Risk Factors for Influenza A(H7N9) Disease—China, 2013

Bo Liu,1,a Fiona Havers,2,a Enfu Chen,3,a Zhengan Yuan,4,a Hui Yuan,5 Jianming Ou,6 Mei Shang,6 Kai Kang,7 Kaiju Liao,1 Fuqiang Liu,8 Dan Li,1 Hua Ding,9 Peng Zhang,1 Weiping Zhu,10 Fan Ding,1 Hualin Su,13 Rui Wang,1 Jian Cai,3 Yang Cao,1 Xianjun Wang,14 Tian Bai,15 Jianjun Wang,16 Zijian Feng,1 Yanping Zhang,1 Marc-Alain Widdowson,17 and Qun Li1

1Public Health Emergency Center, Chinese Center for Disease Control and Prevention, Beijing; 2Epidemic Intelligence Service assigned to the Influenza Division, US Centers for Disease Control and Prevention, Atlanta, Georgia; 3Influenza Division, Zhejiang Provincial Center for Disease Control and Prevention, Hangzhou, 4Shanghai Municipal Center for Disease Control and Prevention, Shanghai, 5Fujian Provincial Center for Disease Control and Prevention, Fuzhou, 6China Office, US Centers for Disease Control and Prevention, Beijing, 7Hebei Provincial Center for Disease Control and Prevention, Shijiazhuang, 8Hunan Provincial Center for Disease Control and Prevention, Changsha, 9Zhejiang Hangzhou Center for Disease Control and Prevention, Hangzhou, 10Shanghai Pudong New Area Center for Disease Control and Prevention, Shanghai, 11Hunan Huzhou Center for Disease Control and Prevention, Hangzhou, 12Jiangxi Provincial Center for Disease Control and Prevention, Nanchang, 13Shanghai Minhang District Center for Disease Control and Prevention, Jinan City, 14Institute for Viral Disease Control and Prevention, Chinese Center for Disease Control and Prevention, Beijing, and 15Anhui Provincial Center for Disease Control and Prevention, Hefei, China; and 16Influenza Division, US Centers for Disease Control and Prevention, Atlanta, Georgia

(See the Editorial Commentary by Vong on pages 795–7.)

Background. The majority of human cases of novel avian influenza A(H7N9), which emerged in China in spring 2013, include reported exposure to poultry. However, specific host and exposure risk factors for disease are unknown, yet critical to design prevention measures.

Methods. In April–June 2013, we conducted a case-control study in 8 Chinese provinces. Patients with laboratory-confirmed A(H7N9) (n = 89) were matched by age, sex, and neighborhood to controls (n = 339). Subjects completed a questionnaire on medical history and potential exposures, including poultry markets and other poultry exposure. We used conditional logistic regression to calculate matched and adjusted odds ratios (ORs) for the association of A(H7N9) virus infection with potential risk factors.

Results. Fifty-five percent of patients compared with 31% of controls reported any contact with poultry (matched OR [mOR], 7.8; 95% confidence interval [CI], 3.3–18.8). Sixty-seven percent of patients compared with 35% of controls visited a live poultry market (mOR, 5.4; CI, 3.0–9.7). Visiting live poultry markets increased risk of infection even after adjusting for poultry contact and other confounders (adjusted OR, 3.4; CI, 1.8–6.7). Backyard poultry were not associated with increased risk; 14% of cases did not report any poultry exposure or market visit. Obesity (mOR, 4.7; CI, 1.8–12.4), chronic obstructive pulmonary disease (mOR, 2.7; CI, 1.1–6.9), and immunosuppressive medications (mOR, 9.0; CI, 1.7–47.2) were associated with A(H7N9) disease.

Conclusion. Exposures to poultry in markets were associated with A(H7N9) virus infection, even without poultry contact. China should consider permanently closing live poultry markets or aggressively pursuing control measures to prevent spread of this emerging pathogen.

Keywords. avian influenza; avian influenza A(H7N9) virus; China; H7N9.

Between March 2013 and 21 April 2014, 427 cases of human infection with the novel avian influenza A(H7N9) virus were reported in mainland China, the Hong Kong Special Administrative Region, Taiwan, and Malaysia, all with mainland China as the presumed place of exposure [1] (unpublished data, Chinese
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METHODS

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upsurge in cases began in October 2013, indicating that the

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epidemiologic features, such as the predominance of elderly men,

remained unexplained and may be due to environmental or host

factors such as underlying disease or behaviors that lead to either

increased risk of infection or severe disease [6, 10–12].

From April to June 2013, the Chinese CDC and provincial

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provinces. After sporadic cases occurred in summer 2013, an

upsurge in cases began in October 2013, indicating that the

virus is still circulating widely in China [1, 9, 13]. Understanding

precise risk factors for A(H7N9) virus infection will inform

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In mainland China, all A(H7N9) cases confirmed by reverse tran-
scription polymerase chain reaction are reported to the China

CDCs [14]. All 102 cases identified from 30 March to 28 May 2013,

from 8 provinces (Shanghai, Anhui, Fujian, Henan, Hunan, Jiang-

xi, Shandong, and Zhejiang) were eligible for inclusion.

Participants

For each case, we aimed to select 4 controls, matched on loca-
tion (same village or community as the case in the 6 months
preceding symptom onset), age (±3 years, but ±5 years if case
was >85 years), and sex.

For urban cases, we randomly selected matched controls from
local population registries. Additional controls were randomly se-
plicated if those initially selected could not be contacted or did not
consent. If no registry was available, we selected households on
randomly selected floors in buildings immediately adjacent to
the case’s home. If households contained no eligible or willing par-
ticipants, we approached adjacent households. For rural cases, we
randomly selected 4 controls from village registries. If the case’s
village lacked controls, we used the adjacent village to the north.

Data Collection

China CDC study investigators, who oversaw quality control,
trained interviewers at provincial CDCs, who then trained
additional interviewers from city or county CDCs. They used
a standard questionnaire, piloted in Henan province, to conduct
face-to-face interviews to collect 2 types of data.

First, interviewers collected information on demographic,
medical history, health behaviors, and backyard, domestically
raised poultry and poultry consumption in the calendar
month prior to symptom onset of case for both cases and
matched controls. For medical history, interviewers examined
cases’ and controls’ medical record handbooks, kept by indi-
viduals in China. Body mass index (BMI) was based on self-
reported weight and height, with obesity defined as those
aged ≥18 years with a BMI ≥30 kg/m² and those aged <18
years with a BMI-for-age ≥95th percentile [15, 16]. Second,
interviewers gathered information regarding risk factors for in-
fection, including exposures in the 10 days prior to illness onset.
Control subjects were interviewed about exposures during the
same calendar period as the matched case. For cases <12
years of age, those who had died, or those who could not be in-
viewed because of illness, a proxy was selected from adult
family members in the same household to fill out the question-
aire on the study subject’s behalf. Age- and sex-associated
poultry exposures in the control population, a sample of the
population at risk for infection, were examined separately.

Exposure was any contact or presence in location with birds.
Contact was either indirect contact (<1 m of poultry, but no
physical contact) or direct contact (physical contact with poul-
try or related biological matter [includes blood, internal organs,
eggs, secretions, feces, or poultry cages]). Direct contact was
subdivided into contact with live poultry prior to slaughter
(no contact with internal organs or blood) and contact during
slaughtering and processing. Contact with live poultry prior to
slaughter includes feeding, capturing, administering medicine,
collecting eggs, and cleaning poultry cage; contact during
slaughtering and processing includes bloodletting, scalding, defeat-
hering, cutting open the chest cavity, evisceration, cleaning in-
ternal organs, and slicing poultry meat. Possible locations for
exposure include the home, live poultry markets, other farm or
poultry-raising household, or aquatic environments with poultry
or wild birds, such as lakes or rice paddies. Live poultry markets
were categorized as wholesale markets, open air retail markets, or
semi-enclosed/enclosed retail markets, which are permanent
structures with a roof and some walls. Backyard poultry was de-
defined as poultry raised by the subject at his or her home. Subjects
were asked about behaviors during poultry contact, such as wear-
ing protective equipment and hand washing.

The China CDC Institutional Ethics Review Board approved
the protocol. Written informed consent was obtained from
adults in the study, from legal guardians for those <18 years
of age, or from family member proxies for deceased patients
or those too ill to participate.

Serological Testing

Serum specimens were collected from controls at the time of in-
terview. Serologic testing was performed at the National Influ-
zenza Center (China CDC, Beijing) as described elsewhere [17].
The antibody response to A(H7N9) virus was screened by a
hemagglutination inhibition (HI) assay using horse red blood cells, and any sera with a HI titer of ≥1:20 was confirmed by microneutralization (MN) assay. MN titer of ≥1:20 was considered seropositive for A(H7N9) virus.

**Statistical Analysis**

We used Epidata for data entry and SAS software version 9.1 for data analysis and employed conditional logistic regression for both univariate and multivariate analysis. We used Fisher exact test when appropriate. For the multivariable models, health conditions with \( P < .1 \) level of significance were included. For other risk factors, variables were chosen based on biologic plausibility and a priori hypotheses.

**RESULTS**

We included 89 (87%) of the 102 confirmed cases of A(H7N9) infection reported in 8 provinces between March 30 and June 4. Thirteen cases, or family members of deceased cases, refused to participate, but these cases did not differ by sex (\( P = .78 \)) or age (\( P = .88 \)) from included cases. Three cases were identified as epidemiologically linked to another case and possibly resulted from human-to-human transmission [9].

We identified 3 or 4 age-, sex-, and neighborhood-matched controls for 76 (85%) cases. Three cases had 2 controls identified, and 10 had >4 controls. Four of the 340 initial controls had an HI assay titer of 1:20. On MN testing, only 1 had a positive MN titer (1:40) and was thus excluded; 339 controls were included in the analysis. Ninety-three percent of matched controls were interviewed within 2 days of their respective case (range, 0–6 days). Cases and controls were similar in sex and median age (71% vs 68% male and 64 vs 63 years, respectively; Table 1). Six (7%) cases had occupational poultry exposure, compared with 3 controls (0.9%). Other demographic features between the groups were similar. A family member served as proxy for 48 (54%) cases and 14 (4%) controls; results including underlying health conditions and exposure variables were unchanged when we limited the analysis only to cases interviewed directly (data not shown). The median time between disease onset and interview for cases was 34 days (range, 4–101 days). Results for health conditions and exposures were unchanged when a sensitivity analysis was performed examining the results among the cases and controls who had interviews performed ≤34 days and >34 days since the case symptom onset (data not shown).

Cases were more likely than controls to have ≥1 underlying condition (46% vs 33%; matched odds ratio \( \text{mOR}, 1.9; 95\% \text{ CI}, 1.1–3.3 \)), and, specifically, were more likely to have chronic obstructive pulmonary disease (COPD) (10% vs 5%; mOR, 2.7; 95% CI, 1.1–6.9) (Table 2). No significant difference in other health conditions was identified. Cases were more likely to be obese (12% vs 3%; mOR, 4.7; 95% CI, 1.8–12.4) and on immunosuppressive medications (among cases, these were cancer chemotherapy, dexamethasone, prednisone or prednisolone; indications included lymphoma, renal transplant, and rheumatoid arthritis) (5.6% vs 0.6%; mOR, 9.0; 95% CI, 1.7–47.2). Smoking habits were similar between cases and controls.

Cases were more likely than controls to have poultry exposure (Table 3). Compared with those with no reported poultry exposure (14% of cases vs 29% of controls), those who reported being in any location with poultry, but having no contact with poultry were at increased risk of disease (mOR, 2.3; 95% CI, 1.0–5.3). This risk further increased among those who additionally reported either direct or indirect contact with poultry (mOR, 7.8; 95% CI, 3.3–18.8). Twelve cases reported no exposure to poultry; none were epidemiologically linked to other cases. Of these, 7 (58%) had data collected by proxy, a similar

| Table 1. Demographic Characteristics of Influenza A(H7N9) Cases and Controls Matched by Age, Sex, and Location |
|---|---|---|
| **Demographic Characteristics** | Cases (n = 89), No. (%) | Controls (n = 339), No. (%) | **\( P \)** Value |
| **Interviewed by proxy** | 48 (54) | 14 (4) | <.01 |
| **Age, y, median (range)** | 64 (2.5–91) | 63 (2–92) | .87* |
| **Age group, y** | | | |
| <18 | 3 (3) | 10 (3) | |
| 18–59 | 34 (38) | 134 (40) | .15 |
| 60–79 | 41 (46) | 165 (49) | |
| ≥80 | 11 (12) | 30 (9) | |
| **Female sex** | 26 (29) | 108 (32) | .99 |
| **Education** | | | |
| Illiterate | 13/86 (15) | 53/325 (16) | |
| Elementary school | 21/86 (24) | 103/325 (32) | .13 |
| High school | 44/86 (51) | 141/325 (43) | |
| College and above | 8/86 (9) | 28/325 (9) | |
| **Average household annual income per capita** | | | |
| <10 000 yuan | 32/88 (36) | 113/337 (34) | |
| 10 000–19 999 yuan | 17/88 (19) | 70/337 (21) | .56 |
| 20 000–29 999 yuan | 16/88 (18) | 56/337 (17) | |
| ≥30 000 yuan | 23/88 (26) | 98/337 (29) | |
| **No. of household members, mean (SD)** | 3.33 (1.7) | 3.58 (1.7) | .64* |
| **Poultry worker** | 6 (6) | 3 (1) | <.01 |
| **Urban residence** | 61 (69) | 229 (67) | .99 |

The \( \chi^2 \) test was used except when noted otherwise. The boldface values indicate \( P < .05 \).

Abbreviation: SD, standard deviation.

* Wilcoxon rank-sum test.

† One yuan = US$0.16.

‡ Paired \( t \) test.

§ Poultry workers include those who derive at least half of their income from work involving poultry, including raising, butchering, trading, and transporting live poultry.
Abbreviations: CI, confidence interval; COPD, chronic obstructive pulmonary disease; OR, odds ratio; Ref, reference exposure category.

The boldface values indicate P < .05.

Table 2. Underlying Health Conditions and Behaviors Among Influenza A(H7N9) Cases and Controls Matched by Age, Sex, and Location

<table>
<thead>
<tr>
<th>Health Condition/Behavior</th>
<th>Cases (n = 89), No. (%)</th>
<th>Controls (n = 339), No. (%)</th>
<th>Matched OR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥1 chronic diseasea</td>
<td>41 (46)</td>
<td>113 (33)</td>
<td>1.9 (1.1–3.3)</td>
<td>.01</td>
</tr>
<tr>
<td>COPD</td>
<td>9 (10)</td>
<td>16 (5)</td>
<td>2.7 (1.1–6.9)</td>
<td>.04</td>
</tr>
<tr>
<td>Other pulmonary disease (tuberculosis, asthma)</td>
<td>0 (0)</td>
<td>8 (2)</td>
<td>. . .</td>
<td>.99</td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>17 (19)</td>
<td>46 (14)</td>
<td>1.5 (0.8–3.0)</td>
<td>.22</td>
</tr>
<tr>
<td>Diabetes</td>
<td>13 (15)</td>
<td>34 (10)</td>
<td>1.6 (0.77–3.3)</td>
<td>.22</td>
</tr>
<tr>
<td>Chronic kidney or liver disease</td>
<td>3 (4)</td>
<td>14 (4)</td>
<td>0.8 (0.2–3.0)</td>
<td>.79</td>
</tr>
<tr>
<td>Cancer</td>
<td>1 (1)</td>
<td>4 (1)</td>
<td>0.9 (0.1–8.6)</td>
<td>.96</td>
</tr>
<tr>
<td>Other chronic diseases</td>
<td>9 (10)</td>
<td>37 (11)</td>
<td>1.0 (0.4–2.1)</td>
<td>.90</td>
</tr>
<tr>
<td>Immunosuppressive medicationsb</td>
<td>5 (6)</td>
<td>2/335 (1)</td>
<td>9.0 (1.7–47.2)</td>
<td>.01</td>
</tr>
<tr>
<td>Obesityc</td>
<td>10/87 (12)</td>
<td>9/338 (3)</td>
<td>4.7 (1.8–12.4)</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Pregnant</td>
<td>1 (1)</td>
<td>0 (0)</td>
<td>. . .</td>
<td>. . .</td>
</tr>
<tr>
<td>Smoking history</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never smoked</td>
<td>54/88 (61)</td>
<td>187 (55)</td>
<td>Ref</td>
<td></td>
</tr>
<tr>
<td>Previous smoker</td>
<td>14/88 (16)</td>
<td>44 (13)</td>
<td>0.95 (0.4–2.0)</td>
<td>.89</td>
</tr>
<tr>
<td>Current smoker</td>
<td>20/88 (23)</td>
<td>108 (32)</td>
<td>0.58 (0.3–1.1)</td>
<td>.10</td>
</tr>
</tbody>
</table>

The values indicate the proportion of cases or controls with the specified health condition or behavior. The Matched OR is calculated for the matched cohort. P-values are calculated using the chi-square test or Fisher's exact test as appropriate.

a Disease diagnosed by medical institutions at county level or above. Excludes hypertension and hypercholesterolemia.

b Includes chronic use of corticosteroids (prednisone, dexamethasone, and prednisolone) and chemotherapy.

c Adults are considered obese if body mass index (BMI) ≥30 kg/m²; for children, if BMI-for-age ≥95th percentile.

Proportion as the cases with poultry exposure (41/77 [53%]); 9 (75%) were from a single urban site. Poultry consumption did not increase risk.

Cases were more likely than controls to have poultry contact at home (45% vs 28%; mOR, 3.9; 95% CI, 2.0–7.5). However, cases and controls were similarly likely to have been exposed to only backyard poultry (23% vs 23%; mOR, 1.23; 95% CI, .6–2.5), whereas cases were significantly more likely than controls to have had contact at home with poultry traded in markets (22% vs 4.7%; mOR, 6.3; 95% CI, 2.9–13.7), suggesting that market and not backyard poultry increased risk. More cases (9%) than controls (1%) reported having backyard poultry that had died from disease in the month prior to symptom onset (mOR, 9.4; 95% CI, 2.5–36.1). Pet bird ownership was not associated with disease, nor was poultry contact in environments besides LBMs, such as farms or lakes with water fowl (mOR, 1.7; 95% CI, 0.5–5.6).

Cases were more likely than controls to visit LBMs (67% vs 35%; mOR, 5.4; 95% CI, 3.0–9.7). Going to an LBM but having no poultry contact was associated with increased risk of infection (mOR, 3.0; 95% CI, 1.6–5.7); this risk tripled if, in addition, direct or indirect contact with poultry was reported at an LBM (mOR, 10.4; 95% CI, 4.9–22.0). Increased frequency of market visits was not associated with increased risk of infection (data not shown). Among 81 cases for whom this information was available, of 52 who went to an LBM, 44% went only once in the 10 days prior to symptom onset.

We examined whether slaughtering poultry posed an increased risk over handling poultry and the various tasks of poultry husbandry. Although this was difficult to assess as behaviors were correlated, slaughtering poultry and exposure to internal organs was not any more associated with increased risk than was direct contact prior to the slaughtering process (mOR, 3.1 vs 3.6; Table 3). Although poultry contact was associated with increased risk of disease, there was no difference between direct and indirect contact (P = .24, data not shown), and no particular type of direct contact was associated with significantly elevated risk (Supplementary Table 1).

Among those with poultry contact, most were exposed to chickens (73% for cases vs 72% for controls), followed by ducks, pigeons, quail, and geese. After controlling for chicken contact, we found no association between contact with other types of birds and increased risk of infection (P = .92, data not shown). Eighty-one percent of cases with available information on market type had visited semienclosed/enclosed retail markets. We therefore could not distinguish between the risk of going to a semienclosed/enclosed market and the risk of going to LBMs in general. However, controlling for LBM exposure, we were unable to identify any association with visiting other types of markets (wholesale and open air retail markets) and increased risk (P = .26, data not shown). Among only those with direct contact, cases used soap to wash hands after contact less frequently than controls, indicating that this behavior was
associated with decreased risk of infection (mOR, 0.12; 95% CI, .04–.35). Other potentially protective behaviors, such as wearing masks, gloves, or goggles, were not significantly more likely to be found in cases than controls.

We wanted to examine whether market exposures explained the predominance of elderly men among cases, but could not compare cases directly to controls given sex and age matching.

Examining controls only, men were no more likely to visit LBMs than women (31% vs 42%, P = .058; age-stratified results: Supplementary Table 2). The difference was more pronounced in urban areas: 32% of men visited LBMs vs 53% of women (P < .01).

In the final multivariable analysis comparing cases and controls, COPD (adjusted OR [aOR], 5.0; 95% CI, 1.7–14.4),

<table>
<thead>
<tr>
<th>Exposure</th>
<th>Cases (n = 89), No. (%)</th>
<th>Controls (n = 340), No. (%)</th>
<th>Matched OR (95% CI)</th>
<th>PValue</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type of exposure&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Poultry consumption</td>
<td>40/88 (46)</td>
<td>144/339 (42)</td>
<td>1.19 (.7–2.0)</td>
<td>.52</td>
</tr>
<tr>
<td>Poultry exposure and contact</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No poultry contact and not in any location with poultry&lt;sup&gt;b&lt;/sup&gt;</td>
<td>12/89 (14)</td>
<td>98/339 (29)</td>
<td>Ref</td>
<td>. . .</td>
</tr>
<tr>
<td>In location with poultry, but no direct/indirect contact&lt;sup&gt;c&lt;/sup&gt;</td>
<td>28/89 (32)</td>
<td>135/339 (40)</td>
<td>2.3 (1.0–5.3)</td>
<td>.059</td>
</tr>
<tr>
<td>Any direct or indirect contact</td>
<td>49/89 (55)</td>
<td>106/339 (31)</td>
<td>7.8 (3.3–18.8)</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Type of direct contact behaviors</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Poultry contact prior to slaughter&lt;sup&gt;d&lt;/sup&gt;</td>
<td>27/89 (30)</td>
<td>62/339 (18)</td>
<td>3.6 (1.7–7.3)</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Poultry contact during slaughtering or processing&lt;sup&gt;e&lt;/sup&gt;</td>
<td>22/89 (25)</td>
<td>37/339 (11)</td>
<td>3.1 (1.7–5.9)</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Direct contact by type of poultry</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chicken</td>
<td>36/89 (40)</td>
<td>76/339 (22)</td>
<td>3.5 (1.9–6.4)</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Nonchicken&lt;sup&gt;f&lt;/sup&gt;</td>
<td>14/89 (16)</td>
<td>33/339 (10)</td>
<td>1.8 (0.8–3.8)</td>
<td>.13</td>
</tr>
<tr>
<td>Location of poultry exposure</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Home</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exposure to backyard poultry&lt;sup&gt;g&lt;/sup&gt;</td>
<td>25/89 (28)</td>
<td>82/339 (24)</td>
<td>2.4 (1.1–5.6)</td>
<td>.038</td>
</tr>
<tr>
<td>Contact at home</td>
<td>40/88 (45)</td>
<td>95/339 (28)</td>
<td>3.9 (2.0–7.5)</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Contact at home only with backyard poultry</td>
<td>20/88 (23)</td>
<td>79/339 (23)</td>
<td>1.2 (6–2.5)</td>
<td>.56</td>
</tr>
<tr>
<td>Contact at home with poultry traded in markets</td>
<td>19/88 (22)</td>
<td>16/339 (5)</td>
<td>6.2 (2.9–13.7)</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Sick or dying backyard poultry&lt;sup&gt;h&lt;/sup&gt;</td>
<td>8/89 (9)</td>
<td>5/339 (1)</td>
<td>9.4 (2.5–36.1)</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Live bird market</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Went to LBM</td>
<td>60/89 (67)</td>
<td>117/339 (35)</td>
<td>5.4 (3.0–9.7)</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>LBMB exposure or contact</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not in LBM</td>
<td>29/89 (33)</td>
<td>222/339 (65)</td>
<td>Ref</td>
<td></td>
</tr>
<tr>
<td>In LBM but no direct/indirect contact&lt;sup&gt;i&lt;/sup&gt;</td>
<td>29/87 (33)</td>
<td>89/339 (26)</td>
<td>3.0 (1.6–5.7)</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Any direct or indirect contact in LBM&lt;sup&gt;j&lt;/sup&gt;</td>
<td>29/87 (33)</td>
<td>28/339 (8)</td>
<td>10.4 (4.9–22.0)</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Other locations&lt;sup&gt;l&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exposure in other locations</td>
<td>28/88 (32)</td>
<td>126/339 (37)</td>
<td>0.8 (0.4–1.4)</td>
<td>.42</td>
</tr>
<tr>
<td>Contact in other locations</td>
<td>4/88 (5)</td>
<td>9/339 (3)</td>
<td>1.7 (0.5–5.6)</td>
<td>.37</td>
</tr>
</tbody>
</table>

The boldface values indicate P < .05.

Abbreviations: CI, confidence interval; LBM, live bird market; OR, odds ratio; Ref, reference exposure category.

<sup>a</sup> All exposures in 10 days prior to symptom onset unless otherwise noted.
<sup>b</sup> Contact includes direct and indirect contact. Locations include home, markets, poultry farms or breeding centers, pet markets, or aquatic environments with birds.
<sup>c</sup> Direct contact: touching poultry or poultry-related substances such as eggs and feces. Indirect contact: being within 1 m but no direct contact.
<sup>d</sup> Poultry contact prior to slaughter: contact with live poultry only, which includes feeding, capturing, and giving medicine to poultry, as well as collecting eggs and cleaning poultry cages.
<sup>e</sup> Types of contact include bloodletting, scalding/defeathering, evisceration and cleaning of poultry body and organs, and butchering/slicing poultry meat.
<sup>f</sup> Among cases, these included ducks (n = 9), geese (n = 1), pigeons (n = 5), quail (n = 1), and pet birds (n = 1).
<sup>g</sup> Backyard poultry: domestically raised poultry.
<sup>h</sup> In month prior to symptom onset.
<sup>i</sup> Other locations include poultry farms or breeding centers, pet markets, or aquatic environments with birds.
obesity (aOR, 3.7; 95% CI, 1.3–10.8), and immunosuppressive medications (aOR, 7.0; 95% CI, 1.7–44.7) remained significantly associated with increased risk of disease (Table 4). Neither consuming poultry (aOR, 0.72; 95% CI, 0.36–1.4) nor raising backyard poultry (aOR, 1.5; 95% CI, 0.5–4.4) was associated with increased risk of illness. Visiting LBMs (aOR, 3.4; 95% CI, 1.8–6.7) and having poultry contact (aOR, 2.9; 95% CI, 1.3–6.3) were both associated with increased risk of illness, as was having had exposure to sick or dying poultry (aOR, 9.8; 95% CI, 2.2–43.2).

### DISCUSSION

Our case-control study indicates that exposure to poultry from LBMs was the main source of A(H7N9) infection in humans. Overall, 68% of cases visited an LBM or were exposed to market poultry. Importantly, our data also provide clues as to how transmission occurred. Merely being in a location with poultry, such as an LBM, was sufficient for infection, even without direct (touching) or indirect (within 1 m) contact. Poultry contact increased the risk of infection sharply, but we found no evidence that slaughtering and processing poultry posed a greater risk than less intense contact. Furthermore, our data suggest that in contrast with influenza A(H5N1) [18], backyard poultry were unlikely a source of A(H7N9) virus; our initial association of infection with backyard poultry exposure can be explained by exposure to poultry traded at LBMs. We also confirmed that poultry consumption is not a risk factor.

This study was conducted in multiple provinces and included the majority of A(H7N9) cases in the initial wave of the A(H7N9) outbreak. Whereas previous descriptive studies and a case-control study from a single province noted that many patients with A(H7N9) infection had underlying medical conditions [3, 6, 9], we compared cases to controls and identify specific conditions that increase risk of severe disease. We found that COPD, obesity, and use of immunosuppressive medications are associated with increased risk of A(H7N9) disease, although these explain only a fraction of cases.

Our study also used the large population of controls to systematically examine poultry-related behavior among the population at risk for A(H7N9). We showed that men—particularly elderly urban men—did not have more chicken contact, nor did they frequent LBMs more than women, as had been postulated previously [11]. This suggests that sex differences in healthcare-seeking behavior or other host factors, such as higher rates of underlying respiratory disease in Chinese men [19–21], may contribute to the higher prevalence of A(H7N9) infections observed in men, and better explain the predominance of A(H7N9) cases in elderly men than sex differences in opportunities for infection through poultry exposure.

The study’s limitations include its retrospective nature, the time between symptom onset and investigation, and the use of proxies for more than half of cases, which may have led to inaccurate information or recall bias. However, results remained unchanged when we restricted the analysis to only those cases interviewed directly. We also did not assess in detail possible human-to-human transmission; previous epidemiologic investigations indicate that this may have occurred in a 3 cases in this study [9, 22]. Finally, the number of cases with certain underlying health conditions or exposures, such as to specific nonchicken bird species, was small, limiting power to detect their association with infection.

The large number of A(H7N9) human infections in a brief period—for greater than A(H5N1) since it reemerged in 2003—suggests that A(H7N9) is more transmissible to humans than A(H5N1) [23]. Unlike a previous small case-control study conducted in a single province [3], which found an association only between >10 visits to an LBM in the 2 weeks before illness onset and increased risk of A(H7N9) infection, we show that many cases had only a single market exposure prior to infection, and may not have had direct or indirect contact with poultry. These findings are suggestive of transmission through environmental contamination or possible aerosolization of infectious particles. Although further studies are needed to confirm these findings, these are suspected modes of transmission for seasonal influenza [24]; limited airborne transmission of A(H7N9) has been shown in ferret experiments, although these studies do not distinguish

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Adjusted Odds Ratio</th>
<th>95% CI</th>
<th>P Value</th>
<th>Prevalence Among Cases, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>COPD</td>
<td>5.0</td>
<td>1.7–14.4</td>
<td>&lt;.01</td>
<td>10</td>
</tr>
<tr>
<td>Immunosuppressive medication&lt;sup&gt;a&lt;/sup&gt;</td>
<td>7.0</td>
<td>1.1–44.7</td>
<td>.04</td>
<td>6</td>
</tr>
<tr>
<td>Obesity&lt;sup&gt;b&lt;/sup&gt;</td>
<td>3.7</td>
<td>1.3–10.8</td>
<td>.02</td>
<td>12</td>
</tr>
<tr>
<td>Visit live bird market&lt;sup&gt;c&lt;/sup&gt;</td>
<td>3.4</td>
<td>1.8–6.7</td>
<td>&lt;.01</td>
<td>67</td>
</tr>
<tr>
<td>Direct/indirect contact with poultry&lt;sup&gt;d&lt;/sup&gt;</td>
<td>2.9</td>
<td>1.3–6.3</td>
<td>&lt;.01</td>
<td>55</td>
</tr>
<tr>
<td>Raised backyard poultry&lt;sup&gt;c&lt;/sup&gt;</td>
<td>1.5</td>
<td>0.5–4.4</td>
<td>.48</td>
<td>28</td>
</tr>
<tr>
<td>Sick or dying backyard poultry&lt;sup&gt;d&lt;/sup&gt;</td>
<td>9.8</td>
<td>2.2–43.2</td>
<td>&lt;.01</td>
<td>9</td>
</tr>
<tr>
<td>Consumed poultry&lt;sup&gt;c&lt;/sup&gt;</td>
<td>0.7</td>
<td>0.4–1.4</td>
<td>.28</td>
<td>46</td>
</tr>
</tbody>
</table>

The boldface values indicate P < .05.

Abbreviations: CI, confidence interval; COPD, chronic obstructive pulmonary disease.
<sup>a</sup> Includes chronic use of corticosteroids (prednisone, dexamethasone, and prednisolone) and chemotherapy.
<sup>b</sup> Adults are considered obese if body mass index (BMI) ≥30 kg/m²; for children, if BMI-for-age ≥95th percentile.
<sup>c</sup> In 10 days prior to symptom onset.
<sup>d</sup> In month prior to symptom onset.
between aerosol and respiratory droplet transmission [25, 26]. Our findings, although not conclusive, have implications for design of LBMs and personal protective equipment.

Despite strong evidence that poultry exposure increases risk, 12 of 89 cases reported no exposure to poultry. Data from 7 of these were obtained from proxies, and may have been incomplete. The majority came from a single site; data quality may have varied between sites. Nevertheless, these cases with no clear source of infection underscore the need for continued detailed epidemiologic investigations in all future A(H7N9) cases. Also, the fact that 1 control subject was excluded due to serologic test results suggestive of A(H7N9) infection underscores the need for surveillance to detect possible cases of mild A(H7N9) disease. We also found an association with ill backyard poultry, which was unexpected given that, as a low pathogenic avian influenza virus, A(H7N9) does not cause severe poultry illness [27, 28]. However, this exposure occurred in a small fraction of cases and may reflect recall bias between cases and controls, perhaps because of the well-publicized association of highly pathogenic A(H5N1) virus infection with sick poultry [18].

Of potential protective health behaviors investigated, washing hands with soap after poultry contact was significantly associated with decreased risk of infection. This finding suggests public health interventions, although its significance is as yet unclear. In addition, self-reported behaviors may be subject to recall bias.

Since A(H7N9) virus was first identified, precautions have been implemented to reduce transmission from market poultry. However, our study suggests that visitors to LBMs can be infected with just 1 visit and no contact with poultry, and this may prompt measures such as LBM design to reduce human exposure to live birds, or permanent closure of markets. Cases of A(H7N9) infections continue to occur [1, 13], and ongoing monitoring of the A(H7N9) virus in the animal population, including backyard poultry, is critical, as spread of the virus to other sectors of the poultry industry may change the risk profile to humans. Vigilant surveillance for A(H7N9) disease and continued assessment of A(H7N9) epidemiology and evolution will be key to identifying measures to prevent the spread of this emerging virus.

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References