Epidemiology of Influenza Virus Reinfection: A Retrospective Analysis of a Nine-year Influenza Surveillance Data

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Abstract

Background

Epidemiological characteristics profile of the reinfection of the influenza virus has not been well described.

Methods

Our study estimated the reinfection rate using nine-year influenza surveillance data and further examined the characteristics associated with the reinfection.

Results

A total of 53,605.6 person-months and the median time of 8.7 months were observed for reinfection. The cumulative reinfection incidence was 2% at 6 months, 4% at 12 months, 5% at 24 months, and 7% after 59 months. Living in the rural area (HR=1.37 [95% CI 1.29-1.45]), and age ≤ 6 years (HR=11.43 [95% CI 9.47-13.80]) were independent risk factors associated with influenza reinfection.

Conclusions

Our findings indicate that the reinfection of the influenza virus in Guangxi independently and positively associated with the rural area and younger age. The unusually high frequency of reinfection points to a need for further prospective longitudinal studies to better investigate sufficient impact on the development of broadly protective or universal vaccines.

Background

Influenza is an acute viral infection of the respiratory tract and yearly seasonal influenza epidemics are associated with excess morbidity and mortality. The World Health Organization (WHO) provides an estimate that influenza infections annually affect about 5-10% of adults and 20-30% of children (WHO, https://www.who.int/ith/diseases/influenza_seasonal/en/) and contribute to approximately 294,000-518,000 respiratory deaths globally [1]. Annual influenza vaccination is recommended as an effective measure to prevent seasonal influenza infections, especially among susceptible individuals including older people and children. Studies estimate that the influenza vaccination can prevent about 59% (95% CI (confidence interval) 51-66%) of laboratory-confirmed influenza [2], and when the vaccine strains and circulating strains match well, vaccination can reduce influenza-like-illness (ILI) visits by 42% (95% CI 9-63%) [3]. However, the effectiveness of influenza vaccines varies from season to season depending on a variety of factors, including age and health status of the recipients, previous exposure to influenza viruses, and the matching degree of circulating virus and strains included in the vaccine.

Several studies have already reported reinfections with the same type or subtype of influenza viruses in humans [4-6]. It was estimated that 3-25% of children experienced reinfections with influenza B

depending on the influenza seasons [5]. Another study reported that about 32% of patients living in a remote island experienced two attacks with influenza A (H3N2) virus [6]. However, most of these studies were established based on a case report, which only focuses on a specific population with a small sample size. It is difficult to systematically analyze the epidemiological characteristics of the influenza reinfections in a population-based. As known, influenza infections are more likely to affect some specific populations, such as child and older people, and more likely to occur in a certain season, typically in fall and winter [7]. Understanding the epidemiological features of the re-infected population would provide useful information for future prevention of seasonal influenza.

China has developed a national influenza surveillance and response system to improve early response to the influenza virus with pandemic potential. All newly diagnosed influenza cases were required to be reported via the National Notifiable Infectious Disease Reporting Information System (NIDRIS) within 24 hours after diagnosis. The establishment of this system provides an opportunity to capture influenza virus reinfections in a diverse population and further analyze the epidemiological characteristics. In this study, we identified demographic characteristics associated with influenza reinfection using data abstracted from NIDRIS. The findings of this study will advance our understanding of characteristics that may increase the risk of reinfections and inform the prevention measures to decrease influenza burden.

Materials And Methods

Data Source

Data of this study included all influenza cases of Guangxi China from January 2011 to December 2019 recorded in NIDRIS. The NIDRIS database encompasses data on demographics including patients' name, the name of either of the patient's guardians (if age <18 years), national identification number, sex, date of birth, age, contact telephone number, living address, and diagnosis classification (clinically diagnosed cases or laboratory-confirmed cases), and date of illness onset and diagnosis, and virus serotype for those laboratory-confirmed cases. Clinically diagnosed cases and laboratory-confirmed cases were defined according to influenza diagnosis and treatment protocol designed by the National Health Commission of the People's Republic of China [8]. Patients were defined as laboratory-confirmed cases if the pharyngeal swabs were positive RT-PCR results tested by the local CDC. The study was approved by the institutional review board of the Guangxi Center for Disease Control and Prevention.

Definition of influenza reinfections

With the approval of Guangxi Center for Disease Control and Prevention, we extracted data on patients' names, the name of either of the patient's parents, national identification number, date of birth, contact telephone number, and living address from NIDRIS. We matched their personal information to identify reinfection episodes. The process of defining influenza reinfections was shown in Figure 1. A total of 150,212 patients with 154,732 episodes were abstracted from NIDRIS. A total of 4710 potential reinfection cases were first identified based on one of the following criteria: 1) having the same name and national identification number; or 2) having the same name and contact telephone number; or 3) having

the same name, birth date, and living address; or 4) having the same name, guardians' name, and birth date; or 5) having the same name, guardians' name, and living address.

Taking into account the incubation period and duration of symptoms, independent attacks were defined with the two infections with >35-day interval, combined with the longest incubation period of influenza reported (7 days) and the longest duration of symptoms onset (28 days). Patients who experienced ≥ 2 independent attacks were defined as influenza reinfection cases. This 35-day criterion was used to define both clinically diagnosed reinfections and laboratory-confirmed reinfections. Finally, we identified 4,007 patients who had influenza reinfection, and 237 cases underwent laboratory tests. Among them, 49 underwent twice laboratory tests that confirmed the types of influenza viruses (i.e. types A and B).

Statistical analysis

Comparisons of characteristics between patients who had one infection and reinfection were performed using the chi-square test for categorical variables and Mann-Whitney U-Test for continuous variables not following a normal distribution. Kaplan-Meier estimate and log-rank tests were used to assess the proportion of influenza reinfections overtime after their first infections. Cox proportional hazards models were used to explore the characteristics associated with reinfection. All patients who experienced twice laboratory-confirmed test were categorized to 4 groups based on the types of the influenza viruses infected: 1) both type A, 2) both type B, 3) type A followed by type B, and 4) type B followed by type A. All analyses were conducted using R Project (version 3.6.3) and $p \leq 0.05$ in 2-tailed was considered statistically significant.

Results

Table 1 shows patients characteristics. The median age at the first infection was 4.5 (IQR=2.0-7.5) years. About half of the patients were males (56.1%) and living in the rural area (52.6%). Among the patients who had reinfection, 10.0% infected three times, and 2.6% infected four times or more. Compared with the patients without reinfection, those with reinfection were younger and more likely to live in a rural area ($p < 0.001$). Figure 2 shows the influenza seasonality across 2011-2019. For the entire sample, while influenza viruses circulated year-round, influenza season generally occurred in the fall and winter. Most of the time influenza activity peaked in fall and winter, but activity could last as late as spring. The incidence of influenza infection increased in recent years, particularly after 2018. The patterns were similar for the patients with reinfection and those with laboratory-confirmed reinfection.

During the observation period, the patients contributed a total of 53,605.6 person-month and a median of 11.1 months (IQR 5.3-19.5) after their first incidence. The recurrent episode occurred 1.2-96.1 months (median 8.7) between two consecutive onsets. Specifically, the cumulative reinfection incidence was 2% at 6 months, 4% at 12 months, 5% at 24 months, and 7% after 59 months. However, in the lower age group (age ≤ 6 years), the rate reached 4% at 6 months, 7% at 12 months, remained 12% after 73 months; for the teenagers (7-18 years), the rate was 1% at 7 months, 2% at 12 months, reached 5% at 45 months; and for the elder patients (> 18 years), the rate still maintained 1% until the end of the observation period

(107 months) (STable). The probability rate in urban and rural area at 12 months, 24 months and 36 months was 3% vs. 5%, 4% vs. 6%, 6% vs.7%, respectively. Multiple Cox regression analysis indicated that living in the rural area (hazard ratio [HR]=1.37 [95% CI 1.29-1.45]), age ≤ 6 year (HR=11.43 [95% CI 9.47-13.80]), and age between 7 and 18 years (HR=3.57 [95% CI 2.95-4.33]) were independent risk factors associated with influenza reinfection (Figure 3). The survival rate was significantly different across age groups of ≤ 6 , 7-18, and >18 years ($p<0.001$) and was different between urban residence and rural residence ($p<0.001$).

Of the 237 patients with recurrent laboratory-confirmed influenza, 219 patients (92.4%) had 2 episodes and 18 patients (8.0%) had ≥ 2 episodes. Among 49 patients experiencing twice laboratory tests, 12 was infected with influenza type A twice, 5 infected with influenza type B twice, 14 infected type A followed by type B, and 18 infected with type B followed by type A. The interval between two consecutive laboratory-confirmed episodes of the four groups differed ($p=0.148$), as the maximum was 72.9 months, and the minimum was 1.2 months (Table 2).

Discussion

Although several studies reported recurrent influenza, most of that was case-report [5, 6, 9], our results showed reinfection of influenza is not a rare phenomenon. We found that a total of 4,007 patients (8,527 episodes) with probable recurrence influenza in Guangxi among 2011-2019. Recurrence of influenza occurred 1.2-96.1 months after the primary infection and reached 7% at 59 months in our study. Living in the rural area and younger age were independent risk factors associated with influenza virus reinfection. During the observational period, 2.7% of people experienced influenza reinfection. Living in a rural area and <18 -year was associated with influenza virus reinfection.

The results of this study showed that the influenza reinfection episodes primarily appeared after 2018, which was similar to the patterns for the entire sample. The consistent trend between infection and reinfection means more infection will undoubtedly lead to an increase in recurrence. Our finding that influenza cases surged in 2019 is consistent with the previous studies that have reported in other countries [10]. One possible reason is that the proportion of a variant with the three-amino-acid deletion was rising, which were antigenically different from the vaccine strain for the 2018-2019 season [11]. Another reason may be due to a rapid increase in the relevant genetic diversity of the influenza A (H1N1) pdm09 virus between 2018-2019 [12].

It seems reasonable that most individuals are probably relatively protected from reinfection with the same or different influenza strains and subtypes for several months [13]. Previous studies showed that vaccination-induced protection gradually waned after 6-12 months [14, 15]. Our study suggests that the influenza reinfection occurred at an average of 8.7 months after the previous infection. The influenza reinfection may be due to the possibility of a suboptimal immune response after the initial natural infection, which led to the failure to protect the reinfection. The study has shown that individuals could be re-infected by the same stain during the multi-wave outbreaks [6, 16]. A recent experiment study reported

that individuals could be re-infected by the identical A (H1N1) pdm09 influenza virus about 1 year after initial infection, and speculated that it could be due to lacking protective immunity induced by the previous infection [4]. Likewise, other studies reported that short-interval sequential infections could be a possible explanation for the multi-wave epidemic of A (H3N2) [6, 17].

Extrinsic properties, such as demographics and environment, have also been associated with influenza reinfection [18]. Consistent with previous studies that have suggested high risks of influenza reinfection among children and juniors [5], we found less than 18 years old was an independent risk factor associated with reinfection. Children might be more vulnerable to be attacked by the influenza virus due to immature immunity or immunodeficiency. On the other hand, in adults protection against A (H3N2) lasted longer than that in children [19], and antibody response induced by one strain was more likely to protect against another related-strains [20, 21], which might reduce the risk of reinfection in adults. In addition, our study suggests that people living in rural areas were more likely to get re-infected, which is consistent with previous studies that showed that rural residences presented a risk factor with respiratory disease [22]. The high risk of reinfection might be attributed to less access to health education and host behavior, such as higher rates of tobacco use, physical inactivity, lower rates of fruit and vegetable intake [23].

Previous studies have reported antibody-dependent enhancement in some communicable diseases, such as dengue virus or other coronaviruses of the SARS type, which increased the transmissibility of the previous infection to the new infections [24, 25]. Thus, further research is needed to explore whether primary influenza infection reduces or increases the susceptibility of reinfection or transmission of reinfection, increasing the probability of reinfection. In addition, a study showed that patients with reinfection had relatively milder symptoms compared with their first infection [26]. We did not examine the association due to a lack of data about the severity of symptoms. Thus, further studies are needed to further testify whether reinfection could aggravate or ease the progress of the illness.

Our study has several limitations. First of all, most recurrent influenza episodes occurred in recent two years 2018-2019, resulting in the observation periods were not sufficient. This may raise concerns that the burden of recurrence influenza we found was underestimated. Meanwhile, this made a little difficult to draft the conclude that influenza reinfection shared a similar seasonal pattern [27]. In addition, the sample size of patients receiving laboratory tests is too small, which may result in insufficient statistical power and impact the accuracy of the results. Also, we could not describe the features of patients with specific influenza classification strains due to a lack of nuclear-acid testing results. Last but not least, lacking immunization records may underestimate the cumulative probability rate of influenza recurrence.

Conclusions

In conclusion, analyzing the nine-year surveillance data, our study demonstrates a high burden of influenza reinfection especially for people less than 18 years and living in a rural area. It is essential to expand the detection of pathogens to further clarify the probability of influenza infection and the

reinfection by different subtypes of influenza. This study also advances our understanding of the cross-immunity effects between different subtypes, providing scientific evidence supporting the development of vaccination strategies. Furthermore, clinical and basic studies are warranted to assess the immune response to influenza reinfection and whether it will aggravate the severity of the disease.

Abbreviations

CI, confidential interval; HR, Hazard Ratio; NIDRIS, National Notifiable Infectious Disease Reporting Information System; RT-PCR, Reverse Transcription-Polymerase Chain Reaction; SARS, Severe Acute Respiratory Syndrome.

Declarations

Ethics approval and consent to participate

The study was approved by the institutional review board of the Guangxi Center for Disease Control and Prevention.

Consent for publication

Not applicable.

Availability of data and materials

All data are available in the manuscript.

Competing interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Authorship contribution statement

Chuanyi Ning: Formal analysis, Supervision. Yi Tan: Writing - review & editing, Supervision.

Jing Wang, Lina Jiang and Yunan Xu: Conceptualization, Methodology, Writing – original draft. Chao Zhang, Weitao He and Fuyin Bi: Data curation.

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Tables

Table 1 Demographic characteristic of patients without or with recurrent influenza in Guangxi, 2011-2019

	Patients with 1 episode (N=146,205)	Patients with ≥ 2 episodes (N=4,007)	Statistics (df)	p- value
Sex, n (%)			$\chi^2 (1) = 1.320$	0.251
Male	80,613 (55.1)	2,246 (56.1)		
Female	65,592 (44.9)	1,761 (43.9)		
Residence, n (%)			$\chi^2 (1) = 22.348$	<0.001
Rural	71,383 (48.8)	2,108 (52.6)		
Unban	74,822 (51.2)	1,899 (47.4)		
Age (yr), n (%)			$\chi^2 (4) = 2293.171$	<0.001
≤ 1	12,696 (8.7)	964 (24.1)		
2-6	38,851 (26.6)	1,820 (45.4)		
7-18	76,131 (52.1)	1,128 (28.2)		
19-59	15,377 (10.5)	77 (1.9)		
≥ 60	3,150 (2.1)	18 (0.4)		
Median (IQR)	8.2 (4.3-13.9)	4.5 (2.0-7.5)	$Z = -42.819$	<0.01
Frequency of infection episode, n (%)				
2	-	4,007 (100.0)	-	-
3	-	400 (10.0)		
≥ 4	-	105 (2.6)		

Note: df, degree of freedom. yr, year. IQR, Inter Quartile Range.

Table 2 Demographic characteristics of patients with recurrent laboratory-confirmed influenza in Guangxi, 2011-2019

	Reinfection after influenza A with influenza A (N=12)	Reinfection after influenza A with influenza B (N=14)	Reinfection after influenza B with influenza A (N=18)	Reinfection after influenza B with influenza B (N=5)
Sex, n (%)				
Male	7(58.3)	10 (71.4)	10 (55.6)	3 (60.0)
Residence, n (%)				
Rural	3 (25.0)	3 (21.4)	7 (38.9)	2 (40.0)
Age at first episode (yr), n (%)				
≤1	2 (16.7)	2 (14.3)	2 (11.1)	0
2-6	6 (50.0)	5 (35.7)	13 (72.2)	4 (80.0)
7-18	4 (33.3)	6 (42.9)	3 (16.7)	0
19-59	0	1 (7.1)	0	0
≥60	0	0	0	1(20.0)
Median (IQR)	4.0 (2.2-6.9)	6.4 (3.9-10.3)	5.2 (1.9-6.2)	3.3 (2.1-63.9)
Interval between two laboratory- confirmed (mo)				
Median (range)	25.1 (8.0-64.8)	14.4 (3.3-59.0)	12.1 (1.2-72.9)	4.7 (2.0-28.4)

Note: yr, year. IQR, Inter Quartile Range. mo, month.

Figures

Figure 1

Flow diagram of selection process for patients with recurrent influenza and laboratory confirmed from NIDRIS in Guangxi, 2011-2019.

Figure 2

Timeline for outbreak of influenza virus in Guangxi, 2011-2019. A) all influenza cases reported; B) all laboratory-confirmed cases reported; C) all influenza recurrence cases. The smaller frames above each figures just reduced the vertical from 2011 to 2017 to get a clearer illustration of the trends by time.

Figure 3

Kaplan-Meier analysis of survival for influenza recurrence after primary episodes in Guangxi, 2011-2019.

A) the cumulative probability of reinfection among all patient with reinfection; B) the cumulative probability of reinfection among patients with different gender; C) the cumulative probability of reinfection among patients with different age group; D) the cumulative probability of reinfection among patients living in rural and urban.