Defining the Epidemiology of Influenza A(H7N9) - A HKU-China CDC Collaboration

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Background

- Novel influenza A(H7N9) virus identified in China in March 2013.
- 132 laboratory-confirmed cases to date including 131 in mainland China.
- 40 of the laboratory-confirmed cases have died, others remain in critical condition.
- Only one new case reported in the last 30 days – opportunity to define the underlying epidemiology of A(H7N9) to date.
- The China-WHO Joint Mission (18-24 April) identified a number of important unanswered questions

China-WHO Joint Mission Report

At this time a number of important uncertainties remain. These include the following:

Why severe disease occurs predominantly in older male urban residents is not clear. It could be that behavioural factors and exposure to live birds in wet markets increased the risk of infection. Alternatively, it could be that they represent only a proportion of a much larger number of mild and symptomatic infections and disease progression is mainly observed in the most vulnerable population, as is the case for seasonal influenza (Figure 4). However, a problem with this hypothesis is how to explain the gender imbalance.

Similarly, it remains to be determined whether the predominance of exposure to live poultry in the cases is in fact a risk factor or simply the norm in the older male urban populations where these infections occur.

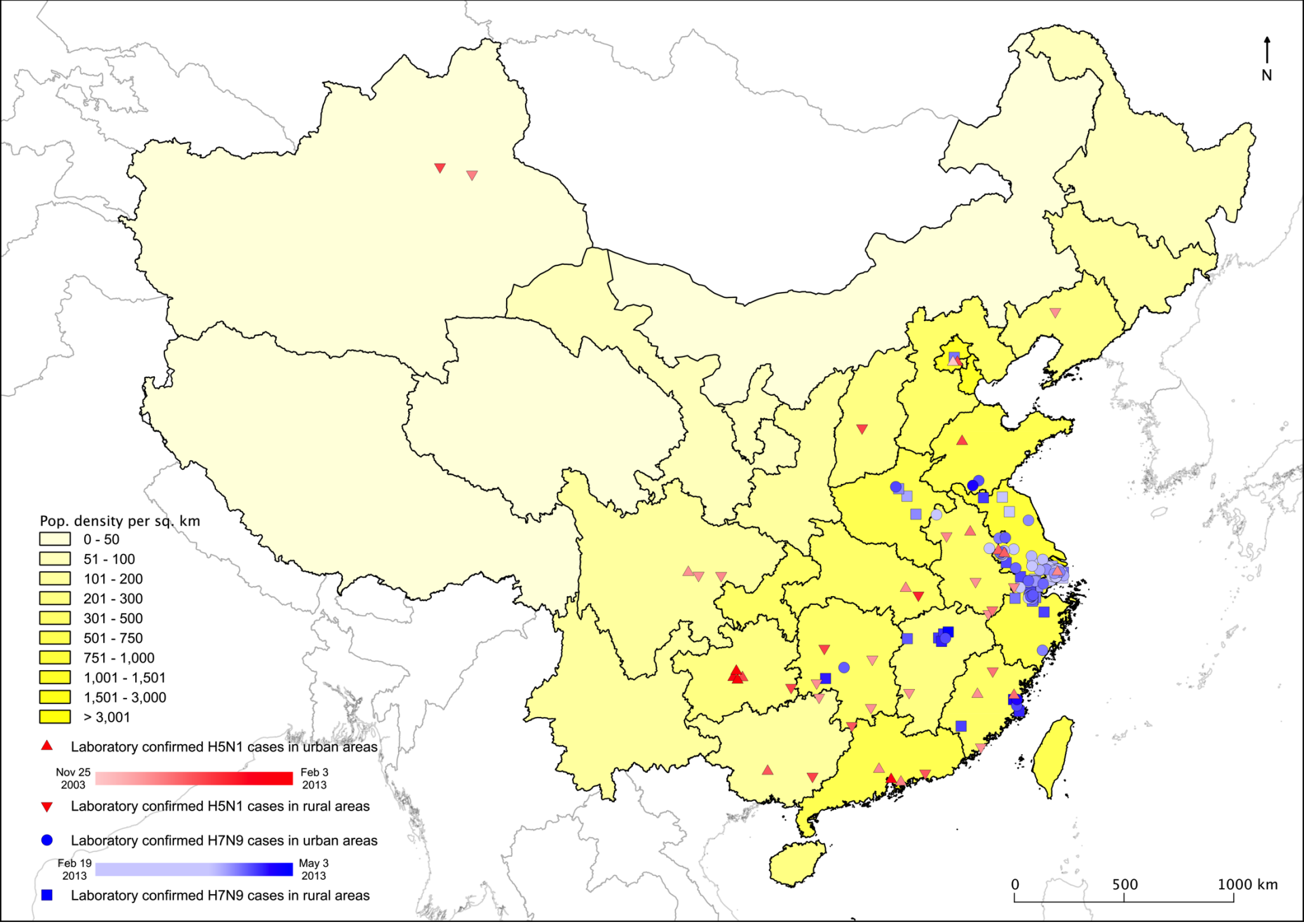
World Health Organization. China—WHO Joint Mission on Human Infection with Avian Influenza A(H7N9) Virus. April 2013
http://www.who.int/influenza/human_animal_interface/influenza_h7n9/ChinaH7N9JointMissionReport2013.pdf

Paper 1 – Lancet

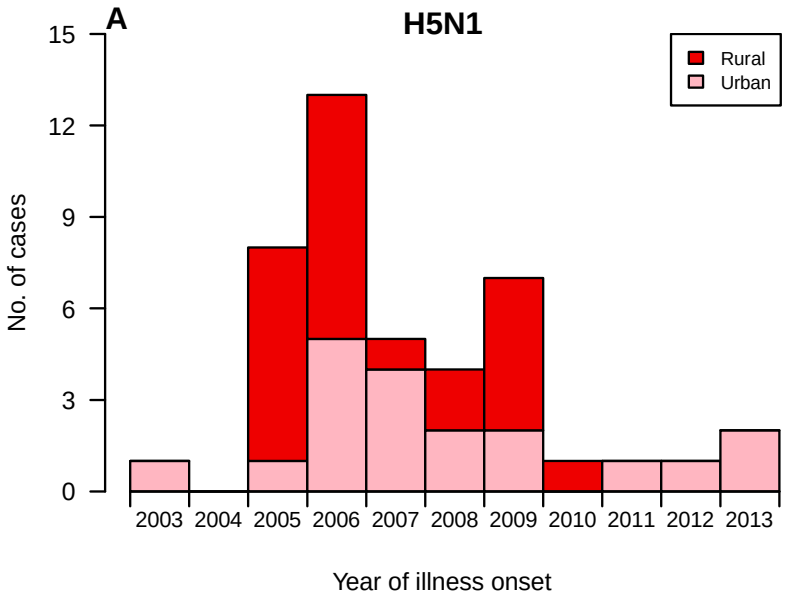
Comparative epidemiology of human infections with avian influenza A H7N9 and H5N1 viruses in China: a population-based study of laboratory-confirmed cases

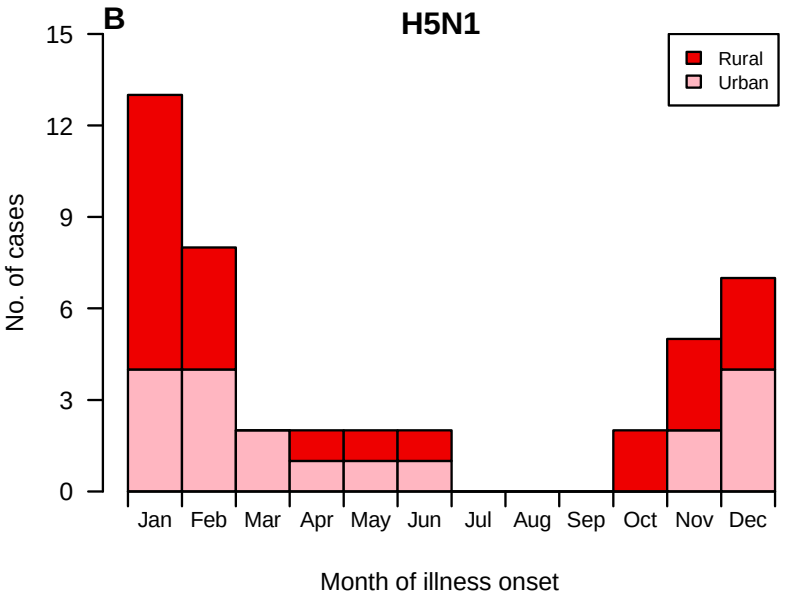
Benjamin J Cowling, Lianmei Jin*, Eric H Y Lau, Qiaohong Liao, Peng Wu, Hui Jiang, Tim K Tsang, Jiandong Zheng, Vicky J Fang, Zhaorui Chang, Michael Y Ni, Qian Zhang, Dennis K M Ip, Jianxing Yu, Yu Li, Liping Wang, Wenxiao Tu, Ling Meng, Joseph T Wu, Huiming Luo, Qun Li, Yuelong Shu, Zhongjie Li, Zijian Feng, Weizhong Yang, Yu Wang, Gabriel M Leung, Hongjie Yu*

Objective: To improve understanding of the characteristics of A(H7N9) and A(H5N1), and to inform public health control measures for both co-circulating viruses.


N
Pop. density per sq. km
0 - 50
51 - 100
101 - 200
201 - 300
301 - 500
501 - 750
751 - 1,000
1,001 - 1,501
1,501 - 3,000
> 3,001
Laboratory confirmed H5N1 cases in urban areas
Nov 25 2003
Feb 3 2013
Laboratory confirmed H5N1 cases in rural areas
Laboratory confirmed H7N9 cases in urban areas
Feb 19 2013
May 3 2013
Laboratory confirmed H7N9 cases in rural areas
0
500
1000 km

Calendar time that cases occurred

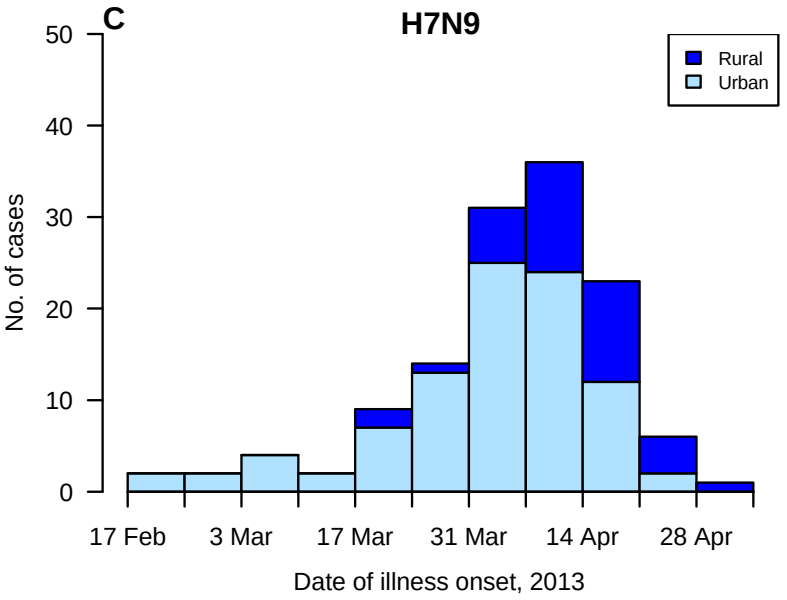




Panel A: Reduction in H5N1 incidence after national poultry vaccination campaign introduced in 2006

Panel B: Strong seasonal pattern in H5N1 incidence

Panel C: Epidemic of H7N9 peaked in April



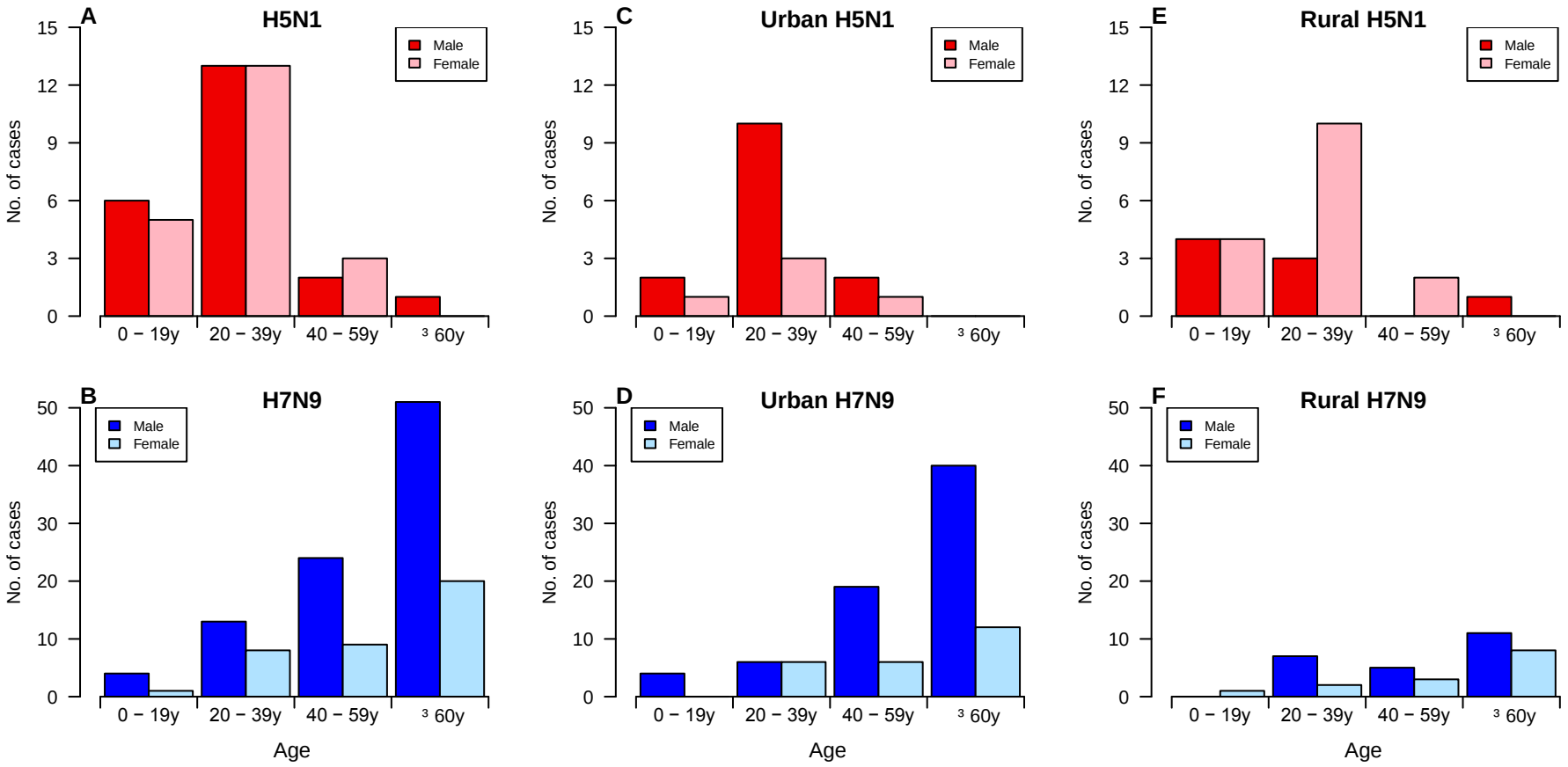
Characteristics of cases

	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[10] were counted here, including chronic respiratory disease, asthma, chronic cardiovascular disease, diabetes, chronic liver disease, chronic kidney disease, immunosuppressed status, and neuromuscular disorders.

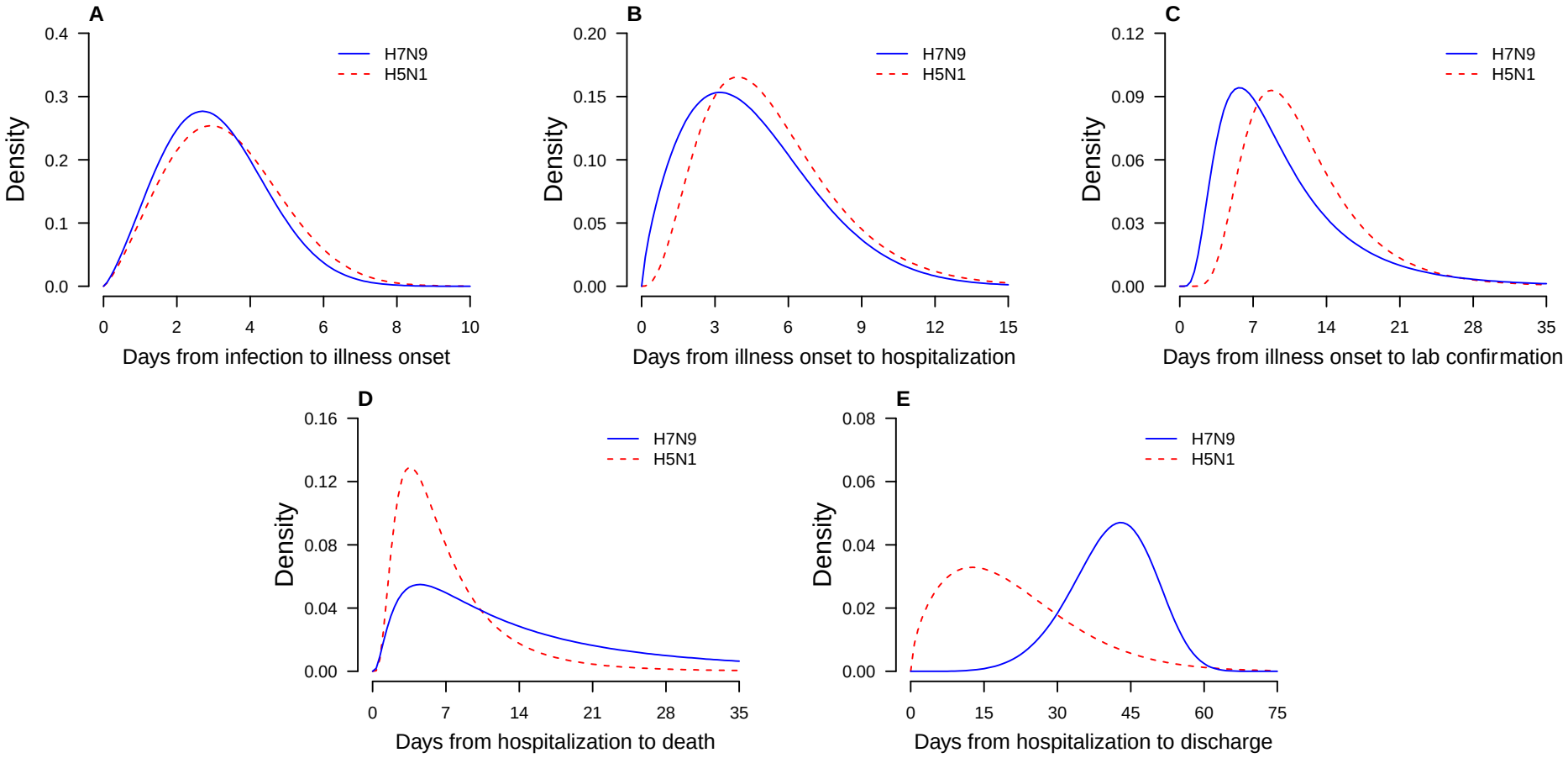
Table 1: **Characteristics of laboratory-confirmed cases of human infection with avian influenza A H7N9 and H5N1 viruses in mainland China**

Sex difference in cases



- **Left:** Increased risk of H7N9 in males, no difference in sex distribution of H5N1 cases
- **Centre:** Increased risk of H7N9 and H5N1 in males in urban areas
- **Right:** Almost no differences in sex distribution of H7N9, but more H5N1 cases in female in rural areas

“Epidemiologic distributions”



Panel A: Incubation period has mean 3.1 and 3.3 days for H7N9 and H5N1 respectively

Panel B: Similar delays from onset to hospitalization

Panel C: Shorter time to laboratory confirmation for H7N9 (improved laboratory capacity)

Panel D: Longer time to death in H7N9 cases who died (improved treatment capacity)

Panel E: Longer time to discharge in H7N9 cases

Summary of findings

- Very different age distribution of H7N9 vs H5N1 cases
- Increased risk of H7N9 and H5N1 among males vs females in urban areas
- Good evidence for low human-to-human transmissibility (only five family clusters, intensive follow-up of 2500 contacts with only 4 potential secondary infections identified.
- Shorter incubation period than previously reported
- Seasonal pattern of H5N1 suggests that H7N9 might reappear in the autumn? – opportunity to prepare definitive public health measures and strengthen response capacity.

Paper 2 – BMJ

BMJ

Detection of mild to moderate influenza A/H7N9 infection by China's national sentinel surveillance system for influenza-like illness: case series

Dennis KM Ip[*1], Qiaohong Liao*[*2], Peng Wu*[*1], Zhancheng Gao*[*3], Bin Cao*[*4], Luzhao Feng[2], Xiaoling Xu[5], Hui Jiang[2], Ming Li[2], Jing Bao[3], Jiandong Zheng[2], Qian Zhang[2], Zhaorui Chang[2], Yu Li[2], Jianxing Yu[2], Fengfeng Liu[2], Michael Y. Ni[1], Joseph T. Wu[1], Benjamin J. Cowling[1], Weizhong Yang[6], Gabriel M. Leung[†1], Hongjie Yu[†2]*

Objective: To characterise the case series of influenza A(H7N9) infections detected by the national sentinel surveillance system for influenza-like illness in China.

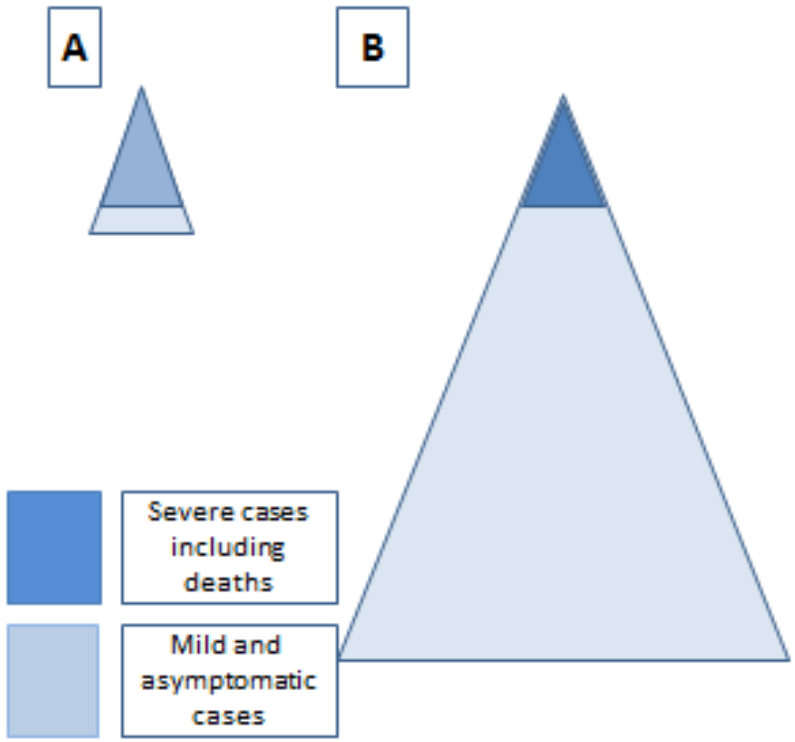
Characteristics of H7N9 infection

- Does human infection with the influenza A(H7N9) virus always present with clinically severe illness, as most early reports suggest?

Two possible scenarios consistent with the current observed human epidemiology of the A(H7N9) cases

A The observed A(H7N9) cases are a high proportion of all cases and there are few mild or asymptomatic cases

B The observed severe A(H7N9) cases are only a proportion of all the cases and there are many mild or asymptomatic cases



- H7N9 infected ferrets in experiments showed relatively mild clinical signs

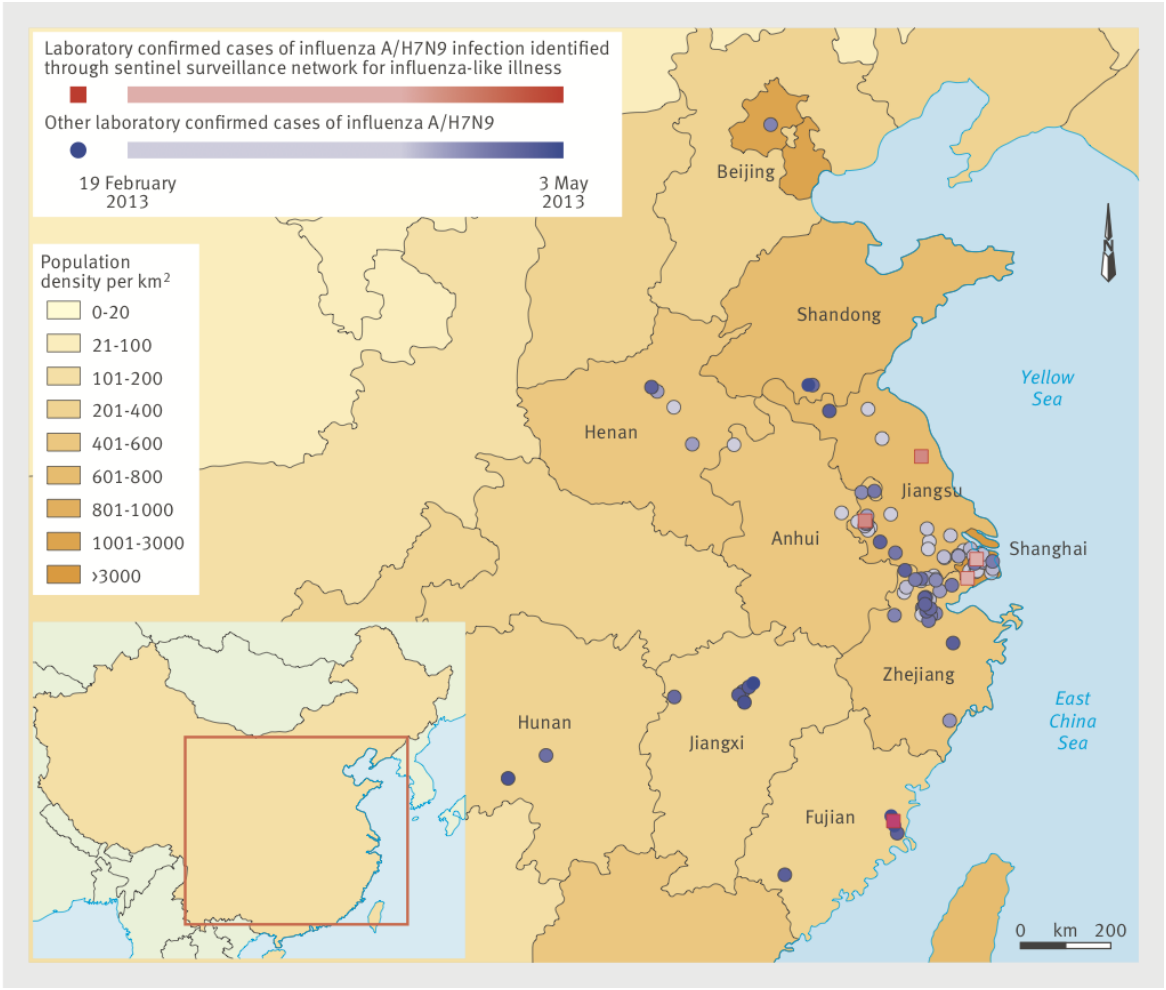
World Health Organization. China—WHO Joint Mission on Human Infection with Avian Influenza A(H7N9) Virus. April 2013
Zhu et al. Science. 2013

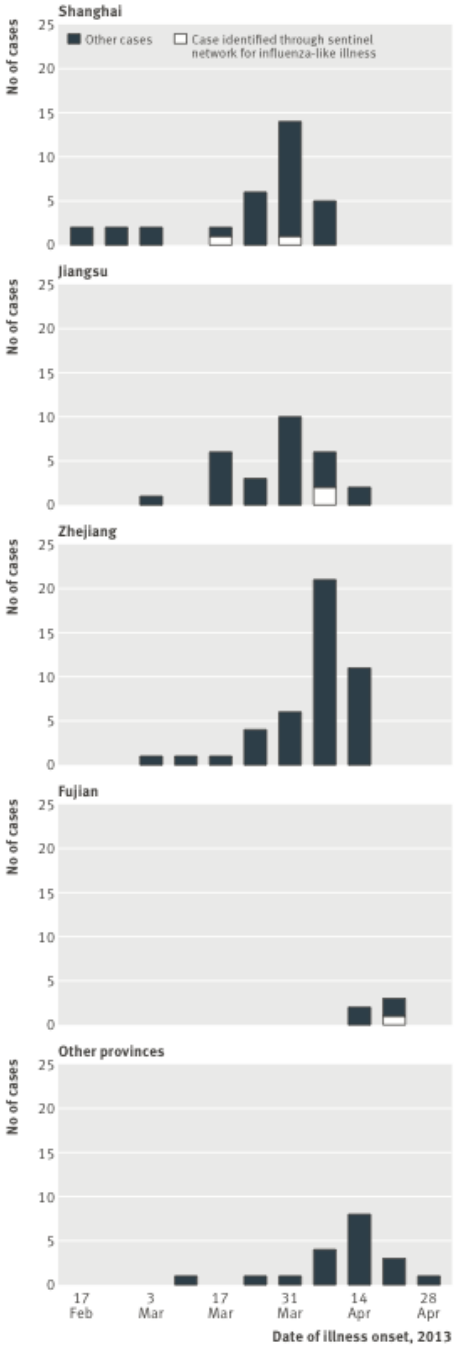
Cases captured by the ILI sentinel surveillance system

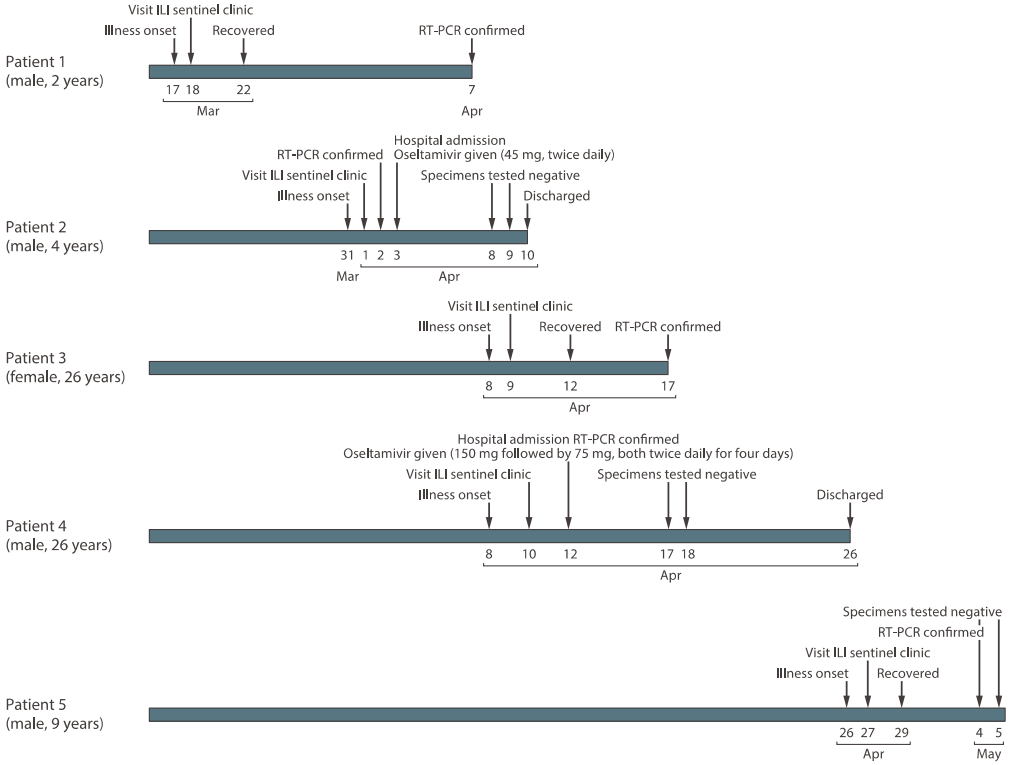
	130 Laboratory confirmed A(H7N9) infection (Based on data up to the manuscript submission - 27 May, 2013)	
	125 cases	5 cases (4%)
Presentation	Presenting with clinical illness to hospitals	Presenting to sentinel ILI surveillance system
Setting	Hospitals in affected provinces	OPDs/ EDs in 544 sentinel hospitals for ILI surveillance over China
A/H7N9 test	As clinically indicated	10-15 nasopharyngeal swabs/ week from ILI patients for routine testing
Relative coverage	More targeted to diagnosis of severe cases	More representative of the disease pattern in community

Epidemiological and clinical data examined in detail

Exposure history, geographical location, and timing of symptom onset of these five A(H7N9) cases were similar to the general cohort of patients with laboratory-confirmed A(H7N9) infection.







	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Age (years)	2	4	26	26	9
Sex	Male	Male	Female	Male	Male
Location	Shanghai	Shanghai	Jiangsu	Jiangsu	Fujian
Underlying medical conditions	None	None	None	None	None
Date of illness onset	17 March 2013	31 March 2013	8 April 2013	8 April 2013	26 April 2013
Presenting symptoms	Fever	Fever, rhinorrhoea	Fever, myalgia	Fever, productive cough	Fever, diarrhoea, malaise
Pneumonia	No	No	No	Yes (left sided)	No
Admitted to hospital	No	Yes	No	Yes	No
Admitted to intensive care unit	No	No	No	No	No
Mechanical ventilation	No	No	No	No	No
Received antiviral treatment	No	Yes	No	Yes	No
Recovered	Yes	Yes	Yes	Yes	Yes

Summary of findings

- Clinical iceberg present - our findings provide indirect evidence for a larger proportion of mild A(H7N9) cases, since the sentinel network only covers a small fraction of outpatient care in China.
- Clinical implications – a need for vigilance to the diverse presentation that can be associated with A/H7N9 infection
- Public health implications – unidentified mild cases in the community may act as a source of infection to other susceptible people if A(H7N9) develops the capacity for human-to-human transmission

Paper 3 – Lancet

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

Hongjie Yu, Benjamin J Cowling*, Luzhao Feng*, Eric H Y Lau*, Qiaohong Liao, Tim K Tsang, Zhibin Peng, Peng Wu, Fengfeng Liu, Vicky J Fang, Honglong Zhang, Ming Li, Lingjia Zeng, Zhen Xu, Zhongjie Li, Huiming Luo, Qun Li, Zijian Feng, Bin Cao, Weizhong Yang, Joseph T Wu, Yu Wang, Gabriel M Leung*

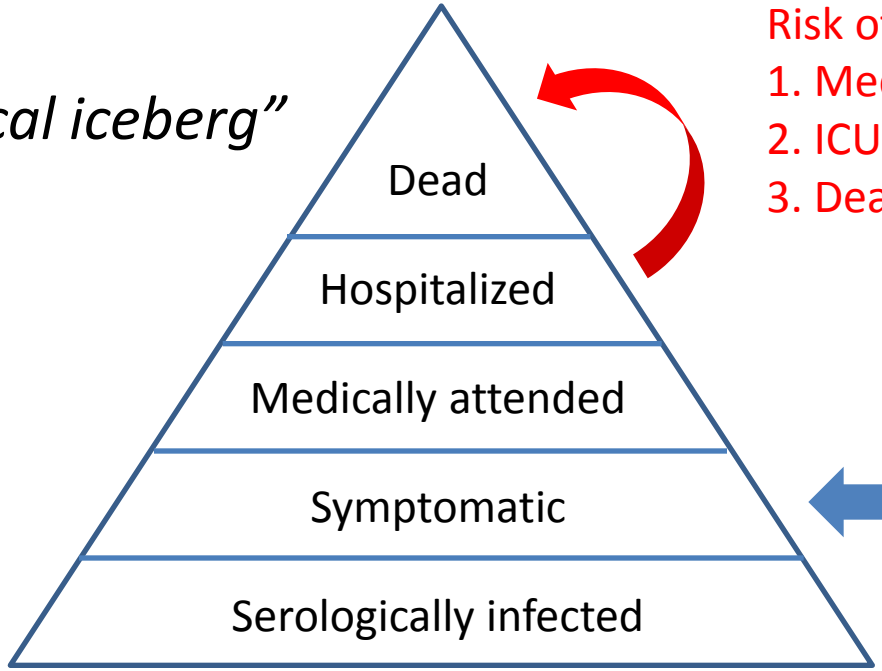
Objective: To characterize the risk of serious illness and severe outcomes among humans infected by the avian influenza A(H7N9) virus.

Clinical Severity

$$\text{Severity} = \frac{\text{Number of severe outcomes}}{\text{Number of infections}}$$

i.e. probability of severe outcome if infected

"Clinical iceberg"



Risk of severe outcomes if hospitalized:
1. Mechanical ventilation
2. ICU admission
3. Death

All symptomatic infections, including mild cases that did not seek medical care

Risk of severe outcomes if hospitalized

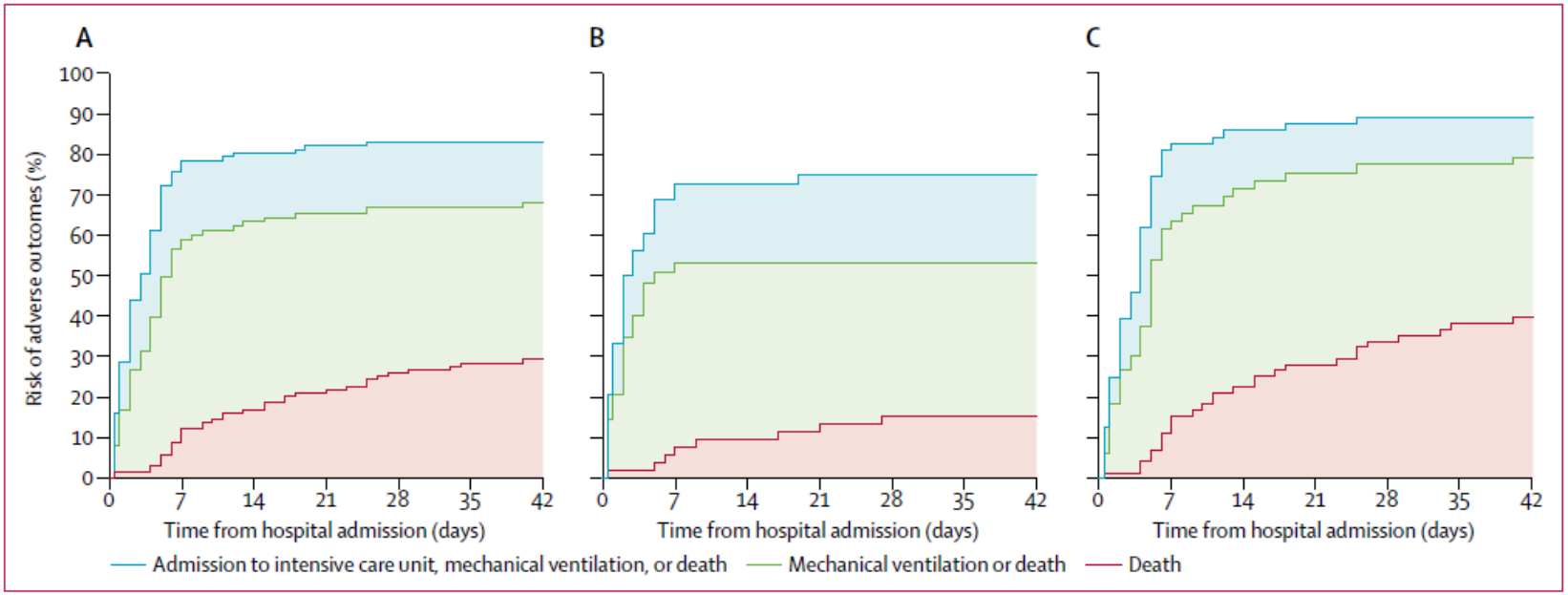


Figure 2: **Risks of adverse outcomes for patients with laboratory-confirmed infection with avian influenza A H7N9 virus who were admitted to hospital**
(A) 123 patients of all ages, (B) 52 patients younger than 60 years, and (C) 71 patients aged at least 60 years.

	All ages	Aged <60 years	Aged ≥60 years
Fatality risk	36% (26–45)	18% (6–29)	49% (36–63)
Risk of mechanical ventilation* or fatality	69% (60–77)	53% (39–68)	80% (71–90)
Risk of ICU admission†, mechanical ventilation*, or fatality	83% (76–90)	75% (63–87)	89% (81–97)

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.

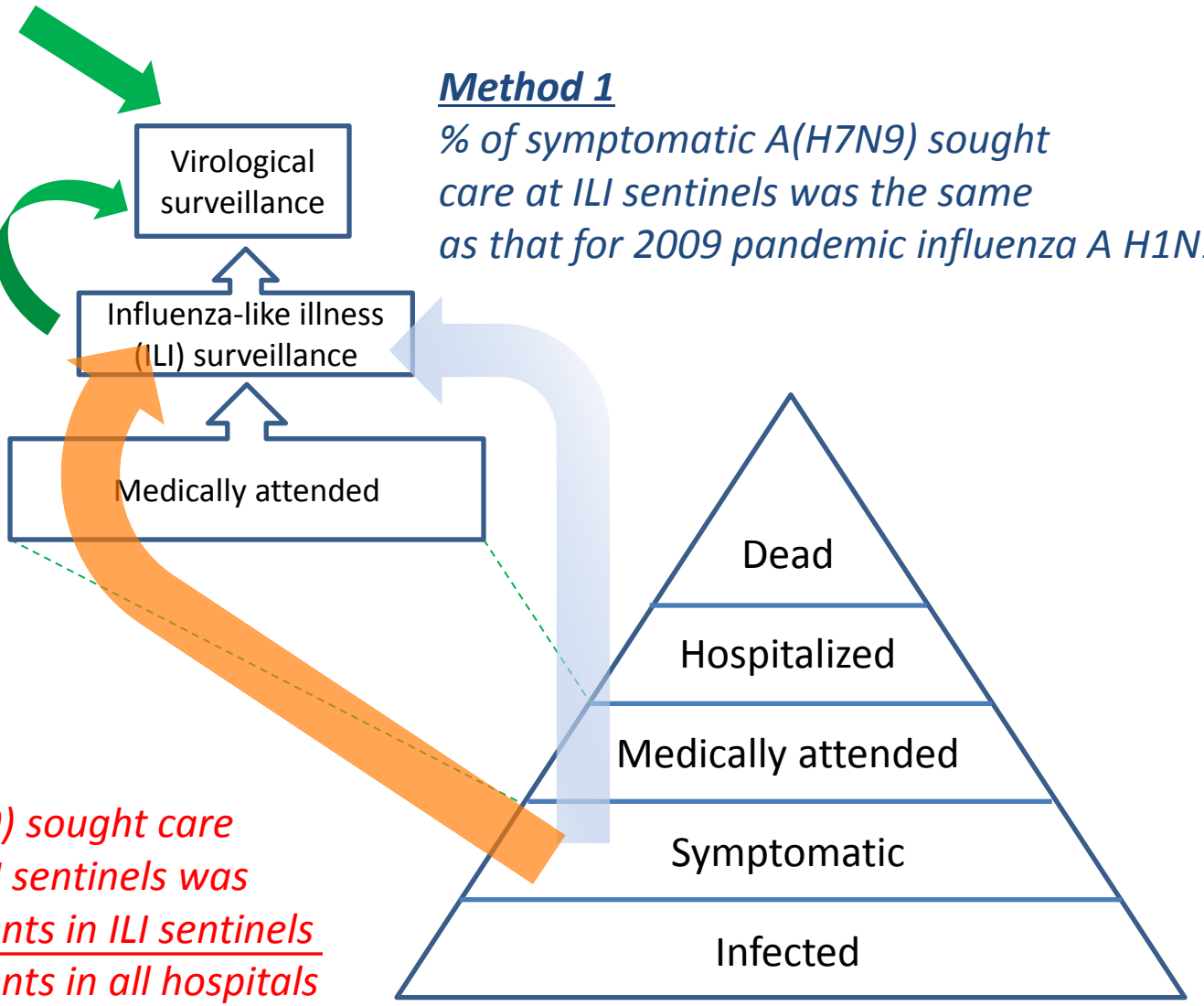
Table 2: **Risks of adverse outcomes for patients with laboratory-confirmed infection with avian influenza A H7N9 virus who were admitted to hospital**

Using data from 123 hospitalized cases as of 28 May 2013

No. of symptomatic infections

2 cases in Shanghai
1 case in Nanjing

Routine % of ILI cases selected for virological testing



Method 1

% of symptomatic A(H7N9) sought care at ILI sentinels was the same as that for 2009 pandemic influenza A H1N1

Method 2

- *All symptomatic A(H7N9) sought care*
- *% who sought care at ILI sentinels was*

$$\frac{\text{Annual no. of outpatients in ILI sentinels}}{\text{Annual no. of outpatients in all hospitals}}$$

Summary of severity

Measure of severity	A(H5N1)	A(H7N9)	2009 pandemic A(H1N1)
Risk of fatality for hospitalized cases	65% (China) 60% (Worldwide)	36%	5 - 20% (China)
Risk of fatality for symptomatic cases	not known	0.16% - 2.8%	0.01% - 0.05% (Worldwide)

Yu et al. 2013 Lancet; Cowling et al. 2013 Lancet; Yu et al. 2011 Clin Infect Dis; Viboud et al. 2013 Lancet; Wong et al. 2013 Epidemiology

Summary of findings

- Symptomatic case fatality risk could be between 160 (63–460) and 2,800 (1000–9,400) per 100,000 symptomatic cases.
- A(H7N9) is not as severe as A(H5N1) but more severe than 2009 pandemic A(H1N1).

Questions