predominant influenza virus subtype was A/H1N1 among these mild infection cases. Influenza B virus was usually observed during the summer months causing mild influenza-like illness throughout 2012–2015. The proportion of influenza-positive ILI cases peaked during March–April in 2012 and 2013, while in 2014 through 2015, the peak was observed during December–January.

Among severe cases hospitalized with SARI, influenza A/H1N1 virus has been the predominant circulating subtype since 2013 (Figure 2B), followed by influenza B virus. The usual season when the influenza-positive SARI cases are expected to peak is November–March. Seasonal influenza activity peaked in the 2014–2015 (Figure 2B).

Based on the 3 years of surveillance data for 2012–2014, the usual season when most of the ILI cases can be expected to be positive for influenza is from November to February (Figure 3A) with peaks expected to exceed the seasonal threshold (base line influenza activity), set at 0.15 influenza-positive samples in the cumulative month. The medians for influenza-positive ILI cases in the 12 cumulative months of the time series 2012–2014 for November to February were 0.16, 0.25, 0.26 and 0.18. Therefore, the seasonality of influenza-positive ILI cases comprises one sharp peak, usually in January, and smaller peaks can be expected starting from November.

On the basis of these 3 years of data, the seasonal pattern of influenza-associated SARI (Figure 3B) is expected to show 1 sharp peak, usually in January, and another smaller peak may be observed in April each year. During the winter months, when the circulation of influenza virus usually peaks, it is possible that such peaks exceed the alert threshold. Using the combined data for both ILI and SARI, the seasonal threshold was defined as consecutive months having a proportion of influenza-positive samples that exceeds 15%, thus influenza seasonality was observed to have typically occurred from November to early May (Kruskal–Wallis test, $P = 0.0043$)

Circulation of Respiratory Synctial Virus

Respiratory syncytial virus (RSV) was observed to have been cocirculating along with influenza virus throughout the year during 2012–2015 in patients with severe acute respiratory infection (Figure 2B). Among the SARI cases enrolled for influenza surveillance, 5% of cases were positive for RSV, highest proportion of cases were observed (22%) in infants under 1 year old (Table 1).

Discussion

We found that during 2012 to 2015, influenza virus caused a substantial proportion of disease among ILI (13%) and SARI (17%) patients in Egypt, and affected all age groups. Among the ILI patients, the age group of 5–15 years had the higher influenza positive rate while among the hospitalized patients the age groups 15 –

Although RSV is known to cause respiratory illness in young children (15), in our analysis we found that RSV was cocirculating along with the predominant influenza virus causing illness among all age-groups, particularly in infants under 1 year old. In other studies from Egypt (16,17) similar findings were observed on the circulation of RSV. These findings are comparable with a study on RSV conducted in Jordan (18).

Patients aged ≥ 15 years were 1.5 times more likely than younger patients to have influenza, and patients who were hospitalized for ≥ 3 days were 1.2 times more likely than those hospitalized for

Our data show that both influenza virus and RSV circulates throughout the year. In our settings, influenza A/H1N1pdm09, which was first detected during the 2009 pandemic, was absent in the 2010–2011 winter season, re-emerged in 2013 and then became the predominant circulating influenza virus. During the 2012–2013 and 2013–2014, influenza A (H3N2) was observed as the predominant circulating influenza virus subtype, especially during the winter months while the influenza B virus was commonly observed during the summer month throughout the 2012–2015. This pattern of influenza virus circulation differs from Thailand (11), Mongolia (14), Pakistan (12), Angola (19), Kenya (13) and other tropical regions of the southern hemisphere (20) and even the northern hemisphere, where Egypt is situated. In all these countries, influenza A/H1N1 was the predominant virus subtype cocirculating with influenza A/H3N2. The influenza seasonal pattern that we observed in Egypt mimics more closely the pattern in Morocco (21) and similar pattern was observed in the central southern hemisphere in 2014 (22), with a predominance of influenza A/H3N2 and cocirculation of influenza B virus.

Reliable data on seasonality and the alert or epidemic threshold for influenza can be used in a forecasting model to detect unusual influenza activity. Despite the year-round presence of the virus, we found that circulation in Egypt peaks during November–February and the seasonal

surge of influenza infection is expected to be observed during this period. In some tropical countries such as Thailand (11) and Pakistan (12) similar increased influenza activity was observed during the winter season. Unfortunately, we found no relevant studies on influenza in the Middle East to compare our findings with. However, data from Jordan (23) and Morocco (21) show a similar circulating pattern for the virus.

Our study has several limitations that warrant discussion. First, the data presented are from a sentinel-based surveillance system and the sentinel sites are located mainly in urban areas. They do not represent the catchment areas of the sites as the public usually consult a pharmacist when they have mild conditions; even if the illness is longer than usual, they tend to visit private clinics or hospitals and the probability of referral to a fever hospital that is an influenza sentinel surveillance site is very low. Therefore, the data presented in this paper cannot be representative or generalized for the whole of Egypt. Furthermore, we sampled only the first two ILI patients of the day, which might lead to biases to our findings as patients who live near the health facility, very ill patients or sick infants might have been preferentially enrolled in our surveillance system. We did not collect data on all ILI patients attending the outpatient clinics in the sentinel sites to ensure that the demography of our sample was representative of all ILI patients visiting the facility. Even for the sampled ILI cases, the data collected in the surveillance system did not include information about comorbid chronic conditions, pregnancy or vaccination status. People are unaware of the importance of influenza vaccination, and, although there has been no study of the prevalence of vaccination in the general population, those who are vaccinated are thought to be upper and upper-middle class people and those who are obliged to be vaccinated, such as health care workers, the military and hajj and umrah travellers. Our data on hospitalized SARI cases could have been augmented to draw meaningful inferences on more-severe clinical forms of the disease and we recognize the importance of enhancing the SARI surveillance system to enrol more hospitalized patients using accurate and consistent case definition. We also need to improve the linkage between the virological and epidemiological data for completeness of surveillance data and to be able to provide information for an early warning system. Despite these limitations, we believe that our system has provided useful information on the epidemiology of influenza in Egypt, including circulating virus types, which can prove useful in developing a prevention and control strategy.

ILI represents milder cases or early symptoms of severe cases. If exposure history was taken properly, the information could be used as a basis for ascertaining exposure during the 10 days prior to symptom onset, such as to birds (avian influenza) or a history of travel to affected countries. Better ILI surveillance could improve early detection, proper diagnosis and effective case management, which, in turn could reduce influenza-related mortality, complications and case severity. While good surveillance data for ILI is useful to determine a high influenza activity season, the data can also be used to determine severity during any influenza epidemic or pandemic. Similarly, good quality surveillance data for SARI will be useful to detect any unusual patterns of pneumonia, monitor trends of severe infection as well help in planning resource

implications during a pandemic influenza in terms of hospitalization needs, requirement for ventilation and intensive care support.

Influenza surveillance data could be used better by decision-makers in setting the epidemic threshold and the alert threshold and for timely detection of unusual events, so that better preparedness and containment strategies could be revised, including the provision of empirical antiviral therapy. Timely detection of the start of the seasonal epidemic should alert the entire health care system and thus mitigate morbidity, mortality and economic costs. The current data from this surveillance system along with studies on disease burden attributed to influenza and influenza-associated pneumonia can be used to introduce influenza vaccines in Egypt as part of prevention and control strategy. The surveillance system also needs to be maintained and enhanced given the fact that Egypt has high burden of infection from influenza A (H5N1) infection (24) and a surge of infection was observed as recently as 2014–2015. Given the pandemic potential of influenza A (H5N1) virus, and the emergence of another new influenza virus type, influenza A H9N2 (25) in, the importance of an enhanced and strengthened influenza surveillance system in the country cannot be over-emphasized.

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