Impact of Influenza Virus-associated Severe Acute Respiratory Infections in Three Districts in 2018 at Gharbia Governorate Egypt

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Impact of Influenza Virus-associated Severe Acute Respiratory Infections in three districts in Gharbia governorate, Egypt, 2018

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بِسْمِ اللَّـهِ الرَّحْمَـٰنِ الرَّحِيمِ

والصلاة والسلام على المبعوث رحمة للعالمين ﷺ

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LIST OF ACRONYMS

MoHP	Ministry of Health and Population
DES	Department of Epidemiology and Surveillance
FETP	Field Epidemiology Training Program
WHO	World Health Organization
SARI	Severe Acute Respiratory Infection
HAS	Hospital Admission Survey
HUS	Health Utilization Survey
ILI	Influenza-Like Illness
ARI	Acute Respiratory Infections
RT-PCR	Real-Time Polymerase Chain Reaction
CI	Confidence Interval
SARS-CoV-1	Severe Acute Respiratory Syndrome Coronavirus 1 (SARS)
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2 (COVID-19)
MERS-CoV	Middle East Respiratory Syndrome Coronavirus
RSV	Respiratory Syncytial Virus
ALRI	Acute Lower Respiratory Infections
DHS	Demographic and Health Survey
CPHL	Central Public Health Laboratories
NEDSS	National Electronic Disease Surveillance System

ABSTRACT

Impact of Influenza Virus-associated Severe Acute Respiratory Infections in Three Districts in 2018 at Gharbia Governorate Egypt

Background

Influenza remains a major contributor to substantial global morbidity and mortality. Reliable influenza burden estimates are needed for a better understanding of the disease impact in vulnerable groups. There are limited data on disease burden in Egypt. Although hospital-based severe acute respiratory illness (SARI) sentinel surveillance was established in El-Mahala Fever hospital at Gharbia governorate in 2009, determining the catchment population for the hospital was one of the biggest challenges.

Objective

This study first aims to determine the catchment population for El-Mahala Fever hospital and calculate the incidence of seasonal influenza infections. Second, the study seeks to estimate the percentage of hospitalizations associated with SARI in public and private sectors in the three districts of Gharbia governorate.

Methods

This study was done by using the World Health Organization (WHO) manual to estimate the incidence of influenza-associated SARI in the sentinel surveillance site of Gharbia governorate. Hospital database for 2018 was screened for SARI patients to obtain demographic, lab testing, and outcome data. Three districts that reported the most SARI cases were identified. Incidence was calculated using influenza-positive SARI cases as the numerator and catchment population as denominator, as defined through the hospital admission survey (HAS). Catchment population was calculated as the proportion of pneumonia cases at El-Mahala fever hospital among all pneumonia admissions in all hospitals in the three districts multiplied by the total population.

Results

The catchment population of El-Mahala Fever hospital was estimated at 10.6% (190,096) persons (95% CI, 10.56-10.65) of the total population residing in the three districts of Gharbia governorate. Meanwhile, hospitalizations of SARI cases in the private sector was estimated at 15.28% (134) cases (95% CI, 12.96-17.83). At El-Mahala fever hospital, 180 SARI cases were identified; their median age was 23 [IQR: 2-53], 45% were males. Of the total SARI cases, 33.3% (60) were confirmed as influenza; their median age was 21 [IQR: 3-51], 42% were males. Influenza A (H3N2) virus predominated, representing 55.0% of patients, followed by A(H1N1) 26.7% and Flu-B virus 18.3%. Influenza prevailed in winters and spring; no deaths from influenza were reported. The overall incidence of influenza-associated SARI was 32/100,000 (95% CI, 25-41). The rate was significantly higher in very young (<2 years) and old (>65 years) patients (282 and 215/100,000 population respectively, $p<0.001$ for both). Incidence was insignificantly higher in females and residents of urban areas than corresponding groups (32 vs 30/100,000 and 34 vs 31/100,000 population, $p=0.8$ and 0.7, respectively).

Conclusions

The methods detailed in the WHO Manual for estimating disease burden associated with seasonal influenza were successfully operationalized in the three districts of Gharbia governorate; it can be used in other districts to estimate catchment population and incidence of influenza-associated SARI. Influenza viruses are associated with a substantial burden of severe illness requiring hospitalization, especially among extreme age groups. In order to estimate influenza burden in other risk groups than those based on age, it is imperative to conduct further research.

Keywords: Influenza; Incidence; Sentinel Surveillance; Respiratory Infections; Egypt

CHAPTER 1: INTRODUCTION

1.1 Background

Viruses that cause seasonal influenza circulate around the world, causing severe respiratory infections, resulting in about 3 to 5 million cases of severe illness and 290,000 to 650,000 deaths each year (WHO, 2018).

There are four types of influenza viruses: A, B, C, and D. Types A and B are normally considered as sources of symptomatic human infection, with Type A having caused human influenza pandemics throughout history. The last influenza pandemic was caused by Flu A (H1N1) in 2009, also known as swine flu (Lee, 2019). Other influenza pandemics include Russian flu in 1977, which was caused by the human H1N1 virus, Hong Kong flu 1968, caused by Influenza A (H3N2), Asian influenza in 1957, caused by Influenza A (H2N2), and Spanish flu in 1919, caused by Influenza A (H1N1) (Kilbourne, 2006).

The population of Egypt is estimated at about 100 million. It is one of the lower middle-income countries of the Eastern Mediterranean Region (EMR) with a tropical to temperate climate. In 1999, Egypt's Ministry of Health and Population (MoHP) implemented sentinel-based influenza surveillance. Following the outbreak of avian influenza, A (H5N1) in 2006, a network of 13 Severe Acute Respiratory Infection (SARI) sentinel sites was established across the country by the MoHP to monitor influenza in hospitals, and to better understand the epidemiology and seasonality of influenza virus infection in the country (MoHP, 2019).

Among the 13 SARI sentinel surveillance sites, El-Mahala Fever hospital targets the Gharbia governorate, and due to lack of information regarding hospital catchment populations, estimates for the incidence rates of seasonal influenza are not available. Countries use various methods to calculate incidence rates, but it is not always possible due to the difficulty of determining the appropriate population count. Historically, as far as our knowledge goes, only one study has been conducted to determine appropriate population denominators through healthcare utilization surveys (HUS) by estimating the catchment area for a hospital through an understanding of the population's healthcare-seeking behavior (Refaey et al., 2016).

According to the WHO's Manual for Estimating Disease Burden Associated with Seasonal Influenza, HAS are an alternative method of measuring disease burden (WHO, 2015). This paper presents an application of HAS methods in three health districts in the Gharbia governorate to estimate the population in the catchment area and to calculate the incidence of influenza-associated SARI at El- Mahalla Fever Hospital.

There are three main players in the Egyptian healthcare system: public, parastatal, and private. The availability of healthcare data for the private sector in Egypt is scant and there are almost no estimates for communicable disease hospitalization proportions. Although 63% of hospitals in Egypt are private, it includes only 28% of hospital bed numbers, with an average of 31 beds per private hospital compared to 96 and 209 beds at governmental and parastatal hospitals, respectively (Colliers, 2021). Through HAS, this study aimed to estimate the proportion of pneumonia hospitalization in the private and government sectors across the three health districts of Gharbia governorate.

1.2 Significance of the study

Influenza is a worldwide phenomenon and causes considerable morbidity and mortality with pandemic, epidemic, or seasonal patterns. Epidemics may become acquire a pandemic status depending on how the viruses have mutated, as was the case in 2009. Baseline data describing the burden of seasonal influenza is needed. Data describing seasonal influenza burden are very scarce in Egypt. As a result of this report, we were able to estimate incidence rate for a specific SARI sentinel site in Egypt during the year 2018.

1.3 Objectives

1.3.1 General Objective

To estimate the burden of influenza virus associated with SARI at three health districts of Gharbia governorate in 2018, to better understand its impact on vulnerable groups and enable policy makers to make informed evidence-based decisions when allocating scarce resources and planning intervention strategies to curtail the burden of the seasonal influenza disease.

1.3.2 Specific Objectives:

- To determine the catchment population of the SARI sentinel surveillance site surrounding El-Mahala Fever hospital and calculate the incidence of seasonal influenza infections.
- To estimate the percentage of hospitalizations associated with SARI in public and private sectors for the three districts of Gharbia governorate.

1.4 Research Questions

- What is the impact of seasonal influenza on the three health districts of Gharbia governorate?
- What is the proportion of SARI hospitalizations in public and private sectors for the three districts of Gharbia governorate?

1.5 Hypothesis

This study hypothesized that: seasonal influenza causes a substantial impact and affects the study population, especially those in extreme age groups.

1.6 Operational Definitions

1.6.1 Seasonal Influenza

It is an acute respiratory infection caused by influenza viruses Types A, B, C, and D. Globally, Types A and B cause seasonal influenza epidemics, triggering a wide range of illnesses, which sometimes require hospitalization and may result in death (WHO, 2018).

It is most common for people to recover from fever and other symptoms without any medical intervention within a week. However, influenza can cause a variety of serious illnesses, and even lead to death in some cases, particularly among high-risk groups including the extreme ages, pregnant women, health workers, and those with serious medical conditions (WHO, 2018).

1.6.2 Pneumonia

It is a type of acute respiratory infection that affects the lungs. When a healthy person breathes, small sacs inside the lungs called alveoli fill with air. When the person has pneumonia infection, the alveoli are filled with pus and fluid, which limits oxygen intake and makes breathing difficult and painful (WHO, 2021).

1.6.3 Severe Acute Respiratory Infection (SARI)

It is an acute respiratory infection with a history of fever or measured fever >38°C and cough with onset within the last 10 days, requiring hospitalization (WHO, 2015).

1.6.4 Burden of the disease

It is the morbidity and mortality associated with the disease (WHO, 2015).

1.6.5 Incidence of Influenza

It is the rate of new influenza cases in a specific period of time divided by people at risk in the same period (WHO, 2015).

1.6.6 Sentinel Surveillance

Type of indicator-based surveillance that enhances certain surveillance sites with suitable resources to better detect a disease in a specific area or population during a certain period of time (MoHP, 2018).

1.6.7 Catchment Area

It is the area located around a defined health unit and most of the outpatient visits or hospitalization to that health unit come from this area (usually more than 80%) (WHO, 2015).

1.6.8 Catchment Population

It is the proportion of the population that is defined for a specific health unit of the total population from the catchment area (WHO, 2015).

1.6.9 Hospital Admission Survey

It is a type of health survey that depends on case admissions/visits to a certain number of hospitals (WHO, 2015).

CHAPTER 2: LITERATURE REVIEW

2.1 Influenza viruses

Acute respiratory infection, which includes influenza, is a serious public health problem that causes severe illness and even death in higher-risk populations. The loss of workforce productivity and strain on health services are the other devastating effects of an influenza pandemic. Two novel Influenza A viruses have emerged in the 21st century; Influenza A/H5N1 in 2004 and Influenza A (H1N1) pdm in 2009, and three other coronaviruses: SARS-CoV-1 in 2003, MERS-CoV in 2012, and SARS-CoV-2 in 2019. These viruses have demonstrated our collective vulnerability to pandemic transmission of respiratory viruses (Guarner, 2020).

In addition to Type A, there are Types B, C, and D seasonal influenza viruses. Seasonal epidemics are caused by Types A and B viruses, and the only influenza virus that has caused pandemics are Type A. Infections caused by Types B and C viruses are typically mild, and cannot enter the pandemic stage. There are no reports of Type D viruses infecting or causing illness in humans, as it primarily affects cattle (WHO, 2018).

An individual suffering from seasonal influenza might experience fever, cough, headache, muscle or joint pains, as well as runny nose and sore throat. It is most common for people to recover from fever and other symptoms without any medical intervention within a week. However, influenza can cause a variety of serious illnesses, and even death in some cases, particularly among high-risk groups, such as the extreme ages, pregnant women, health workers, and those with serious medical conditions (WHO, 2018).

In crowded areas, such as schools and nursing homes, seasonal influenza tends to spread rapidly. As a result of coughing and sneezing, virus-containing droplets can diffuse into the air up to one meter from the infected person. Hands contaminated with influenza viruses can also spread the virus. The seasonal outbreak of influenza occurs mainly in temperate climates during winter, although it may occur throughout the year in tropical regions (WHO, 2018).

2.2 Egypt's influenza surveillance system

There are more than 100 million people in Egypt, making it the most populous country in the Arab world. The median age of the population is 24.6 and 51.6% are males (Colliers, 2021). Egypt has 27 governorates spread over a million kilometers. The Gharbia governorate is located in the northern region, and has a population of more than 5 million (Jan 2018). The largest city in Gharbia is El Mahalla El Kubra.

Healthcare providers in Egypt cater to diverse sectors, ranging from public to private. The Ministry of Health and population (MoHP) regulates the overall healthcare system. In 2019, the nation had around 1,800 hospitals and more than 125,000 beds (Colliers, 2021).

Influenza surveillance activity commenced in 1999 in Egypt, and an influenza-like illness (ILI) sentinel surveillance system was first established at eight sentinel sites. In 2007, SARI sentinel surveillance was launched in eight sentinel sites. In 2016, four pneumonia sentinel sites were founded and subsequently merged with SARI sentinel sites in 2018 (MoHP, 2019) (see Figure 1).

The MoHP has worked to scale up and support influenza surveillance because Egypt has experienced seasonal and avian influenza epidemics repeatedly. ILI, SARI, and ARI surveillance are under the Influenza & Acute Respiratory Illness Unit that reports to the Department of Epidemiology and Surveillance (DES) and the Central Directorate for Preventive Affairs (MoHP, 2019) (Fig. 2).

2.2.1 Components of Egypt's National Acute Respiratory Surveillance System:

1. Nationwide Acute Respiratory Illness.

2. Influenza-Like Illness sentinel surveillance.

3. Sentinel Surveillance for Severe Acute Respiratory Illness and pneumonia.

4. Avian influenza and MERS-CoV surveillance.

5. Hospital-based ARI Syndromic surveillance.

6. Yearly Hajj surveys.

7. Event-based surveillance.

8. Mortality database (MoHP, 2019).

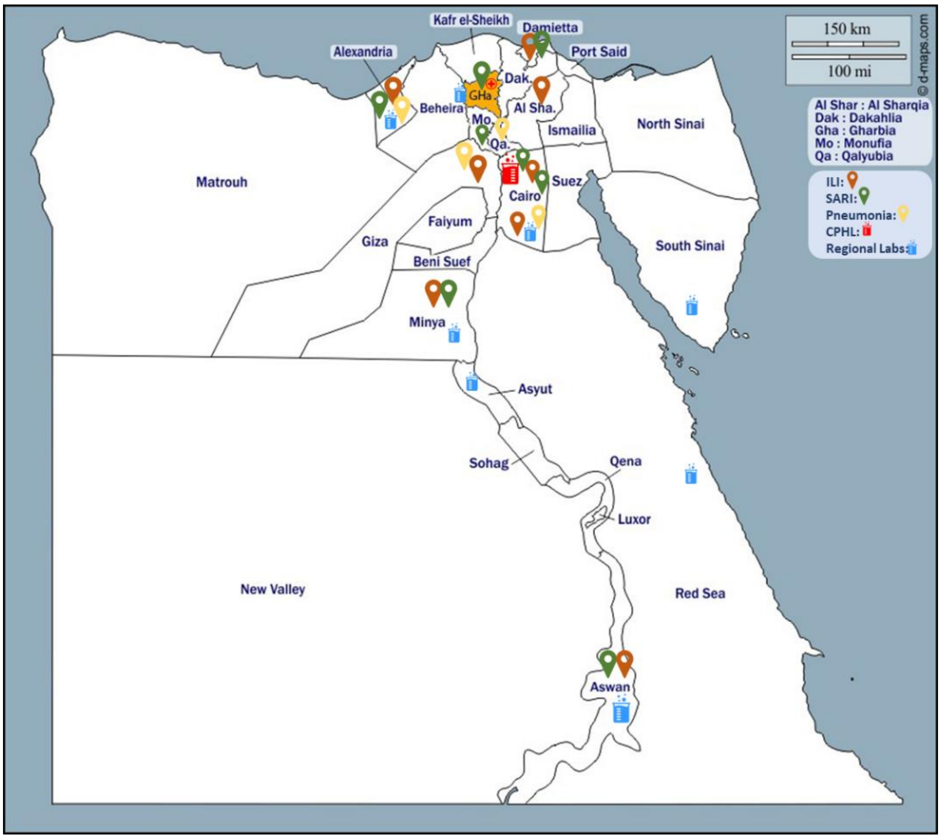

Figure 1 Distribution of SARI, ILI, and pneumonia sentinel sites and regional laboratories across Egypt

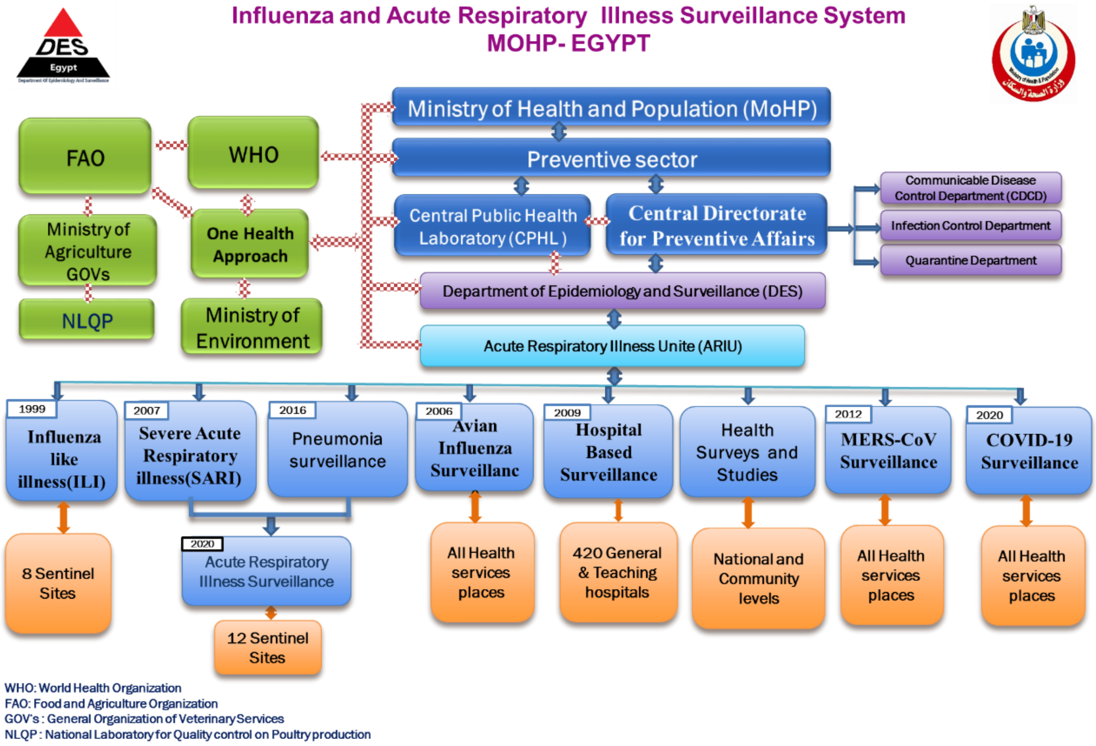

Figure 2 Influenza surveillance program in Egypt

2.3 Sentinel Surveillance for Severe Acute Respiratory Illness:

2.3.1 Surveillance protocol:

Surveillance was established in Egypt in November 2007 in eight governmental and specialized hospitals, selected based on their geographical location that admitted patients from all age groups and socio-economic standards. Most of these hospitals are located in the Delta region or Lower Egypt where population density is high. The advantage of having Fever and Chest hospitals as sentinel sites is that all private and general hospitals tend to refer suspected SARI cases to specialized fever or chest hospitals. Surveillance teams consist of a surveillance focal point, laboratory focal point, nurses, data entry technicians, and other supporting staff. To improve timeliness, reporting was upgraded to a web-based online application starting 2016 (MoHP, 2019).

2.3.2 Surveillance sites:

Table 1 First 8 SARI Sentinel Surveillance Sites in Egypt

N	Governorate	Hospital
1	Cairo	Abbassia Fever Hospital
2		Abbassia Chest Hospital
3	Alexandria	Alexandria Fever Hospital
4	Gharbia	El-Mahalla Fever Hospital
5	Menofiya	Shebin Fever Hospital
6	Damiatta	Damiatta Chest Hospital
7	El-Meniya	El-Meniya Fever Hospital
8	Asawan	Asawan Fever Hospital

All hospitalized patients presenting with acute respiratory symptoms at each sentinel hospital are enrolled according to the WHO SARI standard case definition. The patient's medical history is documented and filled. Throat and nasopharyngeal swabs are collected from all enrolled cases after consent. Patients' information is recorded in a logbook and followed up to record outcome and discharge diagnosis. SARI patients transferred from medical wards to ICUs within the hospital are traced to assess their outcome (MoHP, 2019).

Data are recorded on standardized data collection forms, revised by the surveillance focal person, and entered online through data entry at each sentinel site. The CPHL focal person and/or regional laboratory focal person is responsible for updating influenza test results on a weekly basis to the online web-based application.

Each data entry technician is assigned a username and password on the web-based application. Data are uploaded to the DES server and should be available for influenza surveillance officers, epidemiologists, and the data management team for analysis and report generation. Data are checked for accuracy, and the database is backed up after each data entry session.

Biweekly reports are prepared and shared with Egypt's MoHP decision makers on a regular basis. More extensive data analysis and reports are carried out by the DES team on a quarterly basis. Original data collection forms are stored in a locked cabinet at the MoHP office in Cairo and carbon copies are maintained at each sentinel site (MoHP, 2019).

2.4 WHO manual for estimating disease burden associated with influenza:

There is limited information regarding the burden of influenza-associated diseases in low- and middle-income countries. There are various ways to measure disease burden, but most fall into two categories: medical burden (morbidity and mortality) and economic burden. The WHO has released a manual to estimate the medical burden of influenza, which is a useful tool that focuses on low- and middle-income countries. It is targeted at epidemiologists and data analysts responsible for analyzing and interpreting influenza surveillance site data (WHO, 2015).

The manual describes methods to identify and select different data sources, estimate influenza disease burden (through use; ILI sentinel surveillance data, SARI sentinel surveillance data, and multiple sentinel sites data), and burden estimation for specific risk groups. As a result of these estimates, healthcare planners can make informed decisions and plan accordingly to manage limited resources, prioritize health research investments and healthcare interventions for donor agencies and national governments, and establish a baseline for comparing influenza outbreak data from yearly events to extraordinary events such as pandemics (WHO, 2015).

2.5 Burden of seasonal influenza

Globally, influenza viruses can cause substantial mortality during winter months, affecting up to 20% of the population, depending on the circulating viruses (WHO, Last updated). Seasonal influenza and respiratory syncytial virus (RSV) are the main contributors to Acute Lower Respiratory Infections (ALRI). Among children with ALRI, influenza is the second most commonly identified pathogen (Nair et al., 2011). In the United States during 2018, Rolfes and colleagues estimated that, the number of seasonal influenza cases ranged from 9 million to 35.6 million and hospitalizations ranged from 140,000 to 710,000 (Rolfes et al., 2018), with the average economic burden reaching $11.2 billion ($6.3–$25.3 billion) (Putri et al., 2018).

At present, Egypt's influenza surveillance network is relatively robust, with more sentinel sites located at governmental hospitals and regional laboratories across Upper and Lower Egypt. However, burden estimates are very rare due to the inherent weakness of determining the catchment population for these sentinel sites (Refaey et al., 2016).

During the 2014 Demographic and Health Survey (DHS) in Egypt, the prevalence of ARI among children aged below five in the two weeks before the survey was estimated at 13.6%. Furthermore, 68% of children with ARI requested medical consultations, of which 62% requested consultations from the private sector, and 92.4% of children under five were given various drugs to treat the illness, indicating the burden of mild influenza among children on the health system, especially the private sector (Health et al., 2015).

Refaey and Hassan estimated the incidence of influenza-associated hospitalizations at 44 per 100,000 person–years (95% CI: 39–48) in 3013, with the highest incidence in the 2–4 age group (166 cases per 100,000 person–years; 95% CI:125–220), while the incidence of influenza in pregnant women was 17.3 cases per 100,000 person–years (95% CI: 6–54) (Refaey et al., 2016).

Seasonal influenza vaccines are considered the main pharmaceutical tool to reduce disease burden as defined by the WHO. Five groups are considered particularly vulnerable to seasonal influenza, either because of their greater exposure risk or higher vulnerability to severe illness; healthcare staffs, pregnant women, people with chronic diseases, extreme age groups, i.e., over 65 and below 5 (WHO, 2020).

Data for vaccine coverage in Egypt is limited, especially in the high-risk groups. During the 2009 influenza pandemic, the total number of consumed influenza vaccine doses were 1.37 million, which was less than 2% of the total population number (Ministry of Health and Population, 2018). It was estimated at 1.4 million doses in 2017, which was also considered very low (Al Awaidi et al., 2018).

In a cross-sectional study that included a self-administered structured questionnaire, Sally Hakim and colleagues estimated the percentage of vaccine uptake at 30% among 3,534 healthcare workers in 11 governorates in 2018 (Hakim et al., 2021).

To better understand the impact of influenza in vulnerable communities or subpopulations, reliable disease burden estimates are needed, particularly from low- and middle-income countries. In Zambia, through a prospective SARI hospital-based surveillance, children below 5 are considered to have the highest burden at 82.7% of respiratory admissions due to SARI, while the influenza detection rate was 5.5% of the total tested cases (Theo et al., 2018). Both children and the elderly are the most vulnerable to seasonal influenza infection, as described in another prospective study in Oman, which estimated the incidence of seasonal influenza associated SARI at 0.5 to 15.4 cases per 100,000 population (Al-Awaidy et al., 2015).

HAS and Health Utilization Surveys (HUS) are easy methods for estimating disease burden in low- and middle-income countries, considering the scarcity of data related to health and population (see Table 2). Through HAS, Stewart and Ly estimated the burden of seasonal influenza in 2015 in a Cambodian province at 13.5 per 100,000 persons and the highest incidence of the disease was among individuals aged >65 (Stewart et al., 2018). Meanwhile, Indonesian researchers estimated the burden of seasonal influenza in three provinces at 13–19 per 100,000 population in the 2013–2016 seasons of influenza, and the highest incidence was among children aged below 4 (Susilarini et al., 2018).

Based on the HUS methodology, Ghanaian colleagues estimated the incidence of influenza-associated SARI cases at 30 per 100,000 population (95% CI: 13 to 84), with the highest incidence reported among children below 4, at 135 per 100,000 population (95% CI: 120– 152) (Ntiri et al., 2016). Dawa and Chaves estimated that the incidence of seasonal influenza in ILI cases was four times the SARI cases, which was 21 (95% CI 19–3) per 100,000 persons and the incidence of influenza-associated SARI was the highest in the age group <2 years (147 (95% CI of 134–160) per 100,000 persons), which elucidate the big burden of seasonal influenza in the whole population (Dawa et al., 2018).

Table 2. Burden and incidence rates for seasonal influenza (evidence table)

Author	Title	Data	Period	Population	Results
(Stewart et al., 2018)	Using a hospital admission survey to estimate the burden of influenza-associated severe acute respiratory infections in a province in Cambodia—methods used and lessons learned	Hospital Admission Survey	2015	487,489	13.5/100,000 persons for the catchment area of Svay Rieng Hospital
(Refaey et al., 2016)	Incidence of influenza virus-associated severe acute respiratory infection in Damanhour district, Egypt	Health Utilization S urvey	2013	685,641	44 cases per 100,000 person–years (95% CI: 39–48)
(Al-Awaidy et al., 201 5)	Burden of influenza-associated hospitalizations in Oman	Descriptive prospecti ve study	2008–20 13	2.13 Million	0.5 to 15.4 cases of influenza-associated SARI per 100,000 population

Author	Title	Data	Period	Population	Results
(Dawa et al., 2018)	National burden of hospitalized and non-hospitalized influenza-associated severe acute respiratory illness in Kenya	Health Utilization Survey	2012–2014	80,000 inhabitants	21 (95% CI 19-23) per 100,000 persons
(Ntiri et al., 2016)	Incidence of medically-attended influenza among residents of Shai-Osudoku and Ningo-Prampram Districts, Ghana	Health Utilization Survey	2013–2015	121,943	30 per 100,000 persons (95% CI: 13-84)
(Susilarini et al., 2018)	Estimated incidence of influenza-associated severe acute respiratory infections in Indonesia	Hospital Admission Survey	2013–2016	407,632	13 to 19 per 100,000 population.

2.6 Conceptual Framework:

This study aimed to estimate the burden of seasonal influenza infections associated with SARI at a sentinel surveillance site in Gharbia governorate using the HAS, as described by the WHO manual for estimating disease burden associated with seasonal influenza (WHO, 2015). The study used data on the catchment population (denominator) for El-Mahalla Fever Hospital and the extracted data of influenza-associated SARI (numerator) from the national SARI sentinel surveillance at the National Electronic Disease Surveillance System (NEDSS) database of Egypt to calculate the incidence of SARI in three districts of Gharbia governorate in 2018 (see Figure 3).

It is considered challenging to estimate the whole burden of influenza, since it depends on several changeable factors like number of ILI cases and influenza-related deaths with other comorbidities (WHO, 2020). The severity of influenza is linked mainly to the virus type and new variants of subtypes as it changed periodically within many hosts (humans, animals, and birds) and the severity of the disease ranged from remaining asymptomatic to displaying mild-to-severe symptoms, with variants like avian influenza flu A (H5N1) causing case fatality up to 60% (Adams and Sandrock, 2010).

There are three common seasonal influenza viruses: Flu A (H1N1), Flu A (H3N2), and Flu B (B/Yamagata or B/Victoria lineage). Only influenza Type A viruses are known to have caused pandemics (WHO, 2018). According to the WHO, there are five groups of people who are particularly vulnerable to seasonal influenza, triggered by the risk of exposure or the risk of developing severe diseases: people with chronic diseases, pregnant women, health workers, and individuals aged over 65 or below 5 (WHO, 2020).

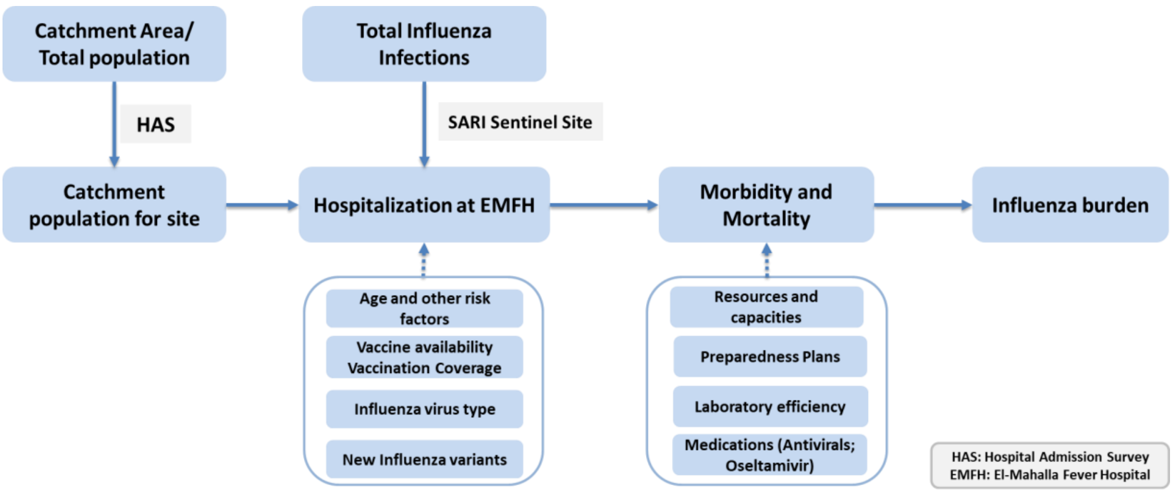

Figure 3 Conceptual Framework, Impact of Seasonal Influenza disease

All factors could not be assessed in this study due to the unavailability of data, but we addressed them in our conceptual framework to formulate a clear overview to most variables that may be related to influenza burden. These variables were categorized into two groups, one affecting the severity of the disease and hospitalizations like age and other risk factors, vaccine availability, influenza virus type, new variants of influenza; and the second related to the health system itself and the availability of resources like human resources and national preparedness plan, vaccination coverage to all vulnerable groups and access to antivirals and how they are used (see Figure 3). It is imperative to consider all the variables that could have an impact on the overall burden of seasonal influenza.

CHAPTER 3: METHODS

3.1 Research design:

This study focused on a cross-sectional design using the HAS, to estimate the catchment population of El-Mahalla Fever Hospital in 2018. The study also used secondary data of influenza-associated SARI from the same hospital.

3.2 Study population:

In this study, the catchment area consists of three health districts and population count was obtained by age group and gender to determine the catchment population of El-Mahalla Fever Hospital. All health districts have an estimated population count every year by age groups and gender, and the total estimated number in the three districts was 1,792,630 in 2018.

3.3 Study setting:

This study focused on a defined catchment area in three districts of Gharbia governorate, representing the majority of enrolled SARI cases in El-Mahalla Fever Hospital in 2018.

3.3.1 Catchment area

This study aimed to visit all 20 hospitals (including El-Mahalla Fever Hospital) located in the catchment area, and counted the number of patients who were hospitalized with pneumonia from January 1–December 31, 2018.

Only patients who resided in the catchment area were considered by gender and age, as recommended by the WHO. This survey reviewed admission and discharge registers for pneumonia cases in all hospitals, including El-Mahalla Fever Hospital. The data were collected using a structured questionnaire by the researchers. The study estimated the proportion of cases (from catchment area) accessing El-Mahalla Fever

Hospital sentinel site for treatment of pneumonia and residing in the catchment area.

Through this study, a spot map was prepared where the population surrounding El-Mahalla Fever Hospital resided, then the lowest administrated level was identified where the majority of SARI cases (recommended not less than 80%) lived, and it was found that 83% of SARI cases live in three districts :

- El-Mahalla Awal district, (50) SARI cases
- El-Mahalla Thane district, (91) SARI cases
- Samanode district, (38) SARI cases

The study identified all hospitals located in the catchment area (7 government and 13 private hospitals), which provided inpatient service for respiratory diseases. As shown in Figure (3), it describes the distribution of the 20 healthcare providers located in the catchment area for El-Mahalla Fever Hospital in 2018. Two districts are overlapping, while the third is very close and connected to them. The three districts represent more than 80% of SARI cases admitted to El-Mahalla Fever Hospital (the lowest administrated level where the majority of patients resided as recommended by the WHO manual).

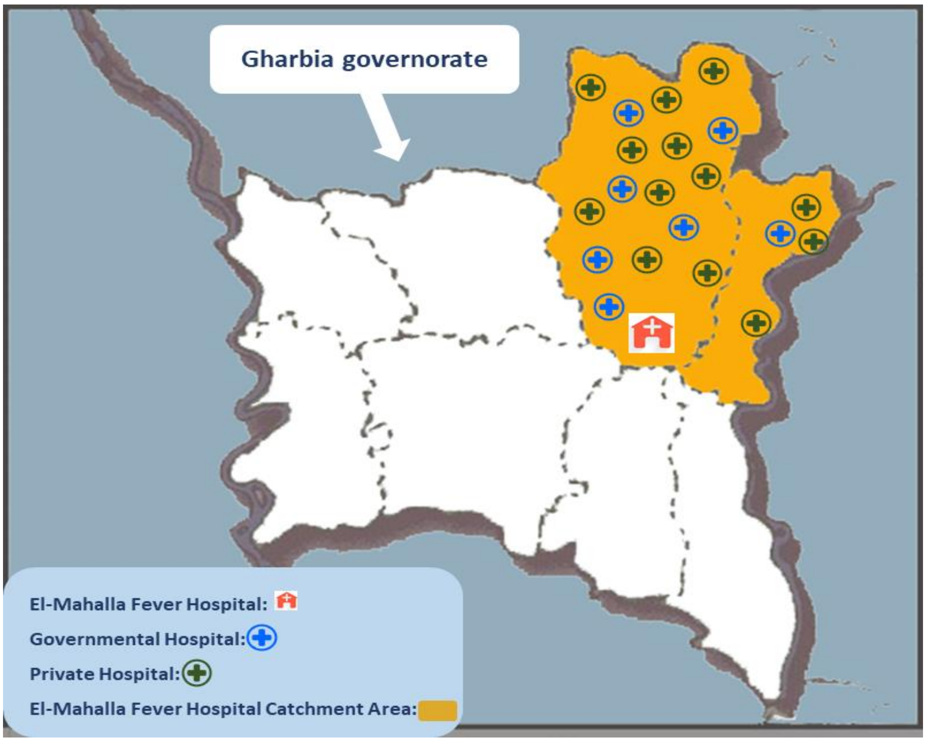

Figure 4. The distribution of the 20 healthcare providers located in the Catchment area for El-Mahalla Fever Hospital in 2018.

3.4 Sampling technique:

In line with the WHO manual for estimating influenza burden, this study included all hospitals located at the catchment area for the HAS, and all SARI cases, which was defined and enrolled by the El-Mahalla Fever Hospital sentinel site in 2018.

3.5 Data sources:

- Primary data related to estimating the catchment population were gathered using a structured questionnaire collected through a HAS at all healthcare facilities in the catchment area.
- Secondary data of El-Mahalla Fever Hospital SARI cases were obtained from the national SARI sentinel surveillance of the NEDSS database.

3.5.1 Variables

The main goal for this research was to estimate the burden (morbidity and mortality) of seasonal influenza disease in 2018.

- Variables for estimating morbidity (incidence) of seasonal influenza included the number of new influenza cases at El-Mahalla Fever Hospital in 2018 and the catchment population for the hospital during the same year.
- Variables for estimating mortality of seasonal influenza included the number of deaths associated with influenza infection and the total number of influenza-positive cases in 2018.

3.6 Data collection:

3.6.1 WHO Manual:

Most low- and middle-income countries lacked data on influenza-associated disease burden. The WHO has provided a manual that outlines a standardized method for estimating the burden of influenza-associated disease. Data analysts and epidemiologists responsible for analyzing and interpreting influenza surveillance site data are the target audience of this manual. This is a very useful tool that focuses on low- and middle-income countries (WHO, 2015).

The manual covers ways to identify and evaluate data sources, as well as evaluate the quality of and relevance of available data, identifying the geographical region where

80% of the sentinel site's case-patients reside (catchment area). It also uses HAS methods to estimate an appropriate population denominator, and outlines how to use HAS, catchment population, and SARI sentinel surveillance data to calculate the burden of influenza-associated SARI (WHO, 2015)

According to the guidelines provided in the WHO manual for disease burden associated with seasonal influenza, this study identified and reviewed data sources for quality and relevance. El-Mahalla Fever Hospital (SARI sentinel site) was chosen as the source of influenza-associated SARI cases and the catchment area of the hospital with the majority of SARI cases was determined. All hospitals in the catchment area were identified and enrolled in the HAS (WHO, 2015).

3.6.2 SARI Sentinel Site data

This study selected El-Mahalla Fever Hospital as a SARI sentinel site. Data from January 1–December 31, 2018, were extracted from the national electronic database of the SARI sentinel surveillance system. All cases that met the standard SARI case definition were enrolled and reported on our national electronic SARI database. In 2018, 216 patients were hospitalized with SARI in El-Mahalla fever Hospital.

3.6.1.1 Sample collection:

Throat and nasopharyngeal swabs were obtained from patients hospitalized with SARI for testing influenza. Clinicians/lab technician or nurses according to each hospital policy is responsible for obtaining throat and nasopharyngeal swabs for laboratory testing from all hospitalized patients who meet the SARI case definition (MoHP, 2019).

- **Oropharyngeal (throat) swabbing:**

A dry sterile tip flocked with nylon fiber swab applicator is used to swab the posterior pharynx. The swab is placed in a 15 ml centrifuge tube labeled with the patient unique ID and containing 2 ml viral transport media (VTM); the applicator stick is then cut off.

- **Nasopharyngeal swabbing:**

A flexible, sterile tip flocked with nylon fiber swab applicator is inserted into the nostril and back to the nasopharynx and left in place for a few seconds before being slowly withdrawn with a rotating motion. For SARI patients, the swab is placed in the same centrifuge tube as the throat swab labeled with the patient's unique ID, and the shaft is cut. The 15 ml tube containing the swab/s are carefully transported to the CPHL as soon as possible.

Nasopharyngeal and oropharyngeal swabs were collected from 215 (99.5%) patients. Overall, 73 (34%) specimens collected from these patients of all ages were tested positive for influenza virus by rRT-PCR. There were 60 positives for influenza patients residing in the catchment area. This study classified all the selected cases by gender and age groups.

3.6.3 Hospital Admission Survey (HAS) data

HAS was conducted in the three health districts surrounding El-Mahalla Fever Hospital using a structured questionnaire, and all hospital records were retrospectively reviewed based on the admission log to identify all patients with diagnosis of pneumonia. Data were gathered from all the study hospitals to determine the proportion of pneumonia admission at El-Mahalla Fever Hospital from all pneumonia hospitalizations in the catchment area.

3.6.4 Overview of Incidence calculation:

Step 1. The study counted SARI patients hospitalized in El-Mahalla Fever Hospital using the national electronic database in 2018. This study followed the WHO-recommended age groups (<2 years, 2<5, 5<15, 15<50, 50<65, and >65).

Step 2. The study analyzed the geographical distribution of SARI cases to identify the catchment area where more than 80% of the cases resided.

Step 3. The study then identified the SARI cases in El-Mahalla Fever Hospital that resided in the catchment area in 2018.

Step 4. The study identified the numerator as influenza-positive SARI cases in 2018 that resided in the catchment area by gender and age group.

Step 5. The study visited all hospitals within the catchment area that provide inpatient services and counted pneumonia admissions in 2018 by gender and age group that resided in the catchment area.

Step 6. The study obtained the estimated total population from the three districts of the catchment area during 2018

Step 7. The study calculated the proportion of pneumonia cases admitted at El-Mahalla Fever Hospital from all pneumonia admissions at all hospitals in the catchment area.

Step 8. By multiplying the proportion of pneumonia admission at El-Mahalla Fever Hospital by the total population number in the catchment area, the study obtained the catchment population of El-Mahalla Fever Hospital by gender and age groups.

Step 9. The study calculated the incidence of influenza-associated SARI cases and divided the influenza positive SARI cases of El-Mahalla Fever Hospital as numerator by the catchment population of El-Mahalla Fever Hospital as denominator and multiplying by 100,000 population.

Step 10. The study estimated the confidence interval for all age groups and gender.

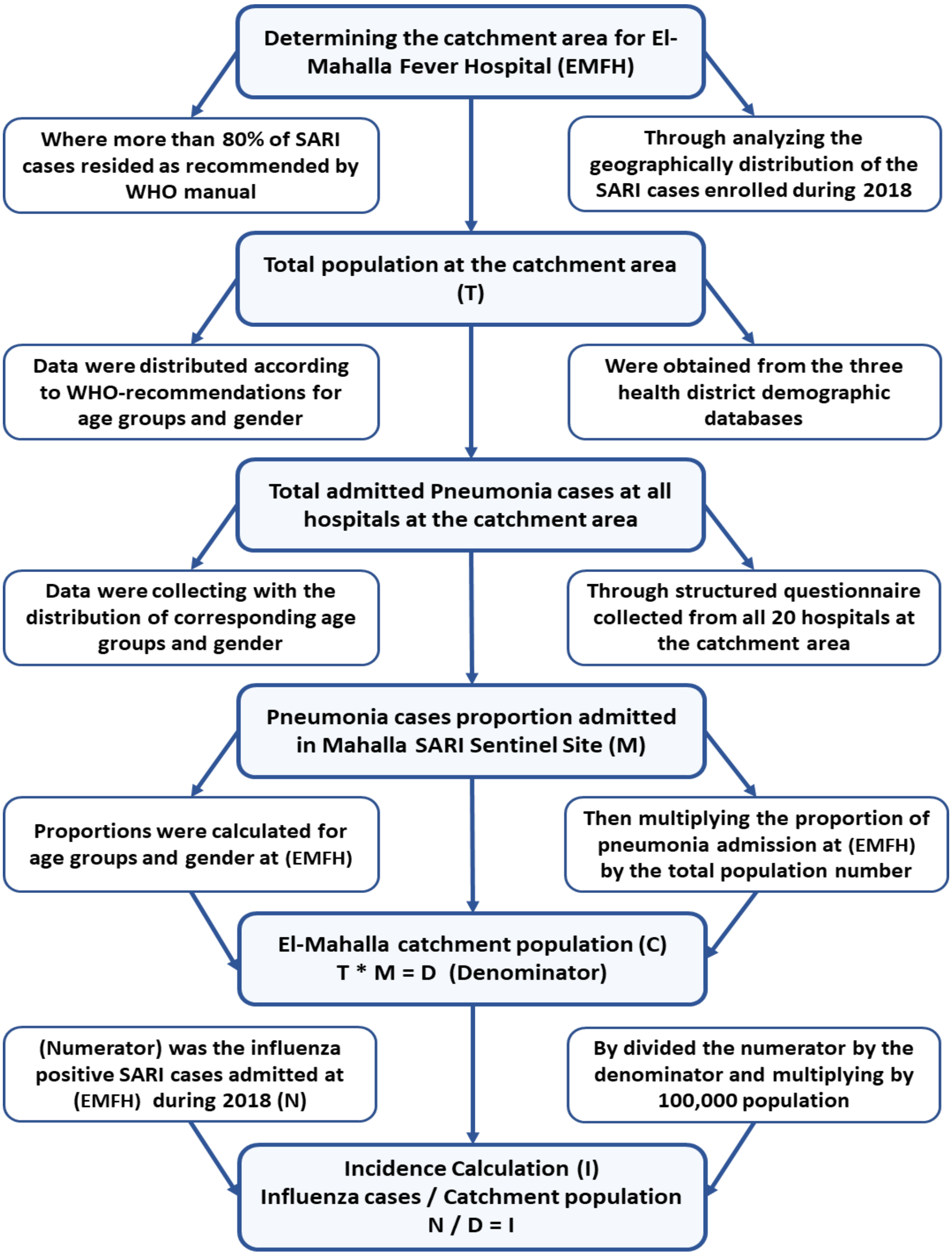

Figure 5 Incidence calculation general procedures

3.7 Ethical statement:

This study was applied, reviewed, and approved by the Egyptian MoHP Research Ethics Committee (REC) under No 18-2022/17 (see annex c).

3.8 Data Analysis:

Demographic characteristics of influenza-positive and influenza-negative SARI cases were tested for differences using Chi-squared test on Epi Info. Annual incidence rates and 95% confidence intervals were calculated according to the WHO manual, using catchment population denominators defined from the HAS and numerator defined from all SARI influenza-positive cases enrolled in the surveillance system. Analyses were conducted in **Microsoft excel© version 2013 and Jamovi 2.2.5.**

CHAPTER 4: RESULTS

The study aimed to determine the burden of seasonal influenza associated with SARI in three health districts of Gharbia governorate in 2018, using data from El-Mahalla Fever Hospital. From January 1–December 31, 2018, physicians enrolled 216 hospitalized patients with SARI who met the standard SARI case definition in El-Mahalla Fever Hospital.

4.1 General characteristics:

Nasopharyngeal and oropharyngeal swabs were collected from 215 (99.5%). Overall, 73 (34%) specimens collected from these patients of all ages tested positive for influenza virus by rRT-PCR. Of the total SARI cases enrolled at the El- Mahalla fever hospital, 180 resided in the catchment area, of which 60 tested positive for influenza. Figure (6) shows the distribution of the population pyramid of SARI cases (n=180) by gender, and Figure (7) shows the distribution of influenza positive-associated SARI by age group and gender (n=60). In total, 45.6% (82/181) of SARI cases were male, 65.6% (118/181) were rural, 6% (11/180) had chronic diseases, and 0.6% (1/181) were pregnant. There were no deaths or cases admitted to the IC unit, and there were no significant differences between influenza-positive and other hospitalized SARI cases at El-Mahalla Fever Hospital (see Table 3).

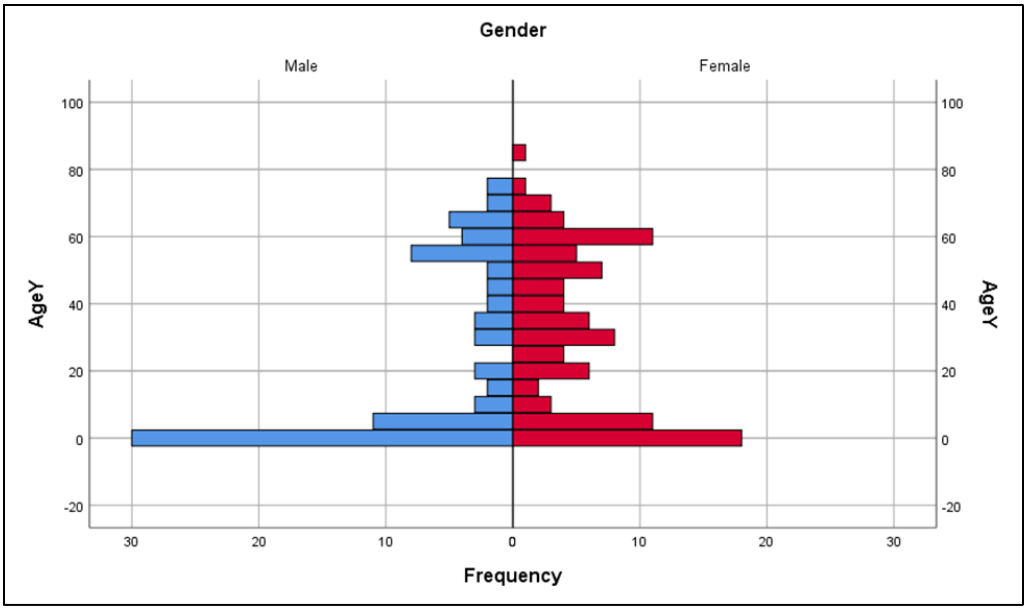

Figure 6 Study group population pyramid and gender distribution at El-Mahalla Fever Hospital in 2018

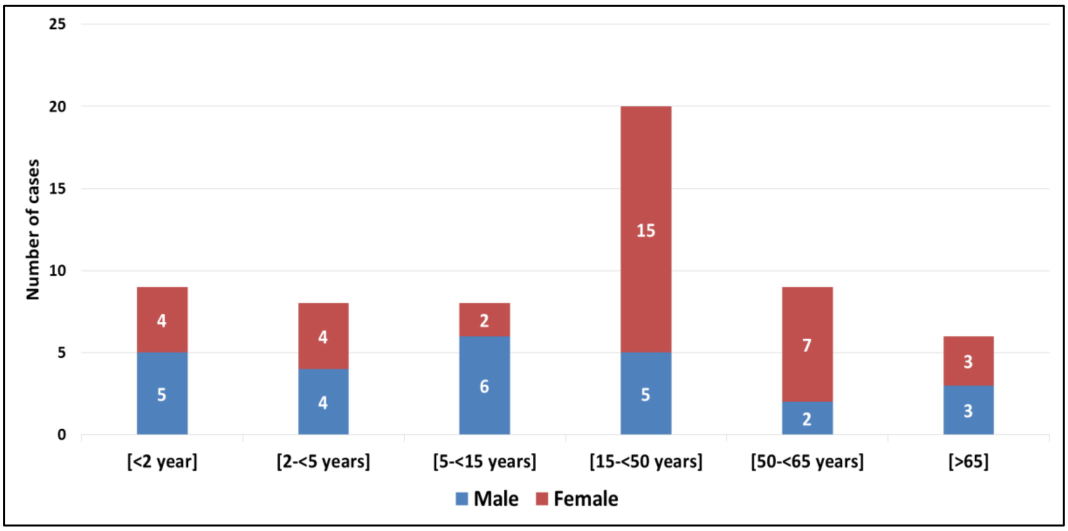

Figure 7 Influenza virus-associated Severe Acute Respiratory illness (SARI) by age groups in El-Mahalla Fever Hospital in 2018

Table 3 General characteristics of influenza-associated SARI cases at El-Mahalla Fever Hospital

	Total	Influenza Positive				P-value
		Yes		No		
sex						0.459
Male	82	25	30.5 %	57	69.5 %	
Female	98	35	35.7 %	63	64.3 %	
Residency						0.912
Rural	118	39	33.1 %	79	66.9 %	
Urban	62	21	33.9 %	41	66.1 %	
Chronic disease						0.379
Yes	11	5	45.5 %	6	54.5 %	
No	169	55	32.5 %	114	67.5 %	
Pregnancy						0.232
Yes	1	1	100.0 %	0	0.0 %	
No	179	59	32.8 %	120	66.7 %	
ICU						
Yes	0	0	0.0 %	0	0.0 %	NA*
No	180	60	33.3 %	120	66.7 %	
Death						
Yes	0	0	0.0 %	0	0.0 %	NA**
No	180	60	33.3 %	120	66.7 %	

NA* There was no ICU at El-Mahalla Fever Hospital
NA** All severe cases were transferred to other hospitals

4.2 Influenza seasonality:

Most cases of influenza in SARI patients occurred in autumn and winter seasons. The percentage of positive influenza virus-associated SARI cases ranged from 0% during summer months and peaked to 76% during January. Furthermore, Influenza A (H3N2) and Influenza A (H1N1) viruses were more commonly reported in winter Figure (8).

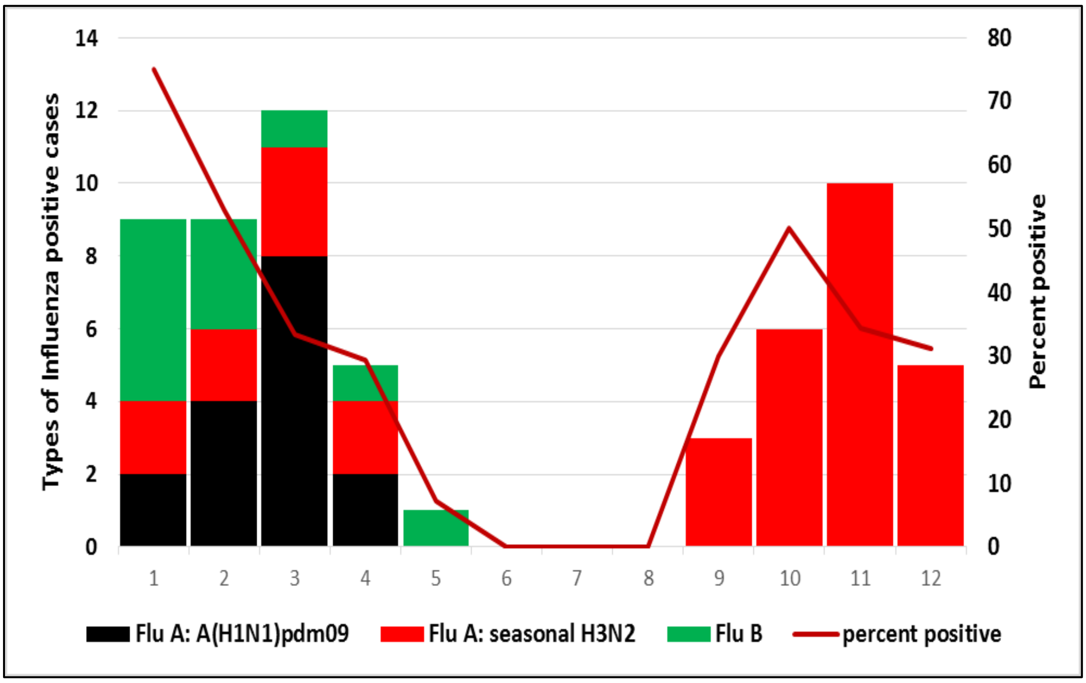

Figure 8 Influenza positive-associated SARI cases at El-Mahalla Fever Hospital by months in 2018

4.3 Population data:

The population in the catchment area in 2018 totaled 1,792,630, of which 924,998 (51.6%) were males and 867,632 (48.4%) females. Data were collected from the three health districts (El-Mahalla Awall, El-Mahalla Thanee, and Samanode) distributed by gender and age groups as the three districts represented the majority of SARI cases admitted to El-Mahalla Fever Hospital, as recommended by the WHO manual, see (Table 4).

Table 4 Total population number at the catchment area of El-Mahalla Fever Hospital, Gharbia governorate in 2018

Total population number at El-Mahalla Awall district distributed by gender and age groups

Age groups	Male	Female	Total
0<2	17871	16762	34633
2<5	34252	32128	66380
5<15	75206	70542	145748
15<50	183174	171815	354989
50<65	47283	44351	91634
>65	14520	13619	28139
Total	372306	349217	721523

Total population number at El-Mahalla Thanee district distributed by gender and age groups

Age groups	Male	Female	Total
0<2	16735	15697	32432
2<5	32075	30086	62161
5<15	70427	66061	136488
15<50	171538	160899	332437
50<65	44278	41533	85811
>65	13598	12755	26353
Total	348651	327031	675682

Total population number at Samanode district distributed by gender and age groups

Age groups	Male	Female	Total
0<2	9794	9186	18980
2<5	18772	17607	36379
5<15	41216	38660	79876
15<50	100388	94161	194549
50<65	25913	24306	50219
>65	7958	7464	15422
Total	204041	191384	395425

Total population number at the catchment area (three districts) distributed by

gender and age groups

Age groups	Male	Female	Total
0<2	44400	41645	86045
2<5	85099	79821	164920
5<15	186849	175263	362112
15<50	455100	426875	881975
50<65	117474	110190	227664
>65	36076	33838	69914
Total	924998	867632	1792630

Among the 20 healthcare facilities in the catchment area, only 12 hospitals recorded inpatient pneumonia cases in 2018 (see Table 5). El-Mahalla Chest hospital reported the highest enrolment of pneumonia cases, followed by El-Mahalla General hospital and the El-Mahalla Fever Hospital. Most pneumonia cases among the elderly (more than 50 years of age) were admitted to El-Mahalla Chest hospital and young patients (below 5) were admitted to El-Mahalla General hospital (see Table 4).

The proportion of pneumonia cases admitted to private hospitals in 2018 was estimated at 15.28% of the total hospitalized pneumonia cases in the catchment area, and it was estimated at 84.72% in the public sector (see Table 5). The highest proportion of hospitalized pneumonia cases was recorded at El-Mahalla Chest hospital (32.72%), followed by El-Mahalla General hospital (26.11%) and the El-Mahalla Fever Hospital (10.6%).

Most pneumonia cases admitted to the private sector involved elderly patients. Hospitals with the most pneumonia cases among private hospitals were El-Waha hospital (5.93%), Madinat Alshefaa (3.65%), and El-Safwa hospital (2.85%), of the total admitted pneumonia cases in the catchment area in 2018 (see Table 6).

The estimated catchment population for El-Mahalla Fever Hospital was 190,096, males were 82,533 (43.4%) and females 107,563 (56.6%). The estimated population residing in urban areas was 62,313 (32.8%) and 127,787 (67.2%) in rural areas.

Table 5 Total pneumonia cases admitted at all healthcare facilities in the catchment area in 2018

	Hospital Name	0<2		2<5		5<15		15<50		50<65		>65	
		M	F	M	F	M	F	M	F	M	F	M	F
1	El-Mahalla Chest H	17	6	9	10	6	7	44	36	37	40	41	30
2	El-Mahalla General H	99	61	11	10	5	9	8	7	5	0	7	7
3	El-Mahalla Fever H	8	2	9	7	5	4	6	17	12	17	2	4
4	El- Mabara H	15	20	9	2	2	2	1	2	5	3	7	1
5	Samanode Central H	18	17	7	2	5	6	8	5	0	0	0	0
6	El-Waha Private	1	2	2	1	6	5	4	9	5	5	4	8
7	Al-Safwa Private	1	3	2	0	2	1	3	2	1	2	4	4
8	Madinat Alshefaa	0	0	0	0	0	0	0	0	9	9	6	8
9	Aldoraa Private	0	0	0	0	0	0	1	2	2	4	6	7
10	Al-Rwad Private	0	0	0	0	0	0	0	0	0	0	0	2
11	Hapaza Private	0	0	0	0	0	0	0	0	0	0	1	0
12	Liver teaching H	0	0	0	0	0	0	0	0	0	0	0	1
13	Charity H	0	0	0	0	0	0	0	0	0	0	0	0
14	Abdelzaher Private	0	0	0	0	0	0	0	0	0	0	0	0
15	Alhoda Private	0	0	0	0	0	0	0	0	0	0	0	0
16	Alrabea Private	0	0	0	0	0	0	0	0	0	0	0	0
17	Alnour Private	0	0	0	0	0	0	0	0	0	0	0	0
18	Ajiad Private	0	0	0	0	0	0	0	0	0	0	0	0
19	Liver centre	0	0	0	0	0	0	0	0	0	0	0	0
20	Alsalam Private	0	0	0	0	0	0	0	0	0	0	0	0
	Total	159	111	49	32	31	34	75	80	76	80	78	72

Table 6 Proportion of pneumonia cases admitted in healthcare facilities in public and private sectors

Sector	No.	Hospital Name	Male	Female	Total	Proportion Total
Public Sector	1	El-Mahalla Chest H	154	129	283	32.27%
	2	El-Mahalla General H	135	94	229	26.11%
	3	El-Mahalla Fever H	42	51	93	10.60%
	4	El- Mabara H	39	30	69	9.29%
	5	Samanode Central H	38	30	68	7.75%
	6	Liver teaching H	0	1	1	0.13%
	7	Liver centre	0	0	0	0.00%
	Total Public		408	335	743	84.72%
Private Sector	1	El-Waha Private	22	30	52	5.93%
	2	Al-Safwa Private	13	12	25	2.85%
	3	Madinat Alshefaa	15	17	32	3.65%
	4	Aldoraa Private	9	13	22	2.51%
	5	Al-Rwad Private	0	2	2	0.23%
	6	Hapaza Private	1	0	1	0.11%
	7	Charity H	0	0	0	0.00%
	8	Abdelzaher Private	0	0	0	0.00%
	9	Alhoda Private	0	0	0	0.00%
	10	Alrabea Private	0	0	0	0.00%
	11	Alnour Private	0	0	0	0.00%
	12	Ajiad Private	0	0	0	0.00%
	13	Alsalam Private	0	0	0	0.00%
	Total private		60	74	134	15.28%
Grand Total					877	

4.4 Influenza burden:

4.4.1 Morbidity:

The term morbidity refers to an episode of illness caused by influenza, which can be described by calculating the incidence of the disease.

Incidence of influenza:

The incidence rate refers to the frequency of new events occurring within a population, and is determined by the number of new incidents or cases occurring over a defined period of time. This is considered the numerator, which is divided by the denominator, representing the population at risk of experiencing this event (WHO, 2015).

This study estimated the total pneumonia cases at 877 in the catchment area; the proportion of people admitted to El-Mahalla Fever Hospital was 10.6%, the estimated catchment population was 190,096 during 2018 for El-Mahalla Fever Hospital, and the estimated total number of influenza cases were 765 in the catchment area (see Table 7),

This study estimated an adjusted influenza-associated 2018 SARI rate of 32/100,000 (95% CI, 25-41) persons for the catchment area of Mahalla Fever Hospital and 765 influenza-associated SARI cases during 2018 in the three districts (El-Mahalla Awal – El-Mahalla Thane- Samanode) after extrapolation, the highest incidence was 282/100,000 (95% CI, 147-542) in the age group less than 2 years followed by the age group more than 65 years at 215/100,000 (95% CI, 97-479), incidence of males was 30/100,000 (95% CI, 20-44), females 32/100,000 (95% CI, 23-45), people residing in urban areas 34/100,000 (95% CI, 22-52) and in rural areas 31/100,000 (95% CI, 23-42) of the total population (see Table 8).

4.4.2 Mortality:

Calculating seasonal influenza mortality is very difficult in LMICs, as a majority of deaths may occur outside the hospital, and laboratory confirmation of all suspected cases within the hospital is very rare (WHO, 2015). Instead, we shall calculate the case fatality ratio (CFR). There were no deaths in El-Mahalla Fever Hospital associated with seasonal influenza in 2018.

Table 7 Detailed calculations incidence rates (per 100,000) of influenza virus-associated severe acute respiratory infection by age group at El-Mahala Fever hospital, Egypt, 2018

Indicators	Age Groups (Y)	0<2		2<5		5<15		15<50		50<65		>65		Total
	Gender	F	M	F	M	F	M	F	M	F	M	F	M	
Total population number		41645	44400	79821	85099	175263	186849	426875	455100	110190	117474	33838	36076	1792630
Total admitted Pneumonia cases in catchment area		111	159	23	49	34	31	80	75	80	76	72	78	877
Pneumonia cases in Mahalla SARI Sentinel Site		2	8	7	9	4	5	17	6	17	12	4	2	93
Proportion of population admitted Mahalla Sentinel Site %		1.8	5	21.88	18.37	11.76	16.13	21.25	8	21.25	15.79	5.56	2.56	10.6
Catchment Population		750	2234	17461	15630	20619	30137	90711	36408	23415	18549	1880	925	190096
Influenza cases in Mahalla SARI Sentinel Site		4	5	4	4	2	6	15	5	7	2	3	3	60
Incidence		533	224	23	26	10	20	17	14	30	11	160	324	32

Y, Years; F, Female; M, Male

Table 8 Incidence rates (per 100,000) of influenza virus-associated severe acute respiratory infection by demographic characteristics at El-Mahala Fever hospital, Egypt, 2018

Characteristics		Estimated catchment population of the Sentinel Site	Number of patients positive for influenza	Incidence per 100,000	(95% CI)	Significance
Age Groups (Years)	0 < 2	3187	9	282	147 - 542	p<0.001
	2 < 5	32577	8	25	13 - 50	
	5 < 15	50139	8	16	8 – 32	
	15 < 50	130874	20	15	10 – 23	
	50 < 65	42322	9	21	11 – 40	
	> 65	2797	6	215	97 – 479	p<0.001
Gender	Male	83013	25	30	20 - 44	
	Female	108189	35	32	23 - 45	p=0. 8
Residency	Urban	62313	21	34	22 – 52	p=0. 7
	Rural	127787	39	31	23 - 42	
Total		**190096**	**60**	**32**	**25 - 41**	

CHAPTER 5: DISCUSSION

Globally, seasonal influenza is one of the most common respiratory infections. Several factors influence the severity and burden of seasonal influenza, especially the virus type and subtype. In 2018, influenza viruses were associated with a substantial burden of severe illness requiring hospitalization, especially among toddlers and older adults at El-Mahalla Fever Hospital. In addition, there were no deaths among all influenza-associated SARI in comparison to other SARI sentinel sites in Egypt.

5.1 Incidence of Seasonal Influenza

Estimating the incidence of influenza-associated SARI was one of the main objectives of our study. The numerator was obtained from the SARI sentinel surveillance site at El-Mahalla Fever Hospital and the denominator was estimated through the HAS in the catchment area of the hospital. Regular estimates of incidence are needed to provide policy makers with the overall burden of influenza disease among the population, as there are many factors that influence the severity of seasonal influenza over time.

Determining the catchment populations for El-Mahalla Fever Hospital was a challenging process, but after applying HAS methods as described in the WHO manual, the catchment population can be easily estimated regularly (every year) for other seasonal influenza sentinel surveillance sites, so that a regular denominator can be used to calculate the seasonal influenza incidence for each hospital.

It is considered impossible to estimate seasonal influenza hospitalizations at all healthcare facilities in a catchment area, since it is impossible to provide laboratory confirmation for all suspected cases in all private and public hospitals for a full year. As recommended by the WHO manual, pneumonia hospitalizations could be used to reflect on influenza hospitalizations. Owing to the unified case definition of pneumonia infections used across all hospitals, calculating pneumonia hospitalization is much easier (WHO, 2015).

Through HAS, this study clarified the distribution of pneumonia hospitalization among both public and private sectors in the catchment area of El-Mahalla Fever Hospital. The majority of pneumonia admission was estimated at 85% in the public sector and at 15% in the private sector, although the number of private hospitals was twice that of public hospitals. The majority of the pneumonia hospitalization cases at private hospitals were from age groups over 50, which indicate the affordability of these age groups to the high cost of the private sector.

Of the total pneumonia hospitalizations, El-Mahalla Chest Hospital (tertiary hospital specializing in chest infections) had the highest number of pneumonia case hospitalization, followed by El-Mahalla General Hospital and El-Mahalla Fever Hospital. El-Mahalla General Hospital had the highest number of pneumonia infections among the age group of less than five as it has the highest capacity and major resources to deal with general cases of children aged below five.

This study estimated the incidence of influenza-associated SARI at 32/100,000 population (95% CI, 25-41), which was comparable to other studies in LMIC, which used positive hospitalized influenza cases (numerator) and the same methodology for estimating the catchment population (denominator). Our results were higher in comparison to Rebeksh J. and Stewart colleagues from Cambodia, as they estimated the incidence of influenza associated SARI at 13.5/100,000 persons in 2015 in Svay Rieng Province, with the highest incidence of 67.8/100 000 (25.8-109.9) reported among individuals aged above 65 (Stewart et al., 2018).

In Egypt, there was only one study (to the best of our knowledge) that estimated the incidence of influenza-associated SARI cases. This study estimated the incidence through HUS methods at Damanhour governorate in 2013 at 44/100,000 person–years

(95% CI, 39-48), our findings were close to each other, but the highest incidence was 166 (95% CI, 125-220) in the 2–5 age group, followed by 89 (95% CI, 71-111) in the 50–65 age group (Refaey et al., 2016).

Our estimates of influenza incidence were very close to estimates by Ntiri MP and colleagues from Ghana, who estimated the incidence among medically-attended influenza cases at 30 per 100,000 population (95% CI, 13-84), with the highest incidence of 135 per 100,000 population (95% CI, 120-152) in the 0–4 age group from 2013 to 2015 (Ntiri et al., 2016). Furthermore, our estimates were higher than colleagues from Kenya, who estimated the influenza incidence among SARI at 21 per 100,000 population (95% CI, 19-23) from 2012 to 2014 (Dawa et al., 2018), and colleagues from Oman, who estimated the influenza incidence among hospitalizations at 0.5–15.4 per 100,000 population from 2008 to 2013, and 7.3–27.5 per 100,000 population (95% CI, 6.4-29.1) from 2012 to 2015 (Abdel-Hady et al., 2018).

The HAS method was also applied by colleagues from Indonesia, who estimated the incidence at 13–19 per 100,000 population (95% CI, 8-30) in 2013–2016, and the highest incidence was estimated at 87–114 (95% CI, 70-137) per 100,000 population in the 0–4 age group (which also was lower than our estimates) (Susilarini et al., 2018).

5.2 Seasonality of Influenza disease

The seasonality of influenza differs according to geographical location, especially in the northern or southern hemisphere. Egypt is located in the northern hemisphere and the seasonality of influenza occurs mostly during the winter months (epi-week 42 to epi-week 12). The severity of influenza seasons significantly depends on the influenza type and subtype. This study found that Flu A (H3N2) predominated the 2018 season at 55%, followed by Flu A (H1N1) at 26.7% and Flu B at 18.3%, and influenza prevailed in winter and spring from epi-week 38 until epi-week 18. In comparison to an Egyptian study conducted in 2013, influenza virus Type A subtype (H3N2) prevailed at 54%, followed by Flu B virus at 29.3% and Flu A (H1N1), but the season of influenza started and surged during autumn and early winter (epi-week 35 to epi-week 51) and continued until the end of spring (Refaey et al., 2016).

In our study, influenza-associated SARI cases had an average positivity of 33.3% and a maximum positivity of 76% in January, in contrast to other colleagues from Egypt (Refaey and H.), who measured the highest positivity during October, at 38% and the average positivity percentage at 19% (Refaey et al., 2016). Doaa and Balushi, colleagues from Oman, measured the peak of seasonal influenza during different years; December 2012, February 2013 and 2014, November 2015, which was the highest peak at 36% positivity and Flu A (H1N1) predominated from 2012 until 2015 at 35% to 64.2% (Abdel-Hady et al., 2018).

5.3 Total Burden of Seasonal Influenza

In order to estimate the total burden of seasonal influenza, we have to estimate the incidence of SARI and ILI cases and the economic burden for both, but estimating ILI is challenging due to various reasons, because mild influenza-associated diseases are not likely to be reported to any health facilities for treatment. Most people will either self-medicate or not undergo any treatment, symptoms of ILI are not specific to influenza (other respiratory viruses result in similar symptoms), and population denominator estimation for ILI sentinel sites may be challenging in most situations (WHO, 2015). According to colleagues from Ghana, the overall influenza-associated ILI infections had a higher incidence than influenza-associated SARI infections, 844 per 100,000 population (95% CI, 501-1099) compared to 30 per 100,000 population (95% CI, 13-84) for influenza-associated SARI from 2013 to 2015 (Ntiri et al., 2016).

5.4 Private Sector:

According to the study, the private sector is less likely to provide health services to SARI patients than the public sector. Only 15.3% of pneumonia cases in the catchment area were hospitalized in private sectors, as private sectors reportedly dismiss suspected influenza cases needing hospitalization amid fears of facing stigma of hospitalizing suspected swine flu cases. Additionally, this study noticed that, the majority of the cases hospitalized in the private sector involved people older than 50, an age group that was able to afford the high cost of services in the private sector.

5.5 Study limitations:

There are a few limitations to the study. First, there was a shortage of quality and completeness in the data for many variables, such as symptoms, residency, occupation, final outcome, final diagnosis, treatments, and vaccination status. Vaccination is considered an effective tool to reduce the overall burden of seasonal influenza. However, in Egypt, seasonal influenza vaccination coverage is considered very low. Al-Awaidy and colleagues estimated the overall influenza vaccination coverage in Egypt at less than 2% of the total population in 2018 (Al Awaidi et al., 2018). A national influenza vaccine policy is needed to reduce the overall burden of seasonal influenza disease, increase preparedness for influenza epidemics and pandemics, strengthen the national health system, and increase vaccination coverage among high-risk groups like healthcare workers, pregnant women, people with chronic disease, and extreme age groups (WHO, 2020).

Second, El-Mahalla Fever Hospital has modest capacity and limited resources in certain departments, such as the pediatric department, and the absence of an intensive care unit. A strong indication can be found in the low enrollment of toddlers under two years of age and the absence of severe cases, as these cases were transferred to El-Mahalla Chest Hospital or El-Mahalla General Hospital.

Furthermore, all hospitals within the catchment area did not have any kind of electronic medical records, making it difficult to collect the data smoothly during the

HAS for calculating the catchment population of El-Mahalla Fever Hospital. Moreover, considering that this study calculated the incidence of influenza-associated SARI for only one year (2018), the cases might have been underestimated or overestimated.

CHAPTER 6: CONCLUSION

Using the methods detailed in the WHO manual and successfully implementing it in Gharbia governorate, Egypt, influenza-associated SARI incidence rates can be estimated in other governorates.

Incidence rates of influenza-associated SARI indicated a substantial burden of influenza hospitalizations, especially among children and older adults. These findings can be used to understand the potential impact of seasonal influenza vaccination in these age groups. Furthermore, influenza prevention, control, and treatment policies can be strengthened by utilizing surveillance data and allocating resources accordingly.

6.1 Recommendations

To better understand influenza seasonality, this study recommends that we extend population-based surveillance to cover more influenza sentinel hospitals (ILI and SARI sentinel sites), conduct further research on other comorbidities and pregnant women, and use surveillance data for more than one calendar year to better estimate influenza burden in the country. These estimates could provide policy makers with the required information about the real burden of seasonal influenza and prioritize actions needed to combat future influenza pandemics.

The study also recommends updating policies and national guidelines for early detection and effective treatment, especially at extreme ages (toddlers and those older than 65 years of age), and establish a vaccination policy guideline that aims to increase the vaccination coverage in general, especially for very high-risk groups, including toddlers and those older than 65 years of age, to reduce the burden of influenza.

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Annexes

A. Questionnaire used for collecting pneumonia cases number by months from all healthcare facilities.

Number of pnumonia cases admitted during 2018 distributed by months, gender and age groups												
Hospital Name												
Months	**0<2**		**2<5**		**5<15**		**15<50**		**50<65**		**>65**	
	Male	**Female**	**Male**	**Female**	**Male**	**Female**	**Male**	**Female**	**Male**	**Female**	**Male**	**Female**
January												
February												
March												
April												
May												
June												
July												
August												
September												
October												
November												
December												
Total												

B. Forms used for summarizing data collected from questionnaire A.

Total pnumonia cases admitted at all healthcare facilities in the catchment area during 2018												
Hospital Name	0<2		2<5		5<15		15<50		50<65		>65	
	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female
Total												

C. Ethical approval from the Egyptian Institutional Review Board (IRB).

Ministry of Health & Population
Training & Research Sector
Cent. Direct. for Research and Health Development

وزارة الصحة والسكان
قطاع التدريب والبحوث
الإدارة المركزية للبحوث والتنمية الصحية

OHRP: FWA00016183 - 23 Mar 2020
IORG0005704 \ IRB0000687 - 8 Nov 2020

REC Decision
قرار لجنة أخلاقيات البحث العلمي

السادة / حسام حسن

إعمالا لقانون تنظيم البحوث الطبية الإكلينيكية رقم 214 لسنة 2020 ولائحته التنفيذية الصادرة بقرار رئيس مجلس الوزراء رقم 927 لسنة 2022 وبناء على قراري معالي أ.د. وزير الصحة والسكان رقم 95 لسنة 2005 بشأن البحوث الصحية ورقم 225 لسنة 2020 بشأن تشكيل لجنة أخلاقيات البحث العلمي وطبقا لقواعد الممارسة الطبية الجيدة (GCP) واعلان هلسنكي وكذلك قواعد منظمة الصحة العالمية اجتمعت لجنة أخلاقيات البحث العلمي بتاريخ 2/ 11 / 2022 الساعة 9 صباحا بالإدارة المركزية للبحوث والتنمية الصحية وتمت مناقشة:

Full Title of The Study الاسم الكامل للدراسة					
Burden of Influenza Virus-associated Severe Acute Respiratory Infections in three districts in Gharbia governorate, Egypt 2018					
Study No. رقم الدراسة	--------------------	PI / Organization الجهة الباحثة / الباحث الرئيسي	حسام حسن	Submission Type غرض العرض	تقديم أول مرة

Submitted Document المستندات المقدمة			Committee Decision قرار اللجنة	
تم التقدم بالمستندات والوثائق الخاصة بالدراسة المذكورة بعالية طبقا لما ورد بالدليل الخاص بلجنة أخلاقيات البحوث وتم تسليمها وعرضها على اللجنة المذكورة بمعرفة الادارة المركزية للبحوث والتنمية الصحية The required Documents are submitted according to the committee guideline & have been received & showed by Central Directorate of Research & Health Development		Received Date تاريخ الإستلام	Approval موافقة	
			Com. No/Dec. No:	18-2022/17

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توصي اللجنة بتقديم نتائج الدراسة فور الإنتهاء منها

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