Calculating the burden of disease of avian-origin H7N9 infections in China

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Burden of diseases in the 21st century:

A case of emerging H7N9 influenza virus infection in China

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Abstract

Objective In China, 134 cases of avian-origin H7N9 infections have been confirmed since February 2013. We aimed to calculate the overall burden of H7N9 cases in China as of May 31, 2013 to give an example of comprehensive burden of disease in the 21st century of an acute animal-borne emerging infectious disease.

Design We present an accurate and operable method for estimating the burden of H7N9 cases in China. The main drivers of economic loss were identified. Costs were broken down into direct (outpatient and inpatient examination and treatment) and indirect costs (cost of DALY and losses in the poultry industry), which were estimated based on field surveys and statistical data.

Setting Models were applied to estimate overall burden of H7N9 cases in China.

Participants 131 Laboratory confirmed H7N9 cases (excluding one Taiwan case) by May 31, 2013.

Outcome measure Burden of H7N9 cases including direct and indirect losses.

Results The total direct medial cost was 16,422,535 CNY. The mean cost for each patient was 10,117 CNY for mild patient, 139,323 CNY for severe cases without death, and 205,976 CNY for severe cases with death. The DALYs were 677.848 and the total cost of DALYs was 17,356,561 CNY. Poultry-industry losses were estimated on three levels: 27 prefectures with cases, 10 affected provinces and eight non-affected adjacent provinces, including the costs of closing the live-poultry market and slaughter. The poultry industry losses amount to 7.75 billion CNY in 10 affected provinces and 3.68 billion CNY in eight non-affected adjacent provinces.

Conclusions The number of H7N9 incidence cases decreased accompanied by closing the live-poultry markets and slaughtering the poultry. However, the medical cost per case and DALY per case were extremely high (esp. addressing the use of modern medical device). Cost-effectiveness assessment for the intervention needs to be done in future study.

Article summary

Strengths and limitations of this study

- This study is the first (to our knowledge) in which comprehensive methods were applied to identified the main drivers of economic losses and estimate the burden of disease due to H7N9 infection including direct cost (medical cost) and indirect cost (death, disability and poultry-industry losses);
- This study has some limitations. Estimation of the medical cost was based on the model and second hand data, not on the H7N9 patients' original costs. The burden of H7N9 might be underestimated since the ongoing costs of existing cases and new cases after May 2013, underreported cases and other losses involved in the livestock-production chain were not included in our study.

Introduction

A novel avian-origin influenza A (H7N9) virus has caused severe disease in humans in China since February 2013. The high number of new cases within a short period and the high case fatality rate have caused public panic and attracted global attention. It was also reported from media that some patients' families undertook large medical costs. According to the literature, exposure to live poultry could be an important risk factor for human infection with H7N9. [1-3] As a result, closing-down the live-poultry markets and slaughtering the poultry were the main intervention measures in affected areas in China. These interventions played an important role in disease prevention, but on the other hand, also caused serious losses to the poultry industry.

The introduction of the novel virus led to numerous investigations on the origin of the virus, its genes, clinical symptoms, laboratory test, treatment and transmission [4-6]; however, the burden of human infection with H7N9 has not yet been measured. It is important to estimate the overall burden of disease (BOD) due to H7N9 in China because this virus is new in humans and could cause a global pandemic in the future. The Global Burden of Disease (GBD) 2010 study presents a comprehensive methodological framework for death and disability loss estimation and has had a pronounced impact on the estimation of BOD [7 8]. In this study, we identified the main drivers of economic losses and summarized the direct and indirect costs of human H7N9 infection. We aimed to present an accurate and operable approach for estimating the overall burden of emerging infectious diseases and to provide evidence on the cost effectiveness of H7N9 prevention and control. We also aim to set up a BOD estimation example for any animal-borne infectious diseases, esp. with the introduction of modern medical device.

Methods

Case category definition

The confirmed human infections of H7N9 were divided into mild and severe cases based on the "Diagnostic and treatment protocol for human infections with avian influenza A (H7N9) (2nd edition, 2013)" .[9] Mild cases presented with influenza-like illness (ILI), while severe cases developed quickly and presented with severe pneumonia, usually accompanied by severe complications and organ failure. Severe illness was divided into 'severe without death' and 'severe with death'. The 11 H7N9 cases of unknown status were classified as 'unknown without death'.

Data source

Data on the 131 confirmed cases of H7N9 by the end of May 31, 2013 came from China's information system for disease control and prevention and included basic information on the onset of illness, epidemiology and emergency event reporting. Disability-adjusted life years (DALYs) were calculated based on two other published sources. The World Health Organization (WHO) provided a table of life expectancy by age for China in 2011,[10] while the Institute for Health Metrics and Evaluation (IHME) published the Global Burden of Disease (GBD) 2010, including the GBD 2010 Disability Weights .[11] Disability weights of general infectious disease (acute episode for mild, moderate and severe) were adopted from IHME based on the clinician's

suggestion though the symptoms of H7N9 cases were more severe than the general infectious disease cases. The 2012 per-capita gross domestic product (GDP), which was used to calculate the cost of lost lives or the cost of disability, was obtained from the National Bureau of Statistics of China.

Poultry production and trade data from27 prefectures with confirmed H7N9 cases, including live-poultry sales, dates of live-market closings and market-stall volumes, were collected from field surveys, local livestock-breeding year books [12] and the 'Chinese Commodities Trading-Market Statistics Yearbook 2012'.[13] Data were gathered from the ten affected provinces and eight unaffected adjacent provinces. These data were used to estimate poultry-industry losses.

Analysis framework of burden of confirmed H7N9 cases

We constructed a framework for BOD analysis (Figure 1). We described the confirmed H7N9 cases category as mild, severe without death, severe with death and unknown without death and examined the spatiotemporal and population characteristics of these cases. Based on the case category and characteristics of case spatiotemporal distribution, costs were broken down into direct medical costs (outpatient and inpatient examination and treatment) and indirect costs (death, disability and poultry-industry losses). To calculate the DALYs attributable to H7N9, the H7N9-specific years of life lost due to premature mortality (YLLs) and years lived with disability (YLDs) were computed and then summed. An intensive analysis of poultry-industry losses would be complex and would require time-consuming field surveys. Meanwhile, indirect effects may lag behind. In this paper, we considered only the poultry industry losses caused from the closing of live-poultry markets and the large-scales laughter of poultry.

Statistical analysis

Descriptive statistics were used to summarize the epidemiologic characteristics of the cases. The distribution of confirmed H7N9 cases by week was also extracted by creating two standard deviational ellipses (covering 95% of the points while calculating the standard deviation of the x-coordinates and y-coordinates from the mean center to define the axes of the ellipse) to summarize the spatial spread of confirmed H7N9 cases (central tendency, dispersion and directional trends). If the number of cases in one week was less than three, those cases were not included in the calculation.

The methods for estimating direct medical costs are traditionally classified into two broad approaches: bottom-up (micro-costing) and top-down (macro-costing) .[14 15] In general, the bottom-up approach usually results in a higher but more accurate estimate.[16] In our study, we used the bottom-up approach to estimate the direct medical costs. Four cost drivers were extracted: cost of outpatient and inpatient examinations in ward, cost of examination in intensive-care units (ICUs), cost of treatment and other costs (including medical consumables, charge for sickbed, general care services, checkup fee, etc). A cost formula was constructed for each driver, as depicted in Table 1. The cost per patient was estimated by experienced hospital financial officers and hospital doctors. The mean number of days (ICU stay, hospital stay and days of treatments) was estimated from the epidemiologic data. The number of patients for each driver was derived

from a previous publication.[6] Professionals' experiences were also considered for some items that were not included in our surveillance system. The costs for the category 'unknown without death' were assumed to be moderate and were set as the average of the costs of mild cases and severe cases without death.

The YLLs for confirmed H7N9 cases in China were calculated from the sum of the number of fatal cases (n) in 5-year age groups (i) multiplied by the remaining expected life span (e) based on the age of death for that age group:[17] (formula 1)

$$YLLs = \sum n_i \times e_i \quad (1)$$

To estimate the burden of H7N9 in YLLs, the Chinese life-expectancy table from WHO 2011 was used.

The YLDs were calculated by multiplying the duration of illness (t) by the disability weights (w) accumulated over all H7N9 cases (d) for each health outcome (j): (formula 2)

$$YLDs = \sum d_j * t_j * w_j \quad (2)$$

As H7N9 is a relatively new infectious disease and the health state of patients after discharge is unknown, we calculated the YLDs only as general acute episodes of infectious disease during the hospital stay. Disability weights were assigned as infectious disease (mild, moderate and severe acute episodes).[11]

The DALYs are calculated by adding YLLs to morbidity and disability, expressed in YLD (formula 3).

$$DALYs = YLLs + YLDs \quad (3)$$

An estimation of the cost of one DALY was based on the traditional human-capital approach for per-capita GDP (formula 4). Considering the different production capabilities at different ages, the weights of production capability were calculated. The following weights were used according to the literature: 0.15 at age 0-14, 0.75 at age 15-44, 0.8 at age 45-59 and 0.1 at age 60+.[18]

$$\text{Cost of DALYs} = \text{DALYs} * \text{per-capita GDP} * \text{weight of production capability} \quad (4)$$

As mentioned above, direct poultry-industry losses (PIL) can be calculated using formula 5:

$$PIL = L_1 + L_2 \quad (5)$$

where L_1 is the loss from poultry slaughter and L_2 is the loss from the closing of live-poultry markets, which includes the lost sales of live poultry (L_{21}) and fees for market-stall leases (L_{22}). A cost formula was constructed for the estimation of poultry industry loses (Table 2).

Results

Epidemiologic characteristics for different case categories

A total of 131 confirmed H7N9 cases in ten provinces in China were mapped as individual points based on detailed addresses (Figure 2). Most (81%) of the patients were located in the Jiangsu, Shanghai and Zhejiang provinces. Most of the cases (73% or above) in ten provinces were severe. There were 25 mild cases, 56 severe cases without death, 39 severe cases with death and 11 unknown cases without death in China through May 31, 2013.

Figure S1 is the presentation of the rate, direction and scope of the H7N9 spread. Each ellipse covers 95% of the incident cases for one week. The location of the first week of H7N9 onset was in Shanghai. Over the next few weeks, the epidemic extended to the Jiangsu and Zhejiang provinces and continued to grow. The virus quickly spread from the northwest to the north and south regions.

The onset of most H7N9 cases was relatively clustered. Within the total event timeframe (2/19–5/21), 74% of the cases were infected between 3/28-4/17 (Figure S2). Severe cases with death were found in the initial and intermediate stages. The median age of patients with confirmed H7N9 virus infection was 61 years (range, 3 to 91). Severe symptoms tended to occur in older people. The median age of patients who were severely ill without death was 60 years, while the median age of patients who were severely ill with death was 69 years. The number of mild cases distributed on all age groups under 80 years (Figure S3).

Direct medical costs of confirmed H7N9 cases

After the confirmed H7N9 cases occurred in China, the patients' clinical manifestations, examinations and treatments were published,[6] which allowed us to estimate the direct medical costs using a cost model. We separated the examination data into examinations conducted in ward and examinations in ICU, as the latter were more frequent. The main treatments for confirmed H7N9 cases were selected. In our cost formula, three main factors were considered: cost per day, number of days and number of patients. For the cost-per-day estimation, we selected a Grade-III Class-A hospital (general large-scale hospital in China). Costs per day were obtained from the hospital financial officers and hospital doctors based on the average costs of patients with same treatments from Jan.1, 2013 to May 31, 2013 in this hospital (Table S1). Differences in costs among the regions in China were approximately 10%.

The mean number of days and number of cases were estimated from a subset of the investigated cases (Table 3). Data regarding hospital stay were available for 11 of the 25 mild cases, 19 of the 56 severe cases without death and 19 of the 39 severe cases with death. The mean length of stay was 9 days for mild cases, 18 days for severe cases without death and 20 days for severe cases with death. Data on the duration of ICU stay were available for ten of the 56 severe cases without death and 11 of the 39 severe cases with death. Severe cases without death stayed in

the ICU for a mean of 12 days, while severe cases with death stayed for a mean of 16 days. We assumed that the mean hospital stay of severe cases with complications was equal to the length of the ICU stay, although complications might occur incrementally. The mean durations of different treatments lasting were also estimated based on a subset of investigated patients, except for glucocorticoids and intravenous immune globulin, for which estimates were obtained from professionals' experiences. Treatment for complications required drugs and examinations in addition to the treatment listed above. Treatment was described for 111 confirmed H7N9 cases, along with the proportion of patients who received each treatment.[6] We assumed that the proportions were generalizable to all cases because it covered 85% of cases.

Table S2 is the summary of all of the direct medical costs. The total cost for all 131 patients with confirmed H7N9 virus infection was 16,422,535 CNY (2,627,606 USD). The mean cost for each patient was 10,117 CNY (1,619 USD) for mild patient, 139,323 CNY (22,292USD) for severe cases without death, and 205,976 CNY (32,956USD) for severe cases with death. The mean cost per day was 1,124 CNY (180 USD) for mild cases, 8,293 CNY (1,327 USD) for severe cases without death and 8,978 CNY (1,437 USD) for severe cases with death. As the severity of the illness increased, the costs increased correspondingly.

Cost of DALYs on H7N9

A total of 39 deaths from confirmed H7N9, including 30 males and 9 females, were reported from the National Health and Family Planning Commission of China by 31 May 2013. For more details on the number of cases in each age group, see Table S3.The total YLLs were 676.89. There were 131 H7N9 cases, including 25 mild cases, 95 severe cases and 11 of unknown category (assumed to be moderate). YLD calculations were based on the case category. The total YLDs were 1.064 (Table S4). The DALYs combine the time lived with disability and the time lost due to premature mortality; thus, the DALYs were 677.848 for all confirmed H7N9 patients. We adopted 2012 per-capita GDP of the ten provinces and estimated the cases adjusted per-capita GDP (65,655 CNY). By calculating the weight of production capability for each age group, we got the average weight of production capability to be 0.39 for all confirmed H7N9 cases. The total cost of DALYs was 17,356,561 CNY (2,777,050 USD) according to the formula 4.

Poultry-industry losses

Poultry-industry losses were estimated for three categories (Figure 3): 1)27 prefectures with confirmed H7N9 cases (region 1, in brown in Figure 3), 2)10 affected provinces (region 2, in yellow in Figure 3) and 3) eight non-affected adjacent provinces (region 3, shadowed in Figure 3).

In region1, three types of losses were calculated: losses from poultry slaughter, lost sales of live poultry and fees for market-stall leases. In the ten affected provinces (region 2), in addition to the losses in region1, the losses mainly arose from the closing-down of live-poultry markets in each province. These two losses were then summed to estimate poultry-industry losses caused by H7N9 outbreaks. Most of the main live-poultry markets in the affected provinces (presented in Figure 3) were obtained from Google Earth; the retail locations were excluded.

Poultry-industry losses in eight non-affected adjacent provinces (region 3) were also calculated as potential economic losses. The direct poultry-industry losses of 27 prefectures for the H7N9 cases are described in detail in Table 4.

The cost of closing-down live-poultry markets includes the lost sales of live poultry and fees for market-stall leases. The cost of lost sales of live poultry was calculated according to the daily live-poultry sales, the cost per animal (assumed to be 10 CNY in this paper) and the number of days the market was closed. The cost of market-stall leases was calculated based on the average lease per stall per day in the corresponding city, the number of stalls and the number of days the market was closed in each city. The cost of poultry slaughter was obtained from the number of poultry slaughtered and the cost per animal. The number of days the market was closed was counted through May 31 because there have been only one confirmed H7N9 cases since then. The total poultry-industry losses in the ten affected provinces, including 27 prefectures with H7N9 cases, are listed in Table 5. The poultry-industry losses of each province are presented in Figure S4.

In general, China's poultry industry suffered direct losses amounting to 7.75 billion CNY from when the first case of H7N9 was confirmed through May 31, 2013. Losses from the live-poultry trade account for 98% of the total losses. Although it had only a fewH7N9 cases, Shandong Province ranked first in losses among all ten provinces at 1.81 billion CNY; Jiangsu, Henan and Anhui ranked next, with 1.28 billion CNY, 1.15 billion CNY and 1.14 billion CNY, respectively. These provinces have large poultry markets. Zhejiang Province had the highest number of confirmed cases; however, the losses in that region were not very high, as the sales of live poultry were lower. Strict prevention and control measures, such as daily cleaning of the market, weekly disinfection of the market and monthly closings of the live market, were conducted in Guangdong Province, which reported no H7N9 cases till 31 May 2013 during the emergency response. Meanwhile, these prevention and control measures affected the poultry industry. For this reason, the poultry-industry losses in Guangdong Province are also given in Table 5.

Due to timely control measures, the H7N9-affected regions were limited to the 27 prefectures in ten provinces in China. In this study, the potential economic risks were also calculated for the eight non-affected adjacent provinces (region 3, shadowed in Figure 3). Table S5 shows that the potential losses to the poultry industry in those regions amount to 3.6 billion CNY.

Discussion

This study was based on illness severity and spatiotemporal aspects of the recent avian-origin influenza A (H7N9) infections. Our results indicate that there were clusters of patients infected with H7N9 in China. Of the 131 patients, 81% resided in the Jiangsu, Shanghai and Zhejiang provinces, and 74% were infected during the period of 3/28-4/17. Patients over 50 years of age accounted for 72% of the total, and 95 patients (73.1%) were diagnosed as severe cases. The fatality rate of confirmed H7N9 cases in China was 26.9%.

We assumed that cases of the same severity resulted in similar medical costs. Therefore, mild cases, severe cases without death, severe cases with death and unknown cases without death were estimated separately by calculating the mean number of days, number of cases and cost per day. The mean cost per patient was 8,880 CNY (1,421 USD) for mild cases, 144,788 CNY (23,166 USD) for severe cases without death and184, 211 CNY (29,474 USD) for severe cases with death. The total direct medical cost for all patients was 15,963,935 CNY (2,554,230 USD). The DALYs, which were determined from the YLLs and YLDs, were 677.848 years for all confirmed H7N9 cases. The total cost of the DALYs was 17,356,561 CNY (2,777,050 USD) according to the average GDP per capita and average weight of production capability.

Compared to the poultry-industry losses, the direct medical losses and DALY losses were relatively small. To a large extent, the small number of patients in the H7N9 outbreak in China was due to quick and effective interventions, which prevented a pandemic. The estimation of direct medical cost and DALY cost, especially the mean cost per patient and mean cost per day for different case categories, can be used to guide those counties in which H7N9 cases did not occur in the prevention and control of H7N9. DALY per H7N9 case (5176 DALYs per 1000 cases) was much higher than the other respiratory infectious diseases according to the 2010 GBD study.[19] A comparison to outbreaks of other infectious diseases (with similar clinical symptom) was also considered in this report. The health care cost per SARS patient in Beijing was 17,150 CNY (1,886USD) while the average medical cost per H7N9 patient was 99,691 CNY(15,951 USD) because of the higher fatality rate of H7N9 patients and more expensive modern medical device had been used.[20]

As of the end of May, China's poultry industry suffered direct losses amounting to 7.75 billion CNY, including the cost of closing live-poultry markets and slaughtering poultry in the ten affected provinces. Poultry-industry losses were estimated at three levels: 27 prefectures with confirmed H7N9 cases, 10 affected provinces and eight non-affected adjacent provinces. The outbreak of H7N9 may reduce the demand for poultry products in other regions of China, due to public perceptions. These effects were not considered in this paper. The cost of closing-down the live-poultry markets and the cost of poultry slaughter were calculated as direct poultry-industry losses. We assumed that the cost per animal is 10 CNY and the date for the end of closing the live-poultry markets was May 31, 2013 because there has been only one confirmed H7N9 case since then. Losses from the live-poultry industry account for 98% of the total losses, with the lost sales of live poultry constituting the majority of that amount. Strict prevention and control measures have been enacted in Guangdong Province, which had few reported cases of H7N9. This finding will be significant for similar cases in the future. Due to timely control measures, the effects of the outbreak were limited to 27 prefectures in ten provinces in China.

Our study had several limitations. First, there were 11 confirmed H7N9 cases without death whose case categories were unknown. The cost estimation for these unknown patients was replaced by the average cost of mild and severe cases without death. Second, in the cost model, some of the data (e.g., mean number of days of ECMO for severe without death cases) were obtained from a small proportion of investigated cases, which could result in an estimation bias. Third, the direct medical cost did not include opportunity cost,[21] the cost that is incurred because a limited resource is used to treat a preventable disease and cannot therefore be used to treat another

disease.[22] The medical practitioners' salary, research funding and loss of working time for family numbers of patients on H7N9 were excluded in our study. Fourth, estimations of the direct medical cost per day might show large differences for specific cases because the drug cost could grow considerably if imported and nutritional drugs were used. We considered only the average severity for patients in ward and in ICU. Fifth, 17 patients were still in hospital by May 28, 2013 according to the literature.[23] The mean numbers of days in ward and in ICU of severe cases and fatality rate were thus underestimated. And some of the mild cases may not be reported which also resulted in the underestimation of the cost. Sixth, in this paper, we considered only direct losses from the closing-down of live-poultry markets and large-scale poultry slaughter, which could be estimated accurately and quickly. This estimation is useful for early control and decision-making; however, other losses involved in the livestock-production chain, such as increased breeding costs, poultry seeding, the prices of poultry meat and eggs and the decreasing production of poultry-feather industries, should be considered in further studies.[24]

In conclusion, we presented a quick, operable and accurate framework for estimating the burden of human infections with H7N9.This framework could be used in the BOD analysis of future H7N9 or similar outbreaks. The results, including direct and indirect costs, provide fundamental information for researchers, the public and policy makers to support timely and effective interventions.

Contributors

All authors participated in the conception and design of the report. XQ and GFG designed and supervised the study, and applied the grants. XQ, DJ, HW, DZ, JM, JF, JQ, YS, GW, KX collected data. XQ, DJ, JF, SY, YM, YH, LX, YL, YW, XS and GF analyzed data. QZ, MW, LX and YL took literature search, XQ and DJ drafted the manuscript, and all authors contributed to review and revision and have seen and approved the final version.

Competing interests

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: no support from any organization for the submitted work; no financial relationships with any organizations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

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Data sharing No additional data available.

Supplementary material

Figure S1 The directional distribution of confirmed H7N9 cases by week

Figure S2 Date of illness onset by case category

Figure S3 Age distribution of each case category

Figure S4 Poultry-industry losses of each province
Table S1 Estimation of costs per day for confirmed H7N9 cases
Table S2 Summary of direct medical costs
Table S3 YLLs of confirmed H7N9 cases
Table S4 YLDs of confirmed H7N9 cases
Table S5 Potential poultry-industry losses of eight non-affected adjacent provinces
(DOC)

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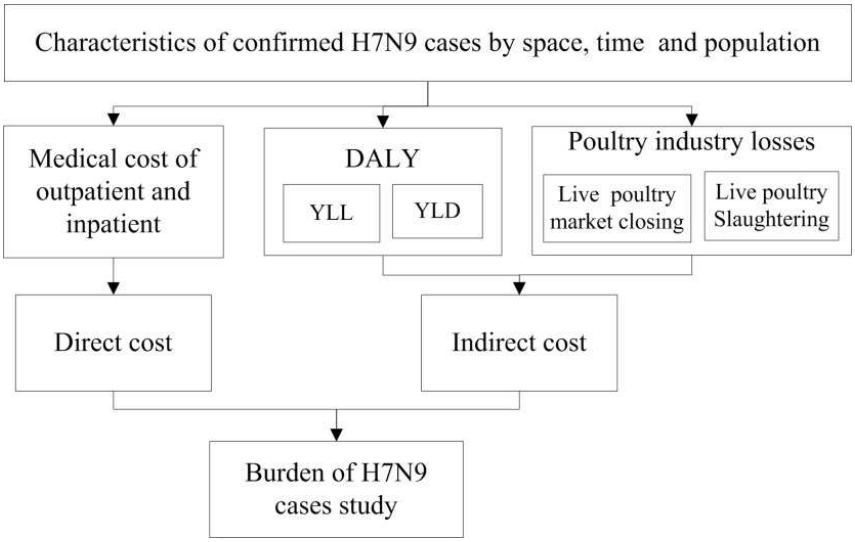

Figure 1. Framework for calculating the burden of confirmed H7N9 cases. (Figure 1 described the analysis route of direct cost and indirect cost, which were integrated into the overall burden of confirmed H7N9 cases. The framework was drawn with Microsoft Office Visio 2003 software.)

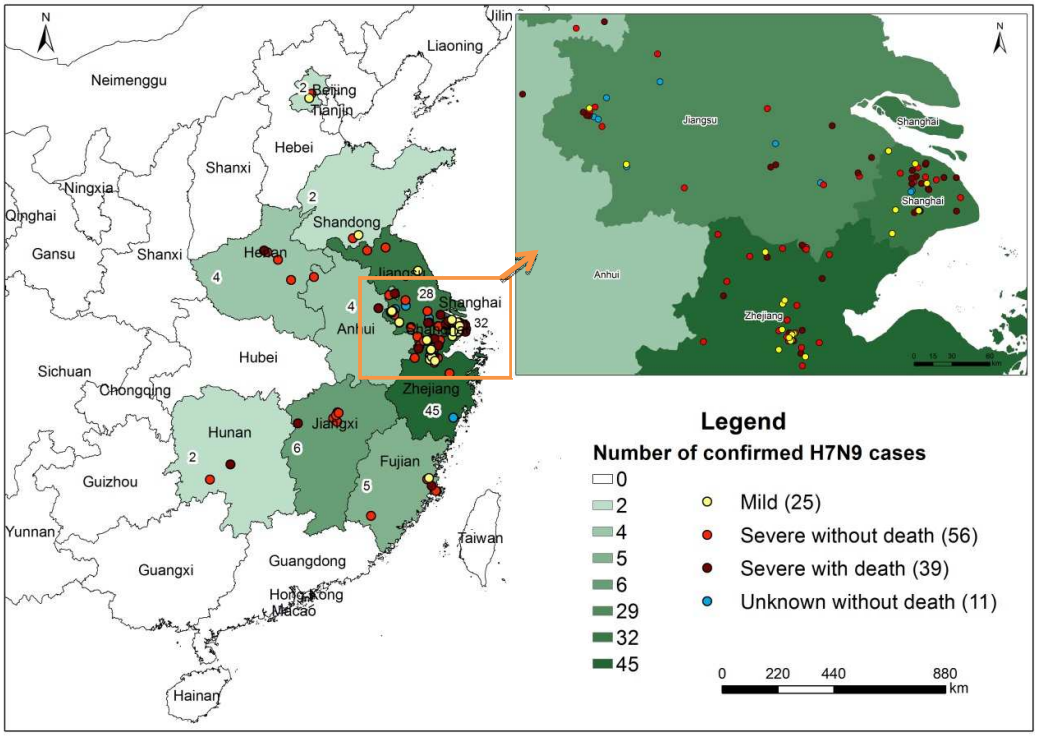

Figure 2. Spatial distribution of 131 confirmed H7N9 cases. (Figure 2 presented the spatial distribution of 131 confirmed H7N9 cases severity in China. Mild, severity without death, severity with death and unknown without death cases were differentiated by diverse colors. The points were mapped based on the coordinates of the addresses. Areas with high density of cases were magnified on the top right corner. The map was drawn with ArcGIS 10.0 software.)

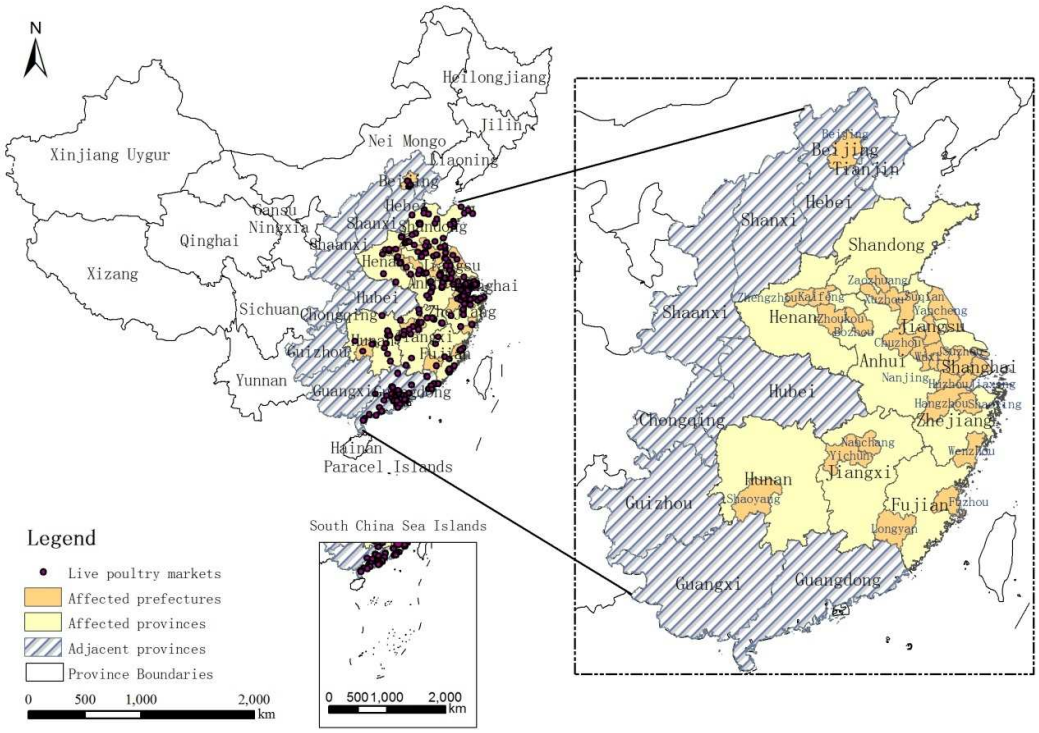

Figure 3. Three types of regions for poultry-industry losses estimation. (Figure 3 presented poultry-industry losses which were estimated for three categories including 27 prefectures, 10 affected provinces and eight non-affected adjacent provinces. Points represented most of the main live-poultry markets which were obtained from Google Earth excluding the retail locations. The map was drawn with ArcGIS 10.0 software.)

Table 1. Formula for calculating direct medical costs

Cost	Formula
Cost of examination for outpatient and inpatient in ward (laboratory and radiology)	Cost per patient * number of patients
Cost of examination in ICU (laboratory and radiology)	Cost per day * mean number of days of ICU stay * number of patients
Cost of treatment	
Antiviral	Cost per day * mean number of days * number of patients
Antibiotics	Cost per day * mean number of days * number of patients
Other drugs	Cost per day * mean number of days * number of patients
Glucocorticoids	Cost per day * mean number of days * number of patients
Intravenous immune globulin	Cost per day * mean number of days * number of patients
Oxygen therapy	Cost per day * mean number of days of hospital stay * number of patients
ICU care	Cost per day * mean number of days of ICU stay * number of patients
ICU monitor	Cost per day * mean number of days of ICU stay * number of patients
Mechanical ventilation	
Noninvasive	Cost per day * mean number of days * number of patients
Invasive	Cost per day * mean number of days * number of patients
Artificial-liver-support-system therapy	Cost per day * mean number of days * number of patients
Continuous renal-replacement therapy	Cost per day * mean number of days * number of patients
Extracorporeal membrane oxygenation (ECMO)	Cost per day * mean number of days * number of patients
Complications	
ARDS	Cost per day * mean number of days of ICU stay * number of patients
Shock	Cost per day * mean number of days of ICU stay * number of patients
Acute kidney injury	Cost per day * mean number of days of ICU stay * number of patients
Rhabdomyolysis	Cost per day * mean number of days of ICU stay * number of patients
Other costs [$]	Cost per day * mean number of days of hospital stay * number of patients

[$] Other costs include medical consumables, charge for sickbed, general care services, checkup fee, etc.

Table 2. Formula for calculating poultry-industry losses

Cost	Formula
Cost of poultry slaughter (L_1)	Cost per animal* number of poultry killed
Cost of closing live-poultry markets (L_2)	
Cost of live-poultry sales(L_{21})	Live-poultry sales per day * cost per animal * number of days
Cost of market-stall leases **(L_{22})**	Cost of lease per stall per day * number of stalls * number of days

Table 3. Driver measurement

Category	Mild		Severe without death		Severe with death		Unknown without death		Reference proportion of patients (%)*
	Mean number of days (no. of cases investigated/total cases)	Number of cases	Mean number of days (no. of cases investigated/total cases)	Number of cases	Mean number of days (no. of cases investigated/total cases)	Number of cases	Mean number of days¶	Number of cases	
Hospital stay	9(11/25)	25	18(19/56)	55	20(19/39)	38	14	11	98.2
ICU stay	0	0	12(10/56)	55	16(11/39)	38	6	7	76.6
Treatment									
Antiviral	7(3/25)	24	7(20/56)	54	11(11/39)	38	7	11	97.3
Antibiotics	8(4/25)	17	11(21/56)	40	14(16/39)	28	9	8	71.2
Other drugs	9(11/25)	25	12(10/56)	55	16(11/39)	38	11	11	98.2
Glucocorticoids	0	0	7§	43	7§	30	4	8	62.2
Intravenous immune globulin	0	0	5§	37	5§	26	3	7	53.2
Oxygen therapy	9(11/25)	25	18(19/56)	56	20(19/39)	39	9	11	100.0
Mechanical ventilation									
Noninvasive	0	0	9(7/56)	19	3(6/39)	13	5	4	27.9
Invasive	0	0	8(7/56)	41	10(15/39)	28	4	8	58.6
Artificial-liver-support-system therapy	0	0	4§	11	4§	7	2	2	15.3
Continuous renal-replacement therapy	0	0	7§	18	7§	13	4	4	26.1
Extracorporeal membrane oxygenation (ECMO)	0	0	6(1/56)	12	7(2/39)	9	3	2	18.0
Complications									
ARDS	0	0	12(10/56)	50	16(11/39)	35	6	10	71.2
Shock	0	0	12(10/56)	18	16(11/39)	13	6	4	26.1
Acute kidney injury	0	0	12(10/56)	11	16(11/39)	8	6	2	16.2
Rhabdomyolysis	0	0	12(10/56)	7	16(11/39)	5	6	1	9.9
Other costs	9(11/25)	25	18(19/56)	55	20(19/39)	38	14	11	98.2

* Referenced from the literature "Clinical Findings in 111 Cases of Influenza A (H7N9) Virus Infection"[6]

§ Based on the professionals' experiences

¶ The mean number of days for patient with unknown without death was estimated as the average days for the mild and the severe cases without death

Table 4. Poultry-industry losses of 27 prefectures with H7N9 cases

Affected provinces (number of cases)	Affected prefectures (number of cases)	Date	Cost of closing live-poultry markets				Cost of poultry slaughter (10^4 CNY)
			Live-poultry sales per day(10^4)	Number of days	Cost of live-poultry sales(10^4 CNY)	Market-stall leases(10^4 CNY)	
Beijing(2)	Beijing(2)	4.13	3.00	49	1470.00	6.93	0.50
Shanghai(32)	Shanghai(32)	4.05	11.94	57	6805.80	1703.16	20.54
Jiangsu(29)	Wuxi(4)	4.09	12.87	53	6821.10	527.40	0.40
	Yancheng(1)	4.15	8.18	47	3844.60	387.11	5.00
	Nanjing(12)	4.06	8.91	56	4989.60	567.84	8.00
	Zhenjiang(1)	4.09	8.55	53	4531.50	342.12	0.31
	Suzhou(7)	4.08	17.73	54	9574.20	265.03	0.01
	Yangzhou(1)	4.15	11.52	47	5414.40	180.17	0.20
	Xuzhou(1)	4.24	14.80	38	5624.00	380.30	0.10
	Changzhou(1)	4.11	8.94	51	4559.40	167.71	1.30
	Suqian(1)	4.02	10.14	60	6084.00	200.00	0.10
Zhejiang(45)	Huzhou(12)	4.11	6.14	51	3131.40	269.79	0.70
	Shaoxing(1)	4.22	5.31	40	2124.00	585.14	10.00
	Hangzhou(29)	4.15	12.48	47	5865.60	1200.20	24.66
	Jiaxing(2)	4.19	6.97	43	2997.10	1565.77	10.00
	Wenzhou(1)	4.21	7.02	41	2878.20	49.78	0.50
Auhui(4)	Bozhou(1)	4.09	2.89	53	1531.70	100.33	10.00
	Chuzhou(3)	3.30	6.19	63	3899.70	65.01	0.72
Fujian(5)	Longyan(1)	5.07	6.73	25	1682.50	77.40	0.82
	Fuzhou(4)	4.29	6.61	33	2181.30	287.76	100.00
Jiangxi(6)	Nanchang(5)	4.26	12.62	36	4543.20	45.72	0.10
	Yichun(1)	4.29	10.46	33	3451.80	14.09	0.08
Henan(4)	Zhoukou(1)	4.16	13.59	46	6251.40	18.28	1.60
	Kaifeng(1)	4.15	9.22	47	4333.40	14.81	1.80
	Zhengzhou(2)	4.15	9.01	47	4234.70	20.68	3.90
Hunan(2)	Shaoyang(2)	4.28	7.80	34	2652.00	70.10	100.00
Shandong(2)	Zaozhuang(2)	4.24	21.20	38	8056.00	52.36	0.66
Total cost (10^4 CNY)		128999.59					
Total cost (10^4 USD)*		20639.93					

Note：'Date' indicates the date on which the live-poultry markets were closed; 'days' is the number of days the live-poultry markets remained closed.

Table 5. Total amount of poultry-industry losses in the ten affected provinces (10^4 CNY)

Affected provinces	Cost of live-poultry sales(10^4 CNY)	Market-stall leases(10^4 CNY)	Cost of poultry slaughter (10^4 CNY)	Total cost (10^4 CNY)	Total cost (10^4USD)
Beijing	14553.98	291.06	0.5	14845.54	2394.59
Shanghai	6805.8	1703.16	20.54	8529.5	1375.81
Jiangsu	124485.53	3181.5	25.62	127692.66	20596.83
Zhejiang	29982.14	2444.4	45.36	32471.9	5237.72
Anhui	113309.59	1113.01	11.52	114434.12	18458.22
Fujian	16723.29	509.04	100.82	17333.15	2795.84
Jiangxi	40832.88	255.36	0.18	41088.42	6627.56
Henan	114473.97	73.09	7.3	114554.36	18477.62
Hunan	32301.37	433.25	100	32834.62	5296.22
Shandong	180421.92	402.76	0.66	180825.34	29167.13
Guangdong	88827.4	1808.59	99.36	90735.35	14635.61
Total cost (10^4CNY)	762717.86	12215.21	411.87	775344.94	125063.14
Total cost (10^4USD)	123026.39	1970.31	66.43	125063.14	2394.59

Note：The date on which the live-poultry markets were closed varied among cities/counties. In table 5, the dates when the first case of H7N9 was confirmed were adopt for estimating the total amount of poultry-industry losses in each affected provinces.

Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Qi XP, Jiang D, Wang HL, et al. Burden of diseases in the 21st century: A case of emerging H7N9 influenza virus infection in China

Supplementary Appendix

Burden of diseases in the 21st century:

A case of emerging H7N9 influenza virus infection in China

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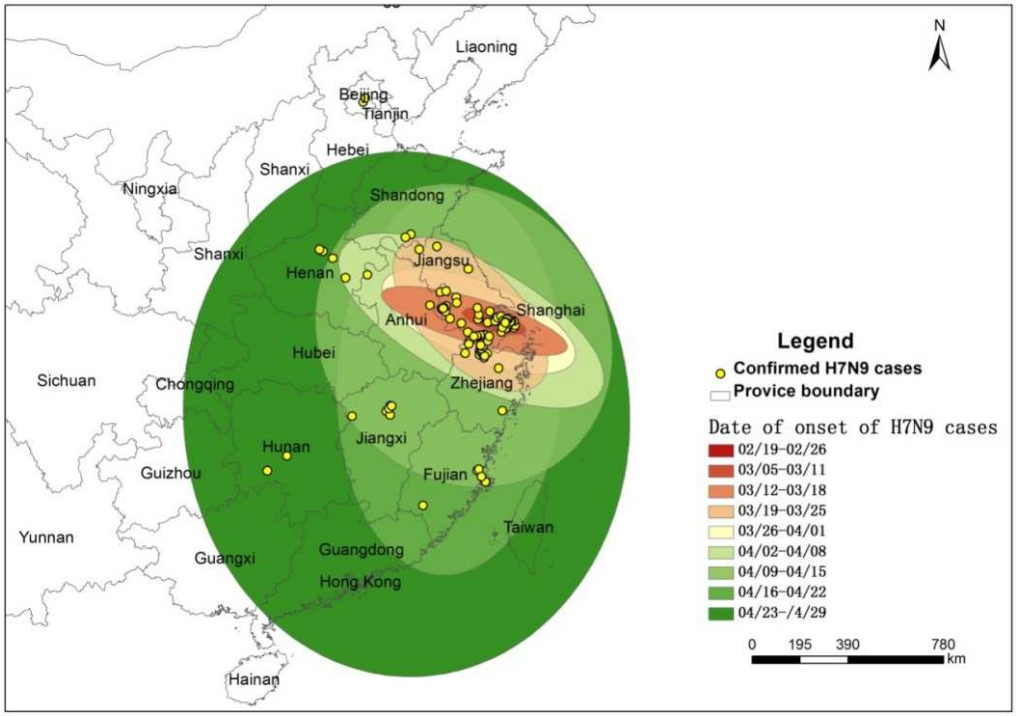

Figure S1. The directional distribution of confirmed H7N9 cases by week (The distribution of new confirmed H7N9 cases by week was extracted by creating two standard deviational ellipses covering 95% of the points in each ellipse to summarize the central tendency, dispersion and directional trends of confirmed H7N9 cases. The map was drawn with ArcGIS 10.0 software)

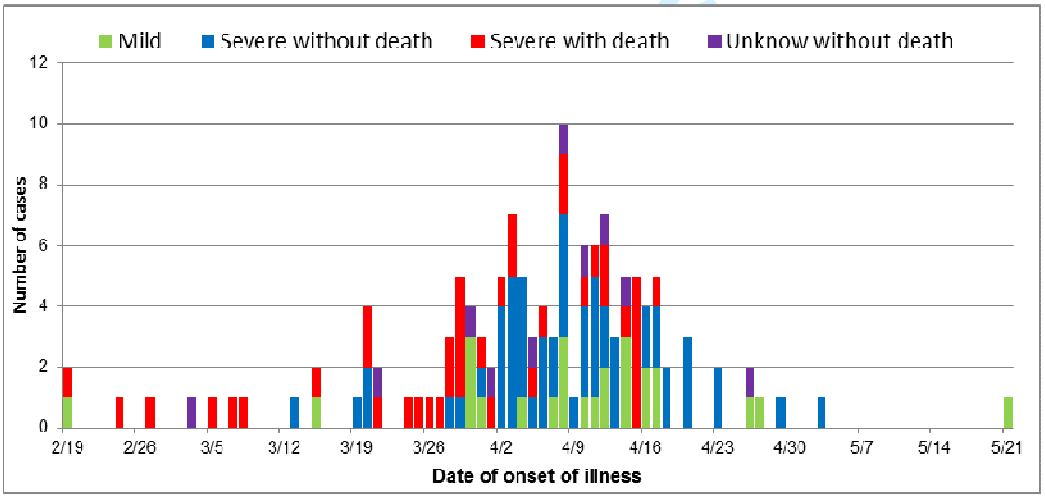

Figure S2. Date of illness onset by case category (Based on the case categories, the graph presented the number of cases within each date of onset of H7N9 cases. It was drawn with Microsoft office Excel 2010 software.)

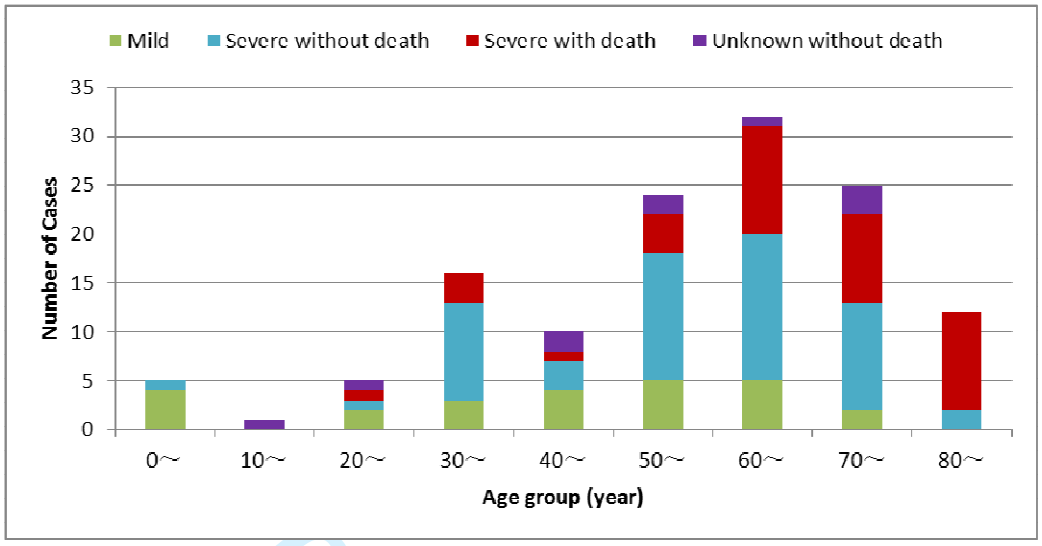

Figure S3. Age distribution of each case category (Based on the case categories, the graph presented the number of cases within each age group of H7N9 cases. It was drawn with Microsoft office Excel 2010 software.)

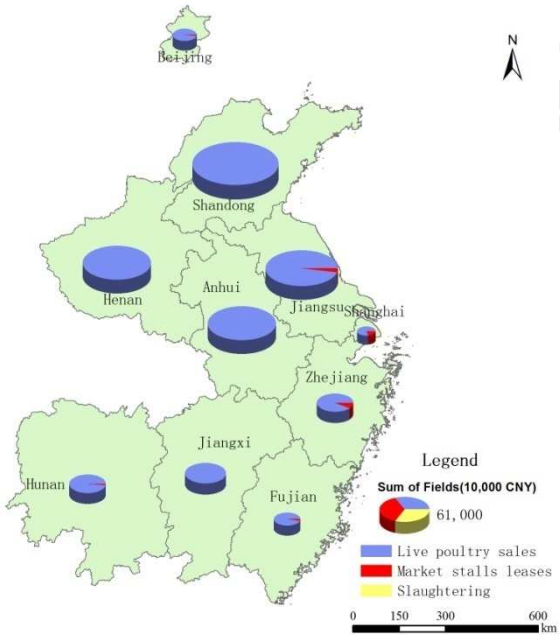

Figure S4. Poultry-industry losses of each province (The map presented the total losses of poultry industry in 10 affected provinces and the proportion of each kind of losses. It was drawn with ArcGIS 10.0 software.)

Table S1. Estimation of costs per day for confirmed H7N9 cases

Cost driver	Cost (CNY)	Note
Cost of examination of outpatients and inpatients in ward (laboratory and radiology)	2,500	Includes tests such as live function test, kidney function test, blood routine examination, routine urinalysis, electrocardiogram, virus detection and isolation, chest radiology, computed tomography(CT), color Doppler ultrasound, antibody testing for hepatitis, human immunodeficiency virus and syphilis, throat swab, drug sensitive test, blood culture, ion test, blood glucose, blood sedimentation, blood gas, troponin, coagulation tests, procalcitonin (PCT), myocardial enzyme, D-dimer, C-reactive protein(CRP), B type natriuretic peptide.
Cost of examination in ICU (laboratory and radiology)	1,700 per day	
Cost of treatment		
Antiviral	60 per day	Oseltamivir and peramivir, etc.
Antibiotics	350 per day	Fluoroquinolones, Piperacillin, Imipenem and Cephalosporin, etc.
Other drugs	Mild: 270 per day	Reducing phlegm, relieving asthma, abating fever, providing antioxidants and nutrition, inducing sedating, etc.
	Severe: 1,600 per day	
Glucocorticoids	70 per day	
Intravenous immune globulin	2,500 per day	
Oxygen therapy	120 per day	
ICU care	1,100 per day	
ICU monitor	500 per day	
Mechanical ventilation		
Noninvasive	400 per day	
Invasive	1,000 per day	
Artificial-liver-support-system therapy	6000 per day	
Continuous renal-replacement therapy	9000 per day	
Extracorporeal membrane oxygenation (ECMO)	10,000 per day	
Complications		Excluding the treatments listed above
Adult respiratory distress syndrome (ARDS)	1,000 per day	Increases drug and special care services
Shock	800 per day	Increases drug, blood, fluid and hemodynamic monitoring
Acute kidney injury	300 per day	Increases drug
Rhabdomyolysis	600 per day	Increases drug use
Other costs	Mild: 200 per day	Medical consumables, charge for sickbed, general care services, checkup fee, etc.
	Severe: 800 per day	

Note: CNY=Chinese Yuan

Table S2. Summary of direct medical costs

Cost driver	Mild (n=25)	Severe without death (n=56)	Severe with death (n=39)	Unknown without death (n=11)	Total cost
Cost of examination for outpatient and inpatient in ward (laboratory and radiology)	62,500	137,500	95,000	27,500	322,500
Cost of examination in ICU (laboratory and radiology)	0	1,122,000	1,033,600	71,400	2,227,000
Cost of treatment					
Antiviral	10,080	22,680	25,080	4,620	62,460
Antibiotics	47,600	154,000	137,200	25,200	364,000
Other drugs	60,750	1,056,000	972,800	113,135	2,202,685
Glucocorticoids	0	21,070	14,700	2,240	38,010
Intravenous immune globulin	0	462,500	325,000	52,500	840,000
Oxygen therapy	27,000	144,000	93,600	11,880	276,480
ICU care	0	726,000	668,800	46,200	1,441,000
ICU monitor	0	330,000	304,000	21,000	655,000
Mechanical ventilation					
Noninvasive	0	68,400	15,600	8,000	92,000
Invasive	0	328,000	280,000	32,000	640,000
Artificial-liver-support-system therapy	0	264,000	168,000	24,000	456,000
Continuous renal-replacement therapy	0	1,134,000	819,000	144,000	2,097,000
Extracorporeal membrane oxygenation (ECMO)	0	720,000	630,000	60,000	1,410,000
Complications					
ARDS	0	600,000	560,000	60,000	1,220,000
Shock	0	172,800	166,400	19,200	358,400
Acute kidney injury	0	1,056,000	1,024,000	96,000	2,176,000
Rhabdomyolysis	0	50,400	48,000	3,600	102,000
Other costs	45,000	806,400	608,000	77,000	1,536,400
Total cost (CNY)	252,930	8,359,350	7,003,180	807,075	16,422,535
Total cost (USD)*	40,469	1,337,496	1,120,509	129,132	2,627,606
Mean cost for each patient (CNY)	10,117	139,323	205,976	73,370	107,197
Mean cost for each patient (USD)*	1,619	22,292	32,956	11,739	17,151
Mean cost per day for each patient (CNY)	1,124	8,293	8,978	5,765	6,040
Mean cost per day for each patient (USD)*	180	1,327	1,437	922	966

*Based on average exchange rate in May,2013: 1CNY=0.16USD

Table S3. YLLs of confirmed H7N9 cases

Age group	Life expectancy at age(Male)	Life expectancy at age(Female)	Number of deaths (Male)	Number of deaths (Female)	YLL(years)*
AGE<1	74.05	77.17	0	0	0.00
AGE1-4	74.01	77.14	0	0	0.00
AGE5-9	70.16	73.29	0	0	0.00
AGE10-14	65.23	68.36	0	0	0.00
AGE15-19	60.31	63.43	0	0	0.00
AGE20-24	55.48	58.57	0	0	0.00
AGE25-29	50.74	53.77	1	0	50.74
AGE30-34	45.99	48.98	0	1	48.98
AGE35-39	41.29	44.21	1	1	85.50
AGE40-44	36.57	39.42	0	0	0.00
AGE45-49	31.96	34.70	1	0	31.96
AGE50-54	27.41	30.06	1	1	57.47
AGE55-59	23.04	25.57	2	0	46.09
AGE60-64	18.88	21.23	6	2	155.73
AGE65-69	15.03	17.15	2	1	47.20
AGE70-74	11.71	13.50	4	1	60.35
AGE75-79	9.00	10.39	3	1	37.40
AGE80-84	6.65	7.68	3	1	27.64
AGE85-89	4.95	5.58	5	0	24.74
AGE90-94	2.99	3.40	1	0	2.99
AGE95-99	2.15	2.37	0	0	0.00
AGE100+	1.53	1.67	0	0	0.00
Total			30	9	676.78

*YLL = years of life lost due to premature mortality.

Table S4. YLDs of confirmed H7N9 cases

	Disability weight*	Number of cases	Duration of disability(years)	YLD(years)¶
Mild	0.005	25	0.025	0.003
Severe	0.21	95	0.052	1.038
Unknown(moderate)	0.053	11	0.038	0.022
Total		131	0.115	1.064

*Disability weight: Institute for Health Metrics and Evaluation (IHME),GBD 2010 Disability Weights

¶YLD = years lived with disability.

Table S5. Potential poultry-industry losses of eight non-affected adjacent provinces

Potential affected provinces	Cost of live-poultry sales(10^4 CNY)	Market-stall leases (10^4 CNY)	Total cost (10^4 CNY)	Total cost (10^4USD)
Guangxi	126671.29	2623.68	129294.97	20687.20
Guizhou	13793.65	256.32	14049.97	2248.00
Chongqing	32341.22	2904.12	35245.34	5639.25
Hubei	76709.59	2097.12	78806.71	12609.07
Shaanxi	7859.11	213.72	8072.83	1291.65
Shanxi	9571.87	473.46	10045.33	1607.25
Hebei	78872.43	1340.10	80212.53	12834.01
Tianjin	11426.38	582.00	12008.38	1921.34
Total cost (10^4CNY)	357245.56	10490.52	367736.08	58837.77
Total cost (10^4USD)	57159.29	1678.48	58837.77	9414.04

Calculating the burden of disease of avian-origin H7N9 infections in China

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Calculating the burden of disease of avian-origin H7N9 infections in China

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Calculating the burden of disease of avian-origin H7N9 infections in China

Abstract

Objective A total of 131 cases of avian-originated H7N9 infection have been confirmed in China mainland from February to May 2013. We calculated the overall burden of H7N9 cases in China as of May 31, 2013 to provide an example of the comprehensive burden of disease in the 21st century from an acute animal-borne emerging infectious disease.

Design We present an accurate and operable method for estimating the burden of H7N9 cases in China. The main drivers of economic loss were identified. Costs were broken down into direct (outpatient and inpatient examination and treatment) and indirect costs (cost of disability-adjusted life years [DALYs] and losses in the poultry industry), which were estimated based on field surveys and china statistical yearbook.

Setting Models were applied to estimate the overall burden of H7N9 cases in China.

Participants One-hundred and thirty-one laboratory-confirmed H7N9 cases by May 31, 2013.

Outcome measure Burden of H7N9 cases including direct and indirect losses.

Results The total direct medical cost was 16,422,535 CNY (2,627,606 USD). The mean cost for each patient was 10,117 CNY(1,619 USD) for mild patients, 139,323 CNY(22,292 USD) for severe cases without death, and 205,976 CNY(32,956 USD) for severe cases with death. The total cost of DALYs was 17,356,561 CNY(2,777,050 USD). The poultry industry losses amounted to 7.75 billion CNY(1.24 billion USD) in 10 affected provinces and 3.68 billion CNY(0.59 billion USD) in eight non-affected adjacent provinces.

Conclusions The huge poultry industry losses followed live poultry markets closing down and poultry slaughtering in some areas. Though the proportion of direct medical losses and DALYs losses in the estimate of H7N9 burden was small, the medical costs per case were extremely high (particularly for addressing the use of modern medical devices). A cost-effectiveness assessment for the intervention should be conducted in a future study.

Article summary

Strengths and limitations of this study

- This study is the first in which comprehensive methods were applied to identify the main drivers of economic losses and estimate the burden of disease due to H7N9 infection

including direct costs (medical cost) and indirect costs (death, disability, and poultry-industry losses);

- This study had some limitations. The estimate of medical costs was based on a model and second-hand data, not on the original costs of patients with H7N9. The burden of H7N9 may have been underestimated, as the ongoing costs of existing cases and new cases after May 2013 were underreported and other losses involved in the livestock-production chain were not included in our study.

Introduction

A novel avian-origin influenza A (H7N9) virus has caused severe disease in humans in China since February 2013. The high number of new cases within a short period and the high case fatality rate have caused public panic and attracted global attention. Some patient's families undertook large medical costs. According to the literature, exposure to live poultry could be an important risk factor for human infection with H7N9. [1-5] As a result, closing down the live-poultry markets and slaughtering the poultry were the main interventional measures in the affected areas of China. These interventions played an important role in disease prevention but also caused serious losses to the poultry industry.

The introduction of the novel virus led to numerous investigations of its origin, its genes, clinical symptoms, laboratory testing, treatment and transmission [6-8]; however, the burden of human infection with H7N9 has not yet been measured. It is important to estimate the overall burden of disease (BOD) due to H7N9 in China because this virus is new to humans and could cause a global pandemic in the future. The Global Burden of Disease (GBD) 2010 study presents a comprehensive methodological framework for death and disability loss estimation and has had a pronounced impact on the BOD estimate [9 10]. In this study, we identified the main drivers of economic loss and summarized the direct and indirect costs of human H7N9 infection. We present an accurate and operable approach for estimating the overall burden of emerging infectious diseases and provide evidence on the cost effectiveness of H7N9 prevention and control. We also set up a BOD estimate example for any animal-borne infectious disease, particularly with the introduction of modern medical devices.

Methods

Case category definition

The confirmed human H7N9 infections were divided into mild and severe cases based on the "Diagnostic and treatment protocol for human infections with avian influenza A (H7N9) (2nd edition, 2013)".[11] Mild cases presented with influenza-like illness, whereas severe cases developed quickly and presented with severe pneumonia, usually accompanied by severe complications and organ failure. Severe illness was divided into "severe without death" and "severe with death". The 11 H7N9 cases of unknown status were classified as "unknown without death".

Data source

Data on the 131 confirmed H7N9 cases by the end of May 31, 2013 came from China Information System for Diseases Control and Prevention and included basic information on the onset of illness, epidemiology and emergency event reporting. Disability-adjusted life years (DALYs) were calculated based on two published sources. The World Health Organization (WHO) provided a table of life expectancy by age for China in 2011,[12] whereas the Institute for Health Metrics and Evaluation (IHME) published the GBD 2010, including the GBD 2010 Disability Weights .[13] Disability weights of general infectious disease (acute episode for mild, moderate, and severe) were adopted from IHME based on clinician's suggestions of symptoms from H7N9 cases

that were more severe than the general infectious disease cases. The 2012 per capita gross domestic product (GDP), which was used to calculate the cost of lost lives and the cost of disability, was obtained from the National Bureau of Statistics of China.

Poultry production and trade data from 27 prefectures with confirmed H7N9 cases, including live-poultry sales, dates of live-market closings, and market-stall volumes were collected from field surveys, *local livestock-breeding year book* [14] and the *Chinese Commodities Trading-Market Statistics Yearbook 2012*.[15] Data were gathered from the 10 affected provinces and 8 unaffected adjacent provinces. These data were used to estimate poultry-industry losses.

Analysis framework for the burden of confirmed H7N9 cases

We constructed a framework for the BOD analysis (Figure 1). We described the confirmed H7N9 cases as mild, severe without death, severe with death, and unknown without death and examined the spatiotemporal and population characteristics of these cases. Based on the case category and characteristics of case spatiotemporal distribution, costs were broken down into direct medical costs (outpatient and inpatient examination and treatment) and indirect costs (death, disability and poultry-industry losses). To calculate the DALYs attributable to H7N9, the H7N9-specific years of life loss due to premature mortality (YLLs) and years lived with disability (YLDs) were computed and summed. An intensive analysis of poultry-industry losses would be complex and would require time-consuming field surveys. Indirect effects may lag behind. In this study, we considered only the poultry industry losses caused from the closing of live-poultry markets and the large-scale slaughtering of poultry.

Statistical analysis

Descriptive statistics were used to summarize the epidemiological characteristics of the cases. The distribution of confirmed H7N9 cases by week was also extracted by creating two standard deviational ellipses (covering 95% of the points while calculating the standard deviation of the x-coordinates and y-coordinates from the mean center to define the axes of the ellipse) to summarize the spatial spread of confirmed H7N9 cases (central tendency, dispersion, and directional trends). If the number of cases in 1 week was less than three, those cases were not included in the calculation.

The methods for estimating direct medical costs are traditionally classified into two broad approaches: bottom-up (micro-costing) and top-down (macro-costing) .[16 17] In general, the bottom-up approach usually results in a higher but more accurate estimate.[18] In our study, we used the bottom-up approach to estimate direct medical costs. Four cost drivers were extracted: cost of outpatient and inpatient examinations in the ward, cost of examinations in intensive-care units (ICUs), cost of treatment, and other costs (including medical consumables, charge for sickbed, general care services, checkup fee, etc.). A cost formula was constructed for each driver, as depicted in Table 1. The cost per patient was estimated by experienced hospital financial officers and hospital doctors. The mean number of days (ICU stay, hospital stay, and days of treatment) was estimated from the epidemiological data. The number of patients for each driver was derived from a previous publication.[6] The professional's experience was also considered for some items

that were not included in our surveillance system. Costs for the category "unknown without death" were assumed to be moderate and were set as the average of the costs of mild cases and severe cases without death.

The YLLs for confirmed H7N9 cases in China were calculated from the sum of the number of fatal cases (n) in 5-year age groups (i) multiplied by the remaining expected life span (e) based on the age of death for that age group:[19] (formula 1)

$$YLLs = \sum n_i \times e_i \quad (1)$$

The Chinese life-expectancy table from WHO 2011 was used to estimate the burden of H7N9 in YLLs.

The YLDs were calculated by multiplying the duration of illness (t) by the disability weights (w) accumulated over all H7N9 cases (d) for each health outcome (j): (formula 2)

$$YLDs = \sum d_j \times t_j \times w_j \quad (2)$$

As H7N9 is a relatively new infectious disease and the health status of patients after discharge is unknown, we calculated the YLDs only as general acute episodes of infectious disease during the hospital stay. Disability weights were assigned as infectious disease (mild, moderate, and severe acute episodes).[13]

DALYs were calculated by adding YLLs to morbidity and disability, expressed in YLD (formula 3).

$$DALYs = YLLs + YLDs \quad (3)$$

An estimate of the cost of one DALY was based on the traditional human-capital approach for per-capita GDP (formula 4). Production capability weights were calculated considering the different production capabilities at different ages. The following weights were used according to the literature: 0.15 at age 0–14 years, 0.75 at age 15–44 years, 0.8 at age 45–59 years, and 0.1 at age 60+ years.[20]

$$\text{Cost of DALYs} = \text{DALYs} \times \text{per-capita GDP} \times \text{weight of production capability} \quad (4)$$

As mentioned above, direct poultry-industry losses (PIL) can be calculated using formula 5:

$$PIL = L_1 + L_2 \quad (5)$$

where L_1 is the loss from poultry slaughter and L_2 is the loss from the closing of live-poultry markets, which includes lost sales of live poultry (L_{21}) and fees for market-stall leases (L_{22}). A cost formula was constructed for the estimate of poultry industry loses (Table 2).

Results

Epidemiological characteristics of case categories

A total of 131 confirmed H7N9 cases in 10 provinces in China were mapped as individual points based on detailed addresses (Figure 2). Most (81%) of the patients were located in Jiangsu, Shanghai, and Zhejiang Provinces. Most of the cases (73% or above) in the ten provinces were severe. There were 25 mild cases, 56 severe cases without death, 39 severe cases with death, and 11 unknown cases without death in China through May 31, 2013.

Figure S1 shows the rate, direction, and scope of H7N9 spread. Each ellipse covers 95% of the incident cases for 1 week. The location of the first week of H7N9 onset was in Shanghai. Over the next few weeks, the epidemic spread to Jiangsu and Zhejiang Provinces and continued to grow. The virus spread quickly from the northwest to the north and south regions.

The onset of most H7N9 cases was relatively clustered. Within the total event timeframe (February 19–May 21), 74% of the cases were infected between March 28–April 17 (Figure S2). Severe cases with death were found in the initial and intermediate stages. The median age of patients with confirmed H7N9 virus infection was 61 years (range, 3–91 years). Severe symptoms tended to occur in older people. The median age of patients who were severely ill without death was 60 years, whereas the median age of patients who were severely ill with death was 69 years. The number of mild cases was distributed in all age groups < 80 years (Figure S3).

Direct medical costs for confirmed H7N9 cases

After the confirmed H7N9 cases occurred in China, the patient's clinical manifestations, examinations, and treatments were published,[6] which allowed us to estimate direct medical costs using a cost model. We separated the examination data into examinations conducted in the ward and examinations conducted in the ICU, as the latter were more frequent. The main treatments for confirmed H7N9 cases were selected. Three main factors were considered in our cost formula: cost per day, number of days, and number of patients. For the cost-per-day estimation, we selected a Grade-III Class-A hospital (general large-scale hospital in China). Cost per day was obtained from the hospital financial officers and hospital doctors based on the average cost of patients with the same treatments from January 1, 2013 to May 31, 2013 in this hospital (Table S1). Differences in costs among the regions in China were approximately 10%.

The mean number of days and number of cases were estimated from a subset of the investigated cases (Table 3). Data regarding hospital stay were available for 11 of the 25 mild cases, 19 of the 56 severe cases without death, and 19 of the 39 severe cases with death. The mean length of stay was 9 days for mild cases, 18 days for severe cases without death, and 20 days for severe cases with death. Data on the duration of ICU stay were available for 10 of the 56 severe cases without death and 11 of the 39 severe cases with death. Severe cases without death stayed in the ICU for a mean of 12 days, whereas severe cases with death stayed for a mean of 16 days. We assumed that the mean hospital stay of severe cases with complications was equal to the length of the ICU stay, although complications might occur incrementally. The mean duration of treatments

was estimated based on a subset of investigated patients, except for glucocorticoids and intravenous immune globulin, for which estimates were obtained from professional experience. Treatment for complications required drugs and examinations in addition to the treatments listed above. Treatment was described for 111 confirmed H7N9 cases, along with the proportion of patients who received each treatment.[8] We assumed that the proportions were generalizable to all cases because it covered 85% of cases.

Table S2 is a summary of all direct medical costs. The total cost for all 131 patients with confirmed H7N9 virus infection was 16,422,535 CNY (2,627,606 USD). The mean cost per patient was 10,117 CNY (1,619 USD) for mild patients, 139,323 CNY (22,292 USD) for severe cases without death, and 205,976 CNY (32,956 USD) for severe cases with death. The mean cost per day was 1,124 CNY (180 USD) for a mild case, 8,293 CNY (1,327 USD) for a severe case without death, and 8,978 CNY (1,437 USD) for a severe case with death. As the severity of the illness increased, the costs increased correspondingly.

Cost of DALYs for H7N9

A total of 39 deaths from confirmed H7N9, including 30 males and 9 females, were reported from the National Health and Family Planning Commission of China by May 31, 2013. See Table S3 for more details on the number of cases in each age group. The total YLLs were 676.89. There were 131 H7N9 cases, including 25 mild cases, 95 severe cases, and 11 of unknown category (assumed to be moderate). The YLD calculations were based on the case category. Total YLDs were 1.064 (Table S4). DALYs combined the time lived with disability and the time lost due to premature mortality; thus, DALYs were 677.848 for all confirmed H7N9 patients. We adopted 2012 per-capita GDP for the 10 provinces and estimated the cases adjusted per capita GDP (65,655 CNY or 10,505USD). By calculating the weight of production capability for each age group, we obtained the average weight of production capability to be 0.39 for all confirmed H7N9 cases. The total cost of DALYs was 17,356,561 CNY (2,777,050 USD) according to formula 4.

Poultry-industry losses

Poultry-industry losses were estimated for three categories (Figure 3): 1) 27 prefectures with confirmed H7N9 cases (region 1, brown in Figure 3), 2) 10 affected provinces (region 2, yellow in Figure 3), and 3) eight non-affected adjacent provinces (region 3, shadowed in Figure 3).

Three types of losses were calculated for region 1: losses from poultry slaughter, lost live poultry sales, and fees for market-stall leases. In the 10 affected provinces (region 2), in addition to the losses in region 1, the losses arose mainly from closing down live-poultry markets in each province. These two losses were then summed to estimate poultry-industry losses caused by H7N9 outbreaks. Most of the main live-poultry markets in the affected provinces (Figure 3) were obtained from Google Earth; the retail locations were excluded.

Poultry-industry losses in eight non-affected adjacent provinces (region 3) were also calculated as potential economic losses. The direct poultry-industry losses of 27 prefectures for the H7N9 cases are described in detail in Table 4.

The cost of closing down live-poultry markets includes the lost live poultry sales and fees for market-stall leases. The cost of lost live poultry sales was calculated according to the daily live-poultry sales, the cost per animal (assumed to be 10 CNY or 1.6USD in this study), and the number of days the market was closed. The cost of market-stall leases was calculated based on the average lease per stall per day in the corresponding city, the number of stalls, and the number of days the market was closed in each city. The cost of poultry slaughter was obtained from the number of poultry slaughtered and the cost per animal. The number of days the market was closed was counted through May 31 because only one confirmed H7N9 case had occurred since then. The total poultry-industry losses in the 10 affected provinces, including 27 prefectures with H7N9 cases, are listed in Table 5. The poultry-industry losses of each province are presented in Figure S4.

China's poultry industry suffered direct losses amounting to 7.75 billion CNY(1.24USD) from when the first case of H7N9 was confirmed through May 31, 2013. Losses from the live-poultry trade accounted for 98% of the total losses. Although it had only a few H7N9 cases, Shandong Province ranked first in losses among all 10 provinces at 1.81 billion CNY(0.29USD); Jiangsu, Henan, and Anhui ranked next with 1.28 billion CNY(0.20USD), 1.15 billion CNY(0.18USD), and 1.14 billion CNY(0.18USD), respectively. These provinces have large poultry markets. Zhejiang Province had the highest number of confirmed cases; however, the losses in that region were not very high, as the sales of live poultry were lower. Strict prevention and control measures, such as daily cleaning of the market, weekly disinfection of the market, and monthly closings of the live market were conducted in Guangdong Province, which reported no H7N9 cases until May 31, 2013 during the emergency response. These prevention and control measures affected the poultry industry. For this reason, the poultry-industry losses in Guangdong Province are also given in Table 5.

Due to timely control measures, the H7N9-affected regions were limited to 27 prefectures in ten provinces in China. In this study, the potential economic risks were also calculated for the eight non-affected adjacent provinces (region 3, shadowed in Figure 3). Table S5 shows that the potential losses to the poultry industry in those regions amounted to 3.6 billion CNY(0.58USD).

Discussion

This study was based on illness severity and spatiotemporal aspects of the recent avian-origin influenza A (H7N9) infection. We assumed that cases of the same severity resulted in similar medical costs. Therefore, mild cases, severe cases without death, severe cases with death, and unknown cases without death were estimated separately by calculating the mean number of days, number of cases, and cost per day.

Compared to the poultry-industry losses, direct medical losses and DALY losses were relatively small. To a large extent, the small number of patients in the H7N9 outbreak in China was due to quick and effective intervention, which prevented a pandemic.[21] The estimate of direct medical costs and DALY costs, particularly the mean cost per patient and mean cost per day for

different case categories, can be used to guide those counties in which no cases occurred during prevention and control of H7N9. DALY per H7N9 case (5,176 DALYs per 1,000 cases) was much higher than most of other respiratory infectious diseases though DALYs per 100,000 population (2.23 DALYs based on affected county population) were lower than most of the infectious diseases according to the 2010 GBD study.[22] A comparison to outbreaks of other infectious diseases (with similar clinical symptoms) was also considered in this report. The healthcare cost per SARS patient in Beijing was 17,150 CNY (1,886 USD), whereas the average medical cost per H7N9 patient was 125,363 CNY (20,058 USD) because of the higher fatality rate of H7N9 patients and use of more expensive modern medical devices.[23]

As of the end of May, China's poultry industry suffered direct losses amounting to 7.75 billion CNY(1.24USD), including the cost of closing live poultry markets and slaughtering poultry in the ten affected provinces. Poultry-industry losses were estimated at three levels: 27 prefectures with confirmed H7N9 cases, 10 affected provinces, and 8 non-affected adjacent provinces. The outbreak of H7N9 may reduce the demand for poultry products in other regions of China due to public perception. These effects were not considered in this study. The cost of closing down the live-poultry markets and the cost of poultry slaughter were calculated as direct poultry-industry losses. We assumed that the cost per animal was 10 CNY(1.6USD) and the date for the end of closing the live-poultry markets was May 31, 2013 because there has been few confirmed H7N9 cases since then. Losses from the live-poultry industry accounted for 98% of the total losses, with the lost sales of live poultry constituting the majority of that amount. Strict prevention and control measures have been enacted in Guangdong Province, which had few reported H7N9 cases. This finding will be significant for similar cases in the future. Due to timely control measures, the effects of the outbreak were limited to 27 prefectures in 10 provinces in China.

Our study had several limitations. First, there were 11 confirmed H7N9 cases without death whose case categories were unknown. The cost estimate for these unknown patients was replaced by the average cost of mild and severe cases without death. Second, in the cost model, some of the data (e.g., mean number of days of extracorporeal membrane oxygenation for severe without death cases) were obtained from a small proportion of investigated cases, which could result in an estimation bias. Third, the direct medical cost did not include opportunity cost,[24] the cost that is incurred because a limited resource is used to treat a preventable disease and cannot therefore be used to treat another disease.[25] The medical practitioner's salary, research funding, and loss of working time for family numbers of patients with H7N9 were excluded from our study. Fourth, estimates of direct medical costs per day might show large differences for specific cases because the drug cost could grow considerably if imported and nutritional drugs were used. We considered only the average severity for patients in the ward and ICU. Fifth, 17 patients were still in the hospital on May 28, 2013 according to the literature.[26] The mean numbers of days in the ward and ICU for severe cases and their fatality rate were thus underestimated. Some of the mild cases may not have been reported, which also resulted in underestimating the cost. Sixth, we considered only direct losses from closing down live-poultry markets and large-scale poultry slaughter, which could be estimated accurately and quickly. This estimate was useful for early control and decision-making; however, other losses involved in the livestock-production chain, such as increased breeding costs, poultry seeding, the prices of poultry meat and eggs, and the decreased production of poultry-feather industries, should be considered in further studies.[27]

In conclusion, we present a rapid, operable, and accurate framework for estimating the burden of human infections from H7N9.This framework could be used in a BOD analysis of future H7N9 or similar outbreaks. The results including direct and indirect costs provide fundamental information for researchers and public and policy makers to support timely and effective interventions. Future study may focus on the cost-effectiveness analysis of poultry industry close down, earlier diagnosis and effective treatments of patients based on more detailed investigation information.

Data sharing

No additional data available.

Contributorship

All authors participated in the conception and design of the report. XQ and GFG designed and supervised the study, and applied the grants. XQ, DJ, HW, DZ, JM, JF, JQ, YS, GW, KX collected data. XQ, DJ, JF, SY, YM, YH, LX, YL, YW, XS and GF analyzed data. QZ, MW, LX and YL took literature search, XQ and DJ drafted the manuscript, and all authors contributed to review and revision and have seen and approved the final version.

Competing Interests

We declare: no support from any organization for the submitted work; no financial relationships with any organizations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

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Figure legends

Figure 1. Framework for calculating the burden of confirmed H7N9 cases. (Figure 1 describes the analytical route of direct and indirect costs, which were integrated into the overall burden of confirmed H7N9 cases. The framework was drawn using the Microsoft Office Visio 2003 software.)

Figure 2. Spatial distribution of the 131 confirmed H7N9 cases. (Figure 2 presents the spatial distribution of the 131 confirmed H7N9 cases by severity in China. Mild, severe without death, severe with death, and unknown without death cases are distinguished by different colors. The points are mapped based on the coordinates of the addresses. Areas with a high density of cases are magnified in the top right corner. The map was drawn using the ArcGIS 10.0 software.)

Figure 3. Three regions for poultry-industry loss estimates. (Figure 3 presents estimated poultry-industry losses for three categories including 27 prefectures, 10 affected provinces, and 8 non-affected adjacent provinces. Points represent most of the main live-poultry markets, which were obtained from Google Earth excluding the retail locations. The map was drawn using the ArcGIS 10.0 software.)

Table 1. Formula for calculating direct medical costs.

Cost	Formula
Cost of examination for outpatient and inpatient in ward (laboratory and radiology)	Cost per patient × number of patients
Cost of examination in ICU (laboratory and radiology)	Cost per day × mean number of days of ICU stay × number of patients
Cost of treatment	
Antiviral	Cost per day × mean number of days × number of patients
Antibiotics	Cost per day × mean number of days × number of patients
Other drugs	Cost per day × mean number of days × number of patients
Glucocorticoids	Cost per day × mean number of days × number of patients
Intravenous immune globulin	Cost per day × mean number of days × number of patients
Oxygen therapy	Cost per day × mean number of days of hospital stay × number of patients
ICU care	Cost per day × mean number of days of ICU stay × number of patients
ICU monitor	Cost per day × mean number of days of ICU stay × number of patients
Mechanical ventilation	
Noninvasive	Cost per day × mean number of days × number of patients
Invasive	Cost per day × mean number of days × number of patients
Artificial-liver-support-system therapy	Cost per day × mean number of days × number of patients
Continuous renal-replacement therapy	Cost per day × mean number of days × number of patients
Extracorporeal membrane oxygenation (ECMO)	Cost per day × mean number of days × number of patients
Complications	
ARDS	Cost per day × mean number of days of ICU stay × number of patients
Shock	Cost per day × mean number of days of ICU stay × number of patients
Acute kidney injury	Cost per day × mean number of days of ICU stay × number of patients
Rhabdomyolysis	Cost per day × mean number of days of ICU stay × number of patients
Other costs [§]	Cost per day ×mean number of days of hospital stay × number of patients

[§]Other costs include medical consumables, charge for sickbed, general care services, checkup fees, etc.

Table 2. Formula for calculating poultry-industry losses.

Cost	Formula
Cost of poultry slaughter (L_1)	Cost per animal × number of poultry killed
Cost of closing live-poultry markets (L_2)	
Cost of live-poultry sales(L_{21})	Live-poultry sales per day × cost per animal × number of days
Cost of market-stall leases (L_{22})	Cost of lease per stall per day × number of stalls × number of days

Table 3. Driver measurement.

Category	Mild		Severe without death		Severe with death		Unknown without death		Reference proportion of patients (%)*
	Mean number of days (no. of cases investigated/total cases)	Number of cases	Mean number of days (no. of cases investigated/total cases)	Number of cases	Mean number of days (no. of cases investigated/total cases)	Number of cases	Mean number of days¶	Number of cases	
Hospital stay	9 (11/25)	25	18 (19/56)	55	20 (19/39)	38	14	11	98.2
ICU stay	0	0	12 (10/56)	55	16 (11/39)	38	6	7	76.6
Treatment									
Antiviral	7 (3/25)	24	7 (20/56)	54	11 (11/39)	38	7	11	97.3
Antibiotics	8 (4/25)	17	11 (21/56)	40	14 (16/39)	28	9	8	71.2
Other drugs	9 (11/25)	25	12 (10/56)	55	16 (11/39)	38	11	11	98.2
Glucocorticoids	0	0	7§	43	7§	30	4	8	62.2
Intravenous immune globulin	0	0	5§	37	5§	26	3	7	53.2
Oxygen therapy	9 (11/25)	25	18 (19/56)	56	20 (19/39)	39	9	11	100.0
Mechanical ventilation									
Noninvasive	0	0	9 (7/56)	19	3 (6/39)	13	5	4	27.9
Invasive	0	0	8 (7/56)	41	10 (15/39)	28	4	8	58.6
Artificial-liver-support-system therapy	0	0	4§	11	4§	7	2	2	15.3
Continuous renal-replacement therapy	0	0	7§	18	7§	13	4	4	26.1
Extracorporeal membrane oxygenation (ECMO)	0	0	6(1/56)	12	7 (2/39)	9	3	2	18.0
Complications									
ARDS	0	0	12 (10/56)	50	16 (11/39)	35	6	10	71.2
Shock	0	0	12 (10/56)	18	16 (11/39)	13	6	4	26.1
Acute kidney injury	0	0	12 (10/56)	11	16 (11/39)	8	6	2	16.2
Rhabdomyolysis	0	0	12 (10/56)	7	16 (11/39)	5	6	1	9.9
Other costs	9 (11/25)	25	18 (19/56)	55	20 (19/39)	38	14	11	98.2

* Referenced from the literature "Clinical Findings in 111 Cases of Influenza A (H7N9) Virus Infection"[6]

§ Based on professional experience

¶ Mean number of days for patients with unknown without death was estimated as the average number of days for mild and severe cases without death.

Table 4. Poultry-industry losses of 27 prefectures with H7N9 cases.

Affected provinces (number of cases)	Affected prefectures (number of cases)	Date	Cost of closing live-poultry markets				Cost of poultry slaughter (10^4 CNY)
			Live-poultry sales per day (10^4)	Number of days	Cost of live-poultry sales(10^4 CNY)	Market-stall leases (10^4 CNY)	
Beijing (2)	Beijing (2)	4.13	3.00	49	1470.00	6.93	0.50
Shanghai (32)	Shanghai (32)	4.05	11.94	57	6805.80	1703.16	20.54
Jiangsu (29)	Wuxi (4)	4.09	12.87	53	6821.10	527.40	0.40
	Yancheng (1)	4.15	8.18	47	3844.60	387.11	5.00
	Nanjing (12)	4.06	8.91	56	4989.60	567.84	8.00
	Zhenjiang (1)	4.09	8.55	53	4531.50	342.12	0.31
	Suzhou (7)	4.08	17.73	54	9574.20	265.03	0.01
	Yangzhou (1)	4.15	11.52	47	5414.40	180.17	0.20
	Xuzhou (1)	4.24	14.80	38	5624.00	380.30	0.10
	Changzhou (1)	4.11	8.94	51	4559.40	167.71	1.30
	Suqian (1)	4.02	10.14	60	6084.00	200.00	0.10
Zhejiang (45)	Huzhou (12)	4.11	6.14	51	3131.40	269.79	0.70
	Shaoxing (1)	4.22	5.31	40	2124.00	585.14	10.00
	Hangzhou (29)	4.15	12.48	47	5865.60	1200.20	24.66
	Jiaxing (2)	4.19	6.97	43	2997.10	1565.77	10.00
	Wenzhou (1)	4.21	7.02	41	2878.20	49.78	0.50
Auhui (4)	Bozhou (1)	4.09	2.89	53	1531.70	100.33	10.00
	Chuzhou (3)	3.30	6.19	63	3899.70	65.01	0.72
Fujian (5)	Longyan (1)	5.07	6.73	25	1682.50	77.40	0.82
	Fuzhou (4)	4.29	6.61	33	2181.30	287.76	100.00
Jiangxi (6)	Nanchang (5)	4.26	12.62	36	4543.20	45.72	0.10
	Yichun (1)	4.29	10.46	33	3451.80	14.09	0.08
Henan (4)	Zhoukou (1)	4.16	13.59	46	6251.40	18.28	1.60
	Kaifeng (1)	4.15	9.22	47	4333.40	14.81	1.80
	Zhengzhou (2)	4.15	9.01	47	4234.70	20.68	3.90
Hunan (2)	Shaoyang (2)	4.28	7.80	34	2652.00	70.10	100.00
Shandong (2)	Zaozhuang (2)	4.24	21.20	38	8056.00	52.36	0.66
Total cost (10^4 CNY)		128999.59					
Total cost (10^4 USD)*		20639.93					

Note: 'Date' indicates the date on which the live-poultry markets were closed; 'days' is the number of days the live-poultry markets remained closed.

Table 5. Total poultry-industry losses in the 10 affected provinces.

Affected provinces	Cost of live-poultry sales (10^4 CNY)	Market-stall leases (10^4 CNY)	Cost of poultry slaughter (10^4 CNY)	Total cost (10^4 CNY)	Total cost (10^4 USD)
Beijing	14553.98	291.06	0.5	14845.54	2394.59
Shanghai	6805.8	1703.16	20.54	8529.5	1375.81
Jiangsu	124485.53	3181.5	25.62	127692.66	20596.83
Zhejiang	29982.14	2444.4	45.36	32471.9	5237.72
Anhui	113309.59	1113.01	11.52	114434.12	18458.22
Fujian	16723.29	509.04	100.82	17333.15	2795.84
Jiangxi	40832.88	255.36	0.18	41088.42	6627.56
Henan	114473.97	73.09	7.3	114554.36	18477.62
Hunan	32301.37	433.25	100	32834.62	5296.22
Shandong	180421.92	402.76	0.66	180825.34	29167.13
Guangdong	88827.4	1808.59	99.36	90735.35	14635.61
Total cost (10^4 CNY)	762717.86	12215.21	411.87	775344.94	125063.14
Total cost (10^4 USD)	123026.39	1970.31	66.43	125063.14	2394.59

Note: Date on which the live-poultry markets were closed varied among cities/counties. In Table 5, the dates when the first case of H7N9 was confirmed were adopted for estimating the total amount of poultry-industry losses in each affected province.

Calculating the burden of disease of avian-origin H7N9 infections in China

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Calculating the burden of disease of avian-origin H7N9 infections in China

Abstract

Objective ~~In China,~~A total of ~~134~~ 131 cases of avian-~~origin~~originated H7N9 ~~infections~~infection have been confirmed in China mainland ~~since~~ between February to May 2013. We ~~aimed to calculate~~calculated the overall burden of H7N9 cases in China as of May 31, 2013 to ~~give~~provide an example of the comprehensive burden of disease in the 21st century ~~of~~from an acute animal-borne emerging infectious disease.

Design We present an accurate and operable method for estimating the burden of H7N9 cases in China. The main drivers of economic loss were identified. Costs were broken down into direct (outpatient and inpatient examination and treatment) and indirect costs (cost of ~~DALY~~disability-adjusted life years [DALYs] and losses in the poultry industry), which were estimated based on field surveys and china statistical yearbook ~~and statistical data~~.

Setting Models were applied to estimate the overall burden of H7N9 cases in China.

Participants ~~131 Laboratory~~ One-hundred and thirty-one laboratory-confirmed H7N9 cases ~~(excluding one Taiwan case)~~ by May 31, 2013.

Outcome measure Burden of H7N9 cases including direct and indirect losses.

Results The total direct ~~medial~~medical cost was 16,422,535 CNY (2,627,606 USD). The mean cost for each patient was 10,117 CNY(1,619 USD) for mild ~~patient~~patients, 139,323 CNY-22,292 USD for severe cases without death, and 205,976 CNY(32,956 USD) for severe cases with death. ~~The DALYs were 677.848 and t~~The total cost of DALYs was 17,356,561 CNY(2,777,050 USD). ~~Poultry-industry losses were estimated on three levels: 27 prefectures with cases, 10 affected provinces, and eight~~8 ~~non-affected adjacent provinces, including the costs~~cost ~~of closing the live-poultry market and slaughter.~~ The poultry industry losses ~~amount~~amounted to 7.75 billion CNY(1.24 billion USD) in 10 affected provinces and 3.68 billion CNY(0.59 billion USD) in eight non-affected adjacent provinces.

Conclusions The huge poultry industry losses followed live poultry markets closing down and poultry slaughtering in some areas. Though the proportion of direct medical losses and DALYs losses in the estimate of H7N9 burden was small, ~~The number of H7N9 incidence cases decreased accompanied by~~in conjunction with ~~closing of~~ the live-poultry markets and slaughtering the poultry. ~~However,~~ the medical costs per case ~~and DALY per case~~ were extremely high (~~esp.~~ particularly for addressing the use of modern medical ~~device). Cost~~devices). A cost-effectiveness

assessment for the intervention ~~needs to~~should be ~~done~~conducted in a future study.

Article summary

Strengths and limitations of this study

- This study is the first ~~(to our knowledge)~~ in which comprehensive methods were applied to ~~identified~~identify the main drivers of economic losses and estimate the burden of disease due to H7N9 infection including direct ~~cost~~costs (medical cost) and indirect ~~cost~~costs (death, disability, and poultry-industry losses);
- This study ~~has~~had some limitations. ~~Estimation~~The estimate of ~~the~~ medical ~~cost~~costs was based on ~~the~~a model and second~~-~~-hand data, not on the ~~H7N9 patients'~~ original costs~~.~~ of patients with H7N9. The burden of H7N9 ~~might be~~may have been underestimated~~ since~~, as the ongoing costs of existing cases and new cases after May 2013~~,~~ were underreported~~ cases~~ and other losses involved in the livestock-production chain were not included in our study.

Introduction

A novel avian-origin influenza A (H7N9) virus has caused severe disease in humans in China since February 2013. The high number of new cases within a short period and the high case fatality rate have caused public panic and attracted global attention. ~~It was also reported from media that some patients'~~Some patient's families undertook large medical costs. According to the literature, exposure to live poultry could be an important risk factor for human infection with H7N9. [1-~~3~~ 5] As a result, closing~~-~~ down the live-poultry markets and slaughtering the poultry were the main ~~intervention~~interventional measures in the affected areas ~~in~~of China. These interventions played an important role in disease prevention~~,~~ but ~~on the other hand,~~ also caused serious losses to the poultry industry.

The introduction of the novel virus led to numerous investigations ~~on the~~of its origin ~~of the virus~~, its genes, clinical symptoms, laboratory ~~test~~testing, treatment and transmission [~~4~~6-~~6~~8]; however, the burden of human infection with H7N9 has not yet been measured. It is important to estimate the overall burden of disease (BOD) due to H7N9 in China because this virus is new ~~in~~to humans and could cause a global pandemic in the future. The Global Burden of Disease (GBD) 2010 study presents a comprehensive methodological framework for death and disability loss estimation and has had a pronounced impact on the ~~estimation of~~ BOD estimate [~~7~~ 9 ~~8~~10]. In this study, we identified the main drivers of economic ~~losses~~loss and summarized the direct and indirect costs of human H7N9 infection. We ~~aimed to~~ present an accurate and operable approach for estimating the overall burden of emerging infectious diseases and ~~to~~ provide evidence on the cost effectiveness of H7N9 prevention and control. We also ~~aim to~~ set up a BOD ~~estimation~~estimate example for any animal-borne infectious ~~diseases, esp.~~disease, particularly with the introduction of modern medical ~~device~~devices.

Methods

Case category definition

The confirmed human H7N9 infections ~~of H7N9~~ were divided into mild and severe cases based on the "Diagnostic and treatment protocol for human infections with avian influenza A (H7N9) (2nd edition, 2013~~)" .~~)". [9-~~11~~] Mild cases presented with influenza-like illness ~~(ILI), while,~~ whereas severe cases developed quickly and presented with severe pneumonia, usually accompanied by severe complications and organ failure. Severe illness was divided into ~~"~~"severe without ~~death'~~death" and ~~"~~"severe with ~~death'.~~death". The 11 H7N9 cases of unknown status were classified as ~~"~~"unknown without ~~death'.~~death".

Data source

Data on the 131 confirmed H7N9 cases ~~of H7N9~~ by the end of May 31, 2013 came from China~~'s information~~ Information ~~system~~ System for ~~disease~~ Diseases ~~control~~ Control and ~~prevention~~Prevention and included basic information on the onset of illness, epidemiology and emergency event reporting. Disability-adjusted life years (DALYs) were calculated based on two ~~other~~ published sources. The World Health Organization (WHO) provided a table of life

expectancy by age for China in 2011,[10-12] whilewhereas the Institute for Health Metrics and Evaluation (IHME) published the Global Burden of Disease (GBD) 2010, including the GBD 2010 Disability Weights .[11-13] Disability weights of general infectious disease (acute episode for mild, moderate, and severe) were adopted from IHME based on the clinician's suggestion though the suggestions of symptoms offrom H7N9 cases that were more severe than the general infectious disease cases. The 2012 per- capita gross domestic product (GDP), which was used to calculate the cost of lost lives orand the cost of disability, was obtained from the National Bureau of Statistics of China.

Poultry production and trade data from27from 27 prefectures with confirmed H7N9 cases, including live-poultry sales, dates of live-market closings, and market-stall volumes, were collected from field surveys, *local livestock-breeding year book* [12-14] and the '*Chinese Commodities Trading-Market Statistics Yearbook* 2012'*2012*.[13-15] Data were gathered from the ten10 affected provinces and eight8 unaffected adjacent provinces. These data were used to estimate poultry-industry losses.

Analysis framework offor the burden of confirmed H7N9 cases

We constructed a framework for the BOD analysis (Figure 1). We described the confirmed H7N9 cases category as mild, severe without death, severe with death, and unknown without death and examined the spatiotemporal and population characteristics of these cases. Based on the case category and characteristics of case spatiotemporal distribution, costs were broken down into direct medical costs (outpatient and inpatient examination and treatment) and indirect costs (death, disability and poultry-industry losses). To calculate the DALYs attributable to H7N9, the H7N9-specific years of life lossst due to premature mortality (YLLs) and years lived with disability (YLDs) were computed and then summed. An intensive analysis of poultry-industry losses would be complex and would require time-consuming field surveys. Meanwhile, indirectIndirect effects may lag behind. In this paperstudy, we considered only the poultry industry losses caused from the closing of live-poultry markets and the large-scales laughterscale slaughtering of poultry.

Statistical analysis

Descriptive statistics were used to summarize the epidemiologicepidemiological characteristics of the cases. The distribution of confirmed H7N9 cases by week was also extracted by creating two standard deviational ellipses (covering 95% of the points while calculating the standard deviation of the x-coordinates and y-coordinates from the mean center to define the axes of the ellipse) to summarize the spatial spread of confirmed H7N9 cases (central tendency, dispersion, and directional trends). If the number of cases in one1 week was less than three, those cases were not included in the calculation.

The methods for estimating direct medical costs are traditionally classified into two broad approaches: bottom-up (micro-costing) and top-down (macro-costing) .[14 15 16 17] In general, the bottom-up approach usually results in a higher but more accurate estimate.[16-18] In our study, we used the bottom-up approach to estimate the direct medical costs. Four cost drivers were extracted: cost of outpatient and inpatient examinations in the ward, cost of examinationexaminations in

intensive-care units (ICUs), cost of treatment, and other costs (including medical consumables, charge for sickbed, general care services, checkup fee, etc~~).~~.). A cost formula was constructed for each driver, as depicted in Table 1. The cost per patient was estimated by experienced hospital financial officers and hospital doctors. The mean number of days (ICU stay, hospital stay, and days of ~~treatments~~treatment) was estimated from the ~~epidemiologic~~epidemiological data. The number of patients for each driver was derived from a previous publication.[6] ~~Professionals' experiences were~~The professional's experience was also considered for some items that were not included in our surveillance system. ~~The costs~~Costs for the category ~~'~~"unknown without ~~death'~~death" were assumed to be moderate and were set as the average of the costs of mild cases and severe cases without death.

The YLLs for confirmed H7N9 cases in China were calculated from the sum of the number of fatal cases (n) in 5-year age groups (i) multiplied by the remaining expected life span (e) based on the age of death for that age group:~~17~~ ~~19~~ (formula 1)

$$YLLs = \sum n_i \times e_i \quad (1)$$

~~To estimate the burden of H7N9 in YLLs, the~~The Chinese life-expectancy table from WHO 2011 was used to estimate the burden of H7N9 in YLLs.

The YLDs were calculated by multiplying the duration of illness (t) by the disability weights (w) accumulated over all H7N9 cases (d) for each health outcome (j): (formula 2)

$$YLDs = \sum d_j \times t_j \times w_j \quad (2)$$

As H7N9 is a relatively new infectious disease and the health ~~state~~status of patients after discharge is unknown, we calculated the YLDs only as general acute episodes of infectious disease during the hospital stay. Disability weights were assigned as infectious disease (mild, moderate, and severe acute episodes).~~11~~13

~~The~~ DALYs ~~are~~were calculated by adding YLLs to morbidity and disability, expressed in YLD (formula 3).

$$DALYs = YLLs + YLDs \quad (3)$$

An ~~estimation~~estimate of the cost of one DALY was based on the traditional human-capital approach for per-capita GDP (formula 4). ~~Considering~~Production capability weights were calculated considering the different production capabilities at different ages~~, the weights of production capability were calculated~~. The following weights were used according to the literature: 0.15 at age 0~~-~~–14 years, 0.75 at age 15~~-~~–44 years, 0.8 at age 45~~-~~–59 years, and 0.1 at age 60~~+~~.+ years.~~18~~20

Cost of DALYs = DALYs ~~*~~× per-capita GDP ~~*~~× weight of production capability (4)

As mentioned above, direct poultry-industry losses (PIL) can be calculated using formula 5:

$$PIL = L_1 + L_2 \quad (5)$$

where L_1 is the loss from poultry slaughter and L_2 is the loss from the closing of live-poultry markets, which includes ~~the~~ lost sales of live poultry (L_{21}) and fees for market-stall leases (L_{22}). A cost formula was constructed for the ~~estimation~~estimate of poultry industry loses (Table 2).

Results

~~Epidemiologic~~Epidemiological characteristics ~~for different~~ of case categories

A total of 131 confirmed H7N9 cases in ~~ten~~01 provinces in China were mapped as individual points based on detailed addresses (Figure 2). Most (81%) of the patients were located in ~~the~~ Jiangsu, Shanghai, and Zhejiang ~~provinces~~Provinces. Most of the cases (73% or above) in the ten provinces were severe. There were 25 mild cases, 56 severe cases without death, 39 severe cases with death, and 11 unknown cases without death in China through May 31, 2013.

Figure S1 ~~is the presentation of~~shows the rate, direction, and scope of ~~the~~ H7N9 spread. Each ellipse covers 95% of the incident cases for ~~one~~1 week. The location of the first week of H7N9 onset was in Shanghai. Over the next few weeks, the epidemic ~~extended~~spread to ~~the~~ Jiangsu and Zhejiang ~~provinces~~Provinces and continued to grow. The virus spread quickly ~~spread~~ from the northwest to the north and south regions.

The onset of most H7N9 cases was relatively clustered. Within the total event timeframe (~~2/~~February 19–~~5/~~May 21), 74% of the cases were infected between ~~3/~~March 28–~~4/~~–April 17 (Figure S2). Severe cases with death were found in the initial and intermediate stages. The median age of patients with confirmed H7N9 virus infection was 61 years (range, 3 ~~to~~ –91 years). Severe symptoms tended to occur in older people. The median age of patients who were severely ill without death was 60 years, ~~while~~whereas the median age of patients who were severely ill with death was 69 years. The number of mild cases was distributed ~~on~~in all age groups ~~under~~< 80 years (Figure S3).

Direct medical costs ~~of~~for confirmed H7N9 cases

After the confirmed H7N9 cases occurred in China, the ~~patients'~~patient's clinical manifestations, examinations, and treatments were published,[6] which allowed us to estimate ~~the~~ direct medical costs using a cost model. We separated the examination data into examinations conducted in the ward and examinations conducted in the ICU, as the latter were more frequent. The main treatments for confirmed H7N9 cases were selected. ~~In our cost formula, three~~ Three main factors were considered in our cost formula: cost per day, number of days, and number of patients. For the cost-per-day estimation, we selected a Grade-III Class-A hospital (general large-scale hospital in China). ~~Costs~~Cost per day ~~were~~was obtained from the hospital financial officers and hospital doctors based on the average ~~costs~~cost of patients with the same treatments from ~~Jan.~~January 1, 2013 to May 31, 2013 in this hospital (Table S1). Differences in costs among

the regions in China were approximately 10%.

The mean number of days and number of cases were estimated from a subset of the investigated cases (Table 3). Data regarding hospital stay were available for 11 of the 25 mild cases, 19 of the 56 severe cases without death, and 19 of the 39 severe cases with death. The mean length of stay was 9 days for mild cases, 18 days for severe cases without death, and 20 days for severe cases with death. Data on the duration of ICU stay were available for ~~ten~~10 of the 56 severe cases without death and 11 of the 39 severe cases with death. Severe cases without death stayed in the ICU for a mean of 12 days, ~~while~~whereas severe cases with death stayed for a mean of 16 days. We assumed that the mean hospital stay of severe cases with complications was equal to the length of the ICU stay, although complications might occur incrementally. The mean ~~durations~~duration of ~~different~~ treatments ~~lasting were also~~was estimated based on a subset of investigated patients, except for glucocorticoids and intravenous immune globulin, for which estimates were obtained from ~~professionals' experiences.~~professional experience. Treatment for complications required drugs and examinations in addition to the ~~treatment~~treatments listed above. Treatment was described for 111 confirmed H7N9 cases, along with the proportion of patients who received each treatment.[6 8] We assumed that the proportions were generalizable to all cases because it covered 85% of cases.

Table S2 is ~~the~~a summary of all ~~of the~~ direct medical costs. The total cost for all 131 patients with confirmed H7N9 virus infection was 16,422,535 CNY (2,627,606 USD). The mean cost ~~for each~~per patient was 10,117 CNY (1,619 USD) for mild ~~patient~~patients, 139,323 CNY (22,~~292USD~~292 USD) for severe cases without death, and 205,976 CNY (32,~~956USD~~956 USD) for severe cases with death. The mean cost per day was 1,124 CNY (180 USD) for mild cases, 8,293 CNY (1,327 USD) for severe cases without death, and 8,978 CNY (1,437 USD) for severe cases with death. As the severity of the illness increased, the costs increased correspondingly.

Cost of DALYs ~~on~~for H7N9

A total of 39 deaths from confirmed H7N9, including 30 males and 9 females, were reported from the National Health and Family Planning Commission of China by ~~31~~ May 31, 2013. ~~For~~ See Table S3 for more details on the number of cases in each age group~~, see Table S3.~~. The total YLLs were 676.89. There were 131 H7N9 cases, including 25 mild cases, 95 severe cases, and 11 of unknown category (assumed to be moderate). The YLD calculations were based on the case category. ~~The total~~Total YLDs were 1.064 (Table S4). ~~The~~ DALYs ~~combine~~combined the time lived with disability and the time lost due to premature mortality; thus, ~~the~~ DALYs were 677.848 for all confirmed H7N9 patients. We adopted 2012 per-capita GDP ~~of~~for the ~~ten~~10 provinces and estimated the cases adjusted per- capita GDP (65,655 CNY or 10,505USD). By calculating the weight of production capability for each age group, we ~~got~~obtained the average weight of production capability to be 0.39 for all confirmed H7N9 cases. The total cost of DALYs was 17,356,561 CNY (2,777,050 USD) according to ~~the~~ formula 4.

Poultry-industry losses

Poultry-industry losses were estimated for three categories (Figure 3): 1) 27 prefectures with confirmed H7N9 cases (region 1, ~~in~~ brown in Figure 3), 2) 10 affected provinces (region 2, ~~in~~ yellow in Figure 3~~)~~), and 3) eight non-affected adjacent provinces (region 3, shadowed in Figure 3).

~~In region1, three~~Three types of losses were calculated for region 1: losses from poultry slaughter, lost ~~sales of~~ live poultry sales, and fees for market-stall leases. In the ~~ten~~10 affected provinces (region 2), in addition to the losses in ~~region1~~region 1, the losses arose mainly ~~arose~~ from ~~the~~ closing~~-~~ down ~~of~~ live-poultry markets in each province. These two losses were then summed to estimate poultry-industry losses caused by H7N9 outbreaks. Most of the main live-poultry markets in the affected provinces (~~presented in~~ Figure 3) were obtained from Google Earth; the retail locations were excluded.

Poultry-industry losses in eight non-affected adjacent provinces (region 3) were also calculated as potential economic losses. The direct poultry-industry losses of 27 prefectures for the H7N9 cases are described in detail in Table 4.

The cost of closing~~-~~ down live-poultry markets includes the lost ~~sales of~~ live poultry sales and fees for market-stall leases. The cost of lost ~~sales of~~ live poultry sales was calculated according to the daily live-poultry sales, the cost per animal (assumed to be 10 CNY or 1.6USD in this ~~paper)~~study), and the number of days the market was closed. The cost of market-stall leases was calculated based on the average lease per stall per day in the corresponding city, the number of stalls, and the number of days the market was closed in each city. The cost of poultry slaughter was obtained from the number of poultry slaughtered and the cost per animal. The number of days the market was closed was counted through May 31 because ~~there have been~~ only one confirmed H7N9 ~~cases~~case had occurred since then. The total poultry-industry losses in the ~~ten~~10 affected provinces, including 27 prefectures with H7N9 cases, are listed in Table 5. The poultry-industry losses of each province are presented in Figure S4.

~~In general, China's~~China's poultry industry suffered direct losses amounting to 7.75 billion CNY(1.24USD) from when the first case of H7N9 was confirmed through May 31, 2013. Losses from the live-poultry trade ~~account~~accounted for 98% of the total losses. Although it had only a ~~fewH7N9~~few H7N9 cases, Shandong Province ranked first in losses among all ~~ten~~10 provinces at 1.81 billion CNY(0.29USD); Jiangsu, Henan, and Anhui ranked next~~,~~ with 1.28 billion CNY(0.20USD), 1.15 billion CNY(0.18USD), and 1.14 billion CNY(0.18USD), respectively. These provinces have large poultry markets. Zhejiang Province had the highest number of confirmed cases; however, the losses in that region were not very high, as the sales of live poultry were lower. Strict prevention and control measures, such as daily cleaning of the market, weekly disinfection of the market, and monthly closings of the live market~~,~~ were conducted in Guangdong Province, which reported no H7N9 cases ~~till 31~~until May 31, 2013 during the emergency response. ~~Meanwhile, these~~ These prevention and control measures affected the poultry industry. For this reason, the poultry-industry losses in Guangdong Province are also given in Table 5.

Due to timely control measures, the H7N9-affected regions were limited to ~~the~~ 27 prefectures in ten provinces in China. In this study, the potential economic risks were also calculated for the eight non-affected adjacent provinces (region 3, shadowed in Figure 3). Table S5 shows that the potential losses to the poultry industry in those regions ~~amount~~amounted to 3.6 billion CNY(0.58USD).

Discussion

This study was based on illness severity and spatiotemporal aspects of the recent avian-origin influenza A (H7N9) ~~infections~~infection. ~~Our results indicate that there were clusters of patients infected with H7N9 in China. Of the 131 patients, 81% resided in the Jiangsu, Shanghai and, or Zhejiang provinces~~Provinces, and 74% were infected during the period of 3/March 28 4/ April 17. ~~Patients over~~≥ 50 ~~years of age accounted for 72% of the total, and 95 patients (73.1%) were diagnosed as severe cases. The fatality rate of confirmed H7N9 cases in China was 26.9%.~~ We assumed that cases of the same severity resulted in similar medical costs. Therefore, mild cases, severe cases without death, severe cases with death, and unknown cases without death were estimated separately by calculating the mean number of days, number of cases, and cost per day. The mean cost per patient was 8,880 CNY (1,421 USD) for mild cases, 144,788 CNY (23,166 USD) for severe cases without death ~~and184~~, and 184, 211 CNY (29,474 USD) for severe cases with death. ~~The total~~Total direct medical ~~cost~~costs for all patients ~~was~~were 15,963,935 CNY (2,554,230 USD). ~~The~~ DALYs, which were determined from the YLLs and YLDs, were 677.848 years for all confirmed H7N9 cases. The total cost of the DALYs was 17,356,561 CNY (2,777,050 USD) according to the average GDP per capita and average weight of production capability.

Compared to the poultry-industry losses, ~~the~~ direct medical losses and DALY losses were relatively small. To a large extent, the small number of patients in the H7N9 outbreak in China was due to quick and effective ~~interventions~~intervention, which prevented a pandemic.[21] The ~~estimation~~estimate of direct medical ~~cost~~costs and DALY ~~cost, especially~~costs, particularly the mean cost per patient and mean cost per day for different case categories, can be used to guide those counties in which ~~H7N9~~no cases ~~did not occur in the~~occurred during prevention and control of H7N9. DALY per H7N9 case (~~5176~~5,176 DALYs per ~~1000~~1,000 cases) was much higher than ~~the~~ most of other respiratory infectious diseases ~~according to the 2010 GBD study~~ though DALYs per 100,000 population (2.23 DALYs based on affected county population) were lower than most of the infectious diseases according to the 2010 GBD study.[~~19~~ 22] A comparison to outbreaks of other infectious diseases (with similar clinical ~~symptoms~~symptoms) was also considered in this report. The ~~health care~~healthcare cost per SARS patient in Beijing was 17,150 CNY (1,~~886USD) while~~886 USD), whereas the average medical cost per H7N9 patient was 99,691 CNY (15,951 USD) because of the higher fatality rate of H7N9 patients and use of more expensive modern medical ~~device had been used~~devices.[~~20~~23]

As of the end of May, ~~China's~~China's poultry industry suffered direct losses amounting to 7.75 billion CNY(1.24USD), including the cost of closing live- poultry markets and slaughtering poultry in the ten affected provinces. Poultry-industry losses were estimated at three levels: 27 prefectures with confirmed H7N9 cases, 10 affected provinces, and ~~eight~~8 non-affected adjacent provinces. The outbreak of H7N9 may reduce the demand for poultry products in other regions of

China~~,~~ due to public ~~perceptions~~perception. These effects were not considered in this ~~paper~~study. The cost of closing~~-~~ down the live-poultry markets and the cost of poultry slaughter were calculated as direct poultry-industry losses. We assumed that the cost per animal ~~is~~was 10 CNY(1.6USD) and the date for the end of closing the live-poultry markets was May 31, 2013 because there has been ~~only one~~few confirmed H7N9 case~~s~~ since then. Losses from the live-poultry industry ~~account~~accounted for 98% of the total losses, with the lost sales of live poultry constituting the majority of that amount. Strict prevention and control measures have been enacted in Guangdong Province, which had few reported H7N9 cases~~ of H7N9~~. This finding will be significant for similar cases in the future. Due to timely control measures, the effects of the outbreak were limited to 27 prefectures in ~~ten~~10 provinces in China.

Our study had several limitations. First, there were 11 confirmed H7N9 cases without death whose case categories were unknown. The cost ~~estimation~~estimate for these unknown patients was replaced by the average cost of mild and severe cases without death. Second, in the cost model, some of the data (e.g., mean number of days of ~~ECMO~~extracorporeal membrane oxygenation for severe without death cases) were obtained from a small proportion of investigated cases, which could result in an estimation bias. Third, the direct medical cost did not include opportunity cost,[~~21~~ [24]](#) the cost that is incurred because a limited resource is used to treat a preventable disease and cannot therefore be used to treat another disease.[~~22~~ [25]](#) The medical ~~practitioners'~~practitioner's salary, research funding, and loss of working time for family numbers of patients ~~on~~with H7N9 were excluded ~~in~~from our study. Fourth, ~~estimations~~estimates of ~~the~~ direct medical ~~cost~~costs per day might show large differences for specific cases because the drug cost could grow considerably if imported and nutritional drugs were used. We considered only the average severity for patients in the ward and ~~in~~ ICU. Fifth, 17 patients were still in the hospital ~~by~~on May 28, 2013 according to the literature.[~~23~~ [26]](#) The mean numbers of days in the ward and ~~in~~ ICU ~~of~~for severe cases and their fatality rate were thus underestimated. ~~And some~~Some of the mild cases may not ~~be~~have been reported, which also resulted in ~~the underestimation of~~underestimating the cost. Sixth, ~~in this paper,~~ we considered only direct losses from ~~the~~ closing~~-~~ down ~~of~~ live-poultry markets and large-scale poultry slaughter, which could be estimated accurately and quickly. This ~~estimation is~~estimate was useful for early control and decision-making; however, other losses involved in the livestock-production chain, such as increased breeding costs, poultry seeding, the prices of poultry meat and eggs, and the ~~decreasing~~decreased production of poultry-feather industries, should be considered in further studies.[~~24~~27](#)

In conclusion, we ~~presented~~present a ~~quick~~rapid, operable, and accurate framework for estimating the burden of human infections ~~with~~from H7N9.This framework could be used in ~~the~~a BOD analysis of future H7N9 or similar outbreaks. The results~~,~~ including direct and indirect costs~~,~~ provide fundamental information for researchers~~, the~~ and public and policy makers to support timely and effective interventions. Future study may focus on the cost-effectiveness analysis of poultry industry close down, earlier diagnosis and effective treatments of patients based on more detailed investigation information.

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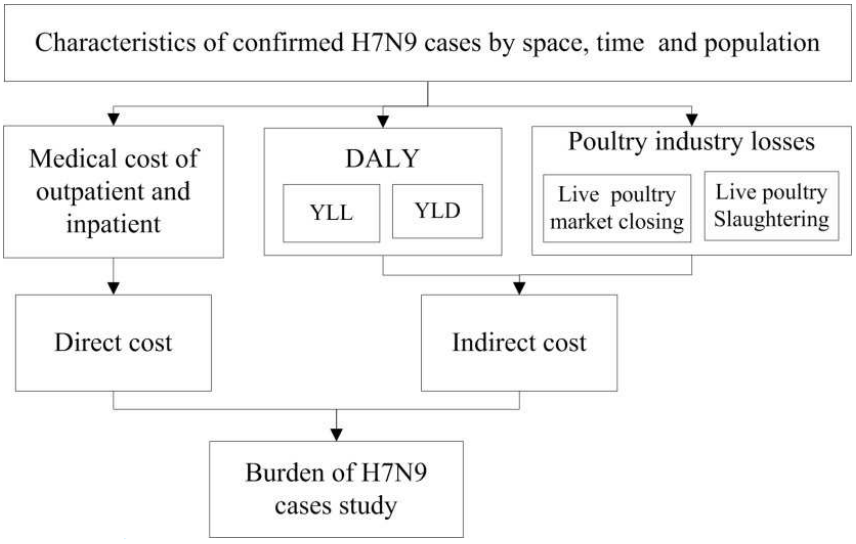

Figure 1. Framework for calculating the burden of confirmed H7N9 cases. (Figure 1 describes the analytical route of direct and indirect costs, which were integrated into the overall burden of confirmed H7N9 cases. The framework was drawn using the Microsoft Office Visio 2003 software.)

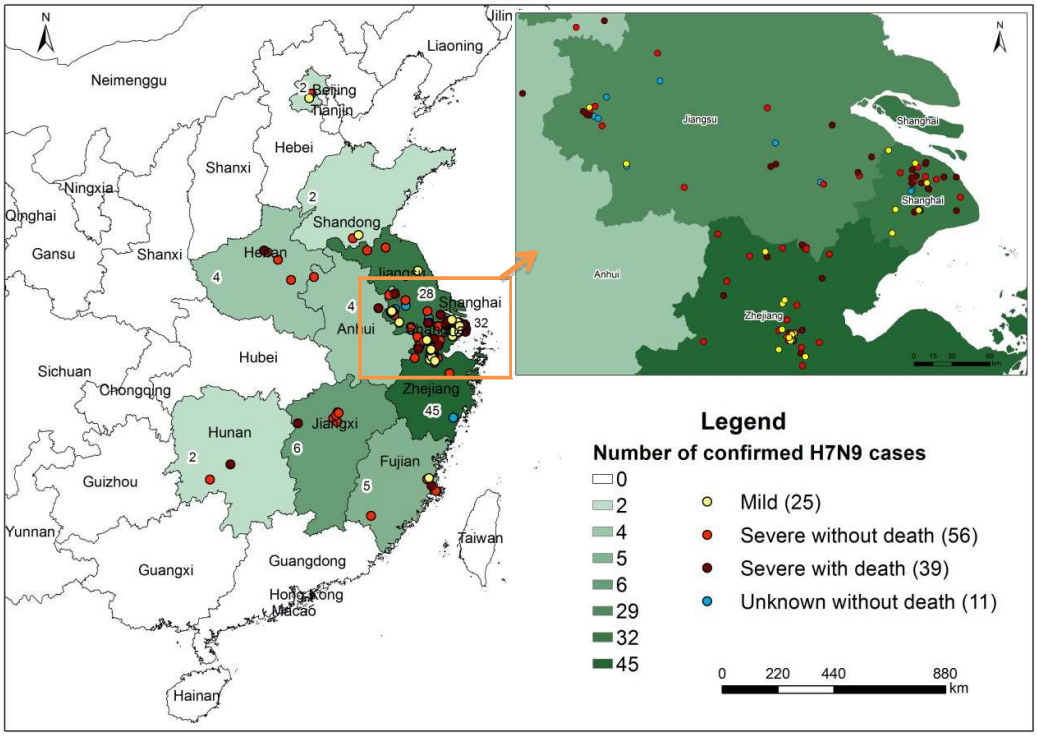

Figure 2. Spatial distribution of the 131 confirmed H7N9 cases. (Figure 2 presents the spatial distribution of the 131 confirmed H7N9 cases by severity in China. Mild, severe without death, severe with death, and unknown without death cases are distinguished by different colors. The points are mapped based on the coordinates of the addresses. Areas with a high density of cases are magnified in the top right corner. The map was drawn using the ArcGIS 10.0 software.)

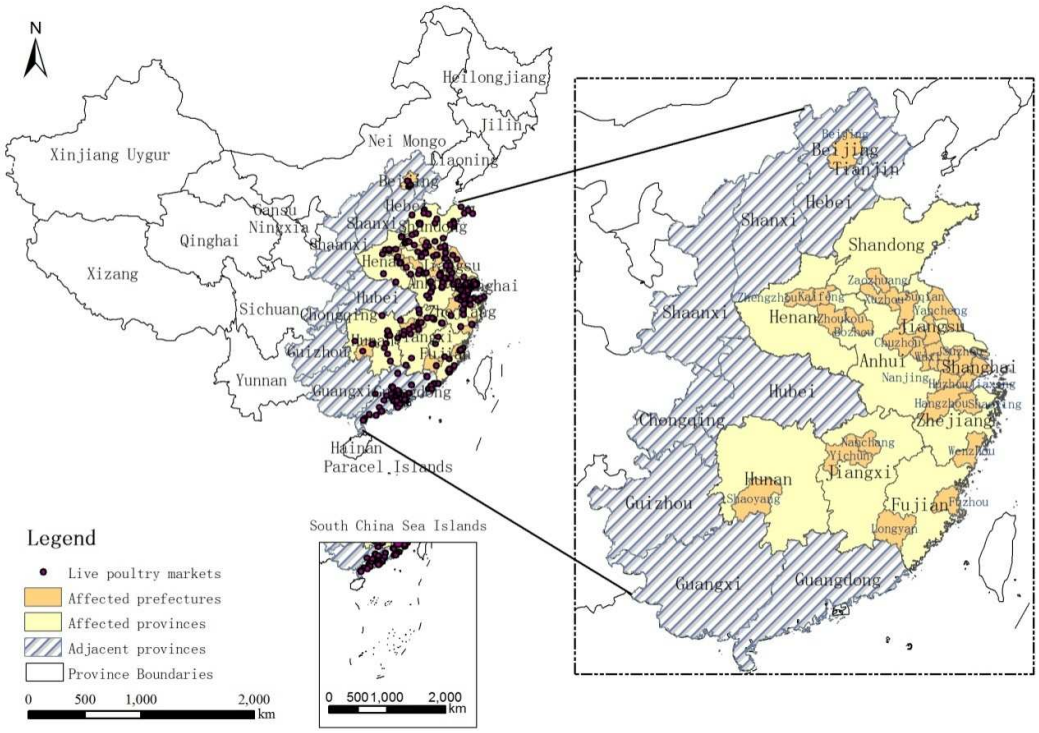

Figure 3. Three regions for poultry-industry loss estimates. (Figure 3 presents estimated poultry-industry losses for three categories including 27 prefectures, 10 affected provinces, and 8 non-affected adjacent provinces. Points represent most of the main live-poultry markets, which were obtained from Google Earth excluding the retail locations. The map was drawn using the ArcGIS 10.0 software.)

Table 1. Formula for calculating direct medical costs.

Cost	Formula
Cost of examination for outpatient and inpatient in ward (laboratory and radiology)	Cost per patient × number of patients
Cost of examination in ICU (laboratory and radiology)	Cost per day × mean number of days of ICU stay × number of patients
Cost of treatment	
Antiviral	Cost per day × mean number of days × number of patients
Antibiotics	Cost per day × mean number of days × number of patients
Other drugs	Cost per day × mean number of days × number of patients
Glucocorticoids	Cost per day × mean number of days × number of patients
Intravenous immune globulin	Cost per day × mean number of days × number of patients
Oxygen therapy	Cost per day × mean number of days of hospital stay × number of patients
ICU care	Cost per day × mean number of days of ICU stay × number of patients
ICU monitor	Cost per day × mean number of days of ICU stay × number of patients
Mechanical ventilation	
Noninvasive	Cost per day × mean number of days × number of patients
Invasive	Cost per day × mean number of days × number of patients
Artificial-liver-support-system therapy	Cost per day × mean number of days × number of patients
Continuous renal-replacement therapy	Cost per day × mean number of days × number of patients
Extracorporeal membrane oxygenation (ECMO)	Cost per day × mean number of days × number of patients
Complications	
ARDS	Cost per day × mean number of days of ICU stay × number of patients
Shock	Cost per day × mean number of days of ICU stay × number of patients
Acute kidney injury	Cost per day × mean number of days of ICU stay × number of patients
Rhabdomyolysis	Cost per day × mean number of days of ICU stay × number of patients
Other costs [§]	Cost per day ×mean number of days of hospital stay × number of patients

[§]Other costs include medical consumables, charge for sickbed, general care services, checkup fees, etc.

Table 2. Formula for calculating poultry-industry losses.

Cost	Formula
Cost of poultry slaughter (L_1)	Cost per animal × number of poultry killed
Cost of closing live-poultry markets (L_2)	
Cost of live-poultry sales(L_{21})	Live-poultry sales per day × cost per animal × number of days
Cost of market-stall leases (L_{22})	Cost of lease per stall per day × number of stalls × number of days

Table 3. Driver measurement.

Category	Mild		Severe without death		Severe with death		Unknown without death		Reference proportion of patients (%)*
	Mean number of days (no. of cases investigated/total cases)	Number of cases	Mean number of days (no. of cases investigated/total cases)	Number of cases	Mean number of days (no. of cases investigated/total cases)	Number of cases	Mean number of days¶	Number of cases	
Hospital stay	9 (11/25)	25	18 (19/56)	55	20 (19/39)	38	14	11	98.2
ICU stay	0	0	12 (10/56)	55	16 (11/39)	38	6	7	76.6
Treatment									
Antiviral	7 (3/25)	24	7 (20/56)	54	11 (11/39)	38	7	11	97.3
Antibiotics	8 (4/25)	17	11 (21/56)	40	14 (16/39)	28	9	8	71.2
Other drugs	9 (11/25)	25	12 (10/56)	55	16 (11/39)	38	11	11	98.2
Glucocorticoids	0	0	7§	43	7§	30	4	8	62.2
Intravenous immune globulin	0	0	5§	37	5§	26	3	7	53.2
Oxygen therapy	9 (11/25)	25	18 (19/56)	56	20 (19/39)	39	9	11	100.0
Mechanical ventilation									
Noninvasive	0	0	9 (7/56)	19	3 (6/39)	13	5	4	27.9
Invasive	0	0	8 (7/56)	41	10 (15/39)	28	4	8	58.6
Artificial-liver-support-system therapy	0	0	4§	11	4§	7	2	2	15.3
Continuous renal-replacement therapy	0	0	7§	18	7§	13	4	4	26.1
Extracorporeal membrane oxygenation (ECMO)	0	0	6(1/56)	12	7 (2/39)	9	3	2	18.0
Complications									
ARDS	0	0	12 (10/56)	50	16 (11/39)	35	6	10	71.2
Shock	0	0	12 (10/56)	18	16 (11/39)	13	6	4	26.1
Acute kidney injury	0	0	12 (10/56)	11	16 (11/39)	8	6	2	16.2
Rhabdomyolysis	0	0	12 (10/56)	7	16 (11/39)	5	6	1	9.9
Other costs	9 (11/25)	25	18 (19/56)	55	20 (19/39)	38	14	11	98.2

* Referenced from the literature "Clinical Findings in 111 Cases of Influenza A (H7N9) Virus Infection"[6]

§ Based on professional experience

¶ Mean number of days for patients with unknown without death was estimated as the average number of days for mild and severe cases without death.

Table 4. Poultry-industry losses of 27 prefectures with H7N9 cases.

Affected provinces (number of cases)	Affected prefectures (number of cases)	Date	Cost of closing live-poultry markets				Cost of poultry slaughter (10^4 CNY)
			Live-poultry sales per day (10^4)	Number of days	Cost of live-poultry sales(10^4 CNY)	Market-stall leases (10^4 CNY)	
Beijing (2)	Beijing (2)	4.13	3.00	49	1470.00	6.93	0.50
Shanghai (32)	Shanghai (32)	4.05	11.94	57	6805.80	1703.16	20.54
Jiangsu (29)	Wuxi (4)	4.09	12.87	53	6821.10	527.40	0.40
	Yancheng (1)	4.15	8.18	47	3844.60	387.11	5.00
	Nanjing (12)	4.06	8.91	56	4989.60	567.84	8.00
	Zhenjiang (1)	4.09	8.55	53	4531.50	342.12	0.31
	Suzhou (7)	4.08	17.73	54	9574.20	265.03	0.01
	Yangzhou (1)	4.15	11.52	47	5414.40	180.17	0.20
	Xuzhou (1)	4.24	14.80	38	5624.00	380.30	0.10
	Changzhou (1)	4.11	8.94	51	4559.40	167.71	1.30
	Suqian (1)	4.02	10.14	60	6084.00	200.00	0.10
Zhejiang (45)	Huzhou (12)	4.11	6.14	51	3131.40	269.79	0.70
	Shaoxing (1)	4.22	5.31	40	2124.00	585.14	10.00
	Hangzhou (29)	4.15	12.48	47	5865.60	1200.20	24.66
	Jiaxing (2)	4.19	6.97	43	2997.10	1565.77	10.00
	Wenzhou (1)	4.21	7.02	41	2878.20	49.78	0.50
Auhui (4)	Bozhou (1)	4.09	2.89	53	1531.70	100.33	10.00
	Chuzhou (3)	3.30	6.19	63	3899.70	65.01	0.72
Fujian (5)	Longyan (1)	5.07	6.73	25	1682.50	77.40	0.82
	Fuzhou (4)	4.29	6.61	33	2181.30	287.76	100.00
Jiangxi (6)	Nanchang (5)	4.26	12.62	36	4543.20	45.72	0.10
	Yichun (1)	4.29	10.46	33	3451.80	14.09	0.08
Henan (4)	Zhoukou (1)	4.16	13.59	46	6251.40	18.28	1.60
	Kaifeng (1)	4.15	9.22	47	4333.40	14.81	1.80
	Zhengzhou (2)	4.15	9.01	47	4234.70	20.68	3.90
Hunan (2)	Shaoyang (2)	4.28	7.80	34	2652.00	70.10	100.00
Shandong (2)	Zaozhuang (2)	4.24	21.20	38	8056.00	52.36	0.66
Total cost (10^4 CNY)		128999.59					
Total cost (10^4 USD)*		20639.93					

Note: 'Date' indicates the date on which the live-poultry markets were closed; 'days' is the number of days the live-poultry markets remained closed.

Table 5. Total poultry-industry losses in the 10 affected provinces ~~(10^4 CNY)~~.

Affected provinces	Cost of live-poultry sales (10^4 CNY)	Market-stall leases (10^4 CNY)	Cost of poultry slaughter (10^4 CNY)	Total cost (10^4 CNY)	Total cost (10^4 USD)
Beijing	14553.98	291.06	0.5	14845.54	2394.59
Shanghai	6805.8	1703.16	20.54	8529.5	1375.81
Jiangsu	124485.53	3181.5	25.62	127692.66	20596.83
Zhejiang	29982.14	2444.4	45.36	32471.9	5237.72
Anhui	113309.59	1113.01	11.52	114434.12	18458.22
Fujian	16723.29	509.04	100.82	17333.15	2795.84
Jiangxi	40832.88	255.36	0.18	41088.42	6627.56
Henan	114473.97	73.09	7.3	114554.36	18477.62
Hunan	32301.37	433.25	100	32834.62	5296.22
Shandong	180421.92	402.76	0.66	180825.34	29167.13
Guangdong	88827.4	1808.59	99.36	90735.35	14635.61
Total cost (10^4 CNY)	762717.86	12215.21	411.87	775344.94	125063.14
Total cost (10^4 USD)	123026.39	1970.31	66.43	125063.14	2394.59

Note: Date on which the live-poultry markets were closed varied among cities/counties. In Table 5, the dates when the first case of H7N9 was confirmed were adopted for estimating the total amount of poultry-industry losses in each affected province.

Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Qi XP, Jiang D, Wang HL, et al. Burden of diseases in the 21st century: A case of emerging H7N9 influenza virus infection in China

Supplementary Appendix

Burden of diseases in the 21st century:

A case of emerging H7N9 influenza virus infection in China

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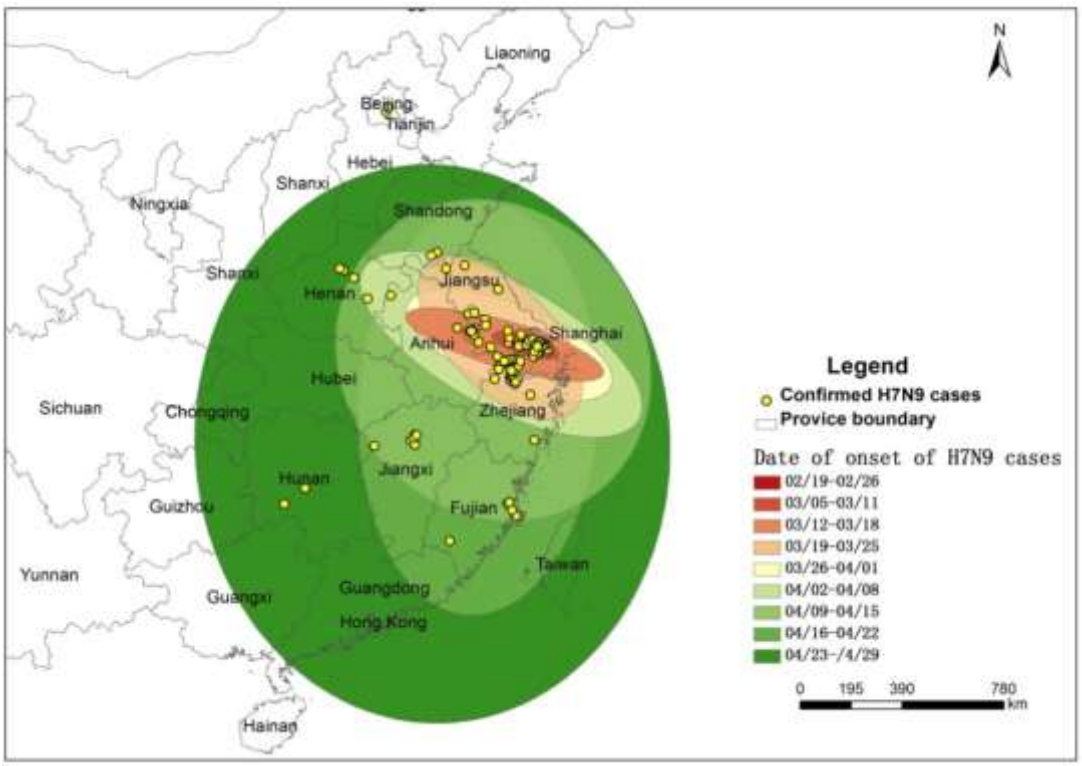


Figure S1. The directional distribution of confirmed H7N9 cases by week (The distribution of new confirmed H7N9 cases by week was extracted by creating two standard deviational ellipses covering 95% of the points in each ellipse to summarize the central tendency, dispersion and directional trends of confirmed H7N9 cases. The map was drawn with ArcGIS 10.0 software)

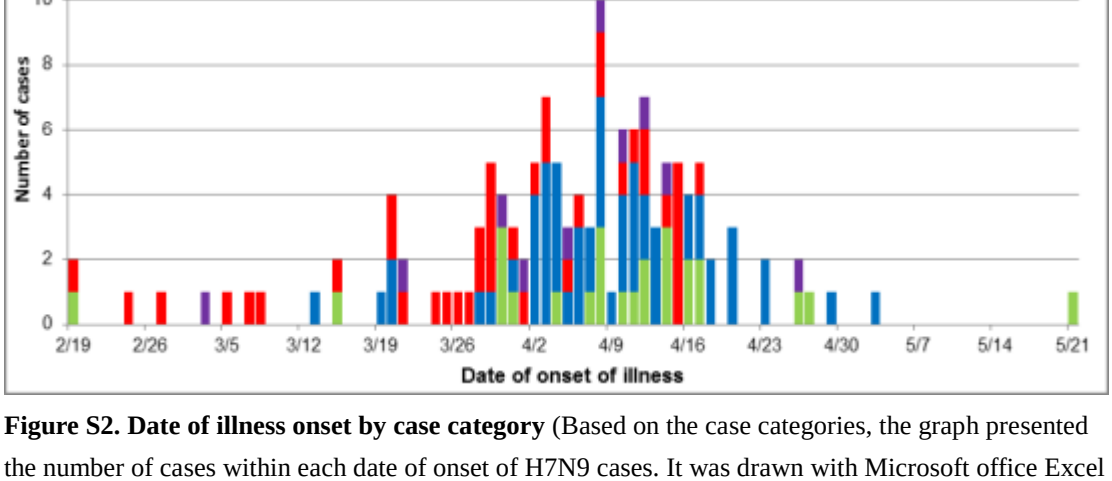


Figure S2. Date of illness onset by case category (Based on the case categories, the graph presented the number of cases within each date of onset of H7N9 cases. It was drawn with Microsoft office Excel 2010 software.)

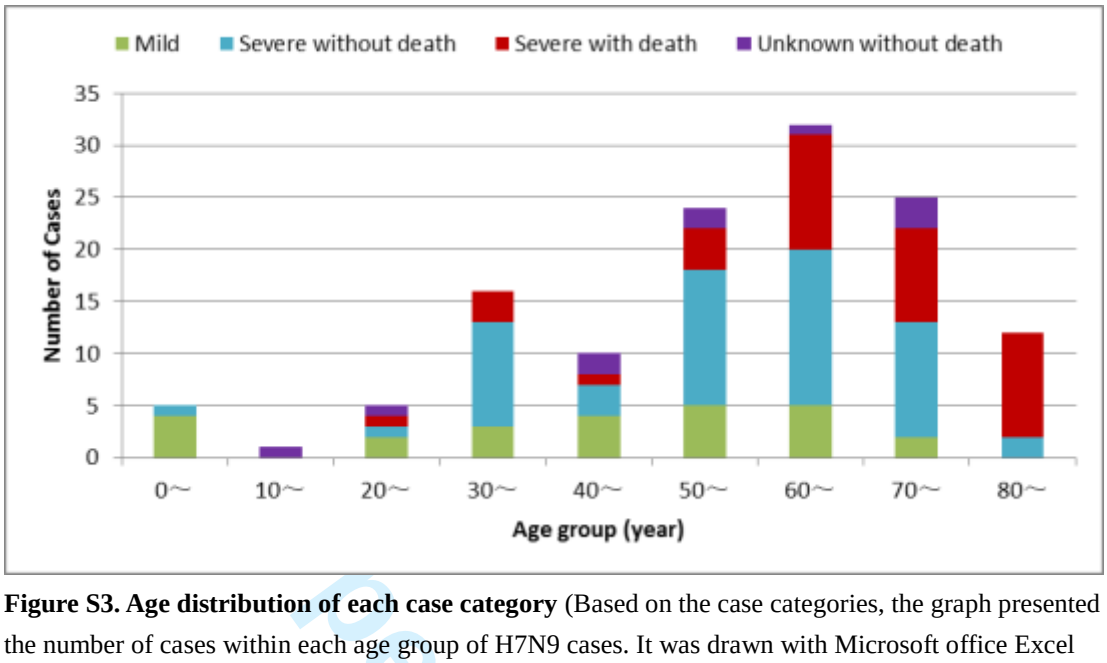


Figure S3. Age distribution of each case category (Based on the case categories, the graph presented the number of cases within each age group of H7N9 cases. It was drawn with Microsoft office Excel 2010 software.)

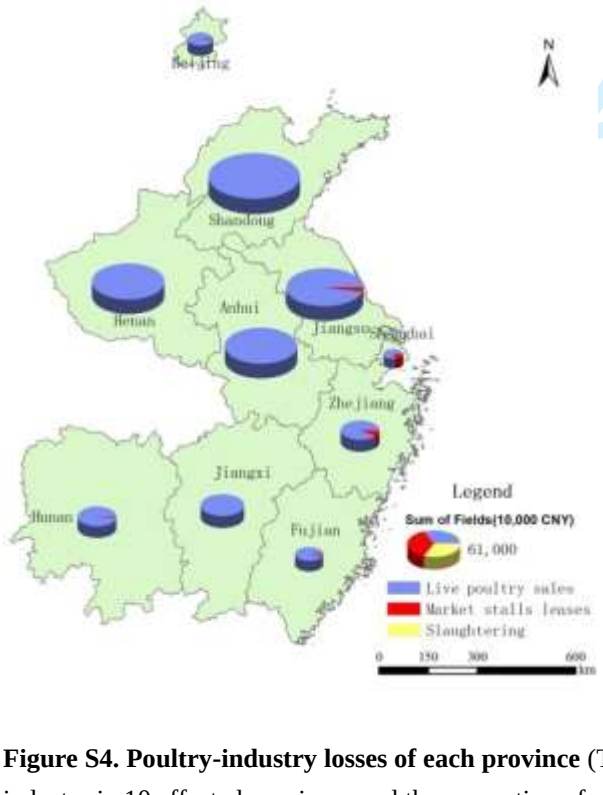


Figure S4. Poultry-industry losses of each province (The map presented the total losses of poultry industry in 10 affected provinces and the proportion of each kind of losses. It was drawn with ArcGIS 10.0 software.)

Table S1. Estimation of costs per day for confirmed H7N9 cases

Cost driver	Cost (CNY)	Note
Cost of examination of outpatients and inpatients in ward (laboratory and radiology)	2,500	Includes tests such as live function test, kidney function test, blood routine examination, routine urinalysis, electrocardiogram, virus detection and isolation, chest radiology, computed tomography(CT), color Doppler ultrasound, antibody testing for hepatitis, human immunodeficiency virus and syphilis, throat swab, drug sensitive test, blood culture, ion test, blood glucose, blood sedimentation, blood gas, troponin, coagulation tests, procalcitonin (PCT), myocardial enzyme, D-dimer, C-reactive protein(CRP), B type natriuretic peptide.
Cost of examination in ICU (laboratory and radiology)	1,700 per day	
Cost of treatment		
Antiviral	60 per day	Oseltamivir and peramivir, etc.
Antibiotics	350 per day	Fluoroquinolones, Piperacillin, Imipenem and Cephalosporin, etc.
Other drugs	Mild: 270 per day	Reducing phlegm, relieving asthma, abating fever, providing antioxidants and nutrition, inducing sedating, etc.
	Severe: 1,600 per day	
Glucocorticoids	70 per day	
Intravenous immune globulin	2,500 per day	
Oxygen therapy	120 per day	
ICU care	1,100 per day	
ICU monitor	500 per day	
Mechanical ventilation		
Noninvasive	400 per day	
Invasive	1,000 per day	
Artificial-liver-support-system therapy	6000 per day	
Continuous renal-replacement therapy	9000 per day	
Extracorporeal membrane oxygenation (ECMO)	10,000 per day	
Complications		Excluding the treatments listed above
Adult respiratory distress syndrome (ARDS)	1,000 per day	Increases drug and special care services
Shock	800 per day	Increases drug, blood, fluid and hemodynamic monitoring
Acute kidney injury	300 per day	Increases drug
Rhabdomyolysis	600 per day	Increases drug use
Other costs	Mild: 200 per day	Medical consumables, charge for sickbed, general care services, checkup fee, etc.
	Severe: 800 per day	

Note: CNY=Chinese Yuan

Table S2. Summary of direct medical costs

Cost driver	Mild (n=25)	Severe without death (n=56)	Severe with death (n=39)	Unknown without death (n=11)	Total cost
Cost of examination for outpatient and inpatient in ward (laboratory and radiology)	62,500	137,500	95,000	27,500	322,500
Cost of examination in ICU (laboratory and radiology)	0	1,122,000	1,033,600	71,400	2,227,000
Cost of treatment					
Antiviral	10,080	22,680	25,080	4,620	62,460
Antibiotics	47,600	154,000	137,200	25,200	364,000
Other drugs	60,750	1,056,000	972,800	113,135	2,202,685
Glucocorticoids	0	21,070	14,700	2,240	38,010
Intravenous immune globulin	0	462,500	325,000	52,500	840,000
Oxygen therapy	27,000	144,000	93,600	11,880	276,480
ICU care	0	726,000	668,800	46,200	1,441,000
ICU monitor	0	330,000	304,000	21,000	655,000
Mechanical ventilation					
Noninvasive	0	68,400	15,600	8,000	92,000
Invasive	0	328,000	280,000	32,000	640,000
Artificial-liver-support-system therapy	0	264,000	168,000	24,000	456,000
Continuous renal-replacement therapy	0	1,134,000	819,000	144,000	2,097,000
Extracorporeal membrane oxygenation (ECMO)	0	720,000	630,000	60,000	1,410,000
Complications					
ARDS	0	600,000	560,000	60,000	1,220,000
Shock	0	172,800	166,400	19,200	358,400
Acute kidney injury	0	1,056,000	1,024,000	96,000	2,176,000
Rhabdomyolysis	0	50,400	48,000	3,600	102,000
Other costs	45,000	806,400	608,000	77,000	1,536,400
Total cost (CNY)	252,930	8,359,350	7,003,180	807,075	16,422,535
Total cost (USD)*	40,469	1,337,496	1,120,509	129,132	2,627,606
Mean cost for each patient (CNY)	10,117	139,323	205,976	73,370	125,363~~107,197~~
Mean cost for each patient (USD)*	1,619	22,292	32,956	11,739	20,058 ~~17,151~~
Mean cost per day for each patient (CNY)	1,124	8,293	8,978	5,765	6,040
Mean cost per day for each patient (USD)*	180	1,327	1,437	922	966

*Based on average exchange rate in May,2013: 1CNY=0.16USD

Table S3. YLLs of confirmed H7N9 cases

Age group	Life expectancy at age(Male)	Life expectancy at age(Female)	Number of deaths (Male)	Number of deaths (Female)	YLL(years)*
AGE<1	74.05	77.17	0	0	0.00
AGE1-4	74.01	77.14	0	0	0.00
AGE5-9	70.16	73.29	0	0	0.00
AGE10-14	65.23	68.36	0	0	0.00
AGE15-19	60.31	63.43	0	0	0.00
AGE20-24	55.48	58.57	0	0	0.00
AGE25-29	50.74	53.77	1	0	50.74
AGE30-34	45.99	48.98	0	1	48.98
AGE35-39	41.29	44.21	1	1	85.50
AGE40-44	36.57	39.42	0	0	0.00
AGE45-49	31.96	34.70	1	0	31.96
AGE50-54	27.41	30.06	1	1	57.47
AGE55-59	23.04	25.57	2	0	46.09
AGE60-64	18.88	21.23	6	2	155.73
AGE65-69	15.03	17.15	2	1	47.20
AGE70-74	11.71	13.50	4	1	60.35
AGE75-79	9.00	10.39	3	1	37.40
AGE80-84	6.65	7.68	3	1	27.64
AGE85-89	4.95	5.58	5	0	24.74
AGE90-94	2.99	3.40	1	0	2.99
AGE95-99	2.15	2.37	0	0	0.00
AGE100+	1.53	1.67	0	0	0.00
Total			30	9	676.78

*YLL = years of life lost due to premature mortality.

Table S4. YLDs of confirmed H7N9 cases

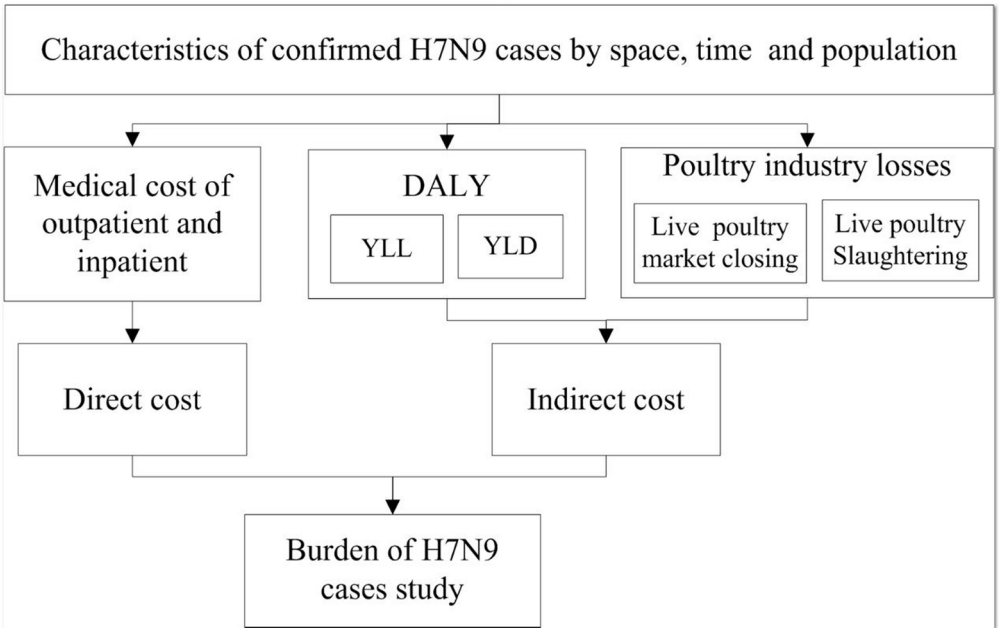
	Disability weight*	Number of cases	Duration of disability(years)	YLD(years)¶
Mild	0.005	25	0.025	0.003
Severe	0.21	95	0.052	1.038
Unknown(moderate)	0.053	11	0.038	0.022
Total		131	0.115	1.064

*Disability weight: Institute for Health Metrics and Evaluation (IHME),GBD 2010 Disability Weights

¶YLD = years lived with disability.

Table S5. Potential poultry-industry losses of eight non-affected adjacent provinces

Potential affected provinces	Cost of live-poultry sales(10^4 CNY)	Market-stall leases (10^4 CNY)	Total cost (10^4 CNY)	Total cost (10^4USD)
Guangxi	126671.29	2623.68	129294.97	20687.20
Guizhou	13793.65	256.32	14049.97	2248.00
Chongqing	32341.22	2904.12	35245.34	5639.25
Hubei	76709.59	2097.12	78806.71	12609.07
Shaanxi	7859.11	213.72	8072.83	1291.65
Shanxi	9571.87	473.46	10045.33	1607.25
Hebei	78872.43	1340.10	80212.53	12834.01
Tianjin	11426.38	582.00	12008.38	1921.34
Total cost (10^4CNY)	357245.56	10490.52	367736.08	58837.77
Total cost (10^4USD)	57159.29	1678.48	58837.77	9414.04



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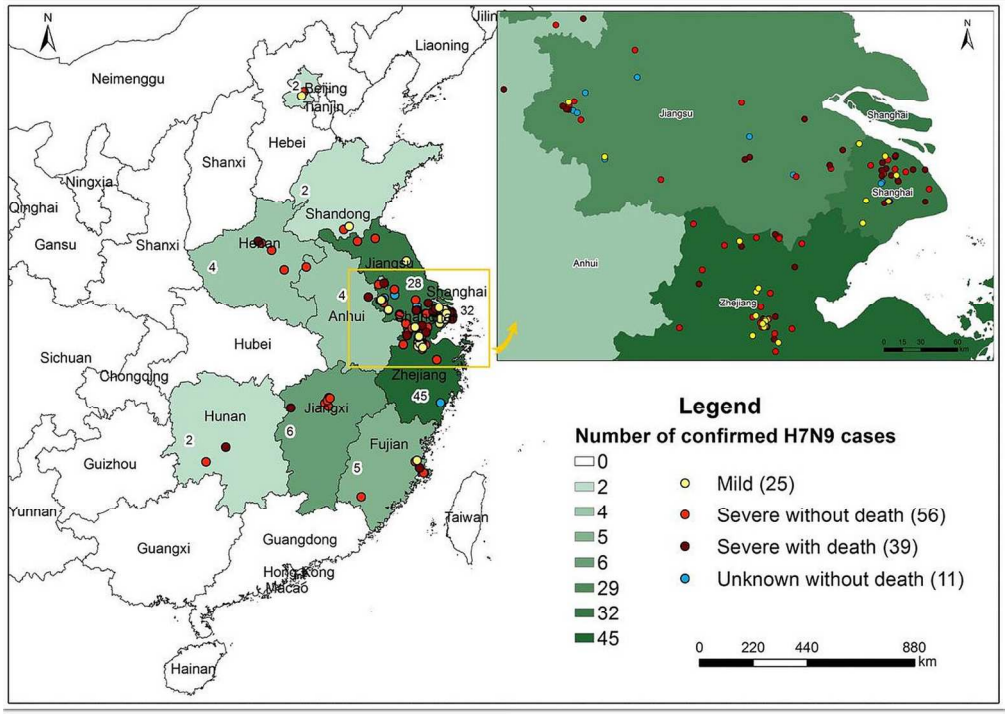

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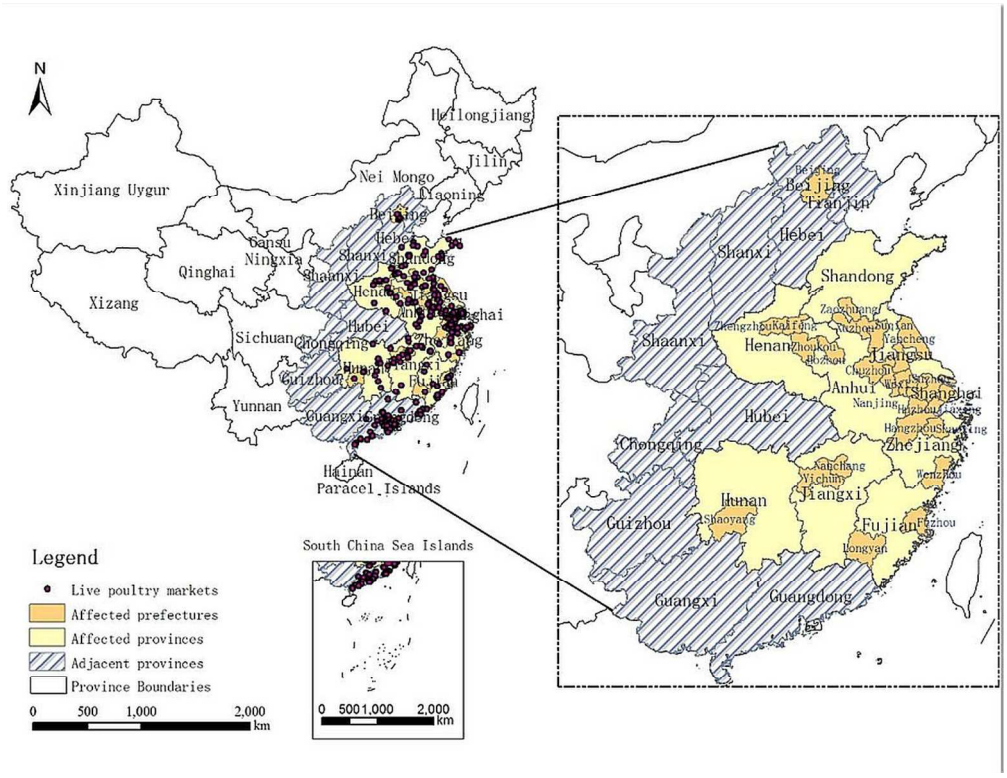

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