Assess transmissibility of different influenza subtypes: Based on a SEIABR model

Haoyun Dai
Hunan Normal University
Nan Zhou
Hunan Normal University
Mengxiang Chen
Hunan Normal University
Guoqun Li
Hunan Normal University
Shanghui Yi
Hunan Normal University
Xiuqin Hong
Hunan Normal University First Hospital: Hunan Provincial People's Hospital
Meifang Quan
Hunan Normal University
Wen-Ting Zha (183259829@qq.com)
Hunan Normal University
Yuan Lv
Hunan Normal University

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Abstract

Background: Influenza is a worldwide public health problem which causes a serious economic and health burden. In order to provide a scientific basis for improving the prevention and control level of influenza, using dynamic model to evaluate the infection rates of influenza different subtypes from 2010 to 2019 in China.

Methods: This article established SEIABR model and calculated the infection rates of different influenza subtypes by using the Berkeley Madonna software.

Results: The average infection rate of influenza was $(7.95\pm1.27)\times10^{-10}$, and influenza A was $(7.25\pm0.82)\times10^{-10}$, influenza B was $(5.88\pm0.97)\times10^{-10}$. In addition, the infection rates of A /H1N1, A/H3N2, B/Yamagata and B/Victoria were $(7.25\pm0.82)\times10^{-10}$, $(6.13\pm0.35)\times10^{-10}$, $(6.01\pm0.52)\times10^{-10}$, $(6.37\pm0.79)\times10^{-10}$.

Conclusion: Between each year, flu transmission capacity had fluctuation. Influenza A was more transmissible than influenza B, and during the major subtypes, influenza A/H1N1 was the most transmissible.

Background

Influenza, as an acute respiratory infection caused by influenza virus, is transmitted through coughing, sneezing or touching surfaces, and then touching the mouth or eyes. Influenza is usually divided into four types: A, B, C, D, main influenza type A virus subtypes are H1N1, H3N2 and in B are Victoria and Yamagata [1]. Influenza viruses often mutate, with epidemiologically important antigenic variants appearing every two to three years under the immune pressure of the population. Because of the high flu virus mutation frequency, the public often lack immunity. And with the short incubation period, infectivity and transmission speed, influenza could suddenly outbreak, trigger a worldwide pandemic or local popular [2]. Go back in history, the flu pandemic in 1918 was the worst, infecting 500 million people worldwide and killing 40 million at least [3]. According to WHO (World Health Organization), every year in the World, 5-10% of adults and 20-30% of children are infected with influenza virus, resulting in 3-5 million severe cases and 290-650,000 deaths [4]. And the outbreak of influenza led to school suspension, business production, increasing number of hospital patients significantly and other phenomena. In 2019, the United States reported that there were at least 36 million cases of influenza, of which 370,000 were hospitalized and 22,000 died [5]. In China, since 2017, the incidence and severity of influenza have been on the rise. And the number of influenza outbreaks was also higher than the same period in previous years [6]. Influenza has become one of the most important public health issues in the world, all countries faced new challenges to prevent and control work particularly through COVID-19 and influenza global pandemic.

Timely surveillance, analysis, understanding of influenza flow characteristics and transmission capacity are important ways to prevent and control influenza outbreaks and pandemics. In recent years, mathematical model has become the mainstream of infectious disease research. Infectious disease dynamics model is a new method in epidemiological studies, mainly according to the law of population growth, study occurrence, development and dissemination to reflect disease characteristics, mechanism and ability. However, in influenza research field, most of dynamic models were limited to research a single outbreak, zone, subtype and prevention, not integrally considered transmission capacity of different subtypes. In addition, viruses mutated constantly, prevention and control measures to continuously upgrade, it is necessary to build a new model to fit recent influenza data again. Therefore, this paper simulated the infectivity of the main infection subtypes of influenza based on the SEIABR model, to provide a scientific basis for the prevention and control of different influenza subtypes.

Methods

Data source

The reported case of influenza from 2010 to 2019 in China were collected from China National Influenza Center(http://www.chinaivdc.cn/cnic). The demographic data came from National Bureau of Statistics of China(http://www.stats.gov.cn).

Models and statistical analysis

SEIABR model

Currently, influenza surveillance system did not cover all the cases in China, some flu patients did not diagnosis in hospital, and because of limited grassroots medical conditions, not all patients had etiological detection. Previous model did not consider the suffering from the flu but did not go to the sentinel hospital patients. In this study, a SEIABR model was developed to simulate the transmission of influenza in China. The human populations were subdivided into six classes, namely Susceptible(S), Exposed(E), Infected (I), Asymptomatic (A), Recovered(R), Untreated Patient(B) (Figure 1).

The model was established based on the following assumptions:1) A patient effective contacted with a susceptible person would transmit flu to a susceptible person, and the infected rate was β; 2) After infected, the exposed person (E) would turn to I, A or B, after an incubation period ($1/\omega$), the number of newly I, A and B per unit time were wE. 3) c meant fatality rate, the fatality of I per unit time was (m+c)I. 4) γrepresented recovery rate, the number of R at time t was (γA+γB+γI). 5) Consider the natural birth and death of populations, set birth rate as μ, and mortality as m.

The differential equation based on SEIABR model was as follows, we set dS/dt, dE/dt, dI/dt, dA/dt , dB/dt and dR/dt to describe the number of population at time t :

$$\begin{cases} dS/dt = \mu N - \beta SE - mS \\ dE/dt = \beta SE - mE - pwE - (1-p)qwE - (1-p)(1-q)wE \\ dI/dt = (1-p)qwE - \gamma I - (m+c)I \\ dA/dt = pwE - \gamma A - mA \\ dB/dt = (1-p)(1-q)wE - \gamma B - (m+c)B \\ dR/dt = \gamma(A+I+B) - mR \end{cases}$$

Parameter estimation

In this study, there were eight parameters, which were infection rate (β), birth rate (μ), mortality(m), the proportion of asymptomatic infection rate of people (p), consultation rate (q) latency coefficient (w), case fatality rate (c) and removal rate of I (γ), all parameters and their sources were listed in Table 1. Through 1stopt, Matlab7.1 and Berkeley Madonna8.3.18, the residual square and least square method were used to estimate the influenza infection rate (β). β represented the probability of infection after a contact between an infected person and a susceptible person, it was also measuring the ability of virus transmission.

All parameters and initial values of each categories were list in Table 2.

1. Birth rate, mortality and Total population came from China Statistical Yearbook.
2. Inapparent infection rate and case fatality rate on the basis of researches [7-10] were 0.33,1%-0.5%.
3. Consultation rate according to the data from National Influenza Center and result of some Literatures [7-10] set as 25-0.70.
4. According to studies [7-10] and data fitting, we supposed A, B and I had the same recovery rate, so we set recovery time as 3-10 days, and the recovery rata(γ) is 1/10-1/3.

Results

Influenza epidemics from 2010 to 2019

From January 1, 2010 to December 31, 2019, 671,693 cases of Influenza were reported. The average incidence was 4.90/10000, the lowest was 1.60/10000 in 2011, and the highest was 8.56/10000. There were 449,042 cases of influenza A, accounting for 66.85%, and 222,651 cases of influenza B, accounting for 33.15%. In influenza A, H3N2 accounted for 38.79% of the reported

cases, followed by H1N1, accounting for 27.01%. Part of influenza B was not classified, and the proportion of Victoria subtype (10.71%) and Yamagata subtype (10.46%) was basically equal. Detail shown in Table 3.

The data showed that onset of influenza was cyclical in every year (Figure 2). In 2011, 2013, 2016, 2018 and 2019, there was only one influenza pandemic cycle in winter spring season. While, in 2010, 2012, 2014, 2015 and 2017, there were two cycles in winter spring season and summer fall season. Influenza A had peak period each year in winter spring season except 2012. H1N1 generally peaked at the beginning of the year, while H3N2 peaked at the middle or end of the year. Influenza B had a distinct epidemic cycle in 2010, 2012, 2016, late 2017 and early 2018.

Influenza transmission capacity assessment

Based on SEIABR model, the annual influenza infection rate (β) was simulated, the range of β is (6.02~9.44) $\times 10^{-10}$ and average was (7.95±1.27) $\times 10^{-10}$. β fluctuated to a certain extent among different years, from 2010 to 2013, the probability of influenza transmission was relatively high; after decreasing in 2014, it remained stable, and after 2017, it showed an upward trend. The result was shown in Table 4.

Comparison of the Different subtypes infection rates (β) of influenza A and B

Fit with actual data by Berkeley Madonna, the average infection rate of influenza A was (7.89±0.78)$\times 10^{-10}$ and influenza B was (5.88±0.97)$\times 10^{-10}$ Influenza A was more transmissible than influenza B. Using the same method to fit the infection rates of different subtypes of influenza. The results showed that the average infection rates of H1N1, H3, Yamagata and Victoria were (7.25±0.82)$\times 10^{-10}$, (6.13±0.35)$\times 10^{-10}$, (6.01±0.52)$\times 10^{-10}$, and (6.37±0.79)$\times 10^{-10}$. Influenza H1N1 had a higher prevalence rate than other influenza types. The detail data were shown in Table 5.

Discussion

Because of the flexibility and unique advantages, dynamic model had become the mainstream mathematical model of infectious disease research [11]. This article, based on SEIABR model, simulated the occurrence of influenza in China from 2010 to 2019, and compared the transmission capacity of influenza different subtypes. The average β was (7.95±1.27) $\times 10^{-10}$ which meant a patient contacted 10 billion person could lead to 6-9 infections. Taking China's 1.4 billion population as an example, one patient could lead to (0.94-1.29) susceptible people becoming infected. It was similar to TRACHT S M's study in the community level [12], but lower than the transmission capacity of influenza outbreak studied by Tianmu Chen et al [13].

This study calculated and compared the probabilities of annual transmission of influenza A and influenza B, and found that between 2010 and 2019, the ability of influenza A to spread was higher than that of influenza B. This meant that a person infected with influenza A had a higher ability to infect vulnerable people than a person who infected with influenza B. Influenza A was the only influenza virus subtype had an animal host [14], its infectivity was manifested by the ability of horizontal gene transfer, which could cause repeated infection of the host [15]. Which may lead to the outbreak of an influenza A virus pandemic. The inherent characteristics of replicase of influenza B virus leaded to slower antigenic characteristics and slower gene evolution [16]. And Influenza B virus didn't have animal host and pandemic potential [17]. Even so, the study found that the transmission ability of influenza B had an upward trend in recent years, which may be related to the antigen drift and antigen transfer of influenza B and how it escaped from the body's immune defense [18,19]. What was more, the Victoria strain in type B was prone to cluster infection [20], people should pay more attention to that.

Then, we compared the transmissibility of several common influenza subtypes. Among them, H1H1 had the strongest transmission capability, and the ability of other influenza subtypes was similar. H1N1 was a new influenza subtype in 2009, which contained the RNA gene fragments of avian influenza, swine influenza and human influenza viruses, and had the characteristics of both Asian swine influenza and African swine influenza viruses. Its strong transmission ability may be one of the main reasons for its worldwide pandemic [21,22]. And H1N1 was prone to mutated strains with an interval of 2 to 3 years. The change of antigen would reduce the protection efficiency of the vaccine, and it was difficult to take effective prevention and control measures in advance [23,24]. Beyond that, H1N1 was more likely to cause pneumonia than H3N1, resulting in a greater

disease burden, which required more attention [25]. We also found that the total transmissible ability of influenza A was higher than that of the two subtypes (H1N1 & H3N2), which may be related to the superimposed epidemics of influenza A and H3N2 in winter and summer. And a phenomenon of co-infection among various subtypes of influenza A may enhance its transmission power [26].

The dynamics model of infectious diseases had better flexibility and could be adjusted according to the actual situation, so that the model was better consistent with reality. However, model was sensitive to the setting of the initial value, which was greatly influenced by subjective factors and empirical factors. Therefore, the setting of the initial value need to be carried out on reading large number of literatures and combining with the actual situation of influenza prevention and control in China.

Conclusion

Based on the SEIABR model, the probability β of influenza infection was calculated to be (7.95±1.27) $\times 10^{-10}$, with a certain fluctuation among different years. Influenza A was more transmissible than influenza B, and of the major subtypes, influenza A (H1N1) was the most transmissible.

Declarations

Ethics approval and consent to participate

Not applicable

Consent for publication

Not applicable

Availability of data and materials

In this study, all data were availability.

The reported case of influenza from 2010 to 2019 in China were collected from China National Influenza Center(http://www.chinaivdc.cn/cnic). The demographic data comes from National Bureau of Statistics of China(http://www.stats.gov.cn).

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

H D, N Z and W Z mainly responsible for analysis data, building model;

H D and W Z mainly draft article and check English writing

X R, M X, G L mainly in charge of the collection of data and searching for relevant parameters;

X H in charge of checking the article;

Y L, WZ and M Q mainly responsible for sponsorship of funds and final check the article.

All authors read and approved the final manuscript.

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Tables

Table 1 SEIABR Model parameters and definitions

Parameters	Definition	Source
S	Susceptible	N-E-I-A-B-R
E	Exposed	Calculated by differential equations
I	Infected	Actual outbreak data
A	Asymptomatic	Actual outbreak data
B	Untreated Patient	Actual outbreak data & Calculation
R	Recovered	The initial value R = 0
N	Population	China Statistical Yearbook
μ	Birth rate	China Statistical Yearbook
m	Mortality	China Statistical Yearbook
β	Infection rate	parameter estimation(OLS)
p	Inapparent infection rate	Literatures [7-10]
q	Consultation rate	National Influenza Center & Literatures [7-10]
w	Incubation relative rate	Literatures [7-10]
c	Case fatality rate	Literatures [7-10]
γ	Removal rate	Literatures [7-10] & Data fitting

Table 2 The original parameters of SEIABR model

Year	Parameters	Value ($\times 10^4$)	Parameters	Value	Parameters	Value
2010	N	134091	μ	1.19%	m	0.71%
2011	N	134735	μ	1.19%	m	0.71%
2012	N	135404	μ	1.21%	m	0.72%
2013	N	136272	μ	1.21%	m	0.72%
2014	N	136782	μ	1.24%	m	0.72%
2015	N	137462	μ	1.21%	m	0.71%
2016	N	138271	μ	1.30%	m	0.71%
2017	N	139008	μ	1.24%	m	0.71%
2018	N	139538	μ	1.09%	m	0.71%
2019	N	140005	μ	1.05%	m	0.71%
2010-2019	p	0.33				
	q	0.25-0.70				
	w	1/7-1				
	c	0.1%-0.5%				
	γ	1/10-1/3				

Table 3 Description of different influenza subtypes in China from 2010 to 2019 N (%)

Year	Different subtypes of influenza									
	Influenza A					Influenza B				Total
	H1N1	H3N2	H5	Not subtyped	Total	Yamagata lineage	Victoria lineage	Not subtyped	Total	
2010	6654 (15.06)	12188 (27.60)	2 (0.00)	3389 (7.67)	22233 (50.34)	1171 (2.65)	2598 (5.88)	18164 (41.13)	21933 (49.66)	44166
2011	10369 (48.19)	2339 (10.87)	0 (0.00)	812 (3.77)	13520 (62.84)	879 (4.09)	1348 (6.27)	5768 (26.81)	7995 (37.16)	21515
2012	352 (0.79)	20885 (47.07)	4 (0.01)	1430 (3.22)	22671 (51.09)	3569 (8.04)	8597 (19.38)	9534 (21.49)	21700 (48.91)	44371
2013	13786 (31.07)	13113 (39.74)	0 (0.00)	396 (1.20)	27295 (82.73)	1666 (5.05)	227 (0.69)	3804 (11.53)	5697 (17.27)	32992
2014	18691 (26.09)	32958 (46.00)	0 (0.00)	294 (0.41)	51943 (72.50)	7884 (11.00)	673 (0.94)	11141 (15.55)	19698 (27.50)	71641
2015	1938 (2.75)	47404 (67.51)	0 (0.00)	114 (0.16)	49456 (70.43)	16639 (23.70)	1058 (1.51)	3066 (4.37)	20763 (29.57)	70219
2016	21363 (24.37)	29502 (33.65)	0 (0.00)	286 (0.33)	51151 (58.34)	5121 (5.84)	20134 (22.97)	11266 (12.85)	36521 (41.66)	87672
2017	16995 (17.16)	58115 (58.68)	0 (0.00)	131 (0.13)	75241 (75.97)	14858 (15.00)	6703 (6.77)	2236 (2.26)	23797 (24.03)	99038
2018	40681 (50.66)	6356 (7.92)	0 (0.00)	72 (0.09)	47109 (58.67)	18097 (22.54)	2345 (2.92)	12745 (15.87)	33187 (41.33)	80296
2019	50620 (42.26)	37709 (31.48)	0 (0.00)	94 (0.08)	88423 (73.82)	360 (0.30)	28261 (23.59)	2739 (2.29)	31360 (26.18)	119783
Total	181448 (27.01)	260570 (38.79)	6 (0.00)	7018 (1.04)	449042 (66.85)	70244 (10.46)	71944 (10.71)	80463 (11.98)	222651 (33.15)	671693

Table 4 Influenza contagiousness (β) assessment

Year	β ($\times 10^{-10}$)	Growth Amount ($\times 10^{-10}$)		Development Speed (%)		Growth speed (%)	
		Accumulated	Year by Year	Fixed Base Relative	Link Relative	Fixed Base Relative	Link Relative
2010	8.17	-	-	100.00	100.00	-	-
2011	9.22	1.05	1.05	112.85	112.85	12.85	12.85
2012	8.85	0.68	-0.37	108.32	95.99	8.32	-4.01
2013	9.66	1.49	0.81	118.24	109.15	18.24	9.15
2014	6.87	-1.30	-2.79	84.09	71.12	-15.91	-28.88
2015	6.62	-1.55	-0.25	81.03	96.36	-18.97	-3.64
2016	7.05	-1.12	0.43	86.29	106.50	-13.71	6.50
2017	6.03	-2.14	-1.02	73.81	85.53	-26.19	14.47
2018	7.79	-0.38	1.76	95.35	129.19	-4.65	29.19
2019	9.25	1.08	1.46	113.22	118.74	13.22	18.74

Table 5 Different subtypes infection rates (β) of influenza A and B ($\times 10^{-10}$)

Year	Influenza A			Influenza B		
	H1N1	H3N2	Total	Yamagata	Victoria	Total
2010	7.93	6.20	8.13	5.35	6.03	5.77
2011	8.50	6.70	9.77	6.80	6.40	6.23
2012	6.85	6.15	7.46	5.83	4.93	4.35
2013	6.62	6.18	7.86	5.97	6.60	5.70
2014	6.15	5.48	6.87	4.56	5.68	4.60
2015	6.90	6.07	7.64	5.90	5.77	5.19
2016	7.10	5.80	7.16	6.09	6.33	6.95
2017	6.60	6.06	7.79	6.58	6.57	7.40
2018	8.56	6.03	8.00	6.54	6.06	6.30
2019	7.27	6.60	8.20	6.48	6.48	6.30

Figures

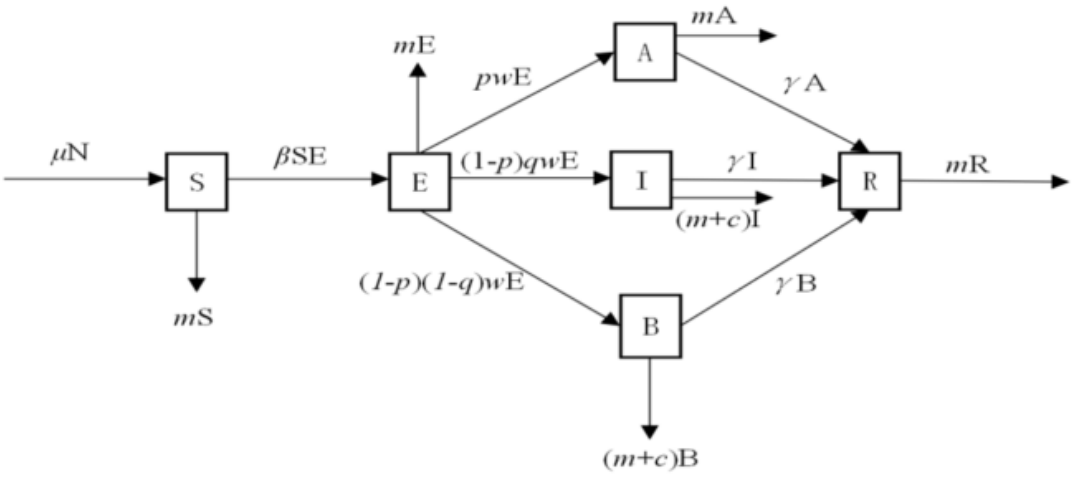

Figure 1

Flow chart of SEIABR model of Influenza

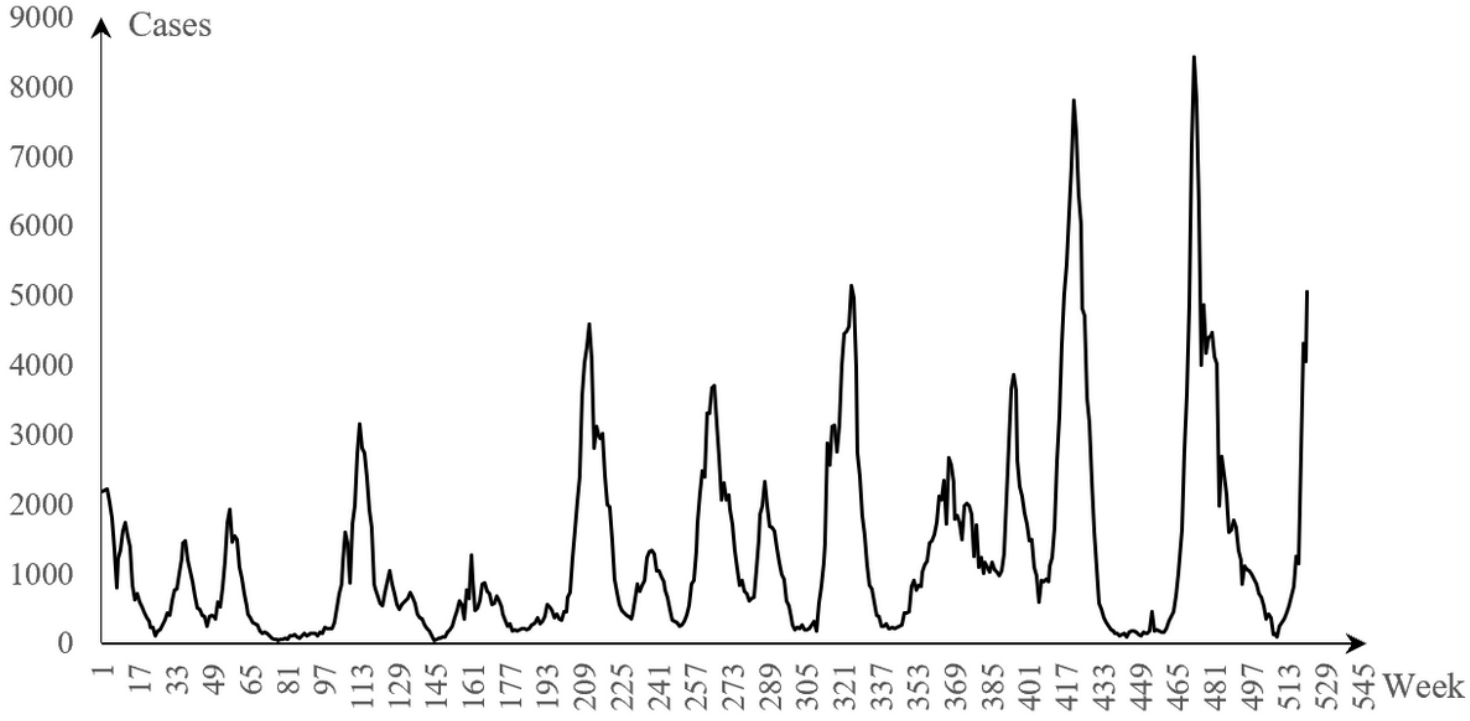

Figure 2

2010-2019 China Influenza Distribution pattern