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[illegible] : [illegible] 31 [illegible] 1 [illegible] - 2013 [illegible] .1856 [illegible] 1727 [illegible] 19% [illegible] .(39-48 :CI 95%) [illegible] 100000 [illegible] 44 [illegible] 4 [illegible] 2 [illegible] . (220–125 :CI 95%) [illegible] 100000 [illegible] 166 [illegible] 17.3 [illegible] .(54–6 :CI 95%) [illegible] 100000 [illegible] . (H3N2)A [illegible] .[illegible]

ABSTRACT The epidemiology, seasonality and risk factors for influenza virus infection remains poorly defined in countries such as Egypt. Between 1 January and 31 December 2013, we used surveillance data on patients hospitalized with severe acute respiratory infection in three Egyptian government hospitals in Damanhour district to estimate the incidence rate of laboratory-confirmed seasonal influenza. Samples were taken from 1727 of 1856 patients; of these, 19% were influenza virus positive. The overall incidence of influenza virus-associated SARI during the study period was estimated to be 44 cases per 100 000 person-years (95% CI: 39–48). The highest incidence of 166 cases per 100 000 person year (95% CI: 125–220) was observed in children aged 2 to 4 years. The incidence of influenza-virus associated SARI cases in pregnant women was estimated to be 17.3 cases per 100 000 person-years (95% CI: 6–54). Majority of influenza virus-associated SARI occurred in autumn and early winter, and influenza

A(H3N2) virus predominated. This was the first ever description of the epidemiology of seasonal influenza in Egypt. However, additional works are needed for greater understanding of influenza burden in Egypt.

Incidence de l'infection respiratoire aiguë sévère associée à la grippe dans le district de Damanhour en Égypte, 2013

RÉSUMÉ L'épidémiologie, la saisonnalité et les facteurs de risque liés à l'infection par le virus de la grippe demeurent mal définis dans des pays tels que l'Égypte. Entre le 1er janvier et le 31 décembre 2013, nous avons utilisé les données de la surveillance des patients hospitalisés pour une infection respiratoire aiguë sévère (IRAS) dans trois hôpitaux publics égyptiens dans le district de Damanhour afin d'estimer le taux d'incidence de la grippe saisonnière confirmée en laboratoire. Des prélèvements ont été réalisés sur 1727 des 1856 patients ; 19 % étaient positifs au virus de la grippe. L'incidence globale des IRAS associées au virus de la grippe durant la période étudiée s'élevait, selon les estimations, à 44 cas pour 100 000 personnes-années (IC 95 % : 39-48). L'incidence la plus élevée, en l'occurrence 166 cas pour 100 000 personnes-années (IC 95 % : 125-220), a été observée chez les enfants âgés de 2 à 4 ans. L'incidence des cas d'IRAS associées au virus de la grippe chez les femmes enceintes s'élevait, selon les estimations, à 17 cas pour 100 000 personnes-années (IC 95 % : 6-54). La majorité des cas d'IRAS associées au virus de la grippe sont survenus en automne et au début de l'hiver, et le virus de la grippe A(H3N2) était prédominant. Toutefois, des études complémentaires sont nécessaires pour mieux comprendre la charge de la grippe en Égypte.

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Introduction

Influenza is a vaccine-preventable disease (1) and long been regarded as an important disease in the elderly because of its high incidence, high rate of hospital admissions and mortality in individuals older than 65 years (2). Studies in the recent past have also revealed that seasonal influenza is associated with a high number of hospital admissions in young children as well (3). The epidemiology, seasonality and risk factors for seasonal influenza are well defined in most of the upper-income and temperate countries (4–6) owing to very good use of surveillance data and availability of study findings on population-based estimates of burden of influenza in these

countries. Such information has generated valuable evidence of the health effects of seasonal influenza.

In tropical regions, on the other hand, in the absence of reliable, consistent and nationally representative surveillance data on seasonal influenza, the occurrence, duration and impact of seasonal influenza on health systems remain unrecognized and influenza remains an under-appreciated public health problem in most of these countries. In temperate climates, surveillance data show that influenza has a distinct seasonality (7). Epidemics of seasonal influenza have been observed to have occurred in temperate climates mainly during the winter time with an annual attack rate going upto 5%–10% in adults and 20%–30% in children (8). In tropical regions, on the other hand, influenza may occur throughout the year (8,9) but its impact remains undetermined.

In the WHO Eastern Mediterranean Region (EMR) there is now an increasing capacity of the countries for laboratory confirmation of influenza infection as well as for collection of good quality epidemiological surveillance data on seasonal influenza. This has resulted in increased recognition of severe influenza-related illness in children and adults and improved understanding of the impact of influenza on healthcare system.

Egypt is a lower middle-income country in the EMR with tropical to temperate climate and has an estimated population of about 90 million. In 1999, the Ministry of Public Health (MoPH) of Egypt initiated sentinel-based influenza surveillance in outpatient settings. Beginning in 2006, after the emergence of avian influenza A (H5N1) virus infection in the country, the ministry of public health established hospital-based influenza surveillance with a network of 13 sentinel sites throughout the country. One of the important goals of the country’s influenza surveillance system has been to better understand the epidemiology and seasonality of influenza virus infection in the country.

Despite improvement in surveillance systems for seasonal influenza, studies measuring the burden of influenza have been sparse in Egypt. This was due to the fact that surveillance system for seasonal influenza in Egypt was sentinel-based and catchment populations of these sentinel surveillance sites, which was needed for denominator in order to calculate the incidence rate of influenza, were difficult to determine or were not available which is an inherent weakness in all sentinel-based surveillance systems.

With a view to increasing our knowledge on the epidemiology of seasonal influenza in Egypt, we

undertook this study to estimate the incidence rate of laboratory-confirmed seasonal influenza from a sentinel-based surveillance system for severe acute respiratory infection (SARI), a project managed jointly by the MoPH of Egypt and International Emerging Infections Program of the United States Centers for Disease Control and Prevention (US-CDC).

The International Emerging Infections Program (IEIP) of the United States Centers for Disease Control and Prevention (US-CDC) works with partners in host countries to build local capacity to detect and respond to emerging threats of infectious disease. A principal activity of each site has been establishment of surveillance for influenza-like illnesses. In addition, these sites conduct health care utilization surveys periodically in order to plan and implement facility-based surveillance systems and to adjust crude calculations of incidence from surveillance data for more accurate estimates of disease burden in the communities under surveillance.

The district of Damanhour, situated in Egypt’s Nile Delta Region, had an estimated population of 685 641 as per the last census held in Egypt in 2006 (10). This has been a project site of the IEIP of US-CDC and the MoPH of Egypt for conducting influenza surveillance amongst hospitalized patients since 2009 (11). Surveillance date on patients hospitalized in three government hospitals of Damanhour district with severe acute respiratory infection over a period of 12 months, from January to December 2013 were used to conduct this study.

Methods

Hospital-based surveillance for severe acute respiratory infection

In May 2009, the Ministry of Public Health of Egypt, in collaboration with International Emerging Infections Program of the US Centers for Disease Control and Prevention and the US Naval Medical Research Unit No. 3 (NAMRU-3) based in Cairo, Egypt initiated a population-based surveillance for infectious diseases including for severe acute respiratory infection (SARI) in Damanhour District. Three secondary level government hospitals in the district of Damanhour were selected for SARI surveillance on the basis of results of a healthcare utilization survey which showed that over 90% of patients hospitalized for an acute respiratory infection in Damanhour district were admitted to these public sector hospitals (10). The administrative boundaries of Damanhour district were considered the catchment area for this surveillance program, and the study population comprised of all people living within the district boundaries.

Case identification

The hospital admission logbooks of these three public sector hospitals of Damanhour district, where the current study was conducted, were reviewed to identify patients hospitalized with severe acute respiratory infection (SARI) in any age group.

Using the WHO case definition of SARI (12), patients of any age group admitted in any of these three hospitals during the period of January to December 2013 were included in the study, i.e. any patient presenting with acute respiratory illness, such as documented or measured fever ≥ 38 °C) or subjective history of fever with acute illness and one or more respiratory symptoms such as cough with the onset in the past 10 days and requiring hospitalization.

Infants aged less than 31 days were excluded from the study because the hospital physicians did not feel comfortable to take nasopharyngeal swabs from ill patients in this age group. Only patients who resided in the Damnhour district belonging to the hospital's main catchment areas, as determined by reviewing hospital logbooks, were included. Therefore, patients who were resident in a district other than Damanhour or had been enrolled previously at another hospital were excluded from this study. After consent had been obtained from the patient or a legal guardian, the study personnel interviewed the patient or guardian and reviewed hospital charts to complete questionnaires on disease history and the patients' current illness. No information was collected from patients or their families after discharge or transfer.

Laboratory testing

Nasopharyngeal and oropharyngeal specimens were collected by physicians from all patients who were included in this study. The specimens were placed in 2 mL of liquid viral transport medium and stored at 4 °C for ≤ 2 days before testing. Microbiologists at the International Emerging Infections Program laboratory in Damanhour tested all specimens with real-time reverse transcription polymerase chain reaction (rRT-PCR) assays for respiratory syncytial virus, influenza A and B viruses, adenovirus, human parainfluenza viruses 1–3 and human meta pneumovirus (13). An aliquot of each specimen was stored in liquid nitrogen and shipped weekly to the US Naval Medical Research Unit No. 3 reference laboratory in Cairo for confirmation.

Health-care utilization survey

To estimate the denominator population for our incidence calculation, we undertook a healthcare utilization survey in Damanhour district between 20 December 2011 and 18 March 2012 in order to determine the size of our sentinel hospital's catchment population as described in WHO's manual for estimating disease burden associated with seasonal influenza in general population (14) and also used in low-income settings (5,6,15)

We used a multistage cluster sampling technique for this survey and on the basis of results of a previous survey conducted in 2009 in Damanhour as part of establishing population-based

surveillance for infectious diseases in the district (11), we estimated that we would needed a sample size of 3000 households (2000 rural and 1000 urban) to estimate the proportion of patients with respiratory illness who sought care either at a hospital or another health care facility in the previous year. We used a simple random sampling technique to select the urban households. While for rural households, we applied a two-stage cluster sampling design. In the first stage, 30 clusters were selected from 57 distinct rural villages by probability proportional to size; some villages contained multiple clusters.

Within each cluster, then, 67 geographical points were randomly selected, and the closest residential structure was identified at each point. In structures with multiple residential units, a single unit was selected from a random numbers table. All household members were enrolled. In each household identified, informed consent was taken by the interviewer from the head of the household or primary caregiver and was asked who, amongst the household members, had a lower respiratory infection during the past year and where the household member had sought care- whether at any of the three sentinel hospitals or to another hospitals and whether or not the household member was admitted to any of the three sentinel hospitals with severe respiratory infection during the preceding year.

We assumed that the pattern of health care used by all age groups remained same every year. As in similar surveys conducted at other International Emerging Infections Program sites (11,16), an episode of lower respiratory infection was defined as self-reported cough and dyspnoea for ≥ 2 days or diagnosis of pneumonia by a health care worker. Participants with a history of lower respiratory infection were asked if they had sought medical care for themselves or their children for the respiratory infection, where they had received medical care and whether they had been hospitalized, defined as admission to an inpatient ward for ≥ 24 h.

Data analysis

We included all patients admitted in any of the three hospitals of Damanhour district between 1 January to 31 December 2013 with lower acute respiratory infection and meeting the WHO case definition for SARI in our analysis.

The numbers and proportions of case patients tested positive for influenza virus were calculated by age group (Less than 2 years, Between 2 to 4 years, 5 to 14 years, 15 to 49 years, 50 to 64 years and above 65 years), gender and residency status and 95% confidence intervals (CIs) were calculated for the proportion of patients hospitalized with influenza virus infection. Odds ratio (OR) and 95% confidence interval (CIs) were also calculated to estimate the risk associated with gender, residency status, demographic and other clinical characteristics such as severity of illness, presence or absence of underlying health conditions of influenza

virus-associated SARI case patients, by comparing with those of influenza virus negative SARI case patients. We assumed that similar proportions of patients who were eligible but who were not included in the study and whose nasopharyngeal and oropharyngeal specimens were not tested for influenza infection had the same proportion of influenza virus infection as patients from whom a specimen was obtained after adjusting for age stratum.

To estimate the annual incidence of influenza-virus associated SARI, we first used the monthly proportion of case patients who tested positive for influenza virus in three hospitals to impute the monthly number of case patients who would have tested positive for influenza virus if all had been tested.

In order to calculate the denominator populations, we first used the population census data of the Damanhour district for 2006, obtained from the Central Agency for Public Mobilization and Statistics of Egypt, and adjusted the census data with the estimated population growth rate of 1.6% for age-specific incidence calculations. The proportions of respondents who reported hospitalization with severe acute respiratory infection in any of these three hospitals in the catchment area and not to any other hospital during the healthcare utilization survey were then multiplied by the population census estimates to calculate the denominator population of the catchment populations of three hospitals where this study was conducted.

Finally, the annual incidence rate of influenza virus-associated SARI, adjusted for patterns of health care use, was estimated by dividing the number of influenza-virus-associated SARI patients with the estimated denominator population of the catchment area, stratified by age-groups and expressed as per 100 000 individuals in each age stratum. Odds ratio (OR) and a 95% CIs were also calculated using X2 tests where appropriate.

Results

Hospital- based influenza surveillance

From 1 January to 31 December 2013, physicians identified 6813 hospitalized patients with severe acute respiratory infection in three hospitals of Damanhour district where this study was undertaken. Of these, 1856 patients (27%) met the WHO case definition for SARI and were included in the study. A nasopharyngeal or oropharyngeal swab was collected from 1727 (93%) out of these total number of 1856 patients who met the WHO case definition for SARI. A total of 320 (19%) specimens collected from these patients of all ages were tested positive for influenza virus by rRT-PCR (Table 1). Amongst these 320 SARI patients of all ages whose samples tested positive for influenza virus, 226 were tested positive for seasonal influenza type A virus (226/320; 71%) and 94 SARI patients were tested positive for influenza type B virus (94/320; 29%).

The proportion of influenza virus-associated SARI patients was highest (Table 1) in the 5 to

Clinical characteristics of influenza-virus associated case patients

There were no significant difference in terms of characteristics of patients hospitalized with SARI patients who were tested positive compared to those who were tested negative for influenza (Table 2 and 3). However, influenza virus-associated SARI case patients who were positive for influenza were less likely to be co-infected with other respiratory virus, such as the respiratory syncytial virus (RSV) and human parainfluenza viruses (Table 3) when compared to those who did not test positive for influenza (P

Similar proportions of influenza virus-positive and influenza virus-negative SARI cases were found amongst pregnant women (19% vs 21%, P = 0.83) or those who had an underlying condition (17% vs 19%, P = 0.53). No deaths due to influenza virus occurred among SARI patients during the period of study.

Survey findings

From December 2011 to March 2012, field workers interviewed participants from 2938 households and obtained information on healthcare utilization for 27 255 household members (mean number of members per household: 9.2) during the survey. This includes 1931 rural and 1017 urban households. Overall, 0.7% household members reported having developed lower respiratory tract infection that started with fever and cough or a sore throat during the year preceding the interview. Of these people, 97.6% respondents sought medical care and 13.0% were hospitalized.

Among those who reported having been hospitalized due to lower respiratory tract infection, 98% were admitted to one of the three sentinel hospitals where the study was undertaken. Additionally, 39% of those who were not hospitalized also sought medical care at one of these three hospitals. During the survey, it was revealed that a higher percentage of children aged less than 5 years were admitted in any of the three sentinel hospitals with lower respiratory tract infection than the people aged equal or more than 5 years.

Influenza incidence

Table 4 summarizes the data used to estimate the incidence of influenza-virus associated SARI case patients reported from three hospitals in Damanhour district in Egypt during 2013. The overall incidence of influenza virus-associated SARI during the study period was estimated

to be 44 cases per 100 000 person-years (95% CI: 39–48). The highest incidence was observed in children aged 2 to 4 years (166 cases per 100 000 person year; 95% CI: 125–220). The incidence of influenza-virus associated SARI cases in pregnant women was estimated to be 17.3 cases per 100 000 person years (CI: 6–54).

Influenza seasonality

Most cases of influenza in SARI patients occurred in autumn and early winter (Figure 1 and 2) when the influenza virus positivity rate amongst SARI patients ranged from 20 to 38%. However, transmission of influenza viruses was seen throughout the year, with a decrease in influenza activity observed during the summer period (Figure-3). In consistency with influenza peak activities, the incidence rate of influenza per 100 000 person years was also observed to have increased during the autumn and winter months (Figure-4).

Discussion

We present the first ever description of the epidemiology of seasonal influenza in Egypt. We estimated the incidence rate of laboratory-confirmed seasonal influenza using the sentinel surveillance data on patients hospitalized with severe acute respiratory infection in a district of Egypt over a period of one year.

We estimated that the incidence rate of influenza virus-associated SARI in Damanhour district was 44 cases per 100 000 person-years (95% CI: 39–48) in 2013 with the highest incidence of 166 cases per 100 000 person years (95% CI: 125–220) in children between the age group of 2-4 years. We also estimated the incidence rate of influenza-associated SARI in pregnant women to be 17 cases per 100 000 person-years (95% CI: 6–54) during the period of study while we did not find any difference in estimated incidence rate of influenza-associated SARI cases between males and females. For our current study, we collected demographic, epidemiological and clinical data on patients hospitalized with severe acute respiratory infection in three government hospitals of Damanhour district in Egypt over a period from January to December 2013. We used the healthcare utilization survey (HUS) data to calculate the catchment populations of these three sentinel hospitals in order to estimate the incidence rate of influenza virus-associated SARI.

In the paucity of regionally representative data on incidence estimates for influenza-associated SARI in the Eastern Mediterranean Region, particularly in the countries of the Middle East, it is difficult to ascertain and compare the rate estimated in our study with those estimated in any other country in the Region. However, in Oman, the annual incidence rate across all age groups varied from 0.5 to 15.4 cases per 100 000 person years (4) which is lower than what we found in our study. To our knowledge, there is no other published information on incidence of

influenza virus- associated SARI from the WHO Eastern Mediterranean Region to which we could compare our rates. We found higher incidence rates of influenza virus associated SARI cases in children between 2 to 4 years compared to other age groups but we did not calculate to see if this difference was statistically significant.

The estimated incidence rate of influenza-virus associated SARI cases in children requiring hospitalization in Damanhour district which we found out in our study was lower than what was reported in some other low-income and lower-middle-income countries including Guatemala, Kenya, El Salvador and the Philippines (6,16,17). This could be due to the fact that our incidence estimation is based on data from one year and from three hospitals only while in all these countries, data were collected over a period of three to five years and this might have resulted in underestimation of our calculated rate.

In our study, overall, 19% of SARI cases of all age groups were influenza positive. Although the influenza positivity among SARI cases was reported to be 8% in Oman, (4) and 9% in Jordan (18), both in the Eastern Mediterranean Region of WHO, the influenza positivity among SARI cases in Asia and Africa found in other studies (5,9,17,19–21) ranged between 8–11%. The reasons why we found a higher percentage of influenza positivity amongst SARI cases could be attributed to the fact that we sampled 93% of all SARI cases that met the WHO case definition for SARI while in all those countries where a low influenza positivity rate was detected amongst SARI cases, not all patients were sampled systematically and different sampling techniques were applied to collect either the nasopharyngeal or oropharyngeal swab.

Majority of influenza virus-associated SARI cases (70%) identified in Damanhour district in the year 2013 were attributed to influenza A virus and overall, 54% of influenza virus-associated SARI cases were attributed to influenza A (H3N2) virus. This was similar to what has been observed in Oman (4) but different than Jordan (18) if we compare our findings from one year with those in Jordan conducted over a four year period. As our data is only from one year while the data on influenza-virus positivity in all these countries are over a period of 3 to 5 years and since we know that the pre-dominant patterns of seasonal influenza virus keeps on changing, there is no surprise that while we found the influenza A (H3N2) virus to be predominantly circulating in 2013 in our study, in all these countries, the iinfluenza A/H1N1 was the predominant virus subtype co-circulating with influenza A/H3N2. However, what we noticed that the influenza seasonal pattern that we observed in Egypt mimic more closely with Tunisia and Morocco (22)

In our study, we found out that the percentage of influenza-positivitty peaked during the autumn and winter season in Egypt (between week no 37 and 50) when the influenza positivity rate

amongst SARI patients reached from 20 to 38%. Accordingly, most of the influenza-virus associated SARI cases occurred during the autumn and early winter. This pattern is similar to Jordan where the proportion of in uenza-positive cases peaked during November–January (14–42%) over a four year period from 2008 to 2014 except during the pandemic influenza of 2009 (18). However, owing to the fact that we collected data for only one year and from only one district in Egypt, this information may not suffice to determine influenza seasonality in the country.

Another finding that of importance was that transmission of influenza viruses was seen throughout the year, with a decrease in summer. This pattern of seasonality is comparable to that of other countries in our Region and in the same latitude such as Oman (4)

This study has several limitations. First, although samples were collected from all SARI cases meeting the WHO case definition, selection biases in identifying SARI case patients and subsequent sampling by surveillance physicians cannot be ruled out. We excluded infants aged

Second, our estimates were based on data from healthcare utilization survey which has several limitations as reported elsewhere (5,11,24). For example, as reported by M. Deutscher et al (24), the specificity of the definition of self-reported lower respiratory infection is unknown, and the survey may have included milder respiratory illnesses that were not consistent with SARI and this might have led to an overestimate of the number of SARI cases. Furthermore, recall bias is likely in such survey since recalling illness in the 12 months preceding the survey may be challenging, especially if the illness was mild. This would lead to biases and eventually might result to an underestimate of the number of people with SARI who did not seek care at a hospital.

It is also plausible that healthcare seeking behaviour documented in the survey differed from those observed during the period the study was undertaken. M. Deutcher et al (24) also reported that such healthcare utilization survey might also be influenced by whether the respondents considered a particular response to be that expected by an interviewer working with the Ministry of Health. For example, the respondents might have been more likely to reply that they sought care at a clinic or hospital and would not seek care from a traditional healer although in reality they would or would not.

Third, the incidence rate of influenza virus associated SARI patients was calculated in our study using sentinel surveillance date from three hospitals of a district and over a period of 12 months only. This might have led to an under or over estimate or a very conservative estimate of the

incidence of influenza virus-associated SARI cases. Therefore, the data presented in this paper needs to be interpreted with caution while generalizing it for whole of Egypt owing to this limitation.

Despite these limitations, our study findings provide a preliminary picture of epidemiology and burden of seasonal influenza in Egypt from a sentinel-based surveillance data adjusted for healthcare utilization patterns. Additional work is certainly needed for better estimates of the influenza burden in the country covering more hospitals and using population-based surveillance-data for more than one calendar year in order to better understand the seasonality including to identify which groups are at greater risk and are disproportionately affected.

The current study could be a good beginning leading to more comprehensive studies in in the future for improved understanding of the epidemiology and seasonality of influenza in Egypt using data that are more representative of the country.

Estimating the burden of influenza is useful for determining the risk of morbidity and mortality in different segments of the population, selecting high priority groups for targeting vaccination against sessional influenza and also for better planning for seasonal epidemics and future pandemics. As influenza is a vaccine preventable disease with high degree of mortality and morbidity in certain age groups (7,25,26) a large number of deaths and hospitalizations attributed to seasonal influenza can be averted if current and future study findings on the burden of influenza in general population is used for evidence-informed prevention and control strategy for influenza in Egypt. It is hoped that the current study will lead to improvement of influenza surveillance system in the country and generate more meaningful data to drive policies and programmes for reducing the burden of seasonal influenza in the country.

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