Human infection with avian influenza A H7N9 virus: an assessment of clinical severity

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Summary

Background Characterisation of the severity profile of human infections with influenza viruses of animal origin is a part of pandemic risk assessment, and an important part of the assessment of disease epidemiology. Our objective was to assess the clinical severity of human infections with avian influenza A H7N9 virus, which emerged in China in early 2013.

Methods We obtained information about laboratory-confirmed cases of avian influenza A H7N9 virus infection reported as of May 28, 2013, from an integrated database built by the Chinese Center for Disease Control and Prevention. We estimated the risk of fatality, mechanical ventilation, and admission to the intensive care unit for patients who required hospital admission for medical reasons. We also used information about laboratory-confirmed cases detected through sentinel influenza-like illness surveillance to estimate the symptomatic case fatality risk.

Findings Of 123 patients with laboratory-confirmed avian influenza A H7N9 virus infection who were admitted to hospital, 37 (30%) had died and 69 (56%) had recovered by May 28, 2013. After we accounted for incomplete data for 17 patients who were still in hospital, we estimated the fatality risk for all ages to be 36% (95% CI 26–45) on admission to hospital. Risks of mechanical ventilation or fatality (69%, 95% CI 60–77) and of admission to an intensive care unit, mechanical ventilation, or fatality (83%, 76–90) were high. With assumptions about coverage of the sentinel surveillance network and health-care-seeking behaviour for patients with influenza-like illness associated with influenza A H7N9 virus infection, and pro-rata extrapolation, we estimated that the symptomatic case fatality risk could be between 160 (63–460) and 2800 (1000–9400) per 100 000 symptomatic cases.

Interpretation Human infections with avian influenza A H7N9 virus seem to be less serious than has been previously reported. Many mild cases might already have occurred. Continued vigilance and sustained intensive control efforts are needed to minimise the risk of human infection.

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Introduction When a new influenza virus that can infect and cause disease in people emerges, such as the avian influenza A H7N9 virus, risk assessment is an urgent public health priority. In guidelines from the US Centers for Disease Control and Prevention, risk assessment metrics were broken down into ten criteria in three categories: properties of the virus, including transmission potential; properties of the population, including pre-existing immunity and the severity of human infections; and ecology and epidemiology in animals and human beings. The second category includes one of the most difficult criteria to assess, but the most important in terms of public health effects—namely, the clinical severity of human infections, which is estimated by measures such as the case fatality risk. The seriousness of infections has major implications for the potential overall severity of an influenza pandemic. However, assessment of severity is challenging because typically the most serious illnesses associated with infection have a much higher probability of being detected and laboratory confirmed than do mild illnesses.

Human infections with the novel influenza A H7N9 virus were first identified in China in March, 2013, and the initial laboratory-confirmed cases were all patients with serious illness. The earliest laboratory-confirmed cases were clustered around the Yangtze River delta, while subsequent laboratory-confirmed cases occurred in neighbouring provinces to the south and north. Most laboratory-confirmed cases occurred in urban areas in people who reported exposure to live poultry in the 7 days before illness onset. Investigation of live poultry markets in Huzhou, Zhejiang Province, identified a high prevalence of infection in poultry, and closure of live poultry markets seems to have been effective in the control of outbreaks. Intensive follow-up of more than 2500 close contacts of laboratory-confirmed cases identified just five potential secondary

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The National Health and Family Planning Commission ruled that the collection of data for laboratory-confirmed cases of avian influenza A H7N9 infection was part of a continuing public health investigation of an emerging outbreak and was therefore exempt from institutional review board assessment.

**Statistical analysis**

We used two approaches to characterise the severity of infection. First, for patients with laboratory-confirmed infection who required hospital admission for medical reasons, we examined the risk of death, admission to ICU, and mechanical ventilation. Second, we sought to estimate the number of symptomatic cases to form the denominator for the symptomatic case fatality risk. Together, these measures characterise the clinical severity profile of avian influenza A H7N9 and allow comparison with other influenza virus infections.

Garske and colleagues\(^*\) discussed two complications with characterisation of severity: the potential for underestimation of cases, and incomplete information about outcomes during a continuing outbreak. We attempted to circumvent the issue of underascertainment of cases and particularly shifts over time in case ascertainment by focusing on cases that required hospital admission. To allow for incomplete information about outcomes, we used survival analyses to allow the inclusion of all cases admitted to hospital in our analysis, incorporating data for patients who were still in hospital at the time of analysis that would be typical of any evolving, incomplete outbreak.

We estimated the fatality risk for patients admitted to hospital within a competing risks framework.\(^{20}\) Specifically, every patient admitted to hospital is assumed to either die of the disease or recover. We estimated the admission to death distribution \(F_1\) and the admission to recovery distribution \(F_2\) with a non-parametric approach, accounting for the competing nature of the outcomes and censoring. We calculated the hospital admission fatality risk with the fraction \(F_1/(F_1+F_2)\) at 6 weeks after admission, and constructed 95% CIs with a bootstrap approach with 1000 resamples.\(^{20}\)

We used the same non-parametric approach to estimate two other serious outcomes of hospital admission: ICU admission and mechanical ventilation. Because some patients died without requiring mechanical ventilation, we grouped two outcomes together to estimate the risk of mechanical ventilation or death, for which the alternative outcome is recovery without ventilation. For the same reason, we estimated risk of ICU admission, mechanical ventilation, or death versus recovery without ICU admission or mechanical ventilation, or both.

Hospital admission dates were unavailable for a few patients. Additionally, the exact date of ICU admission or ventilation was not available in our dataset for a few patients. Therefore, we used multiple imputation with 20 replications to allow for unknown dates of hospital admission, ICU admission, or ventilation.\(^{20}\)

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**Methods**

**Data sources**

In China, all laboratory-confirmed cases of avian influenza A H7N9 virus infection are reported to the Chinese Center for Disease Control and Prevention (China CDC) through a national surveillance system. Case definitions, surveillance for identification of cases, and laboratory assays have been previously described.\(^{20}\)

A joint team comprising staff from local or provincial CDC, or the China CDC, or both, did field investigations of the laboratory-confirmed cases of avian influenza A H7N9 virus infection. Demographic, epidemiological, and basic clinical data were obtained with standardised forms.

An integrated database was built by the China CDC, with detailed epidemiological information about each laboratory-confirmed case of avian influenza A H7N9 infection reported by May 28, 2013. We used information about age, sex, place of residence, dates of illness onset, hospital admission, ICU admission, mechanical ventilation, death, and recovery or discharge.
estimated the distributions of time from illness onset to hospital admission, and from hospital admission to ICU admission or ventilation by complete case analysis. Then, we used the derived distributions, truncated by the duration of follow-up for a specific patient, to impute event dates. We estimated risks of fatality, ICU admission, and mechanical ventilation with 95% CIs from the 20 imputed datasets, and estimated the pooled means across the imputed datasets with Rubin’s formula.22

Additionally, we investigated the risk of fatality, ICU admission, and ventilation for patients admitted to hospital aged younger than 60 years and those aged 60 years or older. To assess the information about severity that was available early in the outbreak for patients who had been admitted to hospital, we did retrospective analyses of the overall fatality risk on the basis of data available on different cutoff dates in April and May, 2013.

To put the clinical severity profile into proper context—ie, by providing a denominator consisting of all infected and symptomatic cases—we estimated the number of symptomatic influenza A H7N9 virus infections in Shanghai and Nanjing (Jiangsu Province) by May 28, on the basis of the numbers of cases detected by routine virological surveillance at ILI sentinel sites. We combined these data with the daily number of all ILI cases reported and specimens tested by ILI surveillance in the two cities to infer the number of infected individuals who would have sought medical care at ILI sentinels (Nili, appendix). We then used two alternative methods to estimate the number of symptomatic infections in Shanghai and Nanjing. With method 1, we assumed that health-care-seeking behaviour of individuals with ILI associated with infection with the influenza A H7N9 virus was the same as health-care-seeking behaviour for those with ILI associated with the 2009 influenza A H1N1 pandemic virus infection. We used data from a nationwide serosurvey and ILI surveillance of the 2009 influenza A H1N1 pandemic virus in China from June, 2009, to January, 2010,23 to estimate the proportion of individuals with symptomatic infections who sought medical care at ILI sentinels. We divided Nili by this proportion (appendix).

With method 2, we assumed that all cases of ILI associated with infection with influenza A H7N9 virus sought medical care, and we estimated the number of symptomatic cases on the basis of the proportions of outpatient consultations at the sentinel locations compared with the total number of consultations in Shanghai and Nanjing (appendix). After estimating the number of mild cases in Shanghai and Nanjing, we extrapolated our estimate to the rest of mainland China on the basis of the proportion of patients with H7N9 admitted to hospital in those two cities (ie, pro rata). Statistical analyses were done in R (version 3.0.1).

Role of the funding source

The sponsors of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The joint first authors had full access to all the data in the study, and the corresponding authors had final responsibility for the decision to submit for publication.

Results

As of May 28, 2013, 131 laboratory-confirmed human cases of avian influenza A H7N9 infection had been officially recorded in mainland China. Of those, 123 patients had to be admitted to hospital for medical reasons and were included in our analyses. Four of the other eight individuals were diagnosed after they had already recovered from mild illness, and four who had mild illness were admitted to hospital for observation (one had been identified through ILI surveillance).

71 (58%) of the 123 individuals who had to be admitted to hospital were aged at least 60 years, and 87 (71%) were male (table 1). Table 2 shows estimated overall fatality risk and risk of other adverse outcomes. Fatality risk was higher for individuals aged 60 years or older than for the rest of mainland China on the basis of the proportions of outpatient consultations at the sentinel locations compared with the total number of consultations in Shanghai and Nanjing (appendix). After estimating the number of mild cases in Shanghai and Nanjing, we extrapolated our estimate to the rest of mainland China on the basis of the proportion of patients with H7N9 admitted to hospital in those two cities (ie, pro rata). Statistical analyses were done in R (version 3.0.1).

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Table 2: Characteristics of 123 patients with laboratory-confirmed infection with avian influenza A H7N9 virus who were admitted to hospital

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Died (n=37)</th>
<th>Recovered (n=69)</th>
<th>Unresolved (n=17)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-15</td>
<td>0</td>
<td>2 (3%)</td>
<td>0</td>
</tr>
<tr>
<td>16-59</td>
<td>8 (22%)</td>
<td>35 (51%)</td>
<td>7 (41%)</td>
</tr>
<tr>
<td>60-74</td>
<td>16 (43%)</td>
<td>21 (30%)</td>
<td>7 (41%)</td>
</tr>
<tr>
<td>≥75</td>
<td>13 (35%)</td>
<td>11 (16%)</td>
<td>3 (18%)</td>
</tr>
<tr>
<td>Men</td>
<td>28 (76%)</td>
<td>47 (68%)</td>
<td>12 (71%)</td>
</tr>
<tr>
<td>Delay from illness onset to hospital admission (days)†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-2</td>
<td>9 (24%)</td>
<td>11 (17%)</td>
<td>3 (18%)</td>
</tr>
<tr>
<td>3-6</td>
<td>21 (57%)</td>
<td>49 (74%)</td>
<td>8 (47%)</td>
</tr>
<tr>
<td>≥7</td>
<td>7 (19%)</td>
<td>6 (9%)</td>
<td>6 (35%)</td>
</tr>
<tr>
<td>Illness onset date (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Feb 19-March 31, 2013</td>
<td>18 (49%)</td>
<td>11 (16%)</td>
<td>5 (29%)</td>
</tr>
<tr>
<td>April 1-14, 2013</td>
<td>15 (41%)</td>
<td>44 (64%)</td>
<td>8 (47%)</td>
</tr>
<tr>
<td>April 15-May 3, 2013</td>
<td>4 (11%)</td>
<td>14 (20%)</td>
<td>4 (24%)</td>
</tr>
<tr>
<td>Residence</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urban</td>
<td>32 (86%)</td>
<td>42 (61%)</td>
<td>14 (82%)</td>
</tr>
<tr>
<td>Rural</td>
<td>5 (14%)</td>
<td>27 (39%)</td>
<td>3 (18%)</td>
</tr>
</tbody>
</table>

Data are n (%). *As of May 28, 17 patients had not died but their disease had not resolved either. †Admission date not known for three patients who recovered.

Table 2: Risks of adverse outcomes for patients with laboratory-confirmed infection with avian influenza A H7N9 virus who were admitted to hospital

<table>
<thead>
<tr>
<th>All ages</th>
<th>Aged &lt;60 years</th>
<th>Aged ≥60 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatality risk</td>
<td>36% (26–45)</td>
<td>18% (6–29)</td>
</tr>
<tr>
<td>Risk of mechanical ventilation* or fatality</td>
<td>69% (60–77)</td>
<td>53% (39–68)</td>
</tr>
<tr>
<td>Risk of admission to intensive care unit*, mechanical ventilation*, or fatality</td>
<td>83% (76–90)</td>
<td>75% (63–87)</td>
</tr>
</tbody>
</table>

Data in parentheses are 95% CIs. 95% CIs were estimated with bootstrapping with 1000 resamples. Accounting for incomplete data for 17 patients who were still in hospital as of May 28, 2013. *Data not available for 15 patients (five aged <60 years; ten aged ≥60 years). †Data not available for 13 patients (four aged <60 years; nine aged ≥60 years).
younger individuals (p=0·0019; figure 1, table 2). For the 37 individuals who died, median time to death was 11 days (IQR 6–23). For the 65 individuals who recovered, median time to recovery was 18 days (14–29).

71 (66%) of 108 patients for whom detailed clinical information was available required mechanical ventilation, and 83 (75%) of 110 were admitted to ICU. We used multiple imputation to account for missing data for dates of ICU admission for one patient and for mechanical ventilation for 23 patients, and censored in 17 patients who were still in hospital as of May 28. We estimated that risks of ICU admission (p=0·08) and mechanical ventilation (p=0·0067) were higher for patients aged 60 years or older than for younger patients (figure 2, table 2). We recorded some evidence that disease progressed or resolved faster in patients younger than 60 years than in older individuals (figures 1, 2), but the small sample size meant that we did not have sufficient statistical power to warrant further investigation.

When we estimated the fatality risk of patients admitted to hospital on the basis of information available on different dates, we noted that the estimated risk gradually decreased (figure 3). Uncertainty was initially substantial, but decreased with time (figure 3), because of the increasing number of cases and follow-up of individuals admitted to hospital.

We estimated that 23 (95% credible interval [CrI] seven to 58) symptomatic individuals infected with avian influenza A H7N9 sought medical care at ILI sentinels in Shanghai up to May 28, on the basis that two cases were identified there by ILI surveillance. Additionally, we estimated that 40 (seven to 129) sought medical care at ILI sentinels in Nanjing on the basis that one case was identified by ILI surveillance. With method 1, we estimated that about 0·75% of individuals with symptomatic 2009 influenza A H1N1 pandemic virus infection sought medical care. With the assumption that a similar proportion of symptomatic individuals infected with avian influenza A H7N9 would have
attended ILI sentinels, we estimated that about 3020 (95% CrI 900–7800) symptomatic infections had occurred in Shanghai and 5310 (880–17 300) in Nanjing (appendix). Pro-rata extrapolation on the basis of 40 total hospital admissions in Shanghai and Nanjing, as of May 28, suggested that 27 000 (95% CrI 9530–65 000) symptomatic infections might have occurred throughout the country as of May 28. This number corresponds to a symptomatic case fatality risk of 160 (63–460) per 100 000 symptomatic cases.

About 21% of outpatient visits in the internal medicine, paediatrics, and emergency departments in Shanghai, and 11% in Nanjing, occurred in sentinel ILI sites. With method 2 and allowing for this coverage, we estimated that about 107 (95% CrI 33–273) symptomatic infections had occurred in Shanghai and 367 (61–1200) in Nanjing (appendix). Pro-rata extrapolation on the basis of number of hospital admissions in these cities (as in method 1) suggested that 1500 (95% CrI 470–4050) symptomatic infections might have occurred throughout the country as of May 28. This number corresponds to a symptomatic case fatality risk of 2800 (1000–9400) per 100 000 symptomatic cases.

Discussion

Our findings represent the most complete picture of the clinical severity profile of avian influenza A H7N9 virus infections in China so far. We have shown that the fatality risk of infected patients admitted to hospital is roughly 36%, and that it increases with age. Our findings put the early reports of severe laboratory-confirmed cases of avian influenza A H7N9 virus infection11 into perspective. Although previous clinical case series have focused on the potential for avian influenza A H7N9 virus infection to cause severe illness,7,9,11 we have estimated that many mild cases might have occurred. Our results thus support continued vigilance and sustained intensive control efforts against the virus to minimise risk of human infection, which is greater than previously recognised.

Notably, our analysis did not contain a metric of confirmed-case fatality risk. We have previously recommended that this term be avoided for epidemiological analysis of pandemic influenza virus,27 and now argue that this term should also be avoided for avian influenza A H7N9 virus. Confirmed cases are apparently biased towards infections associated with serious illnesses,11 although a few confirmed cases of avian influenza A H7N9 virus infection were identified through sentinel ILI surveillance. Because of this under-ascertainment, the confirmed-case fatality risk would apply neither to patients admitted to hospital (for whom the fatality risk is increased), nor to those with mild illness. Shifts in ascertainment of cases with time—eg, by increasing the proportion of ILI specimens tested every week in affected regions—would change the confirmed-case fatality risk, perhaps substantially, without any actual change in the underlying clinical severity profile the infection.

Instead, we used a two-stage approach that was also recommended in the 2009–10 pandemic of influenza A H1N1 virus to provide a stable and robust assessment of severity: estimation of fatality risk and then estimation of number of symptomatic infections.26,27 Our estimation of fatality risk for patients admitted to hospital (36%) is higher than the widely reported risk of less than 25%.11,28,29,36 Our estimate accounted for the unknown outcomes of patients who were still in hospital at time of data cutoff. Our estimate is lower than that for cases of influenza A H5N1 virus infection that has been reported in China (65%)30 and worldwide (60% for all laboratory-confirmed cases),32 but higher than that for 2009 influenza A H1N1 pandemic virus in China (21%).31 Our estimate that between 1500 and 27 000 symptomatic infections with avian influenza A H7N9 virus might have occurred as of May 28, 2013, is much larger than the number of laboratory-confirmed cases. The proportion of patients with symptomatic infections with the virus who sought medical care was probably higher than was assumed with method 1 (which corresponds to the upper limit of our estimates) because laboratory-confirmed cases seemed to have faster and more severe disease progression than did those of infection with the 2009 pandemic virus, and also because residents of the highly developed cities of Shanghai and Nanjing were more likely to seek medical care than the general population of China.

The fatality risk of patients admitted to hospital differed substantially by age. Increasing age is also associated with greater severity of patients infected with seasonal influenza and the 2009 pandemic virus.30,35 However, age-specific ILI surveillance data were not available to allow assessment of age-specific risk of hospital admission for cases of avian influenza A H7N9 virus infection. When possible, an ILI surveillance system that is capitated—ie, based on known population denominators39 rather than on floating consultation...
Our analyses have some limitations. First, our estimates are real time, calculated during the ongoing outbreak of H7N9 while some patients remained critically ill in hospital. Our estimates of fatality risks have fairly wide CIs that will narrow as illnesses resolve. Second, although we could estimate age-specific fatality risks, we could not estimate age-specific symptomatic-case risks in our analyses; further work is needed in this area. Third, our estimates of the number of symptomatic cases by two methods were based on extrapolation from the sentinel ILI network, and necessitated several simplifying assumptions, such as no geographical differences in ascertainment of patients admitted to hospital and no changes in health-care-seeking behaviour in late March, and early April, 2013. Our analysis could be biased if there were additional undetected hospital admissions associated with avian influenza A H7N9—eg, because of poor access to laboratory testing in some areas—or if health-care attendance was increased in view of the perceived severity of this novel infection. Fourth, without data for the proportion of subclinical or asymptomatic infections, we cannot estimate the fatality risk for all infected individuals (ie, not just the risk for those admitted to hospital). Such information might be available from serological studies in future. Finally, clinical information about some laboratory-confirmed cases was not available, and standardised collection and sharing of clinical data would assist risk assessment and treatment.

In conclusion, our estimate of a symptomatic case fatality risk suggests that avian influenza A H7N9 is not as severe as influenza A H5N1, but more severe than 2009 influenza A H1N1 pandemic virus (panel). We are not aware of comparative data for the symptomatic case fatality risks of seasonal influenza viruses, but we speculate that they are similar in size to the 2009 pandemic virus. As with seasonal influenza, the severity of avian influenza A H7N9 virus infection increases with age. Our findings will inform risk assessment and health policy during the present H7N9 outbreak, and will assist preparations for a potential resurgence in human infections towards the end of 2013. Our framework could be used for pandemic risk assessment of future avian influenza viruses that cause disease in people.

denominators—would enable improved characterisation of rates of ILI in the population; laboratory data for a subset of patients could be used to extrapolate the proportion of illnesses associated with influenza. However, this system would be challenging in most settings without a defined population catchment.

Reasonable estimates of the fatality risk were available by mid-May. During the epidemic of severe acute respiratory syndrome, reports of the case fatality risk were low when based on number of deaths divided by number of cases cross-sectionally before complete resolution of all cases, leading to substantial discussion and methodological development during and after that epidemic. 10 years later, during the present H7N9 outbreak, case fatality risks of about 20–25% have frequently been communicated, which is an underestimate. Clearly, more work to disseminate scientific methodological findings and the wider application in public health practice is necessary. We recorded a decrease in the estimated fatality risk over time, because death generally occurred more quickly than recovery. This issue is a limitation of existing methods, and methodological developments would be welcome.

Panels. Research in context

Systematic review

We searched PubMed on May 28, 2013, with the terms “A(H7N9)” or “H7N9” for articles published in English since Jan 1, 2013. We also searched articles available online from international medical and infectious disease journals. We did not identify any reports of human infections with avian influenza A H7N9 virus before 2013. Some reports of the present H7N9 outbreak in people in China divided the number of deaths by the number of laboratory-confirmed cases, and one of these studies clarified that this approach may underestimate the confirmed-case fatality risk, because some patients remain in hospital. Other studies reported the number of laboratory-confirmed cases and the number of deaths without attempts to infer the case fatality risk. One published report suggested that at least 210–550 symptomatic infections with the avian influenza A H7N9 virus in China had occurred by April 21, 2013, on the basis of patterns in incidence compared with presumed patterns in exposure. We did not identify any other report in which estimation of the number of symptomatic cases of avian influenza A H7N9 virus infection or the symptomatic case fatality risk was attempted.

Interpretation

We have shown that human infections with avian influenza A H7N9 virus might be less serious than has been previously reported. Although most patients with laboratory-confirmed infection needed to be admitted to hospital and most of these required admission to intensive care units, the fatality risk for patients with avian influenza A H7N9 infection who were admitted to hospital of 36% seems to be lower than that for influenza A H5N1 in China (65%) and worldwide (60%), but higher than that for the 2009 influenza A H1N1 pandemic virus (21%). Identification of five laboratory-confirmed cases in a network of 554 sentinel hospitals conducting surveillance of influenza-like illness in outpatients in China is indicative of a much larger number of mild cases. Our findings will inform risk assessment and health policy during the present H7N9 outbreak, and will assist preparations for a potential resurgence in human infections towards the end of 2013. Our framework could be used for pandemic risk assessment of future avian influenza viruses that cause disease in people.
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Comparative epidemiology of human infections with avian influenza A H7N9 and H5N1 viruses in China: a population-based study of laboratory-confirmed cases


Summary

Background The novel influenza A H7N9 virus emerged recently in mainland China, whereas the influenza A H5N1 virus has infected people in China since 2003. Both infections are thought to be mainly zoonotic. We aimed to compare the epidemiological characteristics of the complete series of laboratory-confirmed cases of both viruses in mainland China so far.

Methods An integrated database was constructed with information about demographic, epidemiological, and clinical variables of laboratory-confirmed cases of H7N9 (130 patients) and H5N1 (43 patients) that were reported to the Chinese Centre for Disease Control and Prevention until May 24, 2013. We described disease occurrence by age, sex, and geography, and estimated key epidemiological variables. We used survival analysis techniques to estimate the following distributions: infection to onset, onset to admission, onset to laboratory confirmation, admission to death, and admission to discharge.

Findings The median age of the 130 individuals with confirmed infection with H7N9 was 62 years and of the 43 with H5N1 was 26 years. In urban areas, 74% of cases of both viruses were in men, whereas in rural areas the proportions of the viruses in men were 62% for H7N9 and 33% for H5N1. 75% of patients infected with H7N9 and 71% of those with H5N1 reported recent exposure to poultry. The mean incubation period of H7N9 was 3·1 days and of H5N1 was 3·3 days. On average, 21 contacts were traced for each case of H7N9 in urban areas and 18 in rural areas, compared with 90 and 63 for H5N1. The fatality risk on admission to hospital was 36% (95% CI 26–45) for H7N9 and 70% (56–83%) for H5N1.

Interpretation The sex ratios in urban compared with rural cases are consistent with exposure to poultry driving the risk of infection—a higher risk in men was only recorded in urban areas but not in rural areas, and the increased risk for men was of a similar magnitude for H7N9 and H5N1. However, the difference in susceptibility to serious illness with the two different viruses remains unexplained, since most cases of H7N9 were in older adults whereas most cases of H5N1 were in younger people. A limitation of our study is that we compared laboratory-confirmed cases of H7N9 and H5N1 infection, and some infections might not have been ascertained.

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Introduction Since Feb 19, 2013, when the first patient infected with the novel influenza A H7N9 virus from an avian source showed symptoms, 131 laboratory-confirmed cases have been reported in mainland China as of June 9, 2013. This virus seems to exhibit low pathogenicity in birds,1 by contrast with the severe disease that occurs in human beings.2 Such divergent interspecies presentation differs from influenza A H5N1, another influenza virus of direct avian origin, which is highly pathogenic in both human beings and birds.3 Another immediately notable feature of H7N9 is the rapid accumulation of laboratory-confirmed cases of infection in human beings, even though phylogenetic4 and epidemiological5 evidence suggests that transmission is mainly zoonotic. By contrast, H5N1, similarly an exclusive zoonosis with very few exceptions, has caused only 43 laboratory-confirmed cases of infection in human beings since the symptom onset date of Nov 25, 2003, in the first patient in mainland China. To improve our understanding of these different viral characteristics and to inform public health control measures for both co-circulating viruses, we aimed to compare key epidemiological variables of the complete series of laboratory-confirmed human cases of influenza A H7N9 and H5N1 in mainland China so far.

Methods Participants In China, all laboratory-confirmed cases of infection with H7N9 and of H5N1 are reported to the Chinese Centre for Disease Control and Prevention (China CDC) through a national system for reporting of...
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notifiable infectious diseases. Case definitions, surveillance for identification of H7N9 and H5N1 cases, and laboratory test assays are described in previous reports.6–9 A joint field investigation team comprising staff from local or provincial CDC, the China CDC, or both did field investigations of the laboratory-confirmed cases of H7N9 infection. All patients with confirmed H5N1 infection were interviewed by a trained team from the China CDC, except for two military cases. Demographic, epidemiological, and basic clinical data for patients infected with H7N9 and H5N1 were collected on standardised forms. Investigations were generally started within 24 h of diagnosis of suspected infection, clinical circumstances permitting.

China CDC constructed an integrated database, with detailed epidemiological information about each occurrence of laboratory-confirmed H7N9 and H5N1 reported to them by May 24, 2013. Information used in the present analysis included the age, sex, place of residence, number and type of contacts traced, symptoms at illness onset, and underlying medical disorders associated with an increased risk of influenza complications;10 dates of illness onset, hospital admission, death or discharge; and dates of potential exposures to domestic or retail animals and visits to live poultry markets.

The National Health and Family Planning Commission decided that the collection of data from cases of both H5N1 and H7N9 was part of an ongoing public health investigation of an emerging outbreak and thus was exempt from institutional review board assessment.

Statistical analysis
We plotted the geographical locations of cases of H5N1 and H7N9, and did descriptive analyses of the dates of illness onset and the characteristics of the patients. We analysed the number and type of contacts traced for each patient by type of case and exposure history. Close contacts were defined as people known to have been within 1 m of, or to have had direct contact with the respiratory secretions or faecal material of, a patient with laboratory-confirmed H7N9 or H5N1 infection any time from the day before the onset of illness to when the patient

Figure 1: Geographical distribution of 130 and 43 laboratory-confirmed cases of human infection with avian influenza A H7N9 and H5N1 viruses in urban and rural areas of mainland China, with dates of illness onset between Nov 25, 2013, and May 3, 2013
Provinces are shaded according to population density, and H7N9 and H5N1 cases. More recent calendar dates of illness onset are represented by symbols.
was isolated in the hospital or died.\textsuperscript{6,11} We used survival analysis techniques to estimate time-delay distributions, including the incubation period (infection to illness onset), illness onset to admission, illness onset to laboratory confirmation, hospital admission to death, and hospital admission to discharge.\textsuperscript{12,13} We compared alternative parametric distributions, including gamma, Weibull, and lognormal distributions, with non-parametric estimates, and selected the best parametric distribution on the basis of the Akaike information criterion.\textsuperscript{14}

Patients with confirmed infection and their relatives were interviewed to ascertain exposure histories to poultry and swine, and environmental exposures, during the 14 days before illness onset.\textsuperscript{6,15,16} We estimated the incubation period on the basis of dates of reported close contact with live poultry as the proxy for infection, and in sensitivity analyses we explored estimates based on reported exposures to any live animals, and on reported visits to live poultry markets (thus accounting for the possibility of infection by environmental contamination). Information about potential exposures was typically gathered for each of the preceding 14 days, but some cases had repeated exposures and our analysis explicitly allowed for the interval censoring in the exposure data.\textsuperscript{14} In this analysis, we did not include patients who reported recent live poultry exposure but could not recall the exact dates.

Although the case-fatality risk (ie, the risk of death among cases)\textsuperscript{5} is commonly used as an important measure of the severity of infection, the estimated case-fatality risk can be highly dependent on the definition of a case and might sometimes be misinterpreted. Instead, we chose to investigate the fatality risk of patients admitted to hospital, for two reasons. First, mild infections of both H7N9 and H5N1 are less likely to have been detected than serious cases and therefore the risk of death among medically attended and laboratory-confirmed cases would be different, potentially by several orders of magnitude, to the symptomatic case-fatality risk (ie, the risk of death in symptomatic cases of H7N9 and H5N1 virus infections). Second, mild cases identified through sentinel influenza-like illness surveillance or contact tracing should have a substantially lower risk of mortality than serious cases admitted with pneumonia, and one estimated case-fatality risk would misrepresent this heterogeneity. We therefore estimated the fatality risk for patients admitted to hospital with use of a non-parametric approach that accounted for the competing risks of death or discharge, and right-censoring of the outcomes of patients still in hospital.\textsuperscript{9} We estimated 95% CIs for the fatality risk for patients admitted to hospital with bootstrap estimates of the asymptotic variance with 1000 replications.\textsuperscript{18,19} All statistical analyses were done with R version 3.0.1.

Role of the funding source
The sponsors of the study had no role in study design, data collection, data analysis, writing of the report, or the decision to publish. BJC and HY had complete access to the data; the corresponding authors had final responsibility for the decision to submit for publication.

Results
The present analyses included 130 cases of laboratory-confirmed H7N9 infection in mainland China with illness onset dates between Feb 19, 2013 and May 3, 2013. 43 cases of laboratory-confirmed H5N1 infection have been reported so far in mainland China, with the last case documented on Feb 9, 2013, with illness onset dates between Nov 25, 2003, and Feb 3, 2013. Although cases of H5N1 have been distributed across most regions of China, the occurrence of H7N9 in mainland China was initially concentrated in the Yangtze river

![Figure 2](http://dx.doi.org/10.1016/S0140-6736(13)61171-X)
Influenza A H7N9 (n=130) | Influenza A H5N1 (n=43)
---|---
Median age, years | 62 (47–73) | 26 (19–35)
Number of men | 92 (71%) | 22 (51%)
Presence of at least one underlying medical disorder* | 50/111 (45%) | 5/41 (12%)
Urban residence | 93 (72%) | 19 (44%)
Rural residence | 37 (28%) | 24 (56%)
Possible source of infection
Any exposure to poultry | 92/123 (75%) | 29/41 (71%)
Occupational exposure to live poultry | 6 (5%) | 4 (9%)
Visited live poultry market | 43/84 (51%) | 23/41 (56%)
Exposure to sick or dead poultry | 3/123 (2%) | 16/41 (39%)
Exposure to backyard poultry | 19/71 (27%) | 21/41 (51%)

Data are median (IQR), n (%), or n/N (%). *Only underlying medical disorders associated with a high risk for influenza complications—were counted here, including chronic respiratory disease, asthma, chronic cardiovascular disease, diabetes, chronic liver disease, chronic kidney disease, immunosuppressed status, and neuromuscular disorders.

Table 1: Characteristics of laboratory-confirmed cases of human infection with avian influenza A H7N9 and H5N1 viruses in mainland China

Delta in eastern China, with the most recent cases detected away from the initial epicentre to the south and north (figure 1).

93 cases (72%) of infection with H7N9 were in residents of urban areas. By contrast, the incidence rate of cases of infection with H5N1 peaked in 2006, and 24 cases (56%) were in rural residents (figures 1 and 2A). 33 cases (77%) of infection with H5N1 occurred in the winter months (November–February; figure 2B). Incidence of H7N9 peaked in early April, 2013 (figure 2C). A notable difference was recorded in the age and sex distributions of patients overall and by location of residence (figure 3). In urban areas, the viruses were more common in men—the male-to-female ratio for H7N9 was 2.9:1 and for H5N1 was 2.8:1. In rural areas, the male-to-female ratio was 1.6:1 for H7N9 and 0.5:1 for H5N1. Whereas more than half (71 of 130, 55%) of the cases of infection with H7N9 were in people aged 60 years or older (median age 62 years), H5N1 occurred mainly in young adults (figure 3 and table 1).
More than two-thirds of patients reported recent exposure to poultry for both H7N9 and H5N1 (table 1), most often through visits to a live poultry market (for H7N9) or exposure to sick or dead poultry or to backyard poultry (for H5N1). Symptoms at illness onset were similar between the two viruses, with fever and cough the most commonly reported symptoms, albeit less often for H5N1 (table 2). The mean number of contacts traced for each patient was much greater for H5N1 than for H7N9 (table 3). For patients infected with H7N9, 2554 close contacts were reported, all of whom were traced—almost half were health-care-associated contacts. 21 contacts developed acute fever or respiratory symptoms during the medical surveillance period of 7 days after last exposure, without appropriate personal protective equipment, to patients infected with H7N9. Close contacts who developed febrile respiratory illness were transferred to a designated hospital for diagnosis and treatment, and respiratory specimens, paired sera, or both, were collected for laboratory analysis. Four of the ill contacts were laboratory confirmed as cases of infection with H7N9. The mean number of contacts traced for patients infected with H7N9 was higher for urban (21-0) than for rural (18-3) residents (table 3).

Information about dates of recent exposures to live poultry was available for 32 patients (25%) infected with H7N9, and for 27 (63%) infected with H5N1. Weibull models had the best fit to the incubation period distributions for H7N9 and H5N1. We estimated the mean incubation period for H7N9 to be 3-1 days (95% CI 2.6–3.6, SD 1.4 days, 95th percentile 5-5 days). For H5N1, we estimated the mean incubation period to be 3-3 days (95% CI 2.7–3.9, SD 1.5 days, 95th percentile 6-0 days; figure 4A). In sensitivity analyses, estimated incubation period distributions for H7N9 and H5N1 based on contact with any live animals or visits to live poultry markets were very similar (data not shown).

The onset-to-admission interval was also similar for the two viruses (figure 4B): for 123 patients infected with H7N9, the median interval was estimated to be 4-2 days (95% CI 3.7–4.9) based on the best-fitting gamma distribution, whereas for all 43 patients infected with H5N1 the median was estimated to be 4-9 days (3.9–5.9) based on the best-fitting Weibull distribution. For the onset to laboratory confirmation delays, log-normal models fitted best, and the distributions were similar for the two viruses (figure 4C). For H7N9, the median onset to laboratory confirmation delay was 8-3 days (95% CI 7.3–9.5), and for H5N1 the median was 10-7 days (9.1–12.7).

We estimated the fatality risks for patients admitted to hospital, excluding seven patients infected with H7N9 classified as mild and allowing for unresolved outcomes in 17 patients with H7N9 who are still in hospital.13 In 123 patients admitted to hospital with H7N9 and the 43 admitted with H5N1, we estimated respective fatality risks for patients admitted to hospital to be 36% (95% CI 26–45) and 70% (56–83), respectively. Almost all laboratory-confirmed infections with H5N1 had resulted in recovery or death within 3–4 weeks of admission, but duration of hospital stay was typically longer for patients infected with H7N9 than for those infected with H5N1 (figures 4D and 4E). The median time from hospital admission to death for patients infected with H7N9 was 12-0 days, compared with 5-7 days for patients infected with H5N1 based on best-fitting lognormal distributions (figure 4D). Of the patients who survived, the median time from hospital admission to hospital discharge was 10·7 days (9·1–12·7).

### Table 2: Comparison of symptoms at illness onset of laboratory-confirmed cases of human infection with avian influenza A H7N9 and H5N1 viruses in mainland China, based on available data

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Influenza A H7N9 (n=106)</th>
<th>Influenza A H5N1 (n=41)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean health-care contacts traced</td>
<td>Mean other contacts traced</td>
</tr>
<tr>
<td>Urban residence</td>
<td>71</td>
<td>98</td>
</tr>
<tr>
<td>Occupational exposure to live poultry</td>
<td>3</td>
<td>73</td>
</tr>
<tr>
<td>Exposure to retail live poultry</td>
<td>28</td>
<td>80</td>
</tr>
<tr>
<td>Exposure to live poultry elsewhere</td>
<td>27</td>
<td>113</td>
</tr>
<tr>
<td>No known exposure</td>
<td>13</td>
<td>49</td>
</tr>
<tr>
<td>Rural residence</td>
<td>35</td>
<td>67</td>
</tr>
<tr>
<td>Occupational exposure to live poultry</td>
<td>3</td>
<td>69</td>
</tr>
<tr>
<td>Exposure to retail live poultry</td>
<td>11</td>
<td>129</td>
</tr>
<tr>
<td>Exposure to live poultry elsewhere</td>
<td>20</td>
<td>17</td>
</tr>
<tr>
<td>No known exposure</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

Types of exposure were ordered by risk level and categorised to be mutually exclusive by exclusion of overlapping cases with raised risk of exposure. Imputation of missing data was done by assuming the same ratio between health-care contacts and other contacts in the same category. *Other contacts include family and community contacts. †Exposure to poultry elsewhere includes exposure to backyard poultry.

Table 3: Average numbers of close contacts traced for laboratory-confirmed cases of human infection with avian influenza A H7N9 and H5N1 in mainland China, based on available data.

<table>
<thead>
<tr>
<th>Exposures</th>
<th>H7N9 (n=37)</th>
<th>H5N1 (n=37)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No known exposure</td>
<td>1</td>
<td>9</td>
</tr>
<tr>
<td>Rural residence</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Occupational exposure to live poultry</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Exposure to retail live poultry</td>
<td>11</td>
<td>3</td>
</tr>
<tr>
<td>Exposure to live poultry elsewhere</td>
<td>20</td>
<td>28</td>
</tr>
</tbody>
</table>

Types of exposure were ordered by risk level and categorised to be mutually exclusive by exclusion of overlapping cases with raised risk of exposure. Imputation of missing data was done by assuming the same ratio between health-care contacts and other contacts in the same category. *Exposure to poultry elsewhere includes exposure to backyard poultry.
admission to discharge was 41.7 days for those infected with H7N9, whereas it was 18.7 days for patients infected with H5N1 based on best-fitting Weibull distributions (figure 4E).

**Discussion**

We present the comparative epidemiology of human influenza A H7N9 and H5N1 virus infections in China. Although both viruses are of avian origin, and neither has yet acquired the ability for sustained human-to-human transmission, differences exist in their epidemiology.8 Whereas most patients with confirmed H7N9 and H5N1 infection reported exposure to live poultry (table 1), the type of exposure was very different in urban and rural locations. Figure 3 illustrates this finding clearly, since the male-to-female ratio is much higher in urban than in rural areas for both viruses. This result is consistent with sex-based differences in exposure, rather than differences in immunity (panel). In particular, the male-to-female ratio is highest for cases in Shanghai compared with other urban areas (data not shown); anecdotal, Shanghai is the Chinese city where men, rather than women, tend to have the most frequent retail exposures to live poultry.25

Our deduction has at least prima-facie validity in that the age distribution of urban patients infected with H7N9 is consistent with increasing exposure to retail poultry with advancing age.25,26 Whereas some of the cases of H5N1 in rural areas have occurred in regions with low population density and were associated with exposure to backyard live poultry or handling of slaughtered poultry,27 most of the rural cases of H7N9 were in people who live on the outskirts of urban areas and were exposed to retail poultry in live poultry markets; few such patients infected with H7N9 were exposed to backyard poultry (table 1). The preponderance of women among the rural cases of H5N1 might be due to greater exposures to rearing, slaughtering, and cooking of backyard poultry.7 The characteristics of patients infected with H5N1 in China were similar to patients infected with H5N1 in other countries in the region (table 4).

The estimated mean incubation period for H7N9 of about 3 days is much lower than that previously reported,6 which prompted public health authorities to extend the period of medical surveillance for close contacts of confirmed cases from 1 week initially to 10 days now.28–30 Of note, the present findings concur with those estimated by an entirely different method based on inference from the time series of cases (Yu H, Cowling BJ, Wu JT, et al, unpublished). The clarification of the incubation period distribution has important implications. Existing case definitions should be updated, since incubation periods as long as 8–10 days are very unlikely. Quarantine or medical surveillance for close contacts need not last longer than 1 week, since more than 95% of patients would present within 7 days of infection. Accurate estimates of the incubation period distribution can help estimation of epidemic potential in case an avian influenza virus emerges that is efficiently transmissible in humans.

Substantial interest has developed in the case-fatality risk associated with influenza A H7N9 virus infection. Because estimates of the laboratory-confirmed case-fatality risk can be misinterpreted as estimates of the symptomatic case-fatality risk, although they differ substantially, we focused on the risk of death among patients admitted to hospital.25 We found this fatality risk to be about 36% for H7N9—which is much lower than that for H5N1. The fatality risk on hospital admission of 70% for H5N1 was similar to other reports from the region, except for Vietnam (table 4),26,27,31,32 and higher than estimates from Egypt, perhaps because of differences in the viral clade or variations in speed of hospital admissions and levels of care.25,33

The longer average duration of hospital stay for patients with H7N9 before death (figure 4) might represent advances in medical care that can sustain life for longer, but also suggests slower disease progression. However, we did not analyse detailed clinical information in this report, since a separate nationally based effort is already underway. The present relatively long onset to admission intervals

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**Figure 4: Comparisons of time-delay distributions for laboratory-confirmed cases of human infection with avian influenza A H7N9 and H5N1 viruses.**

(A) Estimated incubation period distributions—ie, days from infection to illness onset. (B) Days from illness onset to hospital admission. (C) Days from illness onset to laboratory confirmation of influenza A H7N9 or H5N1 virus infection. (D) Days from hospital admission to death. (E) Days from hospital admission to discharge.
(median 4·2 days) and onset to laboratory confirmation intervals (median 8·3 days) for H7N9 (figures 4B and 4C), could be reduced to permit more timely, and thus more effective, treatment with antivirals.23,24 If preliminary testing can show influenza A virus infection, either by rapid point-of-care tests or by RT-PCR, this could allow early antiviral treatment before the subtype is known.

The authorities have traced more than 2554 close contacts of patients so far, with only four potential secondary infections detected, and those four specific clusters could either be a result of low human-to-human transmission or a common source of infection.6 The high average number of contacts traced for each case (table 3), especially for patients infected with H5N1 who tended to be younger and therefore had more household and community contacts and care involving several hospitals and large medical teams, highlights the potential difficulty that would be faced in a future outbreak of an avian influenza virus that is more transmissible between humans. The higher mean number of contacts for urban than for rural residents is indicative of the increased connectivity associated with urban living and the large medical teams found in tertiary referral hospitals in major cities.

Our analyses have several limitations. First, we have compared laboratory-confirmed cases of infection with H7N9 and H5N1, and some cases of infection might not have been ascertained, particularly those that occurred early in the epidemics, because, for example, of no access to laboratory testing in some areas. Almost all patients with laboratory-confirmed H7N9 infection had serious illness, including pneumonia, and all patients infected with H5N1 had pneumonia. Laboratory confirmation of a few patients infected with H7N9 with mild to moderate disease suggests a greater number of mild to moderate cases.25,26 Additionally, as of May 24, 2013, 17 patients with H7N9 are still in hospital, and the present H7N9 outbreak might not have ended yet, which could lead to some bias in the follow-up data. Second, our estimates of the incubation period are based on a subset of 32 patients with information about single or repeated exposures, whereas accurate and complete information for exposures can be difficult to ascertain. The absence of exposure data for some patients could have caused bias in the estimates of the incubation period distribution.

Our estimates of biological variables, such as the incubation period and to some extent the fatality risk on admission to hospital, should be applicable to other countries. Other variables, such as the onset to hospital admission delay and the onset to laboratory confirmation delay, could also depend on health services and surveillance capacity, whereas the age and sex distribution of cases could also depend on patterns in exposure that could differ in other locations.

In conclusion, we have reported estimates of important epidemiological variables and distributions of influenza A H7N9. However, many important questions remain. The differences in age distribution of patients with laboratory-confirmed infection with H7N9 and H5N1 are intriguing; presumably, immunity associated with different histories of influenza virus exposures has an important role in addition to differences in exposure patterns. Although we have reported the fatality risk for patients admitted to hospital, the symptomatic case-fatality risk remains to be established and a large portion of the “clinical iceberg” of infection might have remained undetected so far. The warm season has now begun in

Panel: Research in context

Systematic review

We searched PubMed on May 27, 2013, with the terms “A(H7N9)” or “H7N9” or “A(H5N1)” or “H5N1”. We also searched articles available online at international medical and infectious disease journals. We did not find any reports of human infections with avian influenza A H7N9 virus before 2013. A total of 628 laboratory-confirmed influenza A H5N1 virus infections in human beings were reported to WHO by April 28, 2013,22–25 including 45 from China since 2003 (43 from mainland China and two from Hong Kong Special Administrative Region). Most cases of H5N1 infection occurred in children and young adults reporting recent exposure to live poultry (table 4).22–25 Preliminary reports of H7N9 epidemiology included three hypotheses for the increased incidence rate of laboratory-confirmed H7N9 in men compared with women: greater risk of exposure in men, worse prognosis for infected men than infected women, and varying health-seeking behaviours.20

Interpretation

Our study showed that the higher incidence rate of cases of H7N9 infection in men than in women was more apparent in urban than in rural areas, and the increased risk for men was also recorded for H5N1 in urban areas (figure 3). This finding is more consistent with exposure playing a major part in the risk of infection, although we cannot rule out the possibility of differences in immunity or health-care-seeking behaviours. Most cases of both viruses reported recent exposure to poultry (table 1) and good evidence suggests low human-to-human transmissibility in view of extensive contact tracing efforts and very few potential secondary cases identified. Some of the epidemiological variables were similar for both viruses (figure 4A–C), whereas patients infected with H5N1 admitted to hospital had a higher risk of death (70% vs 36%) and more rapid disease progression than patients infected with H7N9 (figure 4D). In view of the seasonal pattern in human infections with influenza A H5N1 virus in China (figure 2B), we must be prepared for H7N9 to reappear later this year.

<table>
<thead>
<tr>
<th>Variable</th>
<th>China (n=43)</th>
<th>Vietnam (n=67)</th>
<th>Thailand (n=25)</th>
<th>Indonesia (n=127)</th>
<th>Egypt (n=63)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age, years (range)</td>
<td>26 (2–62)</td>
<td>25 (16–42)</td>
<td>18 (1–62)</td>
<td>20 (1–67)</td>
<td>10 (1–75)</td>
</tr>
<tr>
<td>Proportion of cases in men</td>
<td>51%</td>
<td>55%</td>
<td>64%</td>
<td>50%</td>
<td>36%</td>
</tr>
<tr>
<td>Presence of at least one underlying medical disorder</td>
<td>12%</td>
<td>16%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any recent exposure to poultry</td>
<td>71%</td>
<td>64%</td>
<td>100%</td>
<td>82%</td>
<td>71%</td>
</tr>
<tr>
<td>Fatality risk for those admitted to hospital</td>
<td>70%</td>
<td>39%</td>
<td>68%</td>
<td>82%</td>
<td>39%</td>
</tr>
<tr>
<td>Median duration of hospital stay for fatal cases (days)</td>
<td>6</td>
<td>5</td>
<td>6</td>
<td>3</td>
<td>7</td>
</tr>
<tr>
<td>Median duration of hospital stay for non-fatal cases (days)</td>
<td>21</td>
<td>16</td>
<td>13</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 4: Comparison of epidemiological characteristics of laboratory-confirmed influenza A H5N1 cases reported in China and other countries
China, and only one new laboratory-confirmed case of H7N9 in human beings has been identified since May 8, 2013. If H7N9 follows a similar pattern to H5N1 (figure 2B), the epidemic could reappear in the autumn. This potential lull should be an opportunity for discussion of definitive preventive public health measures, optimisation of clinical management, and capacity building in the region in view of the possibility that H7N9 could spread beyond China’s borders.

Contributors
BJC, GML, and HY designed the study. LJ, QiL, HJ, JZ, ZC, QZ, JY, YL, LW, WT, LM, HL, QUL, YS, ZL, ZF, WT, YW, and HY gathered data. BJC, EHYL, QiL, PW, TKT, VFJ, MYN, and HY analysed the data. BJC wrote the first draft, and all authors contributed to review and revision and have seen and approved the final version.

Conflicts of interest
BJC has received research funding from MedImmune, and consults for Crucell NV. GML has received speaker honoraria from HSBC and CLSIA. The other authors declare that they have no conflicts of interest.

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References


Timely estimates of influenza A H7N9 infection severity

WHO guidance, released in May, 2013, established that estimates of disease severity are key for risk assessment of novel influenza viruses. Unfortunately, epidemiological assessment of severity is difficult in the context of an emerging disease, when estimates are most needed to guide pandemic response. The case fatality risk is an estimate of the proportion of patients with a specific disease who have died; however, both the numerator and denominator of this estimator are elusive. Case detection is typically skewed towards patients with severe disease; laboratory-based case ascertainment can vary geographically and temporally; and there are delays between onset, death, and reporting, potentially leading to overestimation or underestimation of fatality risk.

Much work has been done to refine estimates of case fatality risk in the wake of the 2003 outbreak of severe acute respiratory syndrome and the 2009 influenza pandemic. Different denominators have been considered, including patients who have been admitted to hospital, symptomatic cases, and all individuals with serological evidence of infection. From a statistical point of view, survival analysis provides an appropriate framework to quantify case fatality with right-censored outcome data.

In The Lancet, Hongjie Yu and colleagues assess the clinical severity of human infection with avian influenza A H7N9 virus on the basis of data from 123 patients with laboratory-confirmed infection who were admitted to hospital between March and May, 2013, in mainland China. They estimate that the fatality risk for all ages was 36% (95% CI 26–45), and note that nearly all patients were admitted to an intensive care unit, received mechanical ventilation, or died (83%, 76–90). 71 (58%) of the patients were aged at least 60 years, and fatality risk was higher for these individuals (49%, 36–63) than for younger patients (18%, 6–29; p=0.0019), as is typical of influenza infection.

### Table: Estimates of case fatality risk for the influenza A H7N9 outbreak in China, 2013, influenza A H5N1, and past pandemics

<table>
<thead>
<tr>
<th>Influenza A H7N9, 2013</th>
<th>Case fatality risk in patients admitted to hospital</th>
<th>Case fatality risk in symptomatic patients</th>
<th>Case fatality risk in individuals with serological evidence of infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yu et al (China)³</td>
<td>36% (26–45)</td>
<td>0.16–2.8%* (0.06–9.4)</td>
<td>–</td>
</tr>
<tr>
<td>Influenza A H5N1, 2003–13</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gowling et al (China)¹</td>
<td>70% (56–83)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Fiebig et al (12 countries)⁵</td>
<td>56% (28–87)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>1957 and 1968 pandemics³</td>
<td></td>
<td>0.1%</td>
<td>–</td>
</tr>
<tr>
<td>1918 pandemic³</td>
<td>2–4%</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>2009 pandemic¹</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Earliest estimates: first 1100 laboratory-confirmed cases (Mexico)⁴</td>
<td>–</td>
<td>4%</td>
<td>–</td>
</tr>
<tr>
<td>Fraser et al (Mexico; June, 2009)⁵</td>
<td>–</td>
<td>0.4% (0.03–1.8)</td>
<td>–</td>
</tr>
<tr>
<td>Garske et al (15 countries; July, 2009)⁹</td>
<td>–</td>
<td>0.11–1.47%</td>
<td>–</td>
</tr>
<tr>
<td>Baker et al (New Zealand; August, 2009)²³</td>
<td>1.6%</td>
<td>0.005%</td>
<td>–</td>
</tr>
<tr>
<td>Presanis et al (USA; December, 2009)¹</td>
<td>–</td>
<td>0.048% (0.026–0.096)</td>
<td>–</td>
</tr>
<tr>
<td>Echevarria-Zuno et al (Mexico; December, 2009)²⁴</td>
<td>12%</td>
<td>0.9%</td>
<td>–</td>
</tr>
<tr>
<td>Wu et al (Hong Kong; November, 2010)²⁵</td>
<td>0.6% (0.1)</td>
<td>–</td>
<td>0.004% (0.003–0.017)</td>
</tr>
<tr>
<td>Yu et al (China; February, 2011)²⁶</td>
<td>2.5%</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Riley et al (Hong Kong, June, 2011)²⁷</td>
<td>–</td>
<td>–</td>
<td>0.008% (0.006–0.010%)</td>
</tr>
<tr>
<td>Presanis et al (UK, summer wave; September, 2011)²⁸</td>
<td>5.3%</td>
<td>0.015% (0.010–0.022)</td>
<td>0.05%</td>
</tr>
<tr>
<td>Presanis et al (UK, autumn wave; September, 2011)²⁹</td>
<td>–</td>
<td>0.025% (0.013–0.040)</td>
<td>0.009%</td>
</tr>
</tbody>
</table>

Data in parentheses are 95% CIs, unless otherwise stated. Note the sharp reduction in estimates of case fatality risk in symptomatic patients for the 2009 pandemic as more information became available. By contrast, estimates of case fatality risk in infected individuals are more consistent, although these estimates were not available in the early stages of the 2009 pandemic or the influenza A H7N9 outbreak, and no comparable information for the historical pandemics of 1918, 1957, and 1968 is available. No estimate is available for seasonal influenza. *Range depends on assumptions about number of symptomatic cases of infection with avian influenza A H7N9 virus. †Range across 12 countries. §Estimates sorted by publication date. ¶Range across five regions surveyed. ¶¶limited to individuals aged 5–59 years.
To obtain an estimate of symptomatic case fatality risk, Yu and colleagues extrapolated the total number of symptomatic individuals infected with avian influenza A H7N9 virus on the basis of the number of mild cases detected through routine influenza-like illness surveillance in Shanghai and Nanjing—the most affected cities. They estimate that the symptomatic case fatality risk could be between 160 (95% CI 63–460) and 2800 (1000–9400) per 100 000 symptomatic cases. This estimate is highly sensitive to assumptions about testing propensity, surveillance coverage, and health-care seeking behaviour.

Use of near-real-time estimates of case fatality risk to guide policy is typically limited by broad uncertainty (table). During early assessment of 2009 pandemic influenza disease severity, information about the first 1100 laboratory-confirmed cases produced a severity estimate of 4%, which is even higher than Yu and colleague’s new estimates. However, the 2009 estimate was soon downgraded by more than two orders of magnitude as information accumulated during the summer of 2009 (table). Similarly, severity estimates for avian influenza A H7N9 virus will be refined as the fate of all patients admitted to hospital is resolved and as serological attack rates become available (attack rates could be generated from cross-sectional surveys because background population immunity is low).

It is reassuring that head-to-head comparison of the fatality risk of admitted patients infected with avian influenza A H7N9 or H5N1 suggests a substantially milder disease course for H7N9. Use of these estimates of case fatality risk to extrapolate the potential severity of a full pandemic would be tempting; however, whether global dissemination of these zoonotic influenza viruses would result in a catastrophic pandemic like that in 1918, or worse, or would mirror the mild 2009 pandemic (table) is impossible to predict.

A remaining question relates to the age distribution of symptomatic infections should a zoonotic influenza virus acquire person-to-person transmissibility. So far, the age distribution of reported cases of infection with avian influenza A H7N9 virus has been skewed towards older ages, which is probably explained by behavioural age differences in exposure to the animal reservoir. The age distribution of cases would probably shift towards younger ages in a full pandemic, resulting in a different and potentially decreased case fatality risk. Another issue would be to account for potential changes in disease severity as the virus rapidly evolves. Although conventional wisdom stipulates that virulence attenuates as a pathogen adapts to a new host, animal experiments suggest that influenza virulence could increase simultaneously with genetic drift. Furthermore, evidence from the 1918 pandemic suggests that the situation can escalate: case fatality risk increased by six times from the summer to the autumn of 1918.

The good news is that numbers of cases of avian influenza A H7N9 virus infection have stalled, probably in response to pre-emptive closures of live bird markets. However, the threat of this virus persists, and continued monitoring of infections, together with near-real-time estimation of case fatality risk and serological surveys, remains crucial. Investment in robust hospital surveillance of respiratory infections in a few globally sampled sites, combined with laboratory testing, would help to produce comparative severity estimates for novel and existing viral threats. Yu and colleagues have provided the best severity estimates for avian influenza A H7N9 virus in view of the available information at this point in time; however, public health experts will have to make policy decisions on the basis of uncomfortably broad confidence limits.

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Comment


