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Original Article

Estimation of the actual disease burden of human H7N9 infection in Jiangsu of eastern China from March 2013 to September 2017

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Abstract

The actual incidence of human H7N9 infection is supposed to be much higher than the documented laboratory-confirmed cases. In this study, we estimated the number of the actual H7N9 cases in Jiangsu, China using a probabilistic multiplier model. Then, disability adjusted life years (DALYs), direct and indirect economic loss caused by this disease were calculated and analyzed. Till September 2017, the estimated total number of H7N9 cases was 2 952 [median, 90% probability range (PR): 1 487−22 094], which was 11.8 times (5.9−88.4) as large as the reported number. The median morbidity was estimated to be 4 (90% PR: 2−29) per 100 000 population. The total DALYs loss was 16 548 years, and the total economic loss (direct and indirect) was estimated to be RMB 1 044 618 758 (US$ 16.7 M). The average economic loss for per case and for per year was RMB 353 868 (US$ 56 440) and RMB 232 137 502 (US$ 37.0 M), respectively. The actual burden of human H7N9 infections was much heavier than what was documented. Our study provided an approach to estimate actual burden of infectious diseases using laboratory-confirmation.

Keywords: avian influenza, H7N9, disability adjusted life years, burden of disease, probabilistic multiplier model

Introduction

The avian influenza virus H7N9 was firstly identified in human in March 2013[1]. Since then, the virus has caused five waves of human infections in China. As of 27 September 2017, a total of 1 564 laboratory-confirmed H7N9 cases, including at least 612 deaths, have been documented globally[2]. Jiangsu Province, located in eastern China, is one of the first and most affected regions of H7N9[3]. H7N9 virus has been in continual variation and highly pathogenic strains have emerged[4], which poses a severe threat to the poultry industry and incurs more concerns on its pandemic potential. The Chinese government has made tremen-

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dous efforts, such as slaughtering infected poultry[5] and suspending or closing live poultry markets, to impede the virus transmission from poultry to human[6]. The losses of the poultry industry were estimated to reach RMB 11.43 billion (US$ 1.83 billion) in Chinese mainland from February to May in 2013 alone[7]. The patients' direct medical burden was also heavy. The mean expenditure of each H7N9 hospitalized patient reached RMB 71 060 (US$ 10 996)[8]. The Chinese medical insurance system has offered more support for the clinical treatment of H7N9 patients[9–10]. However, the actual disease burden of human H7N9 infections has not been well established, limiting the full understanding of its health and economic impact, and hindering the formulation of optimized control strategies.

The reported H7N9 cases were only a fraction of total cases, since only a part of the cases sought health care and had the specimens collected, confirmed and reported, resulting in the so-called iceberg phenomenon[11]. Thus, the results of the study based only on the reported H7N9 cases would lead to severely underestimated burden of the disease.

In this study, we estimated the total number of H7N9 cases using a probabilistic multiplier model[12], evaluated the disease burden by DALYs (disability adjusted life years) at the individual level, and calculated the direct and indirect economic burden, aiming to comprehensively depict the disease burden in Jiangsu.

Materials and methods

Data collection

Laboratory-confirmed H7N9 human infection cases were reported through a national system for notifiable infectious diseases in China[13]. Demographic, epidemiological and clinical information of patients with H7N9 infection were collected and investigated by local Center for Disease Control and Prevention (CDC) staff or trained clinicians in Jiangsu and then reported to Jiangsu Provincial CDC and China CDC through this system. All patients infected with H7N9 from March 2013 to September 2017 in Jiangsu were included in this study.

Estimating the total H7N9 cases

We used a probabilistic multiplier model[12] to estimate the total number of human H7N9 infections in Jiangsu from March 2013 to September 2017. The model adjusted the count of laboratory-confirmed cases for each of the following steps: medical care seeking (A), specimen collection (B), submission of specimens for confirmation (C), laboratory detection of H7N9 (D), and reporting of confirmed cases (E). A range of proportions was set at each step, according to the literature or our surveillance data (***Table 1***, ***Supplementary Table 1***, available online).

Disease burden (measured by DALYs)

DALY, an objective quantitative measure of disease burden that considers both premature mortality (years of life lost, YLL) and living with disability (years lived with disability, YLD) caused by a certain disease[17], is widely used in the assessment of global disease burden[18].

The DALY calculation kit developed by the World Health Organization (WHO)[19] was used to compute the DALYs of all reported human H7N9 cases at the individual level in Jiangsu from March 2013 to September 2017. First, the life expectancy of the Jiangsu population was generated by a Life Table template[19] (***Supplementary Table 2***, available online). Next, YLLs and YLDs of reported H7N9 cases were calculated by age groups (0–4, 5–14, 15–29, 30–44, 45–59, 60–69, 70–79, and ≥80 years), and summed. Age weight, disability weight, and time

Table 1 **Parameters of probabilistic multiplier model for estimating the total H7N9 cases in Jiangsu, from March 2013 to September 2017**

Parameters[a]	Proportion ranges in the model (%)		Source[b]
	Not hospitalized	Hospitalized	
A	41–85	100	Xie X[14], Meng H[15], Yuan J[16]
B	0–7	0.2–21	Surveillance data
C	100	100	Surveillance data
D	90–100	90–100	Default
E	95–100	95–100	Default

[a]Medical care seeking (A), specimen collection (B), submission of specimens for confirmation (C), laboratory detection of H7N9 (D), and reporting of confirmed cases (E); [b]Detailed information is presented in ***Supplementary Table 1***, available online.

discount rate were introduced to adjust the value of time lived at different ages, disease severity and future payoffs[17]. In this study, we used full age weight and set other DALY parameters as recommended[19]. Disability weights of moderate and severe hospitalized patients during the disease course were set as 0.051 and 0.133 respectively, and the disability weight of outpatients was set as 0.006, according to the guideline of Global Burden of Disease Study 2016 (GBD 2016)[20].

Economic burden

In a previous study, we estimated that the average direct medical cost of each H7N9 hospitalized patient was RMB 71 060 (US$ 10 996)[8]. And it was reported that the average medical expense of influenza like illness (ILI) per episode (considering both outpatients and those without seeking health care) was RMB 139.6 (US$ 22.41)[21]. Thus, the total direct medical cost of all H7N9 cases was the cost per hospitalization plus the cost before hospitalization, where:

$$\begin{aligned}&\text{Cost of hospitalization}\\&=\text{Total hospitalized H7N9 cases}\\&\times\text{Average cost per hospitalization}\end{aligned}\quad(1)$$

$$\begin{aligned}&\text{Cost before hospitalization}\\&=\text{Total H7N9 cases}\\&\times\text{average cost per episode of ILI patients}\end{aligned}\quad(2)$$

A traditional human-capital approach was used to estimate the indirect cost of reported H7N9 cases (equation 3), multiplying DALYs by the per-capita GDP (gross domestic product) of Jiangsu in 2015 (p) and weight of productivity capability (w) accumulated over all reported H7N9 cases for each age group (k, consistent with the age groups in the DALY computation).

$$\begin{aligned}&\text{Indirect cost of reported H7N9 cases}:\\&\text{ICR}=\text{p}\times\sum_{k=1}^{8}\text{DALYs}_{\text{k}}\times\text{w}_{\text{k}}\end{aligned}\quad(3)$$

The per-capita GDP of Jiangsu in 2015 (p) was taken to be RMB 87 995 (US$ 14 128)[22–23], and the following weights of productivity capability (w) were used: 0.15 at the age of 0–14 years, 0.75 at the age of 15–44 years, 0.8 at the age of 45–59 years and 0.1 at the age of ⩾60 years[7].

Then, the total indirect cost was estimated by multiplying the number of total H7N9 cases by the average indirect cost per reported case (ICR).

$$\text{Total indirect cost}=\text{Total H7N9 cases}\times\text{ICR}\quad(4)$$

Definitions

Five waves of human H7N9 infection had been observed in Jiangsu: March to April 2013, December 2013 to May 2014, October 2014 to May 2015, December 2015 to May 2016 and October 2016 to September 2017. Generally, southern cities in Jiangsu (Nanjing, Suzhou, Changzhou, Wuxi and Zhenjiang) were more developed than northern cities (Xuzhou, Huaian, Suqian, Lianyungang, Nantong, Taizhou, Yangzhou and Yancheng). The exchange rate of RMB against the US dollar used in this study was 6.2284 (in 2015)[23].

Results

Estimation of total H7N9 cases

From March 2013 to September 2017, 250 H7N9 cases with 107 deaths were laboratory-confirmed and reported in Jiangsu through a national system for reporting of notifiable infectious diseases[13], while the estimated total number was as high as 2 952 (median, 90% probability range: 1 487–22 094), with an estimated median morbidity of 4.0 (90% probability range: 2–29) per 100 000 population. Among them, 2 681 patients (median, 90% probability range: 1 320–21 390) were hospitalized and 1 161 patients (median, 90% probability range: 572–9 266) died. Each reported non-hospitalized H7N9 case might represent 50.0 (median, 90% probability range: 23–320) total non-hospitalized cases, and each reported hospitalized H7N9 case might represent 10.9 (median, 90% probability range: 5.4–86.6) total hospitalized cases. Most of the estimated hospitalizations occurred in the age group of 50–64 years, and most estimated deaths occurred in the age group of 65 years or older. However, the rates of hospitalization and death both peaked in the individuals aged 65 years or older (***Table 2***).

DALYs of H7N9 cases

The total DALYs of the 250 reported H7N9 cases in Jiangsu till September 2017 were 1 401.49 years, with an average of 5.61 years for each case. YLLs accounted for an overwhelming majority (1 398.66 years, 99.80%), compared with YLDs (2.83 years). In subgroup analysis of age, the highest DALYs were in individuals aged 45–59 (529.85 years, 37.81% of total), however, the highest average DALYs of each case occurred to individuals aged 15–29 (14.69) years (***Table 3***). Aggregated DALYs of male cases were considerably more than that of female cases (908.49 *vs*. 493.00 years), but the average DALYs were higher in female cases than in male cases (6.94 *vs*. 5.08 years). As most H7N9 cases were reported during the fifth wave (October 2016 to September 2017, 59.6%)

from southern Jiangsu (70.0%), with the highest DALYs in this time period and this region (***Table 4***). DALYs per case were apparently higher during the second (December 2013 to May 2014, 7.49 years) and the third (October 2014 to May 2015, 7.59 years) waves, and in southern Jiangsu (6.42 years), due to the higher case-fatality rates in these time spans and this region (***Table 4***). The total DALYs of H7N9 cases in Jiangsu from March 2013 to September 2017 were calculated by multiplying the average DALYs per reported case (5.61 years) by the estimated number of total H7N9 cases (2 952, median). Thus, the total DALYs were estimated to be 16 548.74 years, with an average of 3 677.50 years per year and a rate of 4.98 years per 100 000 population per year. The DALY rate was adjusted to be 3.50 years per 100 000 population per year after standardization using a global population[24].

Economic burden of H7N9 cases

The total direct medical cost of H7N9 cases in Jiangsu from March 2013 to September 2017 was computed using equations. The total was estimated to be RMB 190 923 959 or US$ 29 546 430 (RMB 42 427 546 or US$ 6 565 873 per year, RMB 64 676 or US$ 10 009 per case), and the cost of hospitalization and before hospitalization were estimated to be RMB 190 511 860 (US$ 29 480 276) and RMB 412 099 (US$ 66 154), respectively.

The total indirect economic cost of H7N9 cases was calculated using the equations. The indirect cost of the 250 observed cases in Jiangsu was RMB 72 298 001 (US$ 11 607 797). Over a half (51.59%) derived from the cases aged 45–59 years (RMB 37 299 111 or US$ 5 988 554). The average indirect cost of each H7N9 case was RMB 289 192 (US$ 46 431) (***Table 3***). Thus, the total indirect cost of 2 952 estimated cases (median) was RMB 853 694 799 (US$ 137 064 864).

In all, the total economic loss was estimated to be RMB 1 044 618 758 (US$ 166 611 294). The average loss for per case and per year was RMB 353 868 (US$ 56 440) and RMB 232 137 502 (US$ 37 024 732), respectively.

Discussion

Most laboratory-confirmed H7N9 cases were severe infections[3,25], which could partly be attributed to the absence of mild infection report to the medical facilities, inadequate coverage of pathogen testing on attended mild and moderate infections due to excessive workload, and the lack of an efficient diag-

Table 2 **Estimated total H7N9 cases in Jiangsu from March 2013 to September 2017**

	Age (year)	Count median (90% limit)	Per 100 000 population median (90% limit)
Total cases	0–4	0 (0, 0)	0 (0, 0)
	5–24	47 (24, 345)	0 (0, 2)
	25–49	897 (452, 6 717)	3 (1, 22)
	50–64	**1 157 (583, 8 661)**	7 (4, 55)
	65+	850 (428, 6 363)	**8 (4, 62)**
	Total	2 952 (1 487, 22 094)	4 (2, 29)
Hospitalizations	0–4	0 (0, 0)	0 (0, 0)
	5–24	43 (21, 342)	0.3 (0.1, 2.1)
	25–49	794 (391, 6 332)	2.6 (1.3, 20.9)
	50–64	**1 064 (524, 8 492)**	6.7 (3.3, 53.8)
	65+	780 (384, 6 225)	**7.6 (3.7, 60.7)**
	Total	2 681 (1 320, 21 390)	3.5 (1.7, 28.0)
Deaths	0–4	0 (0, 0)	0 (0, 0)
	5–24	10 (5, 83)	0.06 (0.03, 0.52)
	25–49	282 (139, 2 252)	0.93 (0.46, 7.42)
	50–64	412 (203, 3 290)	2.61 (1.29, 20.84)
	65+	**456 (225, 3 642)**	**4.45 (2.19, 35.54)**
	Total	1 161 (572, 9 266)	1.52 (0.75, 12.14)

Table 3 **DALYs and indirect economic loss of H7N9 cases by age groups in Jiangsu Province, March 2013–September 2017**

Age (year)	Case (*n*)	Case fatality (%)	YLDs (year)	YLLs (year)	DALYs (year)	Proportion (%)	DALYs per case (year)	Indirect cost, RMB (US$)	Proportion (%)
0–4	0	0.00	0.00	0.00	0.00	0.00	0.00	0 (0)	0.00
5–14	2	0.00	0.04	0.00	0.04	0.00	0.02	484 (78)	0.00
15–29	13	46.15	0.20	190.82	191.02	13.63	**14.69**	12 606 838 (2 024 089)	17.44
30–44	40	27.50	0.60	286.18	286.78	20.46	7.17	18 926 335 (3 038 715)	26.18
45–59	**89**	38.20	**1.07**	**528.77**	**529.85**	**37.81**	5.95	**37 299 111 (5 988 554)**	**51.59**
60–69	59	45.76	0.55	255.42	255.97	18.26	4.34	2 252 450 (361 642)	3.12
70–79	35	60.00	0.31	115.64	115.95	8.27	3.31	1 020 340 (163 820)	1.41
80+	12	**66.67**	0.04	21.83	21.87	1.56	1.82	192 444 (30 898)	0.27
Total	250	42.80	2.83	1 398.66	1 401.49	100.00	5.61	72 298 001 (11 607 797)	100.00

YLLs: years of life lost; YLDs: years of life with disability; DALYs: disability adjusted life years; RMB : US$=6.2284; GDP per capita: RMB 87 995, US$ 14 128.03; Productivity weight: 0.15, 0.15, 0.75, 0.75, 0.80, 0.10, 0.10, and 0.10, for individuals aged 0–4, 5–14, 15–29, 30–44, 45–59, 60–69, 70–79, and 80+ years, respectively.

Table 4 **DALYs and DALYs per case in H7N9 cases with different genders, waves and regions**

Group	Case-fatality rates (%)	Case [*n* (%)]	DALYs (year)	DALYs per case (year)
Gender				
Female	45.07	71 (28.4)	493.00	6.94
Male	41.90	179 (71.6)	908.49	5.08
Wave[a]				
1	32.14	28 (11.2)	77.36	2.76
2	48.15	27 (10.8)	202.13	7.49
3	60.00	20 (8.0)	151.71	7.59
4	46.15	26 (10.4)	160.20	6.16
5	40.94	149 (59.6)	810.09	5.44
Region				
North	32.00	75 (30.0)	278.40	3.71
South	47.43	175 (70.0)	1 123.04	6.42

[a]1: March 2013 to April 2013; 2: December 2013 to May 2014; 3: October 2014 to May 2015; 4: December 2015 to May 2016; 5: October 2016 to September 2017; DALYs: disability adjusted life years.

nostic method, such as point-of-care testing. The iceberg phenomenon of reported H7N9 cases[26–27] led to an underestimation of the burden of this disease. To our best knowledge, this is the first study to estimate the total H7N9 cases quantitatively, which allows the full evaluation of economic burden.

According to our results, the estimated total H7N9 cases in Jiangsu till September 2017 could be 11.8 times (median) as many as those observed. The yearly rank of the incidence of human H7N9 infections

jumped from 18th–22nd (by reported cases) to 11th–13rd (by estimated cases), and the rank of mortality rose from 3rd–6th (by reported cases) to the 1st (by estimated cases) in notifiable infectious diseases (including AIDS, tuberculosis and hydrophobia) in Jiangsu during 2013–2017.

The present disease burden (measured by DALY) of human H7N9 infections was generally moderate (4.98 years per 100 000 population per year, and 3.50 years per 100 000 population per year after standardization), even in Jiangsu, a region severely impacted by H7N9. Due to the limited published data from Jiangsu, we compared the disease burden of human H7N9 infections with that of the other common infectious diseases in China. The DALY per 100 000 population per year of human H7N9 infection (3.5 years) was higher than that of rabies (3.4), acute hepatitis C (2.8), cholera (1.5), malaria (1.0) and diphtheria (0.3), but much lower than that of H influenzae type B pneumonia (114.5), pneumococcal pneumonia (106.0), influenza pneumonia (93.7) and respiratory syncytial virus pneumonia (55.7)[28]. However, the average DALYs per H7N9 case (5.61 years) was much higher than that of most other infectious diseases, such as tuberculosis (4.8), hepatitis B (1.84), intestinal infectious diseases (0.68), measles (0.64), lower respiratory infections (0.27), malaria (0.26), syphilis (0.24), pandemic H1N1 2009 (0.06), seasonal influenza (0.03), hepatitis (0.02) and zika virus disease (0.001), and only lower than that of rabies (57.25), HIV/AIDS (30.87), tetanus (26.29), Africa trypanosomiasis (25.68), diphtheria (21.725) and meningitis (7.75)[29–30].

The significantly elevated numbers of H7N9 cases reported in the recently ended 5th wave (October 2016 to September 2017) in Jiangsu and in China as a whole[3,31], indicate that the H7N9 virus is capable of causing more human infections in scenarios such as favorable climate and widely-contaminated human-avian interfaces. In addition, the virus undergoes continual variation, and drug-resistant and highly pathogenic strains have emerged[3-4]. Thus, it is necessary to closely monitor the virus and implement sufficient measures to impede its transmission in birds, and from birds to humans before it causes more noticeable disease burden.

The number of DALYs per H7N9 case was 5.61 years in our study, which is slightly higher than what was reported by Qi *et al* (5.17 years)[7] and the difference would be largely amplified in an epidemic. The differences in DALYs calculation might be responsible for this. In our study, age weight and time discount rate were introduced as recommended by WHO. Disability weight and disease course were defined for each case rather than group analyses. In addition, regional disparity associated with life expectancy was also accountable.

Male sex and older age were reported to be the main risk factors for human H7N9 infections[32]. In this study, disease burden was found to be heavier in males and older population (⩾45 years) because of larger numbers of cases in these groups. However, the average loss of years of life per case was heavier in females and younger cases (15–29 years) due to the higher case-fatality and longer life expectancy. Similar disparities were also observed between northern and southern cities of Jiangsu and among the 5 epidemic waves.

The economic burden of human infections with H7N9 was heavy. The total economic loss of H7N9 cases was estimated to be RMB 1 044 618 758 (US$ 166 611 294) in Jiangsu since March 2013, and the yearly loss was RMB 232 137 502 (US$ 37 024 732), which accounted for 0.0033% of GDP of Jiangsu (in 2015)[22]. Although this proportion was much lower than those of tuberculosis (0.094%) and AIDS (0.07%)[33–34], the average economic loss per H7N9 case was still huge (RMB 64 676 or US$ 10 009 per case for direct medical cost, and RMB 289 192 or US$ 46 431 per case for indirect cost), which was 4.02 times of the per capita GDP of Jiangsu (in 2015)[22]. The average medical cost per H7N9 case was significantly higher than that of community-acquired pneumonia (RMB 12 147.97 or US$ 1 950.42)[35], tuberculosis (RMB 6 598.3 or US$ 1 059.39)[36], hepatitis B virus (RMB 28 971 or US$ 4 651.44)[37] and hand-foot-and- mouth disease (RMB 3 196.54 to 13 387.76 or US$ 513.22 to 2 149.47)[38]. When using the DALY and human-capital approach to evaluate the total economic burden (direct and indirect) of severe acute respiratory syndrome (SARS) in China, the total economic loss per case was found to be RMB 43 000 (US$ 6 903.86)[39], which was also much lower than that of human H7N9 infections.

Our results show that the disease and economic burden of human H7N9 infection in Jiangsu of eastern China was much heavier than what had been observed, which can deepen and further our understanding of the impact of this disease. The data on the actual disease burden are crucially needed for the cost-effectiveness assessment of various prevention and control measures for this disease. The evaluation approaches of this study could also be used in similar studies in other regions of the world.

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