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Case-control study of risk factors for human infection with avian influenza A(H7N9) virus in Shanghai, China, 2013

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SUMMARY

The first human infection with avian influenza A(H7N9) virus was reported in Shanghai, China in March 2013. An additional 32 cases of human H7N9 infection were identified in the following months from March to April 2013 in Shanghai. Here we conducted a case-control study of the patients with H7N9 infection ($n = 25$) using controls matched by age, sex, and residence to determine risk factors for H7N9 infection. Our findings suggest that chronic disease and frequency of visiting a live poultry market (>10 times, or 1–9 times during the 2 weeks before illness onset) were likely to be significantly associated with H7N9 infection, with the odds ratios being 4·07 [95% confidence interval (CI) 1·32–12·56], 10·61 (95% CI 1·85–60·74), and 3·76 (95% CI 1·31–10·79), respectively. Effective strategies for live poultry market control should be reinforced and ongoing education of the public is warranted to promote behavioural changes that can help to eliminate direct or indirect contact with influenza A(H7N9) virus.

Key words: Avian influenza A(H7N9) virus, case-control study, human infection, risk factor.

INTRODUCTION

Avian influenza A(H7N9) infections are normally seen in animals and are mostly asymptomatic [1]. Human infections with H7N9 are uncommon [2]. The first human case of H7N9 infection was reported on 31 March 2013 in Shanghai, China [3]. As of 31 December 2013, the China National Health and Family Planning Commission has reported 144 laboratory-confirmed case of human H7N9 infection in mainland China, with 46 (31·94%) deaths. This rapid expansion of H7N9 infections has raised concerns regarding the pandemic potential of H7N9 virus. However, investigations of risk factors for human H7N9 infection are rare. Although an analytical study conducted in Jiangsu province identified chronic illness and environment-related exposure as risk factors for human infection with H7N9 [4], current H7N9 outbreaks in China suggest different geographical, sociodemographical, or behavioural contexts might be involved in virus transmission.

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Therefore, further studies are needed to clarify the mode of transmission of H7N9 viruses from animals to humans. Here we conducted a case-control study to identify potential risk factors for H7N9 infection in Shanghai, where the first case of human H7N9 infection occurred, and to guide the strategy for control and prevention of H7N9 infection.

METHODS

Subjects

As of December 2013, 33 laboratory-confirmed cases of human infection with H7N9 have been reported in Shanghai, China, resulting in 18 (54·5%) deaths. All confirmed cases of human H7N9 infection in Shanghai were encouraged to enrol into this study. Of the 33 H7N9 cases, 25, including 11 deceased cases that were confirmed positive for H7N9 using validated real-time RT–PCR TaqMan® assay [5] were finally included in the study. The remaining eight cases (seven fatal cases) were excluded from the study owing to refusal to participate by the cases or their proxies. Cases were defined following the Diagnosis and Treatment Guideline of Human Infection with Avian Influenza A (H7N9) Virus issued by the Chinese National Health and Family Planning Commission [6]. Specifically, all cases of human H7N9 infection in this study had symptoms of fever (oral temperature $\geqslant 38$ °C), cough, headache or severe pneumonia. All cases had a history of poultry exposure or close contact with H7N9 patients during the 2 weeks prior to their illness onset and were seropositive for H7N9 virus. Each case was matched with three controls (75 controls in total) that were of the same gender, had less than 3 years' age difference, and had lived in the same community or village for more than 6 months. All of the controls were seronegative for H7N9, and had no respiratory symptoms and fever ($\geqslant 38$ °C) in the 2 weeks prior to illness onset of the matched cases. If there were not enough eligible controls, the closest neighbours were recruited instead. For example, for H7N9 cases in the urban area, controls were first recruited from the same unit of the block where the cases lived, this was then expanded to the adjacent unit of this block if necessary. For H7N9 cases in the rural area, controls were recruited from the nearest neighbours in the village where the cases lived. The interviewing staff went from door-to-door asking for volunteer controls. Of a total of 80 controls invited to participate, 75 were finally enrolled in this study.

Data and sample collection

Data were collected from 27 May to 7 June 2013. All of the participants were interviewed by the trained employees of the local district Center for Disease Control and Prevention using interviewer-administered questionnaires. The questionnaire was self-developed and a pre-test was performed prior to the official investigation. The questionnaires consisted of demographical characteristics, health status, daily habits, and other related potential risk behaviours including infrequent hand-washing before meals or after using the bathroom and smoking. The questionnaires also included environment-related exposure variables including visiting a live poultry market, visiting a temporary roadside poultry vendor, raising chickens or pigeons in the neighbourhood, or other activities involving direct and indirect contact with live poultry during the 2 weeks before illness onset of the cases. Direct contact was referred to as touching live poultry with bare hands in a live poultry market (slaughtering or purchasing poultry), at home (raising, cleaning or processing poultry), or occupational exposure to live poultry without protection (poultry transportation, restaurant poultry preparation and cooking). Indirect contact was defined as being in close proximity (<1 m away from poultry) at home without direct physical contact. All questions were close-ended. Proxies were interviewed for the deceased patients ($n = 11$), severe H7N9 patients who were too sick to respond to the interviewers ($n = 3$), or subjects aged <6 years ($n = 4$). To ensure accuracy of proxy data, spouses or parents who lived together with the patients for more than 2 weeks before illness onset were interviewed and hospital medical records of the patients were reviewed as well. Data from the medical records were used if there was a discrepancy between the proxy description and the medical records. Following the interview, 5 ml of venous blood from each control was collected for laboratory testing of H7N9 to exclude asymptomatic or past H7N9 infection.

Laboratory analysis

Serum samples from the controls were tested using haemagglutination inhibition (HI) assay with turkey red blood cells against avian influenza A(H7N9) virus strain (A/Shanghai/2/2013). The HI was performed following the Diagnosis and Treatment Guideline of Human Infection with Avian Influenza

A(H7N9) Virus [5]. The serum from a confirmed H7N9 case was used as a positive reference.

Statistics

All tests were performed two-sided at the 5% significance level. The Wilcoxon rank sum test, Pearson's χ^2 test and Fisher's exact test were performed to analyse the difference of general characteristics between cases and controls. Potential risk factors were compared between cases and controls, using univariate logistic regression. Given human H7N9 infection is uncommon and the studies of risk factors for human H7N9 infection are rare, we treated all the variables in this study as potential significant factors. Therefore, we further conducted a backward stepwise (entry and removal probability were 0·05 and 0·10, respectively) multivariate logistic regression analysis including all variables in the univariate analysis to correct possible confounding factors. All statistical analyses were performed using SAS v. 9·2 (SAS Institute Inc., USA).

Ethical approval

The objectives and methods of the study were clearly explained to all participants. Informed written consent from participants or their proxies was obtained before data collection. The ethical approval for the study was obtained from the Ethics Committee of Shanghai Municipal Centre for Disease Control and Prevention and the study was conducted in full compliance with the principles of the Declaration of Helsinki.

RESULTS

General characteristics

Of the 25 cases of human H7N9 infection, only two cases had occupational exposure to live poultry. One was engaged in poultry transportation, and the other worked in a restaurant preparing and cooking poultry. Data for 15 cases (11 fatal and four discharged) and three controls (all aged <6 years) were obtained from their proxies. Data for the remaining 10 cases and 72 controls were provided by the subjects themselves. All of the enrolled controls were seronegative for H7N9.

The demographical and social characteristics of subjects are shown in Table 1. The age of the cases varied from 2·5 to 89 years, with a median age of 69 years. The age of the controls varied from 2 to 92 years (median 67 years). All subjects were aged >25 years except for one case (2·5 years) and three controls (aged 2–5 years). Eighteen (72·0%) cases were aged >60 years and 21 (84·0%) cases were male. Twenty-one cases lived in an urban area. Eighteen cases and 36 controls had been diagnosed with chronic diseases, including chronic bronchitis, hypertension, diabetes, pulmonary disease, or heart disease. The percentage of chronic medical conditions in cases was significantly higher than that in

Table 1. *Demographic and social characteristics of participants in a case-control study of avian influenza A(H7N9) in Shanghai, China*

Variables	Cases ($n = 25$) n (%)	Controls ($n = 75$) n (%)	P value
Age, yr (median, range)	69 (2·5–89·0)	67 (2·0–92·0)	
<60	7 (28·0)	23 (30·7)	0·464*
⩾60	18 (72·0)	52 (69·3)	
Male	21 (84·0)	63 (84·0)	
Location			
Urban	21 (84·0)	63 (84·0)	
Rural	4 (16·0)	12 (16·0)	
Body mass index			0·557†
<20	3 (12·0)	8 (10·7)	
20–25	12 (48·0)	45 (60·0)	
⩾25	10 (40·0)	22 (29·7)	
Diagnosed chronic diseases			
No	7 (28·0)	39 (52·0)	0·037†
Yes	18 (72·0)	36 (48·0)	
Education			
Primary school and below	7 (28·0)	17 (22·7)	0·635†
Junior middle school	8 (32·0)	24 (32·0)	
Senior middle school	5 (20·0)	24 (32·0)	
College and higher	5 (20·0)	10 (13·3)	
Household income *per capita*			0·542‡
<5000 RMB§	4 (16·0)	12 (16·0)	
5000–10 000 RMB	1 (4·0)	7 (9·3)	
10 000–20 000 RMB	3 (12·0)	17 (22·7)	
>20 000 RMB	17 (68·0)	39 (52·0)	

* Wilcoxon rank sum test.
† Pearson's χ^2 test.
‡ Fisher's exact test.
§ 10 RMB = ~1 GBP.

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controls ($P < 0{\cdot}05$). However, there was no statistically significant difference in terms of characteristics including body mass index (BMI), education level and *per capita* household income between cases and controls ($P > 0{\cdot}05$).

Univariate analysis of risk factors for human H7N9 infection

The univariate analysis of possible risk factors for human H7N9 infection is shown in Table 2. Persons with chronic medical conditions appeared to be susceptible to H7N9 infection as 72% of the cases had chronic diseases compared to 48% of the controls [unadjusted odds ratio (OR) 2·79, $P = 0{\cdot}037$]. Indirect contact with poultry at home ($P = 0{\cdot}038$), and environment-related exposures including visiting a live poultry market and visiting a temporary roadside poultry vendor during the 2 weeks before illness onset ($P < 0{\cdot}05$) tended to be associated with H7N9 infection (Table 2). A trend χ^2 analysis ($\chi^2 = 8{\cdot}25$, $P = 0{\cdot}004$) suggested greater frequency of visiting a live poultry market posed a greater risk of H7N9 infection. By contrast, BMI, frequent hand-washing, smoking, direct contact with poultry at a live poultry market, preparing or cooking poultry at home, raising poultry or pigeons at home or in the neighbourhood, occupational contact with poultry and travel history were not significantly different between cases and controls ($P > 0{\cdot}05$).

Multivariate analysis of risk factors for human H7N9 infection

The backward stepwise logistic regression model was fitted to analyse potential risk factors for human H7N9 infection. All variables in univariate analysis were incorporated into a model fitting with multinomial variables converted into dummy variables (Table 3). Two variables, chronic disease and visiting a live poultry market during the 2 weeks before illness onset, were found to be significantly associated with human H7N9 infection. Visiting a live poultry market during the 2 weeks before illness onset was more likely to cause H7N9 infection with odds ratios of 10·61 and 3·76 for frequencies of >10 times and between 1 and 9 times, respectively. Notably, chronic disease appeared to be an independent risk factor for H7N9 infection. Persons with chronic disease were about four times more likely to be infected with H7N9 compared to those without chronic disease (Table 3). Although indirect contact with poultry at home and visiting a temporary roadside poultry vendor in the 2 weeks before illness onset were statistically significant in univariate analysis, they did not enter the ultimate multivariate logistic model. By contrast, other factors had no significant influence on H7N9 infection after adjusting for potential confounding factors.

DISCUSSION

Although poultry infected with avian influenza A (H7N9) virus are usually asymptomatic, H7N9 virus is highly pathogenic in humans. Here we conducted a case-control study to identify risk factors in cases of human H7N9 infection during the first reported outbreak of human H7N9 infections in 2013. To date, it still remains inconclusive whether age, sex and residence are risk factors for human H7N9 infection. In order to minimize possible impact of differences in age, sex and residence on the association of potential risk factors with H7N9 infection, the cases and the controls were matched by these factors. Our study identified that visiting a live poultry market during the 2 weeks prior to illness onset and chronic disease were likely associated independently with human H7N9 infection found in Shanghai, China. Our findings reinforce the hypothesis that visiting a live poultry market and chronic disease are risk factors for H7N9 infection [4], and further prove the consistency of these risk factors in different geographical areas.

Our finding that visiting a live poultry market was probably an independent risk factor for H7N9 infection is also consistent with previous studies on human H5N1 cases [7–9]. Notably, the risk of H7N9 infection appears to increase with increasing frequency of visiting a live poultry market, which implies that the frequency of exposures might have played an important role. The surroundings of live poultry markets are easily contaminated by poultry body secretions, faeces, or processed organs of poultry. In addition, multiple species of live poultry and birds are concentrated at a high density in live poultry markets, which could facilitate viral spread and interspecies transmission [10–12]. The live poultry market is hence considered as a reservoir and amplifier of H7N9 viruses. People in this environment are more likely to be exposed to pathogens including H7N9 carried by live poultry. According to our investigation, cases visiting a live poultry market might just pass by the retail poultry stall, or just observe the live

Table 2. *Univariate analysis of risk factors for human infection with avian influenza A(H7N9) virus in Shanghai, China, 2013*

Variables	Variable level	Cases *n* (%)	Controls *n* (%)	OR (95% CI)	*P* value
Chronic disease	Yes	18 (72·0)	36 (48·0)	2·7 (1·04–7·45)	0·037*
Body mass index	<20	3 (12·0)	8 (10·7)	Reference	
	20–25	12 (48·0)	45 (60·0)	0·7 (0·16–3·10)	0·650
	⩾25	10 (40·0)	22 (29·7)	1·2 (0·26–5·56)	0·804
Frequent hand-washing	No	5 (20·0)	9 (12·0)	1·8 (0·55–6·10)	0·323
Having ever smoked	Yes	10 (40·0)	33 (44·0)	0·8 (0·34–2·13)	0·727
Direct contact with poultry in the live poultry market	Yes	3 (12·0)	11 (14·7)	1·1 (0·57–2·22)	0·740
Preparing or cooking at home†	Yes	4 (16·0)	9 (12·0)	1·4 (0·39–5·00)	0·608
Occupational contact with poultry†	Yes	2 (8·0)	1 (1·3)	6·4 (0·56–74·24)	0·136
Raising poultry or pigeons at home†	Yes	3 (12·0)	3 (4·0)	3·2 (0·62–17·24)	0·160
Indirect contact with poultry at home	Yes	5 (20·0)	4 (5·3)	4·4 (1·09–18·18)	0·038*
Raising poultry or pigeons in the neighbourhood‡	Yes	11(44·0)	31 (41·3)	0·9 (0·36–2·24)	0·815
Visiting a live poultry market‡	No	9 (36·0)	51 (68·0)	Reference	
	1–9 times	12 (48·0)	20 (26·7)	3·4 (1·24–9·31)	0·017*
	⩾10 times	4 (16·0)	4 (5·3)	5·6 (1·20–26·87)	0·029*
Visiting a temporary roadside poultry vendor‡	Yes	4 (16·0)	2 (2·7)	6·95 (1·19–40·63)	0·031*
Travel history§	Yes	6 (24·0)	9 (12·0)	2·32 (0·73–7·33)	0·153

OR, Odds ratio; CI, confidence interval.
† Direct contact with poultry.
‡ Environment-related exposure.
§ Travel to another city where H7N9 cases were reported.
* $P < 0{\cdot}05$

Table 3. *Multivariate logistic regression analysis of risk factors for human infection with avian influenza A (H7N9) virus infection in Shanghai, China, 2013*

Factors	Categories	β	*P* value	OR	95% CI
Constant		−2·69	<0·001	0·07	
Visiting a live poultry market	1–9 times	1·32	0·014	3·76	1·31–10·79
	⩾10 times	2·36	0·008	10·61	1·85–60·74
Chronic disease	Yes	1·40	0·015	4·07	1·32–12·56

OR, Odds ratio; CI, confidence interval.

poultry at close quarters, or they may simply purchase eggs from the egg stall adjacent to the live poultry stall. Evaluation of the airborne transmissibility of the human H7N9 isolates A/Shanghai/2/2013 and A/Anhui/1/2013 suggests the H7N9 viruses could infect ferrets via airborne exposure, albeit the transmission is not as effective as intranasal inoculation of the viruses [13–14]. Transmission of H7N9 virus in animals could select and enrich some mutations similarly seen in influenza A/H5N1 virus that can gain the capacity for airborne transmission between mammals [15]. Although no sustained human-to-human transmission of H7N9 viruses has been confirmed to date, identification of some family clusters of H7N9 infection raised concerns of human-to-human transmission via the aerosol route [16]. Visiting a live poultry market, even for a short period of time, is thus likely to result in contracting H7N9 virus through contaminated aerosols. Consistent with this speculation, H7N9 virus was detected from an environmental specimen collected from the poultry cage at a live poultry market in the epidemic region [17]. This finding suggests that transmission of H7N9 virus via environmental contamination may occur in China. Therefore, effective live poultry market control strategies should be developed and implemented. These strategies include segregating bird species, improving biosecurity, establishing central poultry slaughtering facilities, conducting regular disinfection, and having a periodic rest day [18–20].

Studies have shown that persons with chronic pulmonary disease, renal dysfunction, or haemoglobinopathies are at increased risk of development of complications from influenza infection [21]. Our findings show that having chronic disease(s) is likely to be significantly associated with H7N9 infection. Eighteen (72%) of the 25 cases of human H7N9 infection had pertinent chronic diseases before illness onset, which was higher than that of controls (48%) ($P = 0{\cdot}037$). Persons with chronic disease had compromised immune function, which might have contributed to the increased risk of H7N9 infection. Due to the small numbers of each type of chronic disease, we were not able to further analyse the association of specific underlying medical conditions with H7N9 infection in our study. However, our data suggest that at least some of these medical conditions might be independent risk factors for H7N9 infection. The individuals, especially those with underlying chronic diseases such as chronic bronchitis, hypertension, diabetes, pulmonary disease, or heart disease, should reduce exposure to possibly contaminated environments to minimize the risk of H7N9 infection.

There are several potential limitations to our findings. First, the study may be underpowered to detect the risk factors. In this case-control study, the matched elements including age, gender and residence were excluded from analysis as risk factors. The lack of a statistically significant association between H7N9 infection and direct contact with live poultry in this study may result from the relatively small number of cases ($n = 25$). Further studies to include more cases are warranted to determine whether the frequency and duration of direct contact with poultry are associated with H7N9 infection. Second, data collection bias was likely to have occurred. Although a standardized questionnaire and trained staff were deployed for interview to minimize interviewer bias, masking case-control status from the interviewers was not possible in this study. In addition, a larger proportion of interviews in the case group (15/25) than in the control group (3/75) were completed by proxies. Although the proxies (spouse or parents) lived closely with the cases, it is likely that the proxies might not be aware of some of the activities and poultry exposure history of the cases. The substantial delay (>1 month, range 2–3 months) between illness onset and the interviews could be another potential source of recall bias or inaccuracy both for living and deceased cases. Finally, it is possible that we did not identify all H7N9 cases that occurred in Shanghai during the study period, especially the cases with mild symptoms.

Although our findings indicate that visiting a live poultry market and chronic disease are major risk factors for human H7N9 infection, the exact mechanism of virus transmission is uncertain. Avian influenza viruses have the potential to either reassort with human influenza strains or to undergo genetic mutations and might consequently become more transmissible among humans. In conclusion, interventions based upon our findings may help prevent further avian influenza A(H7N9) transmission to humans. Ongoing education of the public, especially those with chronic medical conditions, is warranted to promote behavioural changes that can help to avoid direct or indirect contact with H7N9 virus. Last, but by no means least, effective strategies for live poultry market control should be reinforced. In addition, the feasibility of wearing protective masks for workers and visitors to live poultry markets could also be considered.

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DECLARATION OF INTEREST

None.

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