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EC NURSING AND HEALTHCARE
Research Article

# Laboratory-Confirmed Seasonal Influenza Virus Infection in Qatar; 2016 - 2018 National Surveillance Data

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**Received:** November 23, 2020; **Published:** February 10, 2021

## Abstract

**Background:** Despite widely available annual immunisation and antiviral therapy, seasonal influenza continues to cause considerable morbidity and mortality. Limited data are available regarding the demographic and virologic characteristics of seasonal influenza in Qatar. The aim of this study was to assess the incidence and clinical impact of laboratory-confirmed influenza infection in Qatar during the years 2016 to 2018.

**Methods:** Qatar Influenza Surveillance Programme involves offering laboratory testing for all individuals who present with an influenza like illness (ILI) to any primary health centre or hospital department. Upper respiratory samples are submitted to the National Virology Laboratory based at Hamad Medical Corporation, Doha, where they are tested using RT-PCR (Xpert Flu, Cepheid, Sunnyvale, California) and multiplex PCR (FTD Respiratory pathogens 21, Fast-Track Diagnostics, Esch-sur-Alzette, Luxembourg). Surveillance results, hospital admissions and mortality data were retrieved retrospectively from electronic databases. All samples tested between January 2016 and December 2018 were included. Stata (StataCorp LLC, College Station, Texas) was used for descriptive statistics. Incidence rates (IR) are reported by 100,000 population. Population data are based on those reported by Qatar Planning and Statistics Authority. The study was approved by the Institutional Review Board at Hamad Medical Corporation.

**Results:** Over the study period, Influenza Virus was detected in 19,339 (1.3%) out of 1,447,636 specimens from individuals with ILI, corresponding to an overall IR of 244 per 100,000 population. Of those with confirmed Influenza, there were significantly more males (56% versus 46% females, $P < 0.001$) and younger age groups (35% from those aged 0 to 4 years and 19% from 5 to 14 years age group). Influenza A (71.0%) predominated, nearly half (48.7%) of which were H1N1pd09 type. Significantly more cases were diagnosed during the months of October to December compared with January to March (63.0% versus 18.0%, $P < 0.001$) (Figure 1). During the year 2018, there were 410 Hospitalizations due to influenza, with a rate of 15.33 (95%CI 13.88; 16.88) per 100,000 hospital admissions due to Influenza and 10 deaths with an in-hospital mortality rate of 0.37 (95%CI 0.22; 0.49) per 100,000.

**Conclusion:** The incidence of laboratory-confirmed seasonal Influenza is high in Qatar. However, children and young adults are most commonly affected, and hence relatively low rates of severe complications and mortality are observed.

***Keywords:*** *Influenza Virus Infection; Qatar; Influenza Like Illness (ILI)*

## Introduction/Background

Influenza is an acute respiratory illness caused by influenza A or B viruses, a major public health problem that can cause hospitalization, respiratory failures and sometimes death in high risk groups Influenza can result in outbreaks and global epidemics, mainly during the winter season [1]. Dry cough, fever with sudden onset, severe malaise, joint and muscle pain and sore throat are the main characteristics of influenza episodes [2]. Despite that the uncomplicated form is the associated with increased morbidity and mortality in children, older adults, pregnant women, people with some chronic illnesses such as diabetes, heart diseases, chronic lung and kidney diseases and weakened immune system, influenza is a self-limiting condition in the general population [3].

On a global scale, seasonal influenza was estimated to be associated with a staggering 291,243 to 645 832 respiratory deaths (4.0 to 8.8 per 100,000 individuals) annually (Iuliano., *et al*. 2018). In 2016, while lower respiratory infections was the six leading cause of death in high-income countries (CDR = 37.3 per 100,000 individuals) and upper-middle-income countries (CDR = 21.8 per 100,000 individuals), it was the third leading cause of death in low-middle income counties (CDR = 48.1 per 100,000 individuals) and the first cause of death in low-income countries (CDR = 75.8 per 100,000 individuals) [4]. This health burden has its significant economic consequences, where average current cost estimates each year in the United States exceeds $1 billion [5].

Children and adolescents appear to play an important role in the transmission of influenza. Given their increased tendency to acquire and shed influenza, children have been identified as predominant vectors in the household spread of influenza [6]. It was also found that type A (H1N1) rates was higher in children aged 5 - 19 years and type B higher in children aged 5 - 14 years compared to other age groups [7].

Estimates during 2017 - 2018 season showed that Influenza was responsible for 810,000 hospitalizations with 4561 deaths per 100,000 hospitalizations in the United states (CDC, 2019). To our knowledge, there is little or no information on influenza trends among the population younger than 15 years old in Qatar. One recent study showed rates from 2012 to 2017 but excluded patients under 15 years of age (Al-Romaihi., *et al*. 2019). Also,influenza-associated hospitalization has been documented in many countries around the world,but such figures are still scarce, especially in the east mediterranean region.Oman for example identified a total of 19 405 influenza-associated hospitalization and 847 deaths from 2012 till 2015.Their Influenza-associated hospitalization incidence rate was 20.6 (95% CI: 19.9 - 21.3) per 100 000 and their hospital death rate was 0.9 (95% CI: 0.7 - 1.0) per 100 000 population [8]. What we know, there are no such published figures for Qatar.

Occupying a small land on the eastern coast of the Arabian Peninsula, the state of Qatar has a dry, subtropical desert climate with low annual rainfall and hot and humid summers. Time from May to September is the hottest. During cool months, there are periodic drops in temperature. The mid-year population in 2016 in Qatar was estimated at 2,617,634 with 14% aged less than 15 years, 85% aged between 15 to 64 years and 1% aged above 65 [9]. Healthcare services in Qatar are provided by a mix of public,private and semi-government providers. Public providers constitute most of the healthcare activity across the country with 23 primary healthcare centers and 15 Hamad Medical Corporation (HMC) hospitals [10]. The Department of Laboratory Medicine and Pathology (DLMP) of HMC is the referral laboratory for the State. Its virology section was recognized to be the National Influenza Center for Qatar (NIC). NICs are national institutions recognized by WHO National Influenza Centers to collect virus specimens in their country and perform preliminary analysis.

A country-wide lab-based surveillance system with daily sampling and reporting was established in HMC in order to assess these ILI trends and monitor its predominant circulating strains.

## Aim of the Study

The aim of this study is to identify the influenza circulating types in Qatar from 2016 to 2018, to have a continuous monitoring of seasonal influenza sub types that can help determine seasonal trends and ultimately help assess the true disease burden, and to provide a better understanding of the impact of influenza in the Qatari community by knowing the hospitalization and deaths rates from Influenza A, H1N1 and Influenza B. Also, these national estimates, if readily available, would enable the Ministry of Public Health in Qatar to make

informed evidence-based decisions when allocating resources and planning intervention strategies to limit the spread of the disease and minimize its associated costs, and to be ready for pandemic preparedness as well.

## Methods

### Case definition and specimen collection

Specimens of ILI patients were collected between January 2016 to December 2018 from Hamad Medical Corporation clinics and all primary healthcare centers in Doha. The WHO standardized ILI case definition that defines ILI more than 38°C fever and cough or sore throat with onset within the last 10 days has been strictly followed [11]. Samples from the throat swabs, nasal and nasopharyngeal swabs, and nasal aspirate were obtained for viral detection. These specimens have been collected in the viral transport medium, placed in 4˚C box and sent to the Hamad Medical Corporation (HMC) Virology Laboratory for analysis. Surveillance results, hospital admissions and mortality data were retrieved retrospectively from electronic databases.

### Laboratory testing

Upper respiratory samples are submitted to HMC National Virology Laboratory where they are tested using RT-PCR (Xpert Flu, Cepheid, Sunnyvale, California) and multiplex PCR (FTD Respiratory pathogens 21, Fast-Track Diagnostics, Esch-sur-Alzette, Luxembourg).

### Statistical analysis

Data that included HMC hospitals and all primary healthcare centers across the country was retrieved from the virology laboratory database for positive Influenza A, H1N1pd09 and Influenza B from 1/1/2016 up to 31/12/2018 and reviewed for a period of 3 months, from September 2019. Specimens positive for viruses other than Influenza were excluded. We had a final sample size of 19,339. Initially, we checked and cleaned the datasheets from duplicates before conducting any analysis.

Those who had similar test results in 14 days have been considered as replicates for accurately assessing infection rates. In order to analyze the demographic and clinical characteristics of the study subjects, we conducted a descriptive statistical analysis and calculated the frequency,percentages, trends and seasonality of the viruses.

The rate of infection of each virus was calculated as the proportion of positive specimens for that particular virus out of the total tested samples per month or year. All sample (n = 1,447,636) were tested for influenza viruses, while 19339 samples were subjected for the detection of influenza.

Accordingly, the estimated numbers of influenza infections were calculated out of 1,447,636, while infection rates of other respiratory pathogens were calculated out of 19339.

We also searched for a temporal distribution of respiratory pathogens throughout the seasonality cycle of the viruses studied.

Categorical data was analyzed using a Pearson's chi-squared test to compare epidemiological factors (age groups, basic demographics and influenza). P values were considered significant if found < 0.05. Stata (StataCorp LLC, College Station, Texas) was used for descriptive statistics.

We estimated incidence of influenza-associated hospitalizations and in-hospital deaths for each year, by multiplying number of hospital discharge records (hospitalizations) with a diagnosis of Influenza by number of tested samples which were positive for influenza virus over the number of tested ILI case-patients samples. We then divided by the population at risk. based on those reported by Qatar Planning and Statistics Authority. We calculated 95% confidence intervals (95% CI) assuming a Poisson distribution.

### Ethics statement

The study included analysis of data obtained the virology laboratory database of Hamad Medical Corporation without patients' identification information. The study was approved by HMC-MRC: approval # 01-18-205.

## Results

### Demographics and circulating viruses

A total of 1,447,636 specimens were collected at different surveillance sites across Qatar from patients with ILIs, between January 2016 and December 2018. 19,339 (1.34%) were positive for at least one influenza type. The age of patients enrolled in this surveillance program was 1 week and or above: median age 9 (3 - 34 years). The majority were aged from 0 to 4 years or between 5 to 14 years (36% and 19% respectively). Males represented 56% (10916) of the study population. Of the positive samples, influenza virus A was the most frequently detected virus, reported in 13,799 (71%) patients. Influenza A viruses accounted for 71% of the positive samples. Among those who tested positive for influenza virus A, 6,718 (48.7%) were typed as H1N1pd09 (Table 1).

| Category | Surveillance year | | | | |
|---|---|---|---|---|---|
| | 2016 | 2017 | 2018 | Total | p-value |
| | N = 2,267 | N = 6,398 | N = 10,674 | N = 19,339 | |
| **Gender** | | | | | < 0.001 |
| Female | 834 (36.8%) | 2,924 (45.7%) | 4,665 (43.7%) | 8,423 (43.6%) | |
| Male | 1,433 (63.2%) | 3,474 (54.3%) | 6,009 (56.3%) | 10,916 (56.4%) | |
| **Age groups** | | | | | < 0.001 |
| 0 - 4 | 310 (13.7%) | 2,146 (33.5%) | 4,405 (41.3%) | 6,861 (35.5%) | |
| 5 - 14 | 357 (15.7%) | 1,643 (25.7%) | 1,677 (15.7%) | 3,677 (19.0%) | |
| 15 - 29 | 435 (19.2%) | 699 (10.9%) | 1,412 (13.2%) | 2,546 (13.2%) | |
| 30 - 44 | 574 (25.3%) | 1,018 (15.9%) | 1,927 (18.1%) | 3,519 (18.2%) | |
| 45 - 59 | 318 (14.0%) | 507 (7.9%) | 795 (7.4%) | 1,620 (8.4%) | |
| ≥ 60 | 273 (12.0%) | 385 (6.0%) | 456 (4.3%) | 1,114 (5.8%) | |
| **Influenza Type** | | | | | < 0.001 |
| Influenza Virus A | 1,273 (56.2%) | 4,915 (76.8%) | 7,611 (71.3%) | 13,799 (71.4%) | |
| A/H1N1 | 272 | 2,686 | 3,760 | 6,718 | |
| Influenza Virus B | 994 (43.8%) | 1,483 (23.2%) | 3,063 (28.7%) | 5,540 (28.6%) | |

***Table 1:*** *Demographic characteristics of the study population.*

### Influenza seasonality

Our data showed strong seasonal peaks for influenza. Both the number and the rate of positive results reported during cooler months increased substantially. Over a span of three years, between November and February each year the largest number of samples collected were reported during winter.

Likewise, in the October to December (12142 cases; 63%), the overall rates of positive cases for at least one influenza virus were significantly higher; followed by Jan to March (3,479 cases; 18%) (p < 0,000) (Figure 1). Influenza viruses spread steadily throughout the year; however, during the colder months, data from the whole three-year period clearly showed significant peaks. Around November and December 2017, the highest rates of influenza outbreaks were seen with up to 3.4%. These levels then declined to less 1.5% in February 2017 and started to peak again in September with a dramatic increase up to 5.3% in December 2018. Figure 2 illustrates the seasonality of influenza viruses during the surveillance years.

### Correlation between influenza and population characteristics

For the available data, the association of gender with the Influenza viruses was explored. Rates of influenza A, and influenza B were comparable between the two groups with no significant correlation. On the other hand, age group distribution of influenza showed that

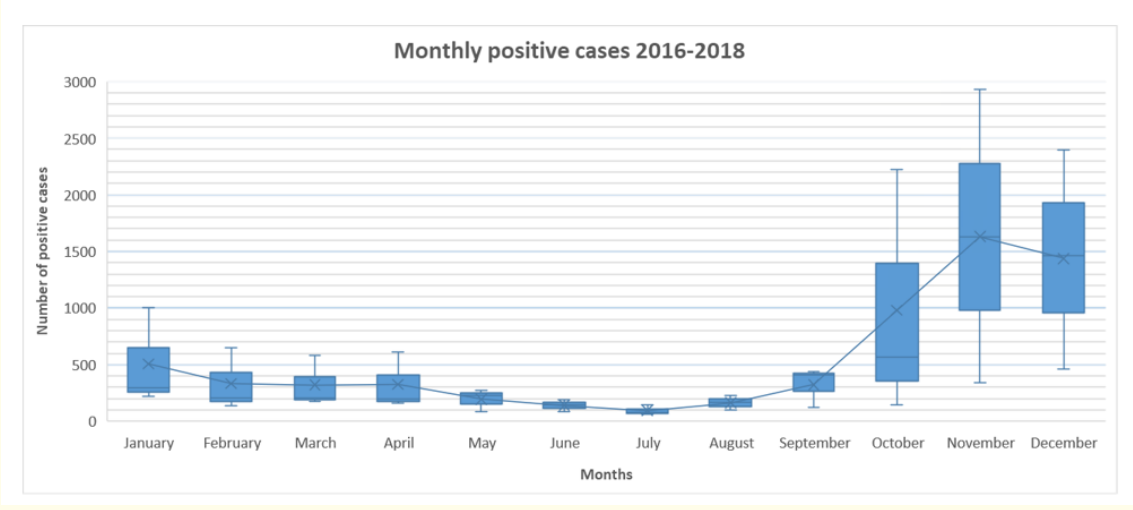


***Figure 1:*** *Monthly distribution of positive cases for at least one influenza virus (2016 - 2018). The box plot shows the median mean differences. X: mean. Bars: standard deviation. The horizontal lines within boxes show the median.*

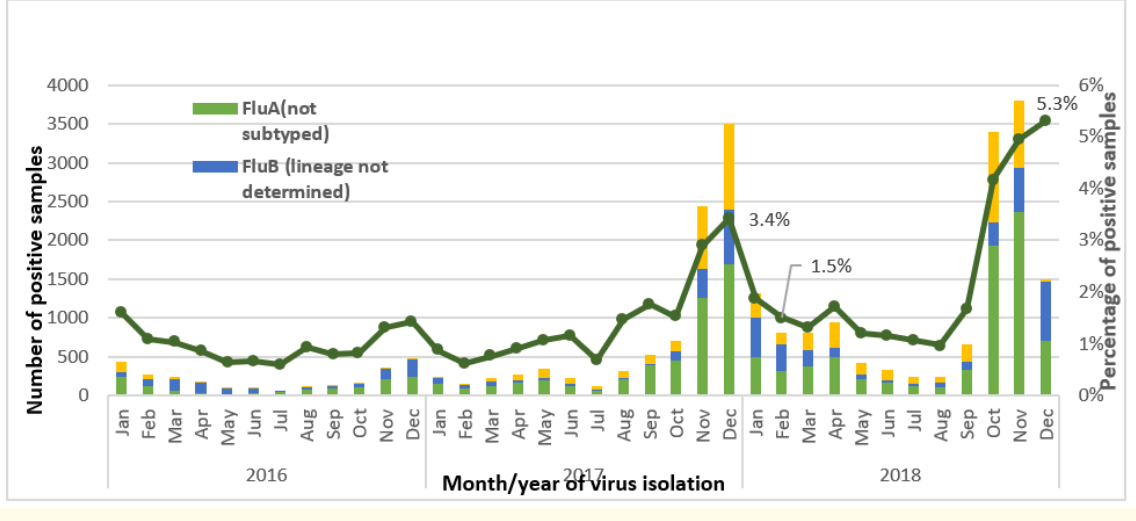


***Figure 2:*** *Seasonality of influenza viruses. The number of positive samples for each influenza type/subtype was calculated per month from 2016 to 2018. The percentage of positive cases was calculated out of the total tested samples for influenza viruses (n = 1,444,855).*

infection rate differed significantly between age groups. Patients aged between 0 and 4 years and those aged 60 and above had the highest rates of Influenza A viruses, with respective prevalence of 78.1 and 71.8 percent. Influenza B virus was observed at 40.1 percent of the positive cases in the 5 - 14 age group and the lowest was for patients aged between 0 and 4 years with a rate of 21.9 percent (Table 2).

| Category | Age groups | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | 0 - 4 | 5-14 | 15 - 29 | 30 - 44 | 45 - 59 | ≥ 60 | Total | p-value |
| | N = 6,861 | N = 3,677 | N = 2,546 | N = 3,519 | N = 1,620 | N = 1,114 | N = 19,337* | |
| **Influenza Type** | | | | | | | | <0.001 |
| Influenza Virus A | 5,358 (78.1%) | 2,204 (59.9%) | 1,672 (65.7%) | 2,560 (72.7%) | 1,203 (74.3%) | 800 (71.8%) | 13,797 (71.4%) | |
| Influenza Virus B | 1,503 (21.9%) | 1,473 (40.1%) | 874 (34.3%) | 959 (27.3%) | 417 (25.7%) | 314 (28.2%) | 5,540 (28.6%) | |
| *2 missing values | | | | | | | | |

***Table 2:*** *Influenza type by age groups.*

## Influenza hospitalization and death rates

We identified a total of 1893 influenza-associated hospitalizations and 27 deaths from 2016 till 2018 with an overall Influenza-associated hospitalization incidence rate of 23.86 (95%CI 22.79; 24.96) per 100,000 population and a hospital death rate 0.34 (95%CI 0.22; 0.49) per 100 000 population. Year 2018 had the lowest influenza-associated hospitalizations (n = 410), with a rate of 15.33 (95%CI 13.88; 16.88) per 100,000 hospital admissions. Compared to year 2016, in-hospital mortality rates for 2017 and 2018 were higher 0.37 vs 0.26 (Table 3). Year 2018 had the highest number of positive Influenza samples (10674) and the lowest flu hospitalization rates: 127 per 100000 admissions compared to 2016 (278) and 2017 (235) (Figure 3).

| | | | | | Estimated influenza-associated (per 100 000) | |
|---|---|---|---|---|---|---|
| Surveillance year | Mid-year Population size* | Hospitalizations due to influenza | Death due to influenza | Annual percentage of influenza positivity | Hospitalizations rate (95% CI) | Deaths rate (95% CI) |
| 2016 | 2617634 | 745 | 7 | 2267/286929 (0.8%) | 28.46(26.45;30.58) | 0.26 (0.10; 0.55) |
| 2017 | 2641669 | 738 | 10 | 6399/525036 (1.2%) | 27.94(25.96;30.03) | 0.37 (0.18; 0.69) |
| 2018 | 2675320 | 410 | 10 | 10673/635671 (1.7%) | 15.33(13.88;16.88) | 0.37 (0.17; 0.68) |
| Overall | 7934623 | 1893 | 27 | 19339/1447636 (1.3%) | 23.86(22.79;24.96) | 0.34 (0.22; 0.49) |
| *MDPS Qatar | | | | | | |

***Table 3:*** *Influenza hospitalization and death rates.*

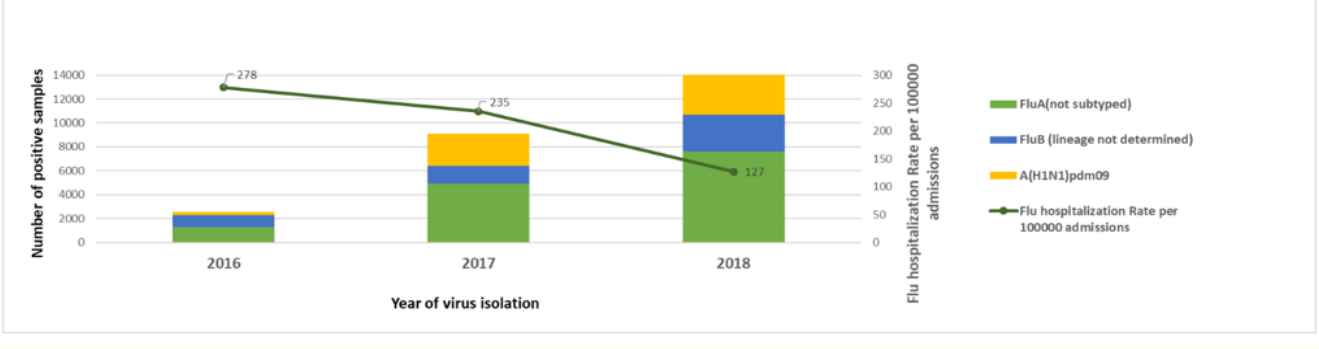


***Figure 3:*** *Annual flu hospitalization rate by virus from 2016-2018.*

## Discussion

Influenza is typically a self-limited and uncomplicated disease. It can, however, be related to extreme morbidity and mortality in certain groups at increased risk of serious or complicated influenza disease. It can cause a significant burden of disease (e.g. absence from school and work, increased frequency of outpatient medical visits) and children are important vectors for disease spread.

Our study is the first in Qatar to gather and analyse influenza specimen that include paediatric group. In 2016,14% of Qatar population was aged less than 15 years. Our findings showed that patients aged between 0 and 4 years had the highest rate of influenza A viruses (78.1%) and those aged between 5 - 14 years accounted for 40.1 % of the positive cases in influenza B. Significantly more cases were diagnosed during the months of October to December compared with January to March (63.0% versus 18.0%, $P < 0.001$). It is also understood that cold temperatures make it easier for viruses to survive and spread (Lowen and Steel, 2014) furthermore, schools are open during the cold months period, which allow infections to spread on.

Similar to our findings, the highest rates of infection occurred in school-age children (5 - 18 years of age) during community-based influenza outbreaks, with rates reaching up to 70 percent in some areas. Since children have the highest rates of infection and shed the virus for longer periods than adults, they play a significant role in the community-wide initiation and dissemination of influenza virus (Carr, 2012). To help prevent flu, CDC recommends that everyone aged 6 months and older get a yearly flu vaccine [12]. Immunization is the most effective way to prevent infection with influenza (Shaw., *et al*. 2002).

Figures from Oman showed an incidence rate of 20.6 per 100 000 of the Influenza-associated hospitalization which is lower than Qatar Influenza-associated hospitalization incidence rate 23.86 per 100,000. Their hospital death rate was 0.9 per 100,000 population higher than Qatar Influenza-associated hospital death rate 0.34 per 100,000 population.

## Conclusion

The incidence of laboratory-confirmed seasonal Influenza is high in Qatar. However, children and young adults are most commonly affected, and hence relatively low rates of severe complications and mortality are observed.

There are some limitations in this study. The reported data is limited to the cases of symptomatic ILI. This did not include patients who did not have normal ILI symptoms as described by the WHO ILI case. This may underestimate the real burden of respiratory infections. In addition, there was no details on the enrolled patients ' vaccination record that prevented further analyzes of vaccine coverage and effectiveness in the population surveyed.

The findings of this study will benefit in improving diagnostic procedures and refine them, as well as management and prevention of respiratory infections. The disease burden estimates will provide a better understanding of the impact of influenza in the Qatari community. These national estimates, would enable governments, nongovernmental agencies to make informed evidence-based decisions when allocating resources and planning intervention strategies to limit the spread of the disease and minimize associated costs. It will also help improving the timing of vaccination through recognizing the seasonality of viruses; encouraging vaccination strategies to target high-risk groups with an increased burden of infection.

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