

Risk Factors for Influenza A(H7N9) Disease in China, a Matched Case Control Study, October 2014 to April 2015

Lei Zhou,^{1,a} Ruiqi Ren,^{1,a} Jianming Ou,^{2,a} Min Kang,^{3,a} Xiaoxiao Wang,^{4,a} Fiona Havers,⁵ Xiang Huo,⁶ Xiaoqing Liu,⁷ Qianlai Sun,⁸ Yongchao He,⁹ Bo Liu,¹ Shenggen Wu,² Yali Wang,¹ Haitian Sui,¹ Yongjie Zhang,^{10,b} Shaopei Tang,^{10,c} Caiyun Chang,^{10,d} Lunhui Xiang,^{10,e} Dong Wang,^{1,f} Shiguang Zhao,^{1,g} Suizan Zhou,⁵ Tao Chen,¹¹ Nijuan Xiang,¹ Carolyn M. Greene,⁵ Yanping Zhang,¹ Yuelong Shu,¹¹ Zijian Feng,¹² and Qun Li¹

¹Public Health Emergency Center, Chinese Center for Disease Control and Prevention, Beijing, ²Fujian Center for Disease Control and Prevention, Fuzhou, ³Guangdong Center for Disease Control and Prevention, Guangzhou, and ⁴Zhejiang Center for Disease Control and Prevention, Hangzhou, China; ⁵United States Centers for Disease Control and Prevention, Atlanta, Georgia; ⁶Jiangsu Center for Disease Control and Prevention, Nanjing, ⁷Jiangxi Center for Disease Control and Prevention, Nanchang, ⁸Hunan Center for Disease Control and Prevention, Changsha, ⁹Shanghai Center for Disease Control and Prevention, ¹⁰Chinese Field Epidemiology Training Program, Chinese Center for Disease Control and Prevention, Beijing, ¹¹National Influenza Center, Chinese Center for Disease Control and Prevention, Beijing, and ¹²Chinese Center for Disease Control and Prevention, Beijing, China

Background. Human infections with avian influenza A(H7N9) virus have been associated with exposure to poultry and live poultry markets (LPMs). We conducted a case-control study to identify additional and more specific risk factors.

Methods. Cases were laboratory-confirmed A(H7N9) infections in persons in China reported from October 1, 2014 to April 30, 2015. Poultry workers, those with insufficient data, and those refusing participation were excluded. We matched up to 4 controls per case by sex, age, and residential community. Using conditional logistic regression, we examined associations between A(H7N9) infection and potential risk factors.

Results. Eighty-five cases and 334 controls were enrolled with similar demographic characteristics. Increased risk of A(H7N9) infection was associated with the following: visiting LPMs (adjusted odds ratio [aOR], 6.3; 95% confidence interval [CI], 2.6–15.3), direct contact with live poultry in LPMs (aOR, 4.1; 95% CI, 1.1–15.6), stopping at a live poultry stall when visiting LPMs (aOR, 2.7; 95% CI, 1.1–6.9), raising backyard poultry at home (aOR, 7.7; 95% CI, 2.0–30.5), direct contact with backyard poultry (aOR, 4.9; 95% CI, 1.1–22.1), and having ≥ 1 chronic disease (aOR, 3.1; 95% CI, 1.5–6.5).

Conclusions. Our study identified raising backyard poultry at home as a risk factor for illness with A(H7N9), suggesting the need for enhanced avian influenza surveillance in rural areas.

Keywords. avian influenza A(H7N9); case-control study; risk factor.

Since the first outbreak of avian influenza A(H7N9) virus in humans was identified in 2013 [1], subsequent seasonal epidemic waves have been documented in Mainland China [2], resulting in 793 confirmed cases and 319 deaths as of July 19, 2016 [3].

Prior studies have consistently identified poultry exposure, including direct and indirect contact with poultry, and visiting live poultry markets (LPMs) as risk factors for infection [4–8].

However, during the epidemic's first wave, exposure to poultry in backyard flocks was not found to be a significant risk factor; at that time, LPMs appeared to be the main source of human infections [6]. These findings have provided scientific evidence needed to design effective control measures. Live poultry market closures occurred in most areas affected by the A(H7N9) virus, including temporary closures in Jiangsu, short-term monthly closures in Guangdong, seasonal long-term annual closures in Shanghai, and permanent closures in the main urban areas of all cities in Zhejiang [9–11]. Although studies demonstrated that LPM closure effectively controlled disease [11, 12], the associated economic burden for the poultry industry, including poultry owners, workers, transporters, and even customers, was substantial.

Further research is needed to identify more specific risk factors for A(H7N9) virus infection, leading to increasingly targeted disease control measures that have less economic impact on China's poultry industry. We conducted a matched case-control study during the third wave of the A(H7N9) outbreak, October 1, 2014 to April 30, 2015, to verify known risk factors for infection, examine whether the epidemiology of A(H7N9) has changed since the first wave of infections in 2013, and to determine more specific additional risk factors that might guide targeted disease control in the future.

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^aL. Z., R. R., J. O., M. K., and X. W. contributed equally to this work.

^bPresent Affiliation: Jiangsu Center for Disease Control and Prevention, Nanjing, China.

^cPresent Affiliation: Bozhou Center for Disease Control and Prevention, Bozhou, China.

^dPresent Affiliation: Jinan Municipal Center for Disease Control and Prevention, Jinan, China.

^ePresent Affiliation: Baoshan Center for Disease Control and Prevention, Baoshan, China.

^fPresent Affiliation: Jinan Municipal Center for Disease Control and Prevention, Jinan, China.

^gPresent Affiliation: Quzhou Center for Disease Control and Prevention, Quzhou, China.

Correspondence: Q. Li, Public Health Emergency Center, Chinese Center for Disease Control and Prevention, Beijing 102206, P. R. China (liqun@chinacdc.cn).

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METHODS

Study Design, Participants and Definitions

We conducted a matched case-control study. Consistent with prior studies, we defined a case as a person with laboratory-confirmed A(H7N9) virus infection verified by real-time reverse-transcriptase polymerase chain reaction assay, viral isolation, or serologic testing [6, 13], reported from October 1, 2014 to April 30, 2015 in mainland China. All suspected A(H7N9) infections in humans were reported to the China Center for Disease Control and Prevention (CDC) through the National Notifiable Surveillance System. The first A(H7N9) case of the influenza season and the first case in the calendar year in each province were confirmed by laboratory testing at China CDC; subsequent cases were confirmed by provincial CDCs. Because LPMs have a greater number and variety of poultry (eg, chicken, duck, geese) than households raising poultry in their backyards, LPM poultry workers have more specific known risk factors for infection compared with other populations, including persons who raise backyard poultry at home. Therefore, we excluded LPM poultry workers given their unique exposures, which may limit comparability with other confirmed cases. We also excluded cases with insufficient epidemiological data, due to death or incomplete original field investigation reports, and those who refused to participate.

We randomly selected up to 4 matched controls for each case using local population registries. Details of control selection are presented elsewhere [6]; in brief, eligible controls were persons who were matched with each case by sex, age (± 3 years for cases ≤ 85 years of age and ± 5 years for cases > 85 years of age), and residential community, defined as where the case was living for the 3 months before their illness onset. We excluded control subjects who refused to participate, or those who reported a fever or acute respiratory illness (defined as new cough or sore throat) during the 7 days before or after the date of the matched case's illness onset.

Data Collection

Investigators from China CDC were trained to collect data using a structured questionnaire. The questionnaire was pretested in Anhui and Fujian provinces in April 2014 and revised by China CDC based on pilot findings. Information collected included demographics, residential setting (urban vs rural, with urban areas defined as cities, towns, and suburbs, and rural areas defined as villages and countryside), underlying medical conditions, smoking status, and handwashing frequency (defined by number of times the subject washed their hands per every 10 contacts with poultry: occasionally, < 5 times; sometimes, 5–8 times; or often, > 8 times).

We collected detailed exposure information from each participant for the 10 days before the case's date of illness onset. Exposure information included details about behavior in LPMs such as number of visits, activities engaged in during market

visits, and direct or indirect contact with live or fresh slaughtered poultry or poultry products. Direct contact was defined as physical contact with poultry or related biologic matter (including blood, internal organs, eggs, secretions, feces, or poultry cages) without the use of personal protective equipment, whereas indirect contact was defined as being within < 1 meter of poultry or poultry products without having any physical contact. The activities during market visits focused on exposures to the live poultry stall such as passing by without stopping at the stall or stopping at a stall to look at, select or buy poultry, and exposure to a slaughtering stall or to a defeathering machine at the stall, regardless of whether the slaughtering/defeathering machine was running. We also collected information about poultry exposure at home, including information on raising poultry, exposure to sick or dead poultry, and source of backyard poultry and/or poultry products. In addition, we asked whether the subject had exposure to a person with acute respiratory illness, had visited another house where poultry was raised, and whether household members had visited a LPM or had contact with a poultry worker.

Study investigators used structured questionnaires to conduct face-to-face interviews with the participant or with a proxy for children < 18 years of age, fatal cases, or cases who were severely ill and unable to respond. For all cases, original field investigation reports completed during the public health emergency response served as supplementary sources of information.

Statistical Analysis

The Wilcoxon test was used to compare median age and range between cases and controls, and a χ^2 test was used to compare frequencies of demographic categorical variables. Conditional logistical regression was performed for univariate and multivariate analysis. Stratified analysis, nonconditional logistical regression, and Fisher exact test were used when appropriate. For the multivariable analysis, we included variables with a P value of $< .1$ in univariate analysis and additional variables based on biological plausibility and our study hypotheses. To examine the effect of proxy use on reported smoking status, we performed a nonconditional logistical regression analysis stratified by whether a study participant required a proxy. Variables with a P value of $< .05$ in the final multivariable model were considered significant. Data were analyzed with SAS 9.1 (SAS Institute Inc., Cary, NC).

Ethics Statement

This study was approved by the China CDC Institutional Ethics Review Board and received a nonengaged determination from the United States CDC. Written informed consent was obtained from all study participants before data collection.

RESULTS

Study Participants

From October 1, 2014 to April 30, 2015, a total of 197 confirmed cases were identified in 11 provinces (Guangdong,

Fujian, Zhejiang, Jiangsu, Anhui, Xinjiang, Shanghai, Hunan, Jiangxi, Shandong and Guizhou). We enrolled 85 (43%) cases from Fujian (32), Guangdong (18), Zhejiang (17), Jiangsu (14), Hunan (2), Shanghai (1), and Jiangxi (1) provinces. Nine cases who were poultry workers were excluded, and 62 fatal cases without detailed exposure information were also excluded. There were no significant differences in the demographic characteristics of the 28 included and the 62 excluded fatal cases (Supplementary Table 1). We also excluded 41 cases who refused to participate. Overall, the proportion of male cases was significantly higher among the 103 excluded nonpoultry worker cases than among the 85 included cases, but there were no other significant differences by age, residential setting (rural vs urban), underlying medical conditions, exposure to LPM, and exposure to backyard poultry (Supplementary Table 2). Interviews and case-related data collection were conducted a median of 80 days (range: 2–145 days) after the date of illness onset of the case.

Table 1. Demographic Characteristics of Influenza A(H7N9) Cases and Controls Matched by Age, Sex, and Location in China, October 2014 to April 2015^a

Characteristics	Cases (n = 85) No. (%)	Controls (n = 334) No. (%)	P Value
Interviewed by proxy, n (%)	26 (31)	33 (10)	<.01
Median age (range), years	53 (2–88)	54 (1–92)	.96
Age group, years, n (%)			
<18	4 (5)	14 (4)	.72
18–29	5 (6)	23 (7)	
30–49	19 (22)	88 (26)	
50–59	26 (31)	80 (24)	
60–79	29 (34)	112 (34)	
≥80	2 (2)	17 (5)	
Male, n (%)	53 (62)	206 (62)	.91
Living area ^b , n (%)			
Urban	44 (52)	172 (51)	.97
Rural	41 (48)	162 (49)	
Occupation, n (%)			
Person who does housework or is unemployed	21 (25)	54 (16)	.11
Person who works in company, industry or institute	19 (22)	47 (14)	
Retiree	17 (20)	68 (20)	
Farmer	11 (13)	68 (20)	
Business service personnel	9 (11)	60 (18)	
Children before school age (<7 years)	4 (5)	14 (4)	
Other ^c	4 (5)	23 (7)	

Boldface indicates statistical significance with $P < .05$, and those variables with $P < .10$ were included in multivariate analyses for the initial model.

^a Median age of cases and controls was compared using Wilcoxon test. Frequencies of 2 groups were compared using χ^2 test.

^b Urban area in our study includes cities, towns and suburbs. Rural area refers to countryside and villages.

^c Other occupations included food service professional (11), independent professional (9), healthcare workers (5), fisherman (1), and herdsman (1).

Three hundred thirty-four controls were selected: 81 cases had 4 controls, 2 cases had 3 controls, and 2 cases had 2 controls. Cases and controls were similar in demographic features, including median age (53 years vs 54 years, respectively), sex (62% male for both cases and controls), and proportion living in an urban setting (52% vs 51%, respectively) (Table 1). The proportion of cases requiring a proxy was significantly higher than among controls (31% vs 10%; $P < .01$). When compared with cases that did not require a proxy, cases that required a proxy reported similar proportions with underlying medical conditions (44% vs 50%; $P = .61$) and LPM exposures (78% vs 81%; $P = .77$).

Table 2. Underlying Medical Conditions and Behaviors of Influenza A(H7N9) Cases and Controls Matched by Age, Sex, and Location in China, October 2014 to April 2015

Characteristics	Cases (n = 85) No. (%)	Controls (n = 334) No. (%)	mOR (95% CI)	P Value
Obesity, n (%) ^a	5 (6)	11 (3)	1.9 (.62–5.7)	.27
≥1 chronic disease, n (%) ^b	39 (46)	84 (25)	3.2 (1.8–5.7)	<.01
COPD	8 (9)	9 (3)	3.7 (1.4–9.9)	<.01
Other pulmonary disease (tuberculosis, asthma)	4 (5)	3 (1)	5.3 (1.2–23.8)	.03
Cardiovascular disease	27 (32)	70 (21)	2.0 (1.1–3.7)	.02
Diabetes	10 (12)	16 (5)	3.0 (1.2–7.3)	.02
Kidney disease	2 (2)	1 (0.3)	8.0 (.72–89.6)	.09
Rheumatoid arthritis	1 (1)	3 (0.9)	1.3 (.14–12.8)	.81
Cancer (all types)	0 (0)	1 (0.3)	—	—
Hepatic disease	7 (8)	0 (0)	—	—
Immunosuppressive medications, n (%) ^c	3 (4)	1 (0.3)	12.2 (1.3–118.6)	.03^d
Current/pervious smoker n (%) ^e	21 (25)	132 (40)	0.32 (.16–.65)	<.01
Handwashing frequency, n (%) ^f				
Occasionally	27 (32)	23 (7)	Ref	
Sometimes	32 (38)	54 (16)	0.67 (.34–1.4)	.26
Often	26 (31)	257 (77)	0.06 (.03–.14)	<.01
Uses soap to wash hands, n (%)	12 (14)	180 (54)	0.10 (.05–.23)	<.01

Boldface indicates statistical significance with $P < .05$, and those variables with $P < .10$ were included in multivariate analyses for the initial model.

Abbreviations: BMI, body mass index; CI, confidence interval; COPD, chronic obstructive pulmonary disease; mOR, matched odds ratio; Ref, reference category.

^a Adults ≥18 years of age were considered obese if their BMI was ≥30 kg/m²; children <18 years were considered obese if their BMI-for-age was ≥95th percentile. BMI was calculated using self-reported height and weight.

^b Chronic diseases included COPD, other pulmonary diseases including tuberculosis and asthma, cardiovascular disease, diabetes, kidney disease, and rheumatoid arthritis. Tumor and hepatic disease were also included in the investigation but cannot be analyzed because of the small value. All chronic diseases were diagnosed by medical institutions at the county level or above. Hypertension and hypercholesterolemia were not included as chronic diseases in this analysis.

^c Immunosuppressive medication was prednisone.

^d Nonconditional logistical regression was used because of limited sample size.

^e We defined smoking status by asking participants to choose one of the following categories: “never smoked”, “currently smoke”, or “smoked in past, but quit”. Those who chose “currently smoke” or “smoked in past, but quit” were defined as current/pervious smokers.

^f Handwashing habit was defined as the frequency of handwashing per 10 times of contact/exposure to poultry (occasionally, <5 times; sometimes, 5–8 times; often, >8 times).

Table 3. Exposures in Live Poultry Market and at Home and Other Possible Exposures of Influenza A(H7N9) Cases and Controls Matched by Age, Sex, and Location in China, October 2014 to April 2015

Exposures ^a	Cases (n = 85) No. (%)	Controls (n = 334) No. (%)	mOR (95% CI)	P Value
Exposure in LPM, n (%)				
Visiting a LPM ^b	67 (79)	148 (44)	9.2 (4.3–20.0)	<.01
Frequency of LPM visits				
1–3 times	29/65 (45)	58/146 (40)	Ref	
≥4 times	36/65 (55)	88/146 (60)	0.89 (.42–1.9)	0.77
Exposure to live poultry stall when visiting a LPM				
Not passing by	10/65 (15)	50/148 (34)	Ref	
Passing by without stopping	24/65 (37)	62/148 (42)	1.6 (.73–3.5)	.23
Stopping at a stall	31/65 (48)	36/148 (24)	3.6 (1.6–7.9)	<.01
Exposure to live poultry slaughtering stall	26/31 (84)	29/36 (81)	1.2 (.16–8.6)	.87
Exposure to defeathering machine at stall	17/31 (55)	21/36 (58)	0.88 (.27–2.9)	.84
Direct contact ^c with live poultry	16/31 (52)	8/36 (22)	3.4 (2.7–16.6)	.02
Direct contact with fresh slaughtered poultry ^d	3/8 (38)	20/52 (38)	0.96 (.21–4.5)	.96 ^e
Indirect contact with poultry ^e	6/31 (19)	10/36 (28)	0.39 (.07–2.2)	.28
Exposure at home, n (%)				
Raised backyard poultry	24 (28)	48 (14)	8.0 (2.6–24.5)	<.01
Backyard poultry was bought from LPM	5/24 (21)	5/48 (10)	2.5 (.34–17.6)	.37
Sick or dead backyard poultry	4/24 (17)	2/48 (4)	3.4 (.27–42.3)	.35
Direct contact ^c with backyard poultry	13/24 (54)	14/48 (29)	5.0 (1.3–18.9)	.02
Contact with live poultry bought from LPM	4/5 (80)	3/5 (60)	2.7 (.16–45.1)	.50 ^e
Slaughtered live poultry bought from LPM	5 (6)	5 (2)	3.9 (1.1–13.4)	.03
Contact with fresh slaughtered poultry bought from LPM	3 (4)	24 (7)	0.48 (.14–1.6)	.24
Contact with frozen poultry bought from LPM	2 (2)	27 (8)	0.26 (.06–1.1)	.07
Indirect contact ^f with backyard poultry	19/24 (79)	34/48 (71)	1.1 (.25–4.9)	.89
Other exposures, n (%)				
Having a household member visit a LPM ^g	33 (39)	116 (35)	1.2 (.71–2.0)	.49
Visited other house where poultry was raised ^h	15 (18)	47 (14)	1.6 (.68–3.7)	.29
Having contact with a poultry worker	10 (12)	18 (5)	2.8 (1.1–6.8)	.03
Exposure to person with acute respiratory illness	3 (4)	16 (5)	0.70 (.20–2.5)	.58

Boldface indicates statistical significance with $P < .05$, and those variables with $P < .10$ were included in multivariate analyses for the initial model.

Abbreviations: CI, confidence interval; LPM, live poultry market; mOR, matched odds ratio; Ref, reference category.

^a All exposures were defined as within the 10 days before the case illness onset date.

^b A univariable analysis of risk factors was conducted among the 18 cases who did not visit a LPM and 72 matched controls. Only having a household member visit a LPM was significantly associated with increased risk of infection with H7N9 virus (mOR, 9.55; 95% CI, 1.9–47.2).

^c Direct contact was defined as physical contact with poultry or related biological matter, such as blood, internal organs, eggs, secretions, feces, or poultry cages.

^d Fresh slaughtered poultry was poultry sold in LPM after being slaughtered in the central processing factory on the same day, usually without frozen storage.

^e Nonconditional logistical regression was used due to the small sample size.

^f Indirect contact was defined as having no physical contact with poultry but being within a distance <1 meter of poultry.

^g Having contact with a poultry worker was defined as direct contact with a poultry worker regardless of whether the case/control had also visited a LPM.

^h Visiting another house where poultry was raised was defined as visiting such a house regardless of whether the case/control also raised backyard poultry at home.

Underlying Medical Conditions and Behaviors

A statistically significantly higher proportion of cases than controls had ≥ 1 chronic disease (46% vs 25%; matched odds ratio [mOR], 3.2; 95% confidence interval [CI], 1.8–5.7) (Table 2). Cases were significantly more likely than controls to have chronic obstructive pulmonary disease, other pulmonary diseases including tuberculosis and asthma, cardiovascular disease, or diabetes, and were more likely to be taking immunosuppressive medications. We did not identify a significant difference in obesity between cases and controls.

Other statistically significant differences between cases and controls included being a current/previous smoker and hand-washing behavior (Table 2). Controls were more likely than

cases to wash hands often after contact with poultry and to use soap when washing hands. The proportion of current/previous smokers among controls (40%) was significantly higher than among cases (25%) (mOR, 0.32; 95% CI, .16–.65).

Exposures

Cases were more likely than controls to have visited a LPM in the 10 days before the case's illness onset (79% vs 44%; mOR, 9.2; 95% CI, 4.3–20.0); however, among cases and controls who had visited a LPM at least once during this timeframe, there was no significant difference in the frequency of their visits (Table 3). Among those who had visited a LPM, the proportion of those who had passed by a live poultry stall without stopping at a stall

was similar among cases and controls (37% vs 42%), whereas more cases than controls had stopped at a live poultry stall to look at, select, or buy poultry (48% vs 24%; mOR, 3.6; 95% CI, 1.6–7.9). Cases were more likely than controls to have had direct contact with live poultry (52% vs 22%; mOR, 3.4; 95% CI, 2.7–16.6) at a LPM. Thirty-one cases and 36 controls provided information regarding exposures to slaughtering or defeathering; no significant difference in exposure to a live poultry slaughtering stall or a defeathering machine was observed. There was no significant difference in indirect contact with poultry at a LPM between cases and controls.

Twice as many cases as controls had raised backyard poultry at home (28% vs 14%, $P < .01$). A nonconditional logistical regression analysis stratified by visiting a LPM showed that the proportion of cases raising backyard poultry at home was significantly higher than that of controls in both those subjects who had visited a LPM and those who had not (24% vs 12% among those who had visited a LPM; OR, 2.3; 95% CI, 1.1–4.8; 44% vs 16% among those who had not visited a LPM; OR, 4.2; 95% CI, 1.5–11.4). Cases were more likely than controls to have direct contact with backyard poultry (54% vs 29%; mOR, 5.0; 95% CI, 1.3–18.9). Five (21%) of 24 cases with backyard poultry reported that their poultry was purchased at a LPM within 2 months before illness onset, compared with 5 (10%) of 48 controls ($P = .37$). A higher proportion of cases than controls had slaughtered live poultry bought from a LPM at home (6% vs 2%; mOR, 3.9; 95% CI, 1.1–13.4).

Among the other exposures investigated, including visiting other houses where poultry was raised, having contact with a

poultry worker, exposure to a person with acute respiratory illness, and having a household member visit a LPM, cases were more likely than controls to have contact with a poultry worker (12% vs 5%; mOR, 2.8; 95% CI, 1.1–6.8).

Multivariate Analysis of Risk Factors

All variables included in the final multivariable model are listed in Table 4. Visiting a LPM in the 10 days before case's illness onset (adjusted OR [aOR], 6.3; 95% CI, 2.6–15.3) remained significantly associated with increased risk of disease. Whereas visiting a LPM, both stopping at a live poultry stall (aOR, 2.7; 95% CI, 1.1–6.9) and having direct contact with poultry (aOR, 4.1; 95% CI, 1.1–15.6), was a risk factor. In addition, raising backyard poultry at home (aOR, 7.7; 95% CI, 2.0–30.5) was associated with increased risk of illness in the final multivariable analysis, and having direct contact with backyard poultry (aOR, 4.9; 95% CI, 1.1–22.1) was also associated with increased risk of illness.

Another factor that remained significant was having ≥ 1 chronic diseases (aOR, 3.1; 95% CI, 1.5–6.5). Being a current/previous smoker (aOR, 0.32; 95% CI, .13–.79) was associated with decreased odds of disease in the final multivariable analysis. Smoking no longer had a significant protective effect when cases and controls were stratified by proxy use (Supplementary Table 3).

DISCUSSION

Our matched case-control study of the third wave of A(H7N9) virus infections confirmed that LPMs remain a major source of human infection with avian influenza A(H7N9) and that underlying chronic medical conditions increase risk of symptomatic infection. More importantly, in contrast to studies conducted when the virus first emerged in 2013 [4–8], we identified that raising and having direct contact with backyard poultry was also associated with increased risk of infection. These findings suggest that the epidemiology of this emerging infection is shifting, with important implications for the control of this disease.

In our study, 24 (28%) cases and 48 (14%) controls stated that they raised backyard poultry at home. Both stratified univariable analysis and multivariable analysis determined that raising backyard poultry was one of the factors associated with increased risk of illness. Raising backyard poultry was not determined to be a risk factor for illness in the prior large case-control study of A(H7N9) virus infections, which used similar methods and questionnaires to the current study [6]. However, backyard poultry exposure has been associated with A(H5N1) virus infection, which has been identified in China primarily in rural areas [14]. According to prior epidemiological analyses of A(H7N9) cases, although visiting a LPM was identified as the key risk factor for infection, the proportion of cases living in rural settings has increased with each subsequent wave

Table 4. Multivariable Analysis of Risk Factors for Infection With Influenza A(H7N9): A Case-Control Study Matched by Age, Sex, and Location in China, October 2014 to April 2015

Risk Factor	Adjusted Odds Ratio	95% CI	<i>P</i> Value
Visiting a LPM ^a	6.3	2.6–15.3	<.01
Stopping at a live poultry stall	2.7	1.1–6.9	.04
Direct contact with poultry in a LPM ^b	4.1	1.1–15.6	.04
Raised backyard poultry at home	7.7	2.0–30.5	<.01
Direct contact with backyard poultry	4.9	1.1–22.1	.04
≥ 1 chronic disease ^c	3.1	1.5–6.5	<.01
Current/previous smoker ^d	0.32	.13–.79	.01

Boldface indicates statistical significance with $P < .05$, and those variables with $P < .10$ were included in multivariate analyses for the initial model.

Abbreviations: CI, confidence interval; LPM, live poultry market.

^a Visiting a LPM in the 10 days before case illness onset.

^b Direct contact with poultry in a LPM included direct contact with live poultry or fresh slaughtered poultry in a LPM.

^c Chronic diseases included chronic obstructive pulmonary disease, other pulmonary diseases including tuberculosis and asthma, cardiovascular disease, diabetes, kidney disease, and rheumatoid arthritis. All chronic diseases were diagnosed by medical institutions at the county level or above. Hypertension and hypercholesterolemia were not included as chronic diseases in this analysis.

^d We defined smoking status by asking participants to choose one of the following categories: "never smoked", "currently smoke", or "smoked in past, but quit". Those who chose "currently smoke" or "smoked in past, but quit" were defined as current/previous smokers.

of the outbreak [6, 15], possibly due to increased exposure to backyard poultry among residents of rural areas [16]. The higher proportion of rural cases identified in later waves suggests that the epidemiology of A(H7N9) virus might be changing, which has important implications for the control of this disease. Our study also suggests that infection among poultry is not limited to LPMs and may be increasing among backyard flocks, indicating that intensified surveillance of these flocks is warranted.

Because A(H7N9) virus does not usually cause symptomatic illness in poultry, it is difficult to detect and stop the silent spread of the virus among poultry populations. Despite the implementation of control measures, human infections with A(H7N9) virus spread geographically in mainland China from the first to the second and third waves of the outbreak [15]. Although a large proportion of poultry is produced and distributed throughout China through integrated industrial production systems that bypass LPMs, LPMs have been identified as important reservoirs and amplifiers of avian influenza virus, including A(H7N9) [4, 5, 9, 17, 18], and sources for the persistence and reintroduction of infection [19]. Most measures to control and prevent avian influenza outbreaks, such as LPM closure, have been implemented in urban areas, where poultry production and distribution involves less movement between the markets and backyard flocks than seen in rural settings. Still, raising backyard poultry in rural areas is an integral part of one of China's 2 largest poultry-producing systems [17], and the possibility of spread from poultry in urban LPMs to poultry in rural settings should be considered. In general, poultry sold in LPMs are provided by large commercial companies or individual commercial poultry traders. Some commercial companies have their own centralized large-scale poultry farms. As in other developing countries, however, some companies and almost all individual traders purchase poultry raised in flocks managed at the individual household or village level in rural areas [20]. At the same time, rural households that produce poultry also consume poultry [21], and they may consume poultry that comes from LPMs. Thus, there is a circular path of poultry trade: from LPMs to backyard flocks, back to LPMs. This urban-rural intermingling of poultry and what appears to be a newly increased risk of human infection from backyard poultry flocks highlights the need to strengthen surveillance for avian influenza in rural areas and perhaps establish pilot interventions to prevent transmission of avian influenza to and from backyard flocks. However, for disease control, closing LPMs in large cities may still offer the most practical solution given the vast numbers and remote locations of backyard poultry farms in small towns and rural villages throughout China.

Consistent with prior studies [4–8], visiting a LPM was associated with increased risk of disease, but there was no dose-response relationship between the frequency of LPM visits and the risk of infection, although we likely lacked the sufficient

power to detect such a relationship. In our study, more detailed risk behaviors during LPM visits were identified. Among those who visited a LPM, stopping at a live poultry stall was identified as a risk factor, whereas passing by a stall without stopping was not associated with increased risk of illness. However, our findings indicate that even though there appears to be some distance around the live poultry stall in which the risk of transmission is increased, merely going to a LPM without having direct contact with poultry or stopping at a live poultry stall increased infection risk.

Having ≥ 1 underlying medical condition was identified as a risk factor for infection with A(H7N9) virus. This finding is consistent with prior studies on A(H7N9), H5N1, and A(H1N1)pdm09 viruses that found that underlying medical conditions were associated with increased risk of infection and illness severity [6–8, 13, 22–25].

Our study has several limitations. First, although we did not identify any significant differences, other than sex, between the included and excluded cases, analyses of specific factors such as exposure to slaughtering and defeathering machines had limited power to detect an association with A(H7N9) virus infection. Second, although our study was conducted in a timely manner during the third wave of A(H7N9) virus, recall bias may still have decreased data quality because of the lag between illness and interviews. When this lag was long, interview questions could be answered using the original field investigation report as a supplementary source of information for cases, but not for controls, and thus documenting specific exposures may have been easier for cases than controls. Although there were no significant observable differences between included and excluded fatal cases, 62 (69%) of the 90 fatal cases were excluded because of insufficient information. Our study may not have sufficient power to detect risk factors specific to fatal cases. In addition, the use of proxies was more common among cases (31%) than controls (10%). These limitations may have impacted our study's smoking-related findings. We were surprised to find that current/previous smoking was associated with decreased risk of illness in the univariable and multivariable analyses. However, smoking no longer had a significant protective effect when cases and controls were stratified by proxy use. Proxies may have been more likely to classify a respondent as nonsmoking. Furthermore, we were unable to collect smoking information from excluded fatal cases, and we do not know whether a higher proportion of these fatal cases were current/previous smokers than nonfatal cases, which could be a potential source of bias. Although it was not verified in this study, numerous prior studies have identified smoking as a risk factor for influenza infection and increased severity of illness [26, 27].

CONCLUSIONS

In addition to risk factors identified in prior studies such as direct contact with poultry in LPMs, visiting LPMs, and having underlying medical conditions, we identified 2 new factors

associated with increased risk of infection with A(H7N9) virus: raising backyard poultry at home and having direct contact with backyard poultry. This finding reflects a potential change in the epidemiology of the A(H7N9) virus from a primarily urban outbreak to one that extends into rural settings, and it highlights the need to strengthen surveillance for avian influenza in rural areas and to pilot culturally and economically appropriate interventions aimed at reducing avian influenza transmission among backyard poultry.

Supplementary Data

Supplementary material is available online at *Open Forum Infectious Diseases* online (<http://OpenForumInfectiousDiseases.oxfordjournals.org/>).

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Author contributions. L. Z., R. Q. R., Y. P. Z., Z. J. F., and Q. L. conceived, designed and supervised the study; F. H. helped with study conception and design; J. M. O., M. K., X. X. W., X. H., X. Q. L., Q. L. S., Y. C. H., B. L., S. G. W., Y. L. W., H. T. S., Y. J. Z., S. P. T., C. Y. C., L. H. X., D. W., S. G. Z., S. Z. Z., and N. J. X. assisted in data collection; T. C. and Y. L. S. assisted in specimens collection and laboratory testing; L. Z. and R. Q. R. analyzed the data; C. M. G., S. Z. Z., and F. H. assisted in data analysis; L. Z. finalized the analysis and wrote the draft of manuscript; C. M. G., S. Z. Z., F. H., Z. J. F., and Q. L. helped interpret the findings; C. M. G., S. Z. Z., and F. H. commented on and helped revise drafts of the manuscript. L. Z. is guarantor.

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