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# Systematic review of clinical and epidemiological features of the pandemic influenza A (H1N1) 2009

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The aim of this systematic review was to summarise the clinical and epidemiological features of the pandemic influenza A (H1N1) 2009. We did a systematic search of published literature reporting clinical features of laboratory-confirmed pandemic influenza A (H1N1) 2009 from 1 April 2009 to 31 January 2010. Forty-four articles met our inclusion criteria for the review. The calculated weighted mean age of confirmed cases was 18·1 years, with the median ranging from 12 to 44 years. Cough (84·9%), fever (84·7%), headache (66·5%), runny nose (60·1%) and muscle pain (58·1%) were the most common symptoms of confirmed cases. One or more pre-existing chronic medical conditions were found in 18·4% of cases. Almost two-thirds (64%) of cases were aged between 10 and 29 years, 5·1% were aged over 50 years and only 1·1% were aged over 60 years. The confirmed case fatality ratio was 2·9% (95% CI 0·0–6·7%), an extracted average from 12 of 42 studies reporting fatal cases (937 fatal cases among 31 980 confirmed cases), which gives an overall estimated infected case fatality ratio of 0·02%. Early in the pandemic, disease occurred overwhelmingly in children and younger adults, with cough and fever as the most prevalent clinical symptoms of the confirmed cases. A high infection rate in children and young adults, with sparing of the elderly population, has implications for pandemic influenza management and control policies.

**Keywords** Clinical features, epidemiology, H1N1 Influenza, pandemic.

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## Background

In June 2009, the World Health Organization (WHO) declared the first human influenza pandemic of the 21st century.[1] The new virus was derived from a triple reassortant North American swine influenza A virus that acquired two virus genes from a Eurasian swine influenza A virus.[2,3] The outbreak began in Mexico in March 2009.[4] By the end of July 2009, more than 168 countries reported confirmed cases of pandemic influenza A (H1N1) 2009, and there were more than 162 380 laboratory-confirmed cases and 1154 deaths.[5]

In seasonal influenza epidemics, 5–15% of the population suffer from upper respiratory tract infections. Although most cases are mild, these annual epidemics cause severe illness in perhaps 3–5 million people and 250 000–500 000 deaths annually worldwide.[6] When an influenza pandemic strikes, it usually causes even more widespread disease and death, as exemplified by the 1918 pandemic which cost 50–60 million lives.[7] Early in the first wave of the pandemic, the potential virulence of a new pandemic strain causes significant concern to the general public, health care professionals and policy makers.

Both morbidity and mortality were concentrated in younger adults, a striking characteristic shared with the 20th century pandemics, especially 1918.[8,9] Estimated mean ages for death in the 1918, 1957 and 1968 pandemics were 27·2, 64·6 and 62·2 years, respectively.[10] Influenza disease surveillance data in 2009 shows that pregnant women, people with underlying medical conditions, the morbidly obese and children under 2 years of age have been most at risk of severe illness from pandemic influenza.[11] However, hospital and intensive care unit (ICU) admission data from different parts of the world suggest that one-third of the patients with severe illness were healthy adults.[12–14] During the first wave of the 2009 influenza pandemic, age-specific death displayed a distinct peak in young adults, consistent especially with the 1918, but also other, pandemics.[15]

The majority of people worldwide infected with the new H1N1 virus experienced uncomplicated influenza-like illness, with full recovery within a week. However, small subsets of patients developed severe progressive pneumonia


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often associated with failure of other organs, or marked worsening of underlying asthma or chronic obstructive airway disease.[12] According to the WHO, in severe cases, patients deteriorated around 3–5 days after symptom onset. Deterioration was rapid, with many progressing to respiratory failure within 24 hours, requiring immediate admission to an intensive care unit. Most of the ICU patients needed immediate respiratory support with mechanical ventilation. However, some patients responded poorly to conventional ventilation and required high-frequency oscillation ventilation and even extracorporeal membrane oxygenation.[16]

During the pandemic, most health authorities (e.g. Centers for Disease Control and Prevention [CDC] in the USA, Health Protection Agency [HPA] in the UK) used clinical definitions for pandemic influenza. These included fever or history of fever (≥38°C), accompanied by respiratory tract symptoms including rhinorrhoea or nasal congestion, sore throat and cough.[17,18] Understanding the presenting clinical features of any new pandemic influenza is important for a sensitive clinical case definition. The aim of this systematic review was to summarise the clinical and epidemiological features of the pandemic influenza A (H1N1) 2009.

## Methods

### Study search strategy

The search strategy and subsequent literature search were performed in consultation with a medical librarian (CK). Searches were undertaken in Ovid MEDLINE (1950 to December Week 5, 2009), Ovid EMBASE (1980–2010 Week 01) and PUBMED in January 2010. To maximise retrieval, a combination of database-specific controlled vocabulary and general free-text terms was used. The primary controlled vocabulary terms used were 'influenza', 'human', 'influenza A virus', 'H1N1 subtype' and 'epidemiology'. Free-text terms representing both influenza (influenza or flu, swine or porcine or H1N1) and clinical/epidemiological concepts (case$ or infection$ or character$ or present$ or symptom$ or sign$ or clinical$ or epidemiolog$) were used in combination with the controlled vocabulary terms to focus the results on clinical and epidemiological presentations. Searches were entry-date limited to include items from 1 April 2009 to 31 January 2010. Searches were limited to human only.

We searched peer-reviewed journals on infectious diseases and viral infection including influenza, hand-searched selected articles and also looked at the websites of the leading health authorities (e.g. WHO, CDC, HPA). To minimise the introduction of bias, no language or publication restrictions were applied. All results were downloaded in a Word document and duplicate citations were identified and removed. Three authors (GK, HR and AD) independently assessed the eligibility of identified studies.

### Study selection

We selected published articles reporting primary data regarding clinical features of laboratory-confirmed pandemic influenza A (H1N1) 2009 infection. The reported use of a valid test to confirm and subtype the pandemic influenza, such as reverse transcription polymerase chain reaction (rt-PCR) or culture was considered necessary for inclusion in this review. Our outcome was the proportion of laboratory-confirmed cases with various clinical symptoms in different age groups and settings.

### Data collection

An Excel spreadsheet was developed and used to retrieve relevant information from selected studies. Three reviewers (GK, HR and AD) independently reviewed and extracted data into the spreadsheet. Disagreements among reviewers were resolved by discussion. Data included the following: study characteristics (e.g. country and study period), data sources, patient setting, number of confirmed cases, age distribution, sex, number of cases with individual clinical/presenting symptoms, clinical attack rate, number of patients with pre-existing medical conditions and number of fatal cases.

### Statistical analysis

We combined the number of cases with individual clinical symptoms for each study and calculated the combined percentage of individual clinical symptoms with 95% confidence interval (95% CI). Subgroup analysis was carried out on clinical symptoms according to patient settings (e.g. community, school, hospital and ICU). Chi-square tests were performed to compare the differences between patient settings and their clinical symptoms. We calculated the weighted mean for age by extracting mean age of the confirmed cases reported in each study. Sex distribution was calculated by extracting data on gender separately. We calculated the confirmed case fatality ratio (cCFR). The cCFR was calculated by using the total number of confirmed cases in 42 (of 44) studies where vitality was determined as the denominator and number of deaths as the numerator.[19] We have estimated the symptomatic case fatality ratio (sCFR) and infected case fatality ratio (iCFR). The sCFR uses the symptomatic cases as denominator, while the iCFR uses the total number of infected cases as denominator. Based on a recent study that only a tenth of the infected individuals developed an influenza-like illness that required medical attention,[20] we estimated sCFR as 0·1 × the cCFR. Further, based on modelling, we estimated the iCFR as 0·1 × the sCFR.[19] We have also estimated the CFR according to the economic status of the countries following the

World Bank classification of the member economies according to gross national income per capita.[21] The groups are low income, $995 or less; lower-middle income, $996–$3945; upper-middle income, $3946–$12 195; and high income, $12 196 or more. The proportion of cases with a pre-existing and chronic health condition was calculated. All analyses were conducted using SPSS Statistics 17.0.1 (SPSS Inc, Chicago, IL, USA).

## Results

Forty-four articles met the inclusion criteria for the review and analysis (Figure 1). These studies reported mainly cases from early in the pandemic of influenza A (H1N1) 2009 (up until September 2009) from different settings including communities, hospitals or both.

The 44 studies reported data from 23 countries from both the southern ($n = 6$) and northern hemispheres ($n = 37$), including one study from a country that lies in both hemispheres.[3,13,14,22–62] The reports are from high-income, upper-middle income and lower-middle-income nations, but none from low-income countries. Details of the included studies are presented in Table S1. All the 33 369 cases included in this study are laboratory-confirmed pandemic influenza A (H1N1) 2009. Of the 44 studies, 31 reported cases from community settings (including five school influenza outbreaks), 10 studies reported cases from hospital settings alone and three studies reported combined community and hospital cases.[3,13,14,22–62] A detailed breakdown of the studies and settings is shown in Table 1.

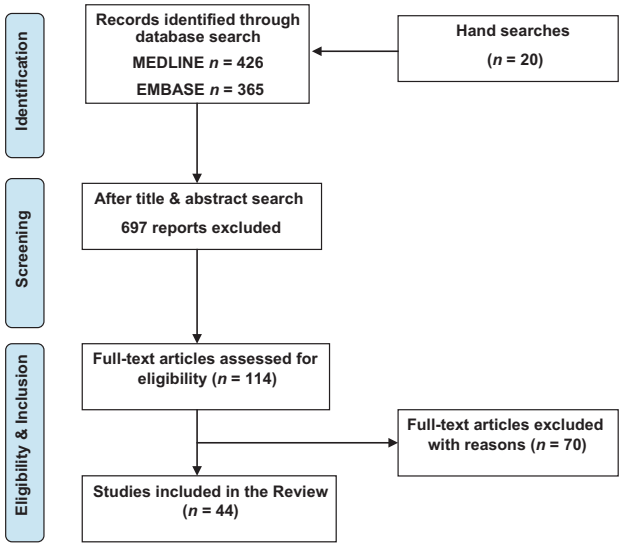


**Figure 1.** Details of articles identified by the literature searches.

**Table 1.** Settings of the laboratory-confirmed H1N1 2009 cases included in this review

| Setting | Number of studies | Number of confirmed cases (%) | Mean age* |
|---|---|---|---|
| Community** | 24 | 22 692 (68·0) | 20·8*** |
| School | 5 | 388 (1·2) | 18·2† |
| Mass gathering | 1 | 12 (0·03) | 23† |
| Community and hospital | 3 | 7618 (22·8) | – |
| H1N1 Clinic | 1 | 117 (0·35) | 19·6† |
| Hospital | 7 | 2309 (6·9) | 24·5*** |
| ICU | 3 | 233 (0·7) | 32·3† |
| Total | 44 | 33 369 (100) | 18·1*** |

A table describing each article is available: see Table S1.
*School outbreaks and studies on paediatric cases were excluded in the mean age calculation.
**Including one study reporting imported cases.
***Weighted mean age calculated from two or more studies.
†Mean age reported only in one study.

### Age and sex distribution

Age range was reported in 34 studies, median age in 31 studies and mean age in 17 studies. The weighted mean age was 18·1 years (none of the school outbreaks and studies on paediatric cases were included in the mean age calculation). The weighted mean age of the confirmed cases according to different settings is presented in Table 1. Median age reported in individual studies ranged from 12 to 44 years. The age range from all the reported studies was 0–93 years.

Fifteen studies reported the age distribution of cases. As they did not follow similar age bands, we were only able to compare data from nine compatible studies; these showed 64% of confirmed influenza cases were aged between 10 and 29 years (pooled data from five studies),[24,37,40,55,59] 5·1% of the cases were aged more than 50 years (pooled data from three studies)[3,53,62] and only 1·1% of the cases were aged over 60 years (pooled data from four studies).[37,40,54,59]

Gender was reported in 35 studies and 50·5% (95% CI 50·0–51·1%) were men.

### Clinical symptoms

Clinical symptoms are presented according to the setting of the patient in Table 2.

Cough, fever, headache, runny nose and muscle pain were the most common symptoms. Common presenting symptoms were different based on the patient's setting. However, cough and fever were the most common symptoms in all settings (84·9% and 84·7%, respectively).


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**Table 2.** Common clinical symptoms of confirmed cases of pandemic influenza A (H1N1) 2009

| Symptoms | All cases inpatient and outpatients (*N* = 33 369)* % | Community cases (*N* = 22 692)* % | School outbreak cases (*N* = 388)* % | Hospitalised cases (*N* = 2309)* % | ICU cases (*N* = 233)* % |
|---|---|---|---|---|---|
| Cough | 84·9 | 83·0 | 95·8 | 81·2 | 76·9 |
| Fever | 84·7 | 81·8 | 76·2 | 85·8 | 93·3 |
| Subjective fever | 67·3 | ** | 73·6 | ** | ** |
| Headache | 66·5 | 65·8 | 48·2 | 18·7*** | 48·2*** |
| Runny nose | 60·1 | 59·0 | 60·0 | 25·7 | ** |
| Muscle pain | 58·1 | 59·5 | 34·2 | 23·6*** | 43·1*** |
| Sore throat | 49·5 | 51·4 | 59·5 | 29·9 | ** |
| Shortness of breath | 31·2 | 14·8† | ** | 51·6 | 61·5† |
| Fatigue | 25·3 | 6·9 | 65·8 | 18·4*** | 54·1*** |
| Vomiting | 19·9 | 22·2 | 17·4 | 11·3 | 23·1 |
| Diarrhoea | 13·0 | 11·2 | 18·8 | 14·5 | ** |

*Individual denominators for each symptom vary: see Table S2.
**No data were available or reported on these symptoms.
***$P$ = 0·0001.
†$P$ = 0·0002.

Two studies reported symptoms in children; fever (89·2%), cough (56·7%) and runny nose (38·8%) were the most common symptoms.[51,61] School outbreak investigations were not included in this analysis as those reported combined symptoms of adult staff and school children.

There were significant differences in clinical symptoms of infection between the hospitalised and ICU cases. Only 18·7% of the hospitalised cases had headache compared to 48·2% in ICU cases ($P$ = 0·0001). Muscle pain (23·6% of hospitalised cases versus 43·1% of ICU cases, $P$ = 0·0001) and fatigue (18·4% of hospitalised cases versus 54·1% of ICU cases, $P$ = 0·0001) were also significantly different.

Shortness of breath was especially common in ICU cases (61·5%) and uncommon in community cases (14·8%) ($P$ = 0·0002).

Five studies reported neurological presentations (seizure, encephalitis, altered mental status). The prevalence of neurological symptoms was low. Seizures were present in 2% of the community cases reported in one study,[24] whereas, in ICU cases, seizure and encephalopathy were each present in 7·7% of the cases.[22] Combined data from two studies reporting hospitalised cases showed 5·5% of the confirmed cases had altered mental status as one of the clinical symptoms.[54,56]

### Pre-existing and chronic health condition

Twenty-one studies have reported laboratory-confirmed pandemic influenza infection in individuals with pre-existing chronic health conditions. Among those, 18·4% (3411/18 515) had one or more pre-existing chronic medical conditions.

### Case fatalities

There were fatalities reported in 12 of 42 studies; in total, 937 out of 31 980 patients died. This equates to an overall cCFR of 2·9% (95% CI 0·0–6·7%) among laboratory-confirmed cases, which gives an estimated sCFR of 0·29% and iCFR of 0·02%. Among all the studies, the highest number of deaths was reported from Brazil, where, out of 5747 confirmed cases with severe acute respiratory infection, 645 patients died (cCFR 11·2%). Excluding the Brazilian study, the overall cCFR comes down to 1·1%. Based on this cCFR, we have estimated the sCFR as 0·11% and iCFR as 0·01%.

We also calculated the cCFR according to the economic status of the reporting countries (Table S3). This showed that the cCFR for 33 reports from high-income countries was 1·1% (95% CI 0·0–3·0%, estimated iCFR 0·01%) versus 4·6% (95% CI 0·0–11·6, estimated iCFR 0·04%) in 11 reports from upper- and lower-middle-income countries. There were no data available from low-income countries. However, these combined estimates based on data from heterogenous sources have many limitations that are discussed later.

## Discussion

To our knowledge, this is the first systematic review of the published literature on clinical and epidemiological features

of pandemic influenza A (H1N1) 2009. We included studies from different settings (hospital, community, school) and different parts of the world (northern and southern hemisphere). It covers a wide geographical and economic area. Also, we report the highest number of laboratory-confirmed cases (33 369 cases), which includes cases from the early stage of the pandemic. Fever and cough were the most common symptoms of confirmed cases with pandemic influenza.

Our review highlights that the majority of proven cases was reported in young adults and children, 64% aged between 10 and 29 years and, extraordinarily, only 1·1% in people aged over 60 years. Most of the studies (7 of 9) included in the age distribution analysis were from community settings. The calculated weighted mean age of cases is 18·1 years, and the median ages reported range from 12 to 44 years. A recent study comparing the community cases of seasonal influenza A (H1N1) versus pandemic influenza found that both seasonal and pandemic influenza A (H1N1) 2009 infections were mainly in the younger age groups. The median age among pandemic cases in the USA (2009) was 20 years, and, among seasonal influenza A (H1N1) cases in Western Australia (WA) and Victoria (both 2007/08), the median ages were 18 and 23 years, respectively. However, the median ages for influenza A (H3N2) were 30 years in Victoria and 31 years in WA.[63]

The low-infection rate among the elderly (1·1% in those aged over 60 years) may be explained by the genetic similarity between the 1918 and 2009 pandemic viruses (HA, NA and M-protein).[2,3] Recent studies have confirmed that individuals alive before and/or during the emergence and initial persistence of the 1918 pandemic virus have higher levels of pandemic influenza A (H1N1) 2009-specific antibodies, which appears to have contributed towards better clinical protection from the pandemic virus.[20,64–68]

Elderly people are considered as a high-risk group of influenza complications and death. Pandemic influenza-specific control and management strategies are also concentrated towards this age group.[69] In Australia, more than 42% of elderly people, aged 65 and older, had received pandemic influenza vaccine by December 2009; in contrast, only 14% of young adults were vaccinated.[70] Our findings suggest that pandemic influenza management and control strategies should have a focus on young adults and children (naïve to the new virus).

## Clinical symptoms

The clinical definitions of pandemic influenza A (H1N1) 2009 used by CDC and HPA are presented in Table 3.

In comparison with the CDC definition of an influenza-like illness, we found only 49% of the confirmed cases had a sore throat; therefore, this symptom is not a sensitive predictor for pandemic influenza A (H1N1) 2009. Also, 'sore throat' was present only in 30% of the hospitalised cases. The HPA definition is, in our opinion, too specific and covers a whole spectrum of clinical symptoms which will be difficult to use in clinical settings for screening purposes. Moreover, the sensitivity of the HPA's clinical case definition has been criticised, and it has been shown that almost 40% of children with H1N1 influenza would not have been diagnosed according to the HPA algorithm.[22] Our review shows that cough and fever are the most prevalent clinical symptoms, present in more than 84% of the confirmed cases, and only these two symptoms could be better used for symptomatic screening. Shortness of breath and fatigue are predictors for more severe illness (higher prevalence in ICU cases). Based on our analysis, we are proposing a more sensitive case definition (cough and fever).

## Pre-existing and chronic health condition

It is well known that patients with chronic diseases are at higher risk of developing serious complications from influenza infection,[71] and immunisation against influenza is rec-

**Table 3.** Comparison of clinical definition of pandemic influenza A (H1N1) 2009 by CDC, HPA and in light of our review findings

| **Definition of pandemic influenza A (H1N1) 2009 during documented influenza activities** | |
|---|---|
| HPA | Fever (pyrexia ≥38°C) or a history of fever and<br>influenza-like illness (two or more of the following symptoms: cough; sore throat; rhinorrhoea; limb or joint pain; headache; vomiting or diarrhoea) or<br>severe and/or life-threatening illness suggestive of an infectious process |
| CDC | influenza-like illness is defined as fever (temperature of 100°F [37·8°C] or greater) and<br>a cough and/or a sore throat in the absence of a known cause other than influenza |
| Review finding | only cough and fever (documented fever) defined more than 84% of confirmed cases<br>shortness of breath (61·5%) and fatigue (54·1%) are predictors for critical illness if present with cough and fever |

HPA, Health Protection Agency.


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ommended. Our study showed that 18% of the confirmed cases had one or more pre-existing medical conditions. We could not extract the data on the outcome for these individuals.

### Case fatalities

The virulence and case fatality of the new pandemic virus is a topic in its own right, and there have been several key publications on the CFR of the new pandemic virus infection.[19,72–79] Our reported cCFR is the tip of the iceberg and biased as we have used the total number of deaths among only laboratory confirmed cases.[75] As suggested by Nishiura[19], the cCFR is always greater than the sCFR, and it has limited utility in assessing the mortality impact.

However, based on our cCFR of 2·9% for all the laboratory-confirmed cases, we have made some admittedly rudimentary adjustments and estimated the overall iCFR to be 0·02%, which is consistent with other studies.[76–78] There was a wide variation in CFR across countries. The rate was significantly lower for high-income compared to upper- and lower-middle-income nations ($P < 0·05$). Our method of estimating sCFR and iCFR from cCFR by using multipliers (0·1) must be interpreted with caution as it is based on data from just one country (UK). Moreover, a wide range in the confidence interval in our cCFR calculation points towards uncertainty in the risk of death.

A striking finding was that there was no published data on the epidemiology and clinical features of the pandemic influenza A (H1N1) 2009 from low-income countries; this is needed. Previous studies on the 1918 pandemic showed the mortality was very much higher in low-income countries, for example, India where as many as 17 million died, about 5% of the population.[80] The 2009 pandemic has resulted in relatively few deaths in comparison with pandemics in the 20th century, although the exact number of deaths from the 2009 pandemic is grossly underestimated and new data are still emerging. A recent study showed that the range of life years lost during the current pandemic were comparable with the impact of mid-20th century influenza epidemics.[10]

### Strengths and limitations

Assessment of the quality of observational studies is more difficult than that of experimental studies like randomised controlled trials. Quality assessment methods for observational studies have not yet been standardised, and, although several assessment scales and checklists are used, none of them have been fully validated or shown to include criteria that are associated with the effect size (outcome) in empirical studies. All the studies included in our review were cross-sectional observational studies. We have reported the clinical and epidemiological features of pandemic influenza A (H1N1) 2009 from reported data until the end of September 2009. There was significant heterogeneity between the studies and comprehensive country-wise data were not available. Moreover, different studies have used different criteria to define fever. Of 44 selected studies, 25 reported documented fever but did not give any cut-off temperature for fever, 10 studies used temperature ≥38°C, five studies used temperature >38°C, two studies used temperature ≥37·8°C, one study used temperature ≥37·5°C and one study used temperature ≥37·3°C as fever. For the review, we have collated all these as 'documented fever'. A cut-off temperature of ≥37·8°C for fever may be more sensitive for screening purposes.

All the studies selected in our review refer to data collected during the early stages of the pandemic (until August/September 2009). Early in the pandemic, screening and laboratory diagnosis of influenza, while more intense, varied significantly and relied on resources and policy. Routine screening and testing became focussed on high-risk groups and hospitalised individuals; thus, laboratory-confirmed data collected during the period in our study will give a higher estimate of hospitalisations and deaths.

Interestingly, within 6 months of the pandemic, more than 100 original research articles were published on our review topic, which may be indicative of the strength of the growing medical press. Several key journals introduced rapid publication processes to expedite the dissemination of pandemic H1N1 information. The WHO and other key agencies also provided frequent and useful information bulletins.[81] The searches undertaken during the period studied attempted to capture information from both published and unpublished sources, including key agency websites, so as to minimise publication bias. One limitation of the study is that conference proceedings were not searched. Given that some countries cancelled medical conferences during the pandemic to mitigate viral spread and to redirect clinical resources,[82] this may be less of an issue in this particular review than it would have been otherwise.

The systematic review of observational studies is always a challenge as there is significant heterogeneity among different studies. Our review is no exception. However, we followed strict inclusion/exclusion criteria and PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines.[83]

## Conclusion

This review shows that, in the early pandemic phase, disease occurred overwhelmingly in children and younger adults, with cough and fever as the most prevalent clinical symptoms, present in more than 80% of the confirmed cases. Based on the largest cohort of confirmed cases of pandemic influenza A (H1N1) 2009, we have explored the clinical presentations of pandemic influenza in different

settings. A high infection rate in children and young adults, with sparing of the elderly population, has implications for pandemic influenza management and control policies. Pandemic influenza control initiatives should have focused more on the young.

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## Supporting Information

Additional Supporting Information may be found in the online version of this article:

**Table S1.** Detail of the included studies in this review.

**Table S2.** Individual denominators for each clinical symptom.

**Table S3.** Detail of the included studies according to the country of origin and economic status.

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