BMJ

RESEARCH

# Effectiveness of oseltamivir on disease progression and viral RNA shedding in patients with mild pandemic 2009 influenza A H1N1: opportunistic retrospective study of medical charts in China

Hongjie Yu, medical epidemiologist/deputy director,[1] Qiaohong Liao, public health officer,[1] Yuan Yuan, respiratory physician,[2] Lei Zhou, public health officer,[1] Nijuan Xiang, public health officer,[1] Yang Huai, public health officer,[1] Xiuhua Guo, professor,[3] Yingdong Zheng, associate professor,[4] H Rogier van Doorn, clinical microbiologist,[5] Jeremy Farrar, professor,[5] Zhancheng Gao, professor/respiratory physician,[2] Zijian Feng, medical epidemiologist/director,[1] Yu Wang, professor/director,[6] Weizhong Yang, medical epidemiologist/deputy director[6]

[1]Office for Disease Control and Emergency Response, Chinese Centre for Disease Control and Prevention, Beijing, China
[2]Department of Respiratory Internal Medicine, Peking University People's Hospital, Peking University Health Science Centre, Beijing
[3]School of Public Health and Family Medicine, Capital Medical University, Beijing
[4]School of Public Health, Peking University Health Science Centre, Beijing
[5]Oxford University Clinical Research Unit, South East Asia Infectious Diseases Clinical Research Network, Hospital for Tropical Diseases, Ho Chi Minh City, Vietnam
[6]Chinese Centre for Disease Control and Prevention, Beijing

**Correspondence to: W Yang yangwz@chinacdc.cn and H Yu yuhj@chinacdc.cn, Chinese Centre for Disease Control and Prevention, 155 Changbai Road, Changping District, Beijing, 102206, People's Republic of China**

Cite this as: *BMJ* 2010;341:c4779
doi:10.1136/bmj.c4779

## ABSTRACT

**Objective** To describe the clinical features and effectiveness of oseltamivir on disease progression and viral RNA shedding in patients with mild pandemic 2009 influenza A(H1N1) virus infection.

**Design** Opportunistic retrospective review of medical charts of patients with confirmed 2009 H1N1 identified through the national surveillance system in China from May to July 2009.

**Setting** Under coordination of the Ministry of Health, local health departments were asked to collect medical records of confirmed patients and send them to the Chinese Centre for Disease Control and Prevention on a voluntary basis as part of the public health response.

**Population** 1291 patients with confirmed 2009 H1N1 infection and available data for chart review.

**Main outcome measures** Demographic characteristics, comorbidities, symptoms and signs, laboratory tests, findings on chest radiography, antiviral treatment, duration of fever, and duration of viral RNA shedding.

**Results** The median age of 1291 patients was 20 years (interquartile range 12-26); 701 (54%) were male. The most common symptoms were fever (820, 64%), cough (864, 67%), sore throat (425, 33%), sputum (239, 19%), and rhinorrhoea (228, 18%). Of 920 patients who underwent chest radiography, 110 (12%) had abnormal findings consistent with pneumonia. Some 983 (76%) patients were treated with oseltamivir from a median of the third day of symptoms (2-4). No patients required admission to the intensive care unit or mechanical ventilation. 2009 H1N1 was shed from one day before onset of symptoms to up to eight days after onset in most (91%) patients, with a median of 5 (3-6) days of shedding after onset. Treatment with oseltamivir significantly protected against subsequent development of radiographically confirmed pneumonia (odds ratio 0.12, 95% confidence interval 0.08 to 0.18), and treatment started within two days of symptom onset reduced the duration of fever and viral RNA shedding.

**Conclusions** Chinese patients with 2009 H1N1 infection predominantly presented with features of uncomplicated, self limiting acute respiratory illness. 2009 H1N1 might be shed longer than seasonal influenza virus. Treatment with oseltamivir was associated with a significantly reduced development of radiographically confirmed pneumonia and a shorter duration of fever and viral RNA shedding. Though these patients benefited from treatment, the findings should be interpreted with caution as the study was retrospective and not all patients underwent chest radiography.

## INTRODUCTION

Pandemic 2009 influenza A(H1N1) virus has spread rapidly, resulting in millions of laboratory confirmed cases and over 18 000 deaths in over 200 countries.[1] In June 2009 the global spread prompted the World Health Organization to declare the first influenza pandemic of the 21st century. Since then, the clinical understanding of 2009 H1N1 infections has increased but has mostly focused on severely ill patients and those admitted to hospital,[2-10] except for one report from China.[11] The spectrum of the disease ranges from asymptomatic to non-febrile and from mild upper respiratory tract illness to severe or fatal pneumonia, and there is controversy about the different impact of antiviral treatment in these groups of patients.[12] Randomised controlled trials conducted on "old" seasonal influenza (1970 to 2008-9) showed that treatment with neuraminidase inhibitors within 48 hours of onset of symptoms can reduce the severity and duration of symptoms and possibly the risk of complications.[13-17] The extent to which treatment with neuraminidase inhibitors might benefit otherwise healthy individuals with mild 2009 H1N1 infection,

**Table 1 | Demographic characteristic and comorbidities of 1291 patients with 2009 H1N1 virus infection in China, May-July 2009. Figures are numbers (percentages) unless stated otherwise**

| Characteristic | All patients (n=1291) | Children <15 years (n=406) | Adults ≥15 years (n=885) |
|---|---|---|---|
| Male | 701 (54) | 215 (53) | 486 (55) |
| Median (IQR) age (years) | 20 (12-26) | 9 (7-11) | 23 (19-33) |
| Age group (years): | | | |
| 0-4 | 35 (3) | 35 (9) | — |
| 5-14 | 371 (29) | 371 (91) | — |
| 15-24 | 511 (40) | — | 511 (58) |
| 25-49 | 315 (24) | — | 315 (36) |
| 50-64 | 52 (4) | — | 52 (6) |
| ≥65 | 7 (0.5) | — | 7 (0.8) |
| Comorbidity associated with severe influenza*: | | | |
| Any | 64 (5) | 14 (3) | 50 (6) |
| Asthma | 29 (2) | 13 (3) | 16 (2) |
| Other chronic pulmonary disease† | 10 (0.8) | 1 (0.2) | 9 (1) |
| Chronic liver disease | 10 (0.8)‡ | 0 (0) | 10 (1)‡ |
| Type 1 or 2 diabetes | 9 (0.7) | 1 (0.2) | 8 (0.9) |
| Coronary artery disease | 4 (0.3) | 0 (0) | 4 (0.5) |
| Pregnancy | 2 (0.2)§ | 0 (0) | 2 (0.2)§ |
| Chronic renal disease | 1 (0.1) | 0 (0) | 1 (0.1) |
| Immunosuppression | 1 (0.1)¶ | 0 (0) | 1 (0.1)¶ |
| Neurological disease | 0 (0) | 0 (0) | 0 (0) |
| Current smoker | 74/1176 (6) | 1/357 (0.3) | 73/819 (9) |
| Influenza vaccination, 2008-9 season | 30/515 (6) | 15/166 (9) | 15/349 (4) |

IQR=interquartile range.
*Comorbidities not mutually exclusive; some patients had multiple chronic comorbid diseases. Data unavailable for three children and three adults.
†Includes chronic bronchitis (5), emphysema (2), bronchiectasis (2), chronic bronchitis and bronchiectasis (1).
‡Includes hepatitis B and fatty liver.
§Both in second trimester (at 13 weeks' gestation).
¶After heart transplantation.

however, remains unknown, although the world will experience a new period of seasonal influenza with 2009 H1N1, the dominant virus worldwide.[18]

China established enhanced national surveillance for patients with 2009 H1N1 on 30 April 2009, and a containment policy was implemented immediately, which included isolation of all confirmed patients, early treatment with oseltamivir, and a set of strict discharge criteria, regardless of clinical severity. On 11 May 2009, the first case of 2009 H1N1 infection was identified in China.

We carried out an opportunistic retrospective review of medical charts to describe the clinical features and effectiveness of oseltamivir on progression of disease and viral RNA shedding in patients with mild 2009 H1N1 infection among 1291 laboratory confirmed cases identified through the national surveillance from May to 31 July 2009.

## METHODS

### National surveillance for pandemic H1N1

All suspected cases of 2009 H1N1 were identified through active surveillance with screening at borders and medical monitoring of close contacts of patients with confirmed disease or through passive reporting by clinicians when those patients sought medical consultations. All suspected and laboratory confirmed cases were reported to the Chinese Centre for Disease Control and Prevention.

A case of acute respiratory illness was defined as a patient with fever (axillary temperature ≥37.3°C) or recent onset of at least one of rhinorrhoea, nasal congestion, sore throat, or cough. A suspected case was defined as a person with acute respiratory illness and onset of illness within seven days of travel to an area with confirmed cases or within seven days of close contact with a confirmed case. A confirmed case was defined as a patient with acute respiratory illness and laboratory evidence of 2009 H1N1 infection diagnosed by real time reverse transcription polymerase chain reaction testing of respiratory specimens.

### Patients

During the early stage of the pandemic (until to 31 July), all patients with suspected 2009 H1N1, regardless of clinical severity, were admitted to designated hospitals and treated with a standard dose of oseltamivir.[19 20] Upper respiratory specimens (nasal, throat, and nasopharyngeal swabs) were collected and placed in sterile viral transport medium for 2009 H1N1 testing. RNA was extracted from specimens with the RNeasy Mini Kit (Qiagen, Valencia, CA, USA) and tested by real time reverse transcription polymerase chain reaction following the protocol of the US Centres for Disease Control and Prevention.[21] Assays were performed in the National Influenza Surveillance Network of 63 laboratories and confirmed by the National Influenza Centre. During the early phase of the 2009 H1N1 outbreak the infectious period was unknown, and the Ministry of Health of China recommended the taking of additional respiratory specimens to determine viral clearance dynamics with molecular analysis.[22] The criteria for discharge from hospital were normal body temperature recorded on two consecutive days, resolution of respiratory symptoms, and two respiratory specimens with negative results collected over two consecutive days.[22]

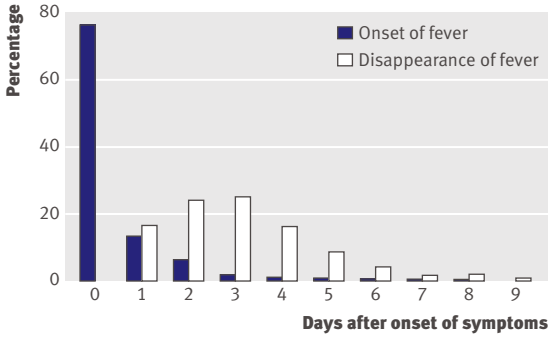


**Fig 1 | Onset and disappearance of fever over clinical course by days after onset of symptoms in 1219 febrile patients with 2009 influenza H1N1 virus infection**

**Table 2 | Clinical symptoms and signs in 1291 patients with 2009 H1N1 virus infection at hospital admission in China, May-July 2009. Figures are numbers (percentages) unless stated otherwise**

| Characteristic | All patients (n=1291) | Children <15 years (n=406) | Adults ≥15 years (n=885) |
|---|---|---|---|
| Clinical symptoms: | | | |
| Fever | 820 (64) | 268 (66) | 552 (62) |
| Cough | 864 (67) | 291 (72) | 573 (65) |
| Sore throat | 425 (33) | 116 (29) | 309 (35) |
| Sputum | 239 (19) | 81 (20) | 158 (18) |
| Rhinorrhoea | 228 (18) | 75 (18) | 153 (17) |
| Headache | 211 (16) | 57 (14) | 154 (17) |
| Weakness | 190 (15) | 47 (12) | 143 (16) |
| Nasal congestion | 149 (12) | 37 (9) | 112 (13) |
| Myalgia | 111 (9) | 20 (5) | 91 (10) |
| Chill | 72 (6) | 17 (4) | 55 (6) |
| Nausea | 22 (2) | 10 (2) | 12 (1) |
| Vomiting | 23 (2) | 13 (3) | 10 (1) |
| Diarrhoea | 19 (1) | 5 (1) | 14 (2) |
| Dyspnoea or shortness of breath | 0 (0) | 0 (0) | 0 (0) |
| Signs: | | | |
| Pharyngeal congestion | 1026 (79) | 325 (80) | 701 (79) |
| Swollen tonsils | 442 (34) | 179 (44) | 263 (30) |

### Data collection

We retrospectively reviewed medical charts to collect data on patients with confirmed infection identified through the national surveillance system from May to 31 July 2009. Beginning in August, as 2009 H1N1 activity expanded, the national policy changed to focus on identifying patients admitted to hospital and continuing routine sentinel influenza surveillance. Only patients who required hospital care were admitted, while patients with milder infection were cared for at home. Under coordination of the Ministry of Health, local health departments were asked to collect medical records of patients with confirmed infection and send them to the Chinese Centre for Disease Control and Prevention on a voluntary basis as part of the public health response. In this study we included patients with available data who were discharged during the study period that ended on 31 July.

Medical epidemiologists reviewed medical charts and extracted data using a standardised form that included demographics, comorbidities, symptoms and signs, laboratory tests, findings on chest radiography, complications, treatment, course, and outcome and results of reverse transcription polymerase chain reaction. The first negative result of two consecutive respiratory specimens was considered to indicate an undetectable viral RNA level. We could not determine the actual onset of fever or the preadmission dynamics of viral RNA shedding and therefore, unlike in another recent report,[11] during hospital admission we defined duration of fever as the number of days between onset of symptoms and return to normal body temperature; duration of viral RNA shedding was defined as the number of days between onset of symptoms and undetectable viral RNA level.

### Statistical analysis

Data were double entered on a computerised database using Microsoft Access. Descriptive statistics included frequency analysis for categorical variables, means and standard deviations for normal distributions, or medians and interquartile ranges for continuous variables. We used two sample *t* tests, Wilcoxon rank sum test, and Kruskal-Wallis H test for continuous variables and $\chi^2$ test or Fisher's exact test for discrete variables in bivariate analyses.

We used multivariable logistic regression models to identify risk factors associated with subsequent development of radiographic pneumonia and calculated odds ratios and 95% confidence intervals. Numbers needed to treat equal to 1/absolute risk reduction were estimated. Based both on relations within the cohort and data from other publications, we considered age, sex, comorbidities, smoking, influenza vaccination, and treatment with oseltamivir and antibiotics as candidate variables. We excluded from the models the variable of days between onset of illness and admission to hospital because of colinearity with the variable of days between onset of illness and initial oseltamivir treatment. To better understand the causal effect of antimicrobial (oseltamivir and antibiotics) intervention and subsequent development of radiographic pneumonia, we considered only oseltamivir and antibiotics given before the presence of radiographic pneumonia.

We used general linear models to identify risk factors associated with prolonged duration of fever and of viral RNA shedding by using log transformed data. Candidate variables considered for analysis of prolonged duration of fever were sex, age, comorbidities, smoking, influenza vaccination, presence of radiographic pneumonia, and treatment with oseltamivir. We also included presence of high fever, cough, sputum, vomiting, and diarrhoea for analysis of prolonged duration of viral RNA shedding, and, as duration of fever and viral RNA shedding were positively correlated (Spearman's ρ 0.417; P<0.001), we included duration of fever in the multivariable model. For variables regarding clinical findings, we included symptoms developed and treatments given during the whole clinical course in the analysis.

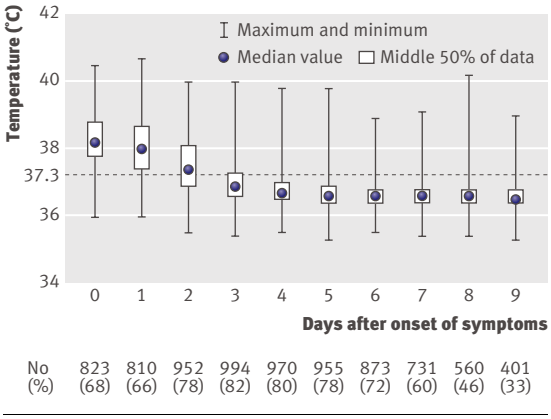


**Fig 2 | Body temperature over clinical course in 1219 febrile patients with 2009 influenza H1N1 virus infection**

**Table 3 | Laboratory findings of 1291 patients with 2009 H1N1 virus infection at hospital admission in China, May-July 2009. Figures are numbers (percentages) unless stated otherwise**

| Characteristic | All patients (n=1291) | Children <15 years (n=406) | Adults ≥15 years (n=885) |
|---|---|---|---|
| Haematology: | | | |
| Leucopenia | 451/1237 (36) | 169/388 (44) | 282/849 (33) |
| Neutropenia | 483/1233 (39) | 182/388 (47) | 301/845 (36) |
| Lymphopenia | 252/1229 (21) | 84/387 (22) | 168/842 (20) |
| Thrombocytopenia | 34/1208 (3) | 9/382 (2) | 25/826 (3) |
| Anaemia | 109/1211 (9) | 74/381 (19) | 35/830 (4) |
| Raised erythrocyte sedimentation rate | 67/228 (29) | 33/86 (38) | 34/142 (24) |
| Serum biochemistry: | | | |
| Alanine aminotransferase >40 U/l | 110/1068 (10) | 17/332 (5) | 93/736 (13) |
| Aspartate aminotransferase >40 U/l | 127/1035 (12) | 62/327 (19) | 65/708 (9) |
| Creatinine >177 μmol/l | 0/1107 (0) | 0/353 (0) | 0/754 (0) |
| Raised creatine kinase | 100/524 (19) | 39/174 (22) | 61/350 (17) |
| Creatine phosphokinase isoenzymes >25 U/l | 51/460 (11) | 31/162 (19) | 20/298 (7) |
| Lactic dehydrogenase >245 U/l | 119/717 (17) | 77/205 (38) | 42/512 (8) |
| C reactive protein >8 mg/l | 271/705 (38) | 41/246 (17) | 230/459 (50) |
| Immunological marker: | | | |
| CD4 <0.35×$10^9$/l | 130/527 (25) | 28/132 (21) | 102/395 (26) |
| CD8 <0.24×$10^9$/l | 121/526 (23) | 21/131 (16) | 100/395 (25) |
| CD4:CD8 ratio <1.4 | 279/528 (53) | 70/131 (53) | 209/397 (53) |
| Invasive bacterial co-infection | 0/36 (0) | 0/19 (0) | 0/17 (0) |
| Radiographic diagnosis of pneumonia during admission: | | | |
| Total | 110/920 (12) | 28/287 (10) | 82/633 (13) |
| Only infiltrate | 105 (95) | 27 (96) | 78 (95) |
| Unilateral infiltrate | 67 (64) | 15 (56) | 52 (67) |
| Bilateral infiltrate | 38 (36) | 12 (44) | 26 (33) |
| Consolidation: | | | |
| Total | 5 (5) | 1 (4) | 4 (5) |
| Unilateral consolidation | 4 (80) | 1 (100) | 3 (75) |
| Bilateral consolidation | 1 (20) | 0 (0) | 1 (25) |
| Median (IQR) time (days) from illness onset to radiographic diagnosis of pneumonia | 2 (1-3) | 2 (1-4) | 2 (1-3) |

IQR=interquartile range.

Statistical analysis was performed with SPSS (v13.0, SPSS, Chicago, IL, USA). For all analyses, probabilities were two tailed and a P value of <0.05 was considered significant.

## RESULTS

### Demographic characteristics and comorbidities

From 11 May to 31 July 2009 a total of 2126 confirmed cases of 2009 H1N1 were reported. We included 1291 (61%) with available data for chart review reported from 94 prefectures in 25 provinces (see appendix 1 on bmj.com), which represented 90% (1291/1438) of patients discharged before 31 July. See bmj.com for details of patients' enrolment (appendix 2) and a comparison of the characteristics of patients with and without medical records for review (appendix 3). Of the 1291 patients, 406 (31%) were aged <15 years and were classed as children.

The median age of the patients was 20 years (interquartile range 12-26) and 54% were male (table 1); most (71%) were aged ≤24. Of the 1291 patients, 64 (5%) had a comorbidity associated with severe influenza; the most common were asthma (2%), other chronic pulmonary disease (0.8%), and chronic liver disease (0.8%). Two patients were pregnant, both in the second trimester.

### Clinical symptoms and laboratory findings

The most common symptoms on admission were fever (820, 64%), cough (864, 67%), sore throat (425, 33%), sputum (239, 19%), and rhinorrhoea (228, 18%) (table 2). Only 4% of the patients reported gastrointestinal tract symptoms including diarrhoea, nausea, or vomiting. The most common signs were pharyngeal congestion (1026, 79%) and swollen tonsils (442, 34%). None of 1291 patients developed symptoms of lower respiratory tract disease such as dyspnoea or shortness of breath. More children than adults experienced cough, vomiting, and swollen tonsils (table 2).

Table 3 gives details of abnormal haematological findings at admission, which included leucopenia (451, 36%), neutropenia (483, 39%), lymphopenia (252, 21%), thrombocytopenia (34, 3%), and anaemia (109, 9%) in children and adults. Some patients had mildly raised biochemical markers including alanine aminotransferase (110, 10%), aspartate aminotransferase (127, 12%), creatine kinase (100, 19%), creatine phosphokinase isoenzymes (51, 11%), lactic dehydrogenase (119, 17%), and C reactive protein (271, 38%). Compared with adults, children more often had leucopenia, anaemia, or raised aspartate aminotransferase, creatine phosphokinase isoenzymes, and lactic dehydrogenase levels (table 3).

Of the 920 patients who underwent chest radiography during their stay in hospital, 110 (12%) had abnormal findings consistent with pneumonia. Radiography was carried out at a median of two days (interquartile range, 1-3) after onset of symptoms in 28 (10%) children and 82 (13%) adults (table 3). Findings included infiltration in 105 patients and consolidation in five. The most common features of these

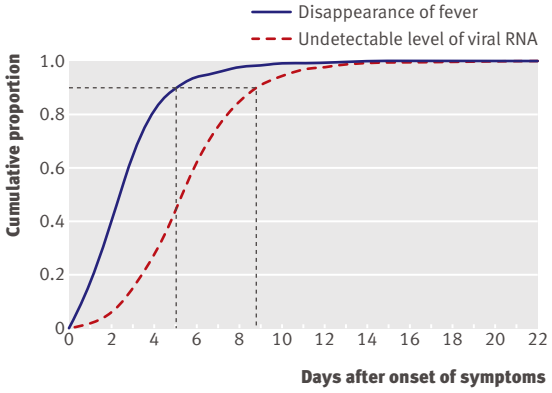


**Fig 3 | Cumulative disappearance of fever and proportion of patients with undetectable viral RNA by days after onset of symptoms**

**Table 4 | Treatments and clinical course of 1291 patients with 2009 H1N1 virus infection in China, May-July 2009. Figures are numbers (percentages) unless stated otherwise**

| Characteristic | All patients (n=1291) | Children <15 years (n=406) | Adults ≥15 years (n=885) |
|---|---|---|---|
| Oseltamivir treatment | 983 (76) | 299 (74) | 684 (77) |
| Oseltamivir initiation time (days after onset of symptoms): | | | |
| Median (IQR) | 3 (2-4) | 3 (2-4) | 3 (2-4) |
| Day 1-2 | 363 (37) | 106 (35) | 257 (38) |
| Day 3-4 | 476 (48) | 153 (51) | 323 (47) |
| Day 5-17 | 144 (15) | 40 (13) | 104 (15) |
| Duration of oseltamivir treatment (days): | | | |
| Median (IQR) | 5 (5-6) | 5 (5-6) | 6 (5-6) |
| 1-4 | 138 (14) | 39 (13) | 99 (14) |
| 5 | 735 (75) | 237 (79) | 498 (73) |
| 6-15 | 110 (11) | 23 (8) | 87 (13) |
| Received antibiotics* | 479 (37) | 129 (32) | 350 (40) |
| Received antipyretics† | 340 (26) | 143 (35) | 197 (22) |
| Supplementary oxygen treatment‡ | 18 (1) | 3 (0.7) | 15 (2) |
| Corticosteroid treatment | 3 (0.2) | 1 (0.2) | 2 (0.2) |
| Median (IQR) time (days) from symptom onset to fever | 0 (0-0) | 0 (0-0) | 0 (0-1) |
| Median (IQR) time (days) from symptom onset to fever disappearance | 3 (2-4) | 3 (2-4) | 3 (2-4) |
| Afebrile though clinical course | 72 (6) | 15 (4) | 57 (6) |
| Median (IQR) time (days) from symptom onset to resolution§ | 5 (4-7) | 5 (4-7) | 5 (4-7) |
| Median (IQR) time (days) from symptom onset to hospital admission | 2 (1-3) | 2 (1-3) | 2 (1-3) |
| Median (IQR) time (days) from symptom onset to discharge | 8 (6-10) | 8 (7-10) | 8 (6-9) |

IQR=interquartile range.
*Some patients received multiple antibiotics. Major antibiotics include cephalosporins (243, 51%), macrolides or azithromycin (221, 46%), fluoroquinolones (83, 17%), penicillins (70, 15%), lincomycin (8, 2%), aminoglycosides (4, 1%).
†Some patients received multiple antipyretics. Major antipyretics include paracetamol non-steroidal anti-inflammatory drugs (199, 46%), arylpropionic acid non-steroidal anti-inflammatory drugs (98, 23%), physical antipyretic measures (51, 12%), salicylic acid non-steroidal anti-inflammatory drugs (31, 7%).
‡Mask oxygen therapy (n=5); nasal catheter oxygen therapy (n=13).
§Resolution of symptoms defined as disappearance of influenza related symptoms including fever, cough, sore throat, nasal congestion, rhinorrhoea, myalgia, weakness, etc.

abnormalities were local patchy shadowing and lobular infiltration. None of 36 patients who were tested had bacterial growth from blood cultures.

### Treatment and clinical course

The 1291 patients were admitted to hospital a median of two days (interquartile range 1-3) after onset of symptoms (table 4). During admission, 983 (76%) patients were treated with oseltamivir from a median of day three of symptom onset (2-4) and 363 (37%) patients within two days of symptom onset. Some 735 (75%) patients received a standard course of oseltamivir (five days), and 110 (11%) received prolonged treatment for persistently positive viral RNA. During hospital admission, 479 (37%) patients received empirical antibiotics, most commonly cephalosporins (51%) and macrolides or azithromycin (46%). Few patients received corticosteroids (three) or supplementary oxygen via either mask (five) or nasal catheter (13). None of 1291 patients required admission to an intensive care unit or invasive mechanical ventilation.

Seventy two (6%) patients had no fever throughout the clinical course. Of the remaining 1219 (94%) patients who developed fever, most (76%) had fever on the same day as onset of symptoms, and fever most commonly disappeared two (24%) or three days (25%) after onset (fig 1and fig 2). Fever persisted for a median of two days (interquartile range 1-3). Overall, the median body temperature of febrile patients had returned to normal (<37.3°C) three days after onset (fig 1), and 90% of fevers had disappeared within five days (fig 3). All 1291 patients' symptoms resolved fully at a median of five days (4-7) after onset, and patients were discharged at a median of eight days (6-10) after

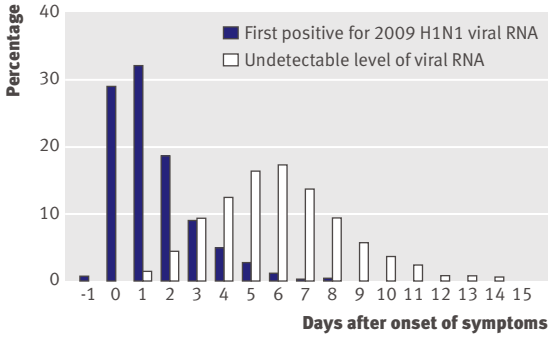


**Fig 4 | Proportion of samples with first positive for viral RNA and samples with undetectable viral RNA by days after onset of symptoms**

Table 5 | Multivariable analyses* of risk factors associated with prolonged duration of fever and duration of viral RNA shedding

| Risk factors | No (%) of patients included in analysis | β (95% CI) | P value |
|---|---|---|---|
| **Duration of fever (n=951)†** | | | |
| Oseltamivir: | | | |
| Started on day 1-2 of symptom onset | 246 (26) | Reference | |
| Started >2 days after symptom onset | 440 (46) | 0.15 (0.11 to 0.19) | <0.001 |
| No oseltamivir treatment | 265 (28) | 0.05 (0.001 to 0.10) | 0.044 |
| Radiographic pneumonia: | | | |
| Not present | 569/643 (88) | Reference | |
| Present | 74/643 (12) | 0.07 (0.01 to 0.12) | 0.018 |
| **Prolonged duration of viral RNA (n=1289)‡** | | | |
| Oseltamivir: | | | |
| Started on day 1-2 of symptom onset | 363 (28) | Reference | |
| Started >2 days after symptom onset | 619 (48) | 0.13 (0.10 to 0.16) | <0.001 |
| No oseltamivir treatment | 307 (24) | 0.04 (0.01 to 0.07) | 0.021 |
| Cough: | | | |
| Not present | 188 (15) | Reference | |
| Present | 1101 (85) | 0.07 (0.03 to 0.10) | <0.001 |
| Sputum: | | | |
| Not present | 715 (55) | Reference | |
| Present | 574 (45) | 0.04 (0.004 to 0.05) | 0.025 |
| Duration (days) of fever after onset of symptoms†§ | 949 (74) | 0.03 (0.02 to 0.03) | <0.001 |

*General linear model. β >0 indicates variable increases duration of fever or duration of viral RNA shedding and β <0 indicates the variable reduces duration of fever or duration of viral RNA shedding. For example, compared with patients with oseltamivir started on day 1-2 of symptoms, duration of fever would be 1.4 (equal to 10β) times that in patients with oseltamivir started on >2 days after symptom onset.
†Excluded 340 patients treated with antipyretics.
‡Excludes two patients because data unavailable on time from onset of illness to first sample negative for 2009 influenza H1N1 virus RNA.
§Considered as continuous variable when included in model.

onset. In the final multivariable model (table 5), no oseltamivir treatment (β 0.05, 95% confidence interval 0.001 to 0.10) or oseltamivir treatment starting more than two days after symptom onset (0.15, 0.11 to 0.19) and presence of radiographic pneumonia (0.07, 0.01 to 0.12) were independent factors associated with a prolonged duration of fever.

### Risk factors associated with radiographic pneumonia

In the final multivariable model, which included 920 patients who underwent chest radiography during their admission to hospital, treatment with oseltamivir starting within two days (odds ratio 0.17, 95% confidence interval 0.10 to 0.29) or more than two days (0.09, 0.05 to 0.15) after onset of symptoms were identified as significant protective factors for radiographic pneumonia (table 6). When we combined oseltamivir treatment starting within two days or after two days for multivariable analyses, there was no significant change in the estimate of overall impact on presence of radiographic pneumonia (0.12, 0.08 to 0.18, P<0.001). To prevent one 2009 H1N1 patient developing radiographic pneumonia, four patients (number needed to treat 4, 3 to 5) would need to be treated with oseltamivir. With regard to development of radiographic pneumonia, there seemed to be no more benefit with early initiation of oseltamivir (within two days of symptom onset) than with initiation after two days.

### Viral RNA shedding

We had data on the first positive and undetectable viral RNA results in respiratory specimens for almost all patients (1289). Those specimens were collected at a median of one day (0-2) and six days (4-7) after the onset of symptoms. Specimens with first positive results were usually collected on the day (29%) of symptom onset or one day (32%) after, while the sample with undetectable viral RNA was most commonly collected at five (16%) or six days (17%) after onset (fig 4). Specimens positive for viral RNA were collected from 11 patients one day before onset of symptoms, while they were under medical observation as close contacts of cases. Overall, viral RNA was undetectable among most patients (91%) within nine days after symptom onset (fig 3). Of the 119 (9%) remaining patients whose first test with undetectable viral RNA was later than nine days after symptom onset, 45 (38%) were children and five (4%) had one comorbidity associated with severe influenza, but none of them were immunosuppressed. The median interval between the first sample positive for viral RNA and the undetectable RNA was four days (3-6), and the median interval between disappearance of fever and an undetectable viral RNA level was three days (1-4).

Two previously healthy men had the longest duration of viral RNA shedding (21 days). One was a 20 year old student with acute respiratory illness; he also had the longest duration of fever of 16 days. He received oseltamivir treatment for five days, beginning two weeks after onset of symptoms. The other was a 28 year old patient with radiographic pneumonia after five days of fever. He received oseltamivir treatment for 15 days, starting two days after onset.

In the final multivariable model (table 5), no oseltamivir treatment (β 0.04, 95% confidence interval, 0.01 to 0.07) or oseltamivir treatment starting more than two days after symptom onset (0.13, 0.10 to 0.16), presence of cough (0.07, 0.03 to 0.10), sputum (0.04, 0.004 to 0.05), and prolonged duration of fever (0.026, 0.020 to 0.032) were independent factors associated with prolonged viral RNA shedding.

## DISCUSSION

### Principal findings

In people with mild H1N1 infection, treatment with oseltamivir significantly protects against subsequent development of radiographically confirmed pneumonia, and early initiation within two days of onset of symptoms reduces the duration of fever and viral RNA shedding. We studied 1300 patients with mild 2009 H1N1 infection, who mostly presented with clinical features of uncomplicated, self limiting acute respiratory illness. A minority (12%) of patients had chest radiography consistent with pneumonia. Three quarters of patients were treated with oseltamivir during admission to hospital. The laboratory analyses showed that 2009 H1N1 is shed from one day before onset of symptoms and might be shed for a longer period of time than seasonal influenza virus.

Table 6 | Multivariable analyses* of risk factors associated with presence of radiographic diagnosis of pneumonia

| | No diagnosis of pneumonia (n=810) | Diagnosis of pneumonia (n=110) | Odds ratio (95% CI) | P value |
|---|---|---|---|---|
| No oseltamivir treatment | 163 (20) | 75 (68) | Reference | |
| Oseltamivir started >2 days after symptom onset | 406 (50) | 16 (15) | 0.09 (0.05 to 0.15) | <0.001 |
| Oseltamivir started on day 1-2 of symptom onset | 241 (30) | 19 (17) | 0.17 (0.10 to 0.29) | <0.001 |

*Multivariable logistic regression model. OR >1 indicates variable is risk factor and OR <1 indicates variable is protective factor.

### Strength and comparison with other studies

At the beginning of the pandemic, China implemented an aggressive containment strategy based on the national pandemic preparedness plan. Rigorous clinical management, which included isolation of all patients with confirmed infection and early oseltamivir treatment, and set discharge criteria, including an undetectable viral RNA level, provided us with a unique opportunity to study the clinical features, effectiveness of oseltamivir treatment, and the viral RNA shedding pattern of patients with mild 2009 H1N1. Our study population was three times the size of one in a recent study[11] and provided us with a more powerful analysis to determine the effect of oseltamivir on the prevention of radiographically confirmed pneumonia.

Most of our patients presented with features of uncomplicated, self limiting acute respiratory illness, similar to seasonal influenza.[23] Fever was an early symptom but was not always present at admission (36%), and 6% of our patients did not have fever throughout their clinical course. A meta-analysis reported that fever occurred in only one third of healthy participants in experimental seasonal influenza virus infection.[24] Consistent with the duration of fever in seasonal influenza (three to four days), fever resolved within five days for most patients. Gastrointestinal symptoms were rare (4%), although consistent with adults infected with seasonal influenza,[23] but much lower than in recent reports of severely affected patients admitted to hospital with 2009 H1N1 infection.[3 4] Seasonal influenza is associated with various signs and symptoms that can vary by age, underlying chronic disease, pregnancy, complications, and host immune status. Clinical features among children and adults in our study were similar, consistent with an absence of immunity to this novel virus, although older people aged >60 might have pre-existing immunity.[25] As with uncomplicated seasonal influenza, in which illness typically resolves after three to seven days,[26] our patients' symptoms resolved fully within five days of illness.

Although upper respiratory illness with systemic symptoms constituted the most common presentation, a minority (12%) of patients had findings on chest radiography consistent with pneumonia, but notably none of them presented with clinical symptoms or signs of lower respiratory tract disease. Of the patients with radiographic evidence of pneumonia, most (92%) received antiviral drugs and 59% received empirical antibiotics. It is difficult to precisely determine the cause of pneumonia from radiography, though most radiographic features of local patchy shadowing and the negative results of blood cultures in our study would not seem to support the use of antibiotics for these mildly affected patients. A current summary of bacterial isolates from 53 children who died from 2009 H1N1[27] highlights a challenge facing clinicians who make decisions about antibiotic treatment in influenza patients with lower respiratory tract disease. Most uncomplicated self limiting acute respiratory illness caused by 2009 H1N1, however, does not require treatment with antibiotics.

Our study suggests that 2009 H1N1 is shed from one day before the onset of symptoms to eight days after onset for most (91%) patients and can be shed up to 21 days. Consistent with two small observational studies in Singapore[28] and Canada,[29] our results show that 2009 H1N1 can be shed for a longer period of time than seasonal influenza virus. The latter is usually shed for five days after onset of symptoms in adults,[30 31] although the virus can be isolated up to two weeks after the onset of symptoms in children and even longer in immunocompromised individuals.[32 33] One study isolated viable pandemic H1N1 virus in 24% of samples taken seven days after the onset of illness in adults.[34] Influenza virus shedding usually stops once the illness has resolved.[33] In our study, however, though viral RNA shedding correlated with the duration of fever, viral RNA negativity lagged behind the resolution of fever by a median of three days. Although the viral RNA shedding by real time reverse transcription polymerase chain reaction might not reflect the true infectious period, our results suggest current infection control guidance[20 35] on the duration of isolation precautions for patients admitted to hospital (24 hours after the resolution of fever and respiratory symptoms) might be too short and patients might be infectious for longer.

Three quarters of our patients received oseltamivir treatment, and 37% of them were given treatment within two days of symptom onset. Thus, we analysed the effectiveness of oseltamivir treatment on the subsequent development of radiographic evidence of pneumonia and on two quantitative indicators—duration of fever and viral RNA shedding—rather than grouping only duration of viral RNA shedding as in a recent study.[11] Our study suggests that oseltamivir reduces the risk of radiographically confirmed pneumonia, and early treatment within two days of symptoms onset can reduce the duration of fever and viral RNA shedding. Two small observational studies on 2009 H1N1 also suggested that early oseltamivir treatment

## WHAT IS ALREADY KNOWN ON THIS TOPIC

Neuraminidase inhibitors (especially oseltamivir) have been widely recommended to treat patients with pandemic 2009 H1N1 infections outside the risk groups

Neuraminidase inhibitors given within 48 hours of symptom onset can reduce severity and duration of symptoms and possibly the risk of complications for seasonal influenza

## WHAT THIS STUDY ADDS

In patients with mild pandemic 2009 H1N1 infection, oseltamivir can protect against subsequent development of radiographic pneumonia, even in those who start treatment more than two days after the onset of symptoms

Early oseltamivir treatment within two days of symptom onset can reduce the duration of fever and viral RNA shedding

Pandemic 2009 H1N1 virus is shed from one day before the onset of clinical symptoms to up to eight days after onset for most patients and is shed for longer than seasonal influenza virus

reduced duration of viral shedding,[28] viral load, and duration of fever.[36] The evidence from previous randomised controlled trials of uncomplicated seasonal influenza is strongest for antiviral treatment started within 48 hours of illness onset.[13-17] Current guidance recommends that antiviral treatment should be initiated immediately and without waiting for laboratory confirmation of diagnosis.[20 37] Observational studies suggest that neuraminidase inhibitor treatment of patients in hospital can reduce disease severity and mortality, both for 2009 H1N1[3 6 10] and seasonal influenza.[38-40] Our results, however, do not suggest that early initiation of oseltamivir (that is, less than two days after onset) was more protective than later initiation. Consistent with the observational studies on seasonal infection[40 41] and human infection with H5N1,[42] our patients still seemed to gain benefit (prevention of radiographically confirmed pneumonia) even when they received antiviral treatment more than 48 hours after symptom onset. Antiviral treatment should ideally be started early after the onset of symptoms, but it can also be used at any stage of active disease if ongoing viral replication is anticipated or documented.[20 43]

We believe the absence of severely affected patients in our series is because of early admission to hospital and early treatment with oseltamivir for most patients. In contrast to previous reports on severely affected patients admitted to hospital in countries with sustained community-wide transmission,[2-9] our case series reflects only the most commonly affected—that is, young healthy adults—at the beginning of the pandemic, which is not representative of the general Chinese population. Also, the prevalence of risk factors associated with severe disease from 2009 H1N1, including chronic comorbidities, pregnancy, and very young age, in our patients is much lower than in recent reports of severely affected patients admitted to hospital.[2-10] These differences are probably because we included all patients positive for reverse transcription polymerase chain reaction, whereas in the other studies requirement for admission to hospital was an additional criterion.

### Limitations of study

Our study was limited to data available for early 2009 H1N1 cases identified through surveillance during the study period, did not include all confirmed patients, and was inevitably retrospective. For timeliness to inform public health policy, we included only 90% of patients discharged during the study period that ended on 31 July, and we have no information on patients who were still in hospital when the study ended. Not all patients underwent radiography, which could have introduced selection bias. Participation in the study was voluntary and was therefore subject to reporting bias. The national surveillance system might not have identified all cases of 2009 H1N1, especially among severely affected people. All laboratory testing was clinically driven, and tests were not carried in a standardised fashion. We did not attempt viral isolation to show the actual viral shedding pattern and conducted antiviral resistance analysis for patients with prolonged antiviral treatment and viral RNA shedding. We also did not collect data on adverse events attributable to oseltamivir and on why 24% of patients did not receive oseltamivir. Inevitably, there was circularity of reporting on clinical features of the illness in patients who were selected according to the case definition that included these features.

### Conclusion

In conclusion, during the early phase of the pandemic, Chinese patients with 2009 H1N1 infection predominantly presented with features of uncomplicated, self limiting acute respiratory illness. 2009 H1N1 is shed for longer than seasonal influenza virus. Oseltamivir treatment was identified as a significant protective factor against subsequent development of radiographic pneumonia, faster fever clearance times, and shorter viral RNA shedding. These findings are consistent with patients with the new 2009 H1N1 benefiting from use of oseltamivir. Given the retrospective design of this work and the fact that not all patients underwent radiography, however, our finding that oseltamivir treatment protected against subsequent radiographic pneumonia should be interpreted with caution. Continued investigation is needed to define the effectiveness of antiviral treatment, pharmacokinetic and pharmacodynamic parameters, viral shedding patterns, and risk factors for an increased severity of illness, which will allow for improvement both in clinical treatment and public health guidance.

We thank the all designated hospitals and local Centres for Disease Control and Prevention for assistance in coordinating data collection, and the Ministry of Health in China for generously facilitating this study.
**Contributors:** HY and WY conceived, designed, and supervised the study, finalised the analysis, and interpreted the findings. QL, YY, LZ, NX, YH, XG, and YZ assisted in data collection and analysis. HY wrote the drafts of the manuscript. HRvanD and JF interpreted the findings and commented on and helped revise drafts of the manuscript. All other coauthors (ZG, ZF, YW) participated in collection and management of data. HY is guarantor.
**Funding:** This study was supported by grants from US National Institutes of Health (Comprehensive International Program for Research on AIDS grant U19 AI51915), the China-US Collaborative Program on Emerging and Re-emerging Infectious Diseases, South East Asia Infectious Disease Clinical Research Network, and Wellcome Trust Major Overseas

Programme, Oxford University Clinical Research Unit, Ho Chi Minh City, Vietnam. None of the funders had any role in the study design and the collection, analysis, and interpretation of data, or in the writing of the article and the decision to submit it for publication. The researchers confirm their independence from funders and sponsors. All authors had full access to all data included in the study and are jointly responsible for the integrity of the data and accuracy of data analyses.

**Competing interests:** All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: no support from any institution for the submitted work; no financial relationships with any institutions that might have an interest in the submitted work in the previous 3 years; no other relationships or activities that could appear to have influenced the submitted work.

**Ethical approval:** This study was considered to be part of a continuing public health outbreak investigation by the Ministry of Health of China and exempt from institutional review board assessment. All data were kept confidential without patient identifiers.

**Data sharing:** Technical appendix, statistical code, and dataset are available from the corresponding author at yuhj@chinacdc.cn for re-analysis.

1 World Health Organization. Pandemic (H1N1) 2009—update 105. 2010. www.who.int/csr/don/2010_06_18/en/index.html.
2 Novel swine-origin influenza A (H1N1) virus investigation team. Emergence of a novel Swine-origin influenza A (H1N1) virus in humans. *N Engl J Med* 2009;260:2605-15.
3 Jain S, Kamimoto L, Bramley AM, Schmitz AM, Benoit SR, Louie J, et al. Hospitalized patients with 2009 H1N1 influenza in the United States, April-June 2009. *N Engl J Med* 2009;361:1935-44.
4 Louie JK, Acosta M, Winter K, Jean C, Gavali S, Schechter R, et al. Factors associated with death or hospitalization due to pandemic 2009 influenza A (H1N1) infection in California. *JAMA* 2009;302:1896-902.
5 Perez-Padilla R, de la Rosa-Zamboni D, Ponce de Leon S, Hernandez M, Quiñones-Falconi F, Bautista E, et al. Pneumonia and respiratory failure from swine-origin influenza A (H1N1) in Mexico. *N Engl J Med* 2009;361:680-9.
6 Dominguez-Cherit G, Lapinsky SE, Macias AE, Pinto R, Espinosa-Perez L, de la Torre A, et al. Critically ill patients with 2009 influenza A (H1N1) in Mexico. *JAMA* 2009;302:1880-7.
7 Canadian Critical Care Trials Group H1N1 Collaborative. Critically ill patients with 2009 influenza A (H1N1) infection in Canada. *JAMA* 2009;302:1872-9.
8 ANZIC Influenza Investigators. Critical care services and 2009 H1N1 influenza in Australia and New Zealand. *N Engl J Med* 2009;361:1925-34.
9 Australia and New Zealand Extracorporeal Membrane Oxygenation (ANZ ECMO) Influenza Investigators. Extracorporeal membrane oxygenation for 2009 influenza A (H1N1) acute respiratory distress syndrome. *JAMA* 2009;302:1888-95.
10 Rello J, Rodríguez A, Ibañez P, Socias L, Cebrian J, Marques A, et al. Intensive care adult patients with severe respiratory failure caused by Influenza A (H1N1)v in Spain. *Crit Care* 2009;13:R148.
11 Cao B, Li XW, Mao Y, Wang J, Lu HZ, Chen YS, et al. Clinical features of the initial cases of 2009 pandemic influenza A (H1N1) virus infection in China. *N Engl J Med* 2009;361:2507-17.
12 Jefferson T, Jones M, Doshi P, Del Mar C. Neuraminidase inhibitors for preventing and treating influenza in healthy adults: systematic review and meta-analysis. *BMJ* 2009;339:b5106.
13 Moscona A. Neuraminidase inhibitors for influenza. *N Engl J Med* 2005;353:1363-73.
14 Hayden FG, Treanor JJ, Fritz RS, Lobo M, Betts RF, Miller M, et al. Use of the oral neuraminidase inhibitor oseltamivir in experimental human influenza: randomized controlled trials for prevention and treatment. *JAMA* 1999;282:1240-6.
15 Nicholson KG, Aoki FY, Osterhaus AD, Trottier S, Carewicz O, Mercier CH, et al. Efficacy and safety of oseltamivir in treatment of acute influenza: a randomised controlled trial. Neuraminidase Inhibitor Flu Treatment Investigator Group. *Lancet* 2000;355:1845-50.
16 Treanor JJ, Hayden FG, Vrooman PS, Barbarash R, Bettis R, Riff D, et al. Efficacy and safety of the oral neuraminidase inhibitor oseltamivir in treating acute influenza: a randomized controlled trial. US Oral Neuraminidase Study Group. *JAMA* 2000;283:1016-24.
17 Ong AK, Hayden FG. John F. Enders lecture 2006: antivirals for influenza. *J Infect Dis* 2007;196:181-90.
18 Nicoll A. A new decade, a new seasonal influenza: the Council of the European Union recommendation on seasonal influenza vaccination. *Euro Surveill* 2010;15:pii:19458.
19 Ministry of Health, China. [Clinical management of human infection with pandemic 2009 influenza A (H1N1) virus: initial guidance.] 2009. www.moh.gov.cn/publicfiles/business/htmlfiles/mohyzs/s3585/200905/40478.htm.
20 World Health Organization. Clinical management of human infection with pandemic (H1N1) 2009: revised guidance. www.who.int/csr/resources/publications/swineflu/clinical_management_h1n1.pdf.
21 World Health Organization. CDC protocol of realtime RTPCR for swine influenza A (H1N1). WHO, 2009.
22 Ministry of Health, China. [Discharge criteria of human infection with pandemic 2009 influenza A (H1N1) virus: initial guidance.] 2009. www.moh.gov.cn/publicfiles/business/htmlfiles/mohyzs/s3585/200905/40645.htm.
23 Nicholson KG. Clinical features of influenza. *Semin Respir Infect* 1992;7:26-37.
24 Carrat F, Vergu E, Ferguson NM, Lemaitre M, Cauchemez S, Leach S, et al. Time lines of infection and disease in human influenza: a review of volunteer challenge studies. *Am J Epidemiol* 2008;167:775-85.
25 Hancock K, Veguilla V, Lu X, Zhong W, Butler EN, Sun H, et al. Cross-reactive antibody responses to the 2009 pandemic H1N1 influenza virus. *N Engl J Med* 2009;361:1945-52.
26 Fiore AE, Shay DK, Broder K, Iskander JK, Uyeki TM, Mootrey G, et al. Prevention and control of influenza: recommendations of the Advisory Committee on Immunization Practices (ACIP), 2008. *MMWR Recomm Rep* 2008;57:1-60.
27 Centers for Disease Control and Prevention. Bacterial coinfections in lung tissue specimens from fatal cases of 2009 pandemic influenza A (H1N1)—United States, May-August 2009. *MMWR Morb Mortal Wkly Rep* 2009;58:1071-4.
28 Ling LM, Chow AL, Lye AC, Tan AS, Krishnan P, Cui L, et al. Effects of early oseltamivir therapy on viral shedding in 2009 pandemic influenza A (H1N1) virus infection. *Clin Infect Dis* 2010;50:963-9.
29 De Serres G, Rouleau I, Hamelin M-E, Quach C, Skowronski D, Flamand L, et al. Contagious period for pandemic (H1N1) 2009. *Emerg Infect Dis* 2010;16:783-8.
30 Leekha S, Zitterkopf NL, Espy MJ, Smith TF, Thompson RL, Sampathkumar P. Duration of influenza A virus shedding in hospitalized patients and implications for infection control. *Infect Control Hosp Epidemiol* 2007;28:1071-6.
31 Frank AL, Taber LH, Wells CR, Wells JM, Glezen WP, Paredes A. Patterns of shedding of myxoviruses and paramyxoviruses in children. *J Infect Dis* 1981;144:433-41.
32 Hall CB, Douglas RG Jr. Nosocomial influenza infection as a cause of intercurrent fevers in infants. *Pediatrics* 1975;55:673-7.
33 Klimov AI, Rocha E, Hayden FG, Shult PA, Roumillat LF, Cox NJ. Prolonged shedding of amantadine-resistant influenza A viruses by immunodeficient patients: detection by polymerase chain reaction-restriction analysis. *J Infect Dis* 1995;172:1352-5.
34 Witkop CT, Duffy MR, Macias EA, Gibbons TF, Escobar JD, Burwell KN, et al. Novel influenza A (H1N1) outbreak at the US Air Force Academy: epidemiology and viral shedding duration. *Am J Prev Med* 2009;38:121-6.
35 Centers for Disease Control and Prevention. Interim guidance on infection control measures for 2009 H1N1 influenza in healthcare settings, including protection of healthcare personnel. CDC, 2009. www.cdc.gov/h1n1flu/guidelines_infection_control.htm.
36 Li IW, Hung IF, To KK, Chan KH, Wong SS, Chan JF, et al. The natural viral load profile of patients with pandemic 2009 influenza A (H1N1) and the effect of oseltamivir treatment. *Chest* 2010;137;759-68.
37 Centers for Disease Control and Prevention. Updated interim recommendations for the use of antiviral medications in the treatment and prevention of influenza for the 2009-2010 season. CDC, 2009. www.cdc.gov/h1n1flu/recommendations.htm.
38 Lee N, Chan PK, Choi KW, Lui G, Wong B, Cockram CS, et al. Factors associated with early hospital discharge of adult influenza patients. *Antivir Ther* 2007;12:501-8.
39 Hanshaoworakul W, Simmerman JM, Narueponjirakul U, Sanasuttipun W, Shinde V, Kaewchana S, et al. Severe human influenza infections in Thailand: oseltamivir treatment and risk factors for fatal outcome. *PLoS One* 2009;4:e6051.
40 McGeer A, Green KA, Plevneshi A, Shigayeva A, Siddiqi N, Raboud J, et al. Antiviral therapy and outcomes of influenza requiring hospitalization in Ontario, Canada. *Clin Infect Dis* 2007;45:1568-75.
41 Lee N, Cockram CS, Chan PK, Hui DS, Choi KW, Sung JJ. Antiviral treatment for patients hospitalized with severe influenza infection may affect clinical outcomes. *Clin Infect Dis* 2008;46:1323-4.
42 Writing Committee of the Second WHO Consultation on Clinical Aspects of Human Infection with Avian Influenza A (H5N1) Virus. Update on avian influenza A (H5N1) virus infection in humans. *N Engl J Med* 2008;358:261-73.
43 Uyeki T. Antiviral treatment for patients hospitalized with 2009 pandemic influenza A (H1N1). N Engl J Med 2009;361:e110.

**Accepted:** 28 June 2010