



**HAL**  
open science

## Epidemiological aspects of 2009 H1N1 influenza: the accumulating experience from the Northern Hemisphere

M. E. Falagas, N. V. Cholevas, A. M. Kapaskelis, E. K. Vouloumanou, A. Michalopoulos, P. I. Rafailidis

► **To cite this version:**

M. E. Falagas, N. V. Cholevas, A. M. Kapaskelis, E. K. Vouloumanou, A. Michalopoulos, et al.. Epidemiological aspects of 2009 H1N1 influenza: the accumulating experience from the Northern Hemisphere. *European Journal of Clinical Microbiology and Infectious Diseases*, 2010, 29 (11), pp.1327-1347. 10.1007/s10096-010-1002-3 . hal-00608423

**HAL Id: hal-00608423**

**<https://hal.science/hal-00608423>**

Submitted on 13 Jul 2011

**HAL** is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

# Epidemiological aspects of 2009 H1N1 influenza: the accumulating experience from the Northern Hemisphere

M. E. Falagas<sup>1□,2,3</sup> <Phone: +30-694-6110000, Fax: +30-210-6839605, Email: m.falagas@aibs.gr>

N. V. Cholevas<sup>1</sup>

A. M. Kapaskelis<sup>1,2</sup>

E. K. Vouloumanou<sup>1</sup>

A. Michalopoulos<sup>1,4</sup>

P. I. Rafailidis<sup>1,2</sup>

<sup>1</sup> Alfa Institute of Biomedical Sciences (AIBS), 9 Neapoleos Street, Marousi, 151 23 Athens, Greece

<sup>2</sup> Department of Medicine, Henry Dunant Hospital, Athens, Greece

<sup>3</sup> Department of Medicine, Tufts University School of Medicine, Boston, MA, USA

<sup>4</sup> Intensive Care Unit, Henry Dunant Hospital, Athens, Greece

## Abstract

Preliminary data regarding the experience of countries of the Northern Hemisphere with pandemic 2009 A(H1N1) influenza have already appeared in the literature. We aimed to evaluate the available published literature describing the epidemiological features of pandemic influenza. We searched ~~the PubMed. Thirty five PubMed;~~ 35 studies (14 referred to European countries, ~~8~~ eight to the USA, ~~5~~ five to Mexico, ~~4~~ four to Canada, ~~2~~ two to Japan, ~~1~~ one to Colombia, and ~~1~~ one reviewed relevant data reported worldwide) were included. Considerably high hospitalization, ~~ICU~~ intensive care unit (ICU) admission, and fatality rates (up to ~~93.8%, 36.4%, 93.8, 36.4, and 38.5%~~ 38.5%, respectively) among the evaluated cases were reported across studies with ~~the~~ available relevant data. Young and middle-aged adults constituted the majority of the evaluated pandemic ~~cases~~ cases, with different disease severity (as indicated by ~~the~~ level of care and outcome). Yet, substantial percentages of elderly individuals were reported among more severely afflicted cases. Otherwise healthy patients constituted substantial percentages among evaluated cases with different disease severity. Pregnant women, ~~obese~~ obese, and morbidly obese patients also constituted substantial percentages of the cases involved in the included ~~studies~~ studies. The evaluation of the currently available published evidence contributes to the clarification of the epidemiological features of pandemic 2009 A(H1N1) influenza, which is useful in terms of ~~the~~ individual and public health ~~perspective~~ perspectives.

## <H1>. Introduction

Influenza is an important clinical entity. The burden of this infection is considerable, as it is associated with considerably high hospitalization and mortality rates, as well as with increased direct and indirect ~~costs.[1]~~ costs [1]. The burden of influenza infection became even more pronounced with the emergence of the current influenza pandemic. Inevitably, the effective management of this new global threat necessitates the epidemiological features of 2009 pandemic influenza.

Evidence deriving from studies presenting the ~~experience,~~ experience of countries of the Southern Hemisphere with pandemic influenza, as well as preliminary data from ~~U.S.A~~ the USA, suggests that 2009 pandemic influenza affects mostly populations of younger ~~age.[2-5]~~ age [2-5], a fact that is contradictory to the knowledge regarding seasonal ~~influenza~~ influenza, in which severe disease as well as mortality is observed more frequently in elderly ~~populations.[6]~~ populations [6].

Additionally, patients with comorbidity ~~and~~and, specifically, sub-populations such as pregnant women and obese individuals also appear to suffer more severely ~~form~~from pandemic ~~influenza~~.~~[4, 5]~~influenza [4, 5].

The aim of this review was to collect and evaluate the available evidence regarding various epidemiological aspects of 2009 H1N1 influenza that ~~was~~ derived from studies, published up to this writing, referring to the experience of countries from the Northern Hemisphere with pandemic influenza.

## <H2>. Data sources

The articles to be included in our review were retrieved from searches performed in the PubMed database. The PubMed database was assessed ~~until~~to the end of ~~November~~,~~November~~ 2009. We used the following search term: “[(swine OR H1N1) AND (flu OR influenza OR virus OR outbreak OR pandemic) AND "last 6 months"]”, ~~that~~~~which~~ is currently provided ~~from~~~~by~~ the PubMed database to its users, in order to enable quick and easy access to the latest H1N1 citations. We also hand-searched the bibliographies of relevant articles.

## <H2>. Study selection criteria

A study was considered as eligible for inclusion in our review if it reported original data regarding epidemiological features of patients of any age with 2009 influenza A (H1N1) infection (either confirmed or ~~probable~~),~~probable~~) and also originated from countries of the Northern Hemisphere. Abstracts presented in scientific conferences were not regarded as eligible for inclusion in our review. Only articles published in ~~the~~ English language were regarded as eligible for inclusion in our review.

## <H2>. Data extraction

Two reviewers (N.V.C and E.K.V.) performed the literature search, assessed the eligibility of relevant studies, and extracted the data, independently. Data obtained from the included articles referred to study characteristics (country, study period, study population), demographic characteristics of the patients (age, sex), any kind of potential risk factors for influenza, comorbidity (such as obesity, pregnancy, respiratory diseases, cardiovascular disease, diabetes mellitus, chronic neurological disease), as well as history of seasonal influenza ~~2008–2009~~~~2008–2009~~ vaccination). The above-mentioned data were extracted for the ~~total of the~~~~whole~~ patient populations involved in each ~~one~~of the included studies, as well as for the sub-populations of patients with pandemic influenza of different severity, as this was indicated by the level of ~~health care~~~~health-care~~ they ~~received~~,~~[hospitalized~~~~received~~ (hospitalized patients, patients admitted in the intensive care unit ~~(ICU)~~~~[ICU]~~), and the outcome of the influenza infection (fatal cases).

## <H2>. Study characteristics

A total of 35 studies were regarded ~~as~~ eligible for inclusion in our ~~review~~.~~[2, review [2, 4, 7–39]~~7–39]. Specifically, ~~fourteen~~14 of the 35 included studies referred to European ~~countries~~,~~[7–20]~~8 countries [7–20], eight to ~~U.S.A.~~,~~[2, the USA [2, 4, 21–26]~~5–21–26], five to ~~Mexico~~,~~[31–35]~~4 Mexico [31–35], four to ~~Canada~~,~~[27–30]~~2–Canada [27–30], two to ~~Japan~~,~~[37, 38]~~1–Japan [37, 38], one to ~~Colombia~~,~~[36]~~Colombia [36], whereas the remaining ~~1~~study referred to a specific number of fatal cases associated with pandemic influenza that were reported worldwide up to a specific time ~~point~~.~~[39]~~point [39]. The data retrieved and evaluated from this specific study referred only to continents or countries of the Northern Hemisphere. The data retrieved from studies originating from European countries, USA and Canada, and from the rest of the world are presented in tabulated form in Table 1, Table 2, and Table 3, respectively.

Four of the 35 included studies referring to ~~Mexico,~~ Mexico covered a time period starting in March and ending in ~~April,[32, 34] May,[35]~~ April [32, 34], May [35], and ~~June,[31]~~ June [31], respectively. Eleven of the 35 included studies referred to a time period starting from April and ending in ~~May,[8; May [8, 9, 12, 21–24, 26, 28, 33, 37]~~ 4–37], four to a period starting from April and ending in ~~June,[2; June [2, 10, 14, 30]~~ 2–30], two to a period from April until ~~July,[16, 39]~~ 4 July [16, 39], four from April until ~~August,[4; August [4, 7, 13, 27]~~ 27], and ~~1~~ one to an extended time period from April to ~~October.[15]~~ October [15]. Four other studies covered a time period from May until ~~June,[11; June [11, 19, 20, 38]~~ 38], whereas ~~2~~ two studies covered a time period from May until ~~July.[29, 36]~~ July [29, 36]. Two other studies covered a time period from June to ~~July,[18, 25]~~ July [18, 25], whereas the remaining ~~1~~ study covered a time period from June to ~~September.[17]~~ September [17]. Additionally, the evaluated population constituted solely of hospitalized cases with 2009 H1N1 ~~influenza,[2; influenza [2, 4, 15, 17, 25, 29, 32, 37]~~ influenza [2, 4, 15, 17, 25, 29, 32, 37] in 8 of the 35 included studies, of patients admitted ~~in-into~~ the ~~intensive care unit (ICU)~~ ICU in ~~3 studies,[7; three studies [7, 18, 27]~~ 3 studies [7, 18, 27], and from fatal cases associated with 2009 H1N1 influenza in ~~1 study.[39]~~ one study [39]. Of note, 2 of the 35 included studies involved only pregnant ~~cases.[22, 25]~~ cases [22, 25].

## <H2>. Hospitalization, ICU admission, and fatality rate

The rate of hospitalization rate among the evaluated pandemic influenza cases ranged between ~~0%–93.8%~~ 0 and 93.8% in 13 studies that provided relevant ~~data.[8; data [8, 10, 11, 13, 14, 19–22, 24, 26, 28, 36]~~ data [8, 10, 11, 13, 14, 19–22, 24, 26, 28, 36]. The rate of admission ~~in-into~~ the ICU among the evaluated pandemic influenza cases ranged between ~~0%–36.4%~~ 0 and 36.4% in ~~4 studies.[14; four studies [14, 21, 22, 28]~~ 4 studies [14, 21, 22, 28]. The rate of admission ~~in-into~~ the ICU among hospitalized cases ranged between ~~9%–66.7%~~ 9 and 66.7% in ~~6 studies.[2; six studies [2, 4, 15, 17, 29, 32]~~ 6 studies [2, 4, 15, 17, 29, 32]. Specific data are presented in Table 1. The fatality rate among the evaluated pandemic influenza cases was 0% in 13 of the included ~~studies.[8–10; studies [8–10, 12–14, 16, 19, 20, 24, 26, 28, 37]~~ studies [8–10, 12–14, 16, 19, 20, 24, 26, 28, 37]. However, the respective rates reported from ~~5~~ five other studies ranged between ~~2%–38.5%~~ 2 and 38.5% [18, 21, 22, 33, 36]. The fatality rate among hospitalized cases ranged between ~~0%–38.9%~~ 0 and 38.9% in ~~6~~ six of the included ~~studies.[2; studies [2, 4, 15, 17, 29, 32]~~ studies [2, 4, 15, 17, 29, 32], whereas the fatality rate among cases admitted ~~in-into~~ the ICU ranged between ~~25%–41.4%~~ 25 and 41.4% in ~~3 studies.[7; three studies [7, 27, 31]~~ 3 studies [7, 27, 31].

## <H2>. Epidemiological characteristics of cases

In Table ~~4~~ 4, we present the percentage of specific epidemiological groups (defined with regard to age, sex, or ~~the~~ the presence of risk factors or comorbid conditions) among the patients involved in the respective included studies (stratified with regard to ~~the~~ the type of diagnosis, level of ~~health care~~ health-care they received, and outcome).

## <H2>. Age and sex

Among the evaluated cases of 2009 H1N1 influenza, young and ~~middle aged~~ middle-aged adults constituted the majority of the reported cases; the percentages ranged ~~between 13.2%–83.7%~~ between 13.2 and 83.7% among studies with available relevant data. Older children and adolescents ~~followed~~ followed, with percentages ranging between ~~6.3%–79.5%~~ 6.3 and 79.5%, and young children with percentages ranging from ~~2.3%–2.3~~ 2.3 to 62.9%. This observation was consistent regarding the evaluated hospitalized cases. Specific data are presented in Table 4. In ~~2~~ two studies with available relevant data, the highest rate of admission ~~in-into~~ the ICU was observed for young and ~~middle aged~~ middle-aged adults (~~50%,[7]~~ 50% [7] and ~~58.8%,[27]~~ 58.8% [27], respectively), whereas the lowest rate was observed for senior patients (~~3.1%,[7]~~ 3.1% [7] and ~~8.3%,[27]~~ 8.3% [27], respectively). Among fatal cases, young and ~~middle aged~~ middle-aged adults constituted the majority, with percentages ranging from ~~65.5%–65.5~~ 65.5 to 91.7%, according to the data provided from ~~6~~ six of the included ~~studies.[27; studies [27, 31, 33–35, 39]~~ studies [27, 31, 33–35, 39]. Yet, substantial percentages ranging from ~~4.2%–4.2~~ 4.2 to 20.7% were observed for ~~seniors.[27; seniors [27, 31, 33–35, 39]~~ seniors [27, 31, 33–35, 39].

Considerable differences were not observed between the male and female sex among the evaluated, hospitalized, ICU, and fatal cases. Specific data are presented in Table 4. Yet, men constituted the majority in ~~3~~ three studies reporting data for 97 ~~laboratory confirmed case, [26]~~ laboratory-confirmed cases [26], 58 hospitalized ~~cases, [29]~~ cases [29], and 32 ICU ~~cases, [7]~~ cases [7]. The respective percentages were ~~75.3%, [26]~~ 60.3%, [29] 75.3% [26], 60.3% [29], and ~~73.3%, [7]~~ 73.3% [7].

## <H2>. Seasonal (~~2008–2009~~) (2008–2009) influenza vaccination

The percentage of patients vaccinated for seasonal (~~2008–2009~~) (2008–2009) influenza ranged between ~~3.4%–66.3%~~ 3.4 and 66.3% among the evaluated cases in ~~8~~ eight studies that provided relevant ~~data, [9, data [9, 12, 14, 22, 24, 26, 28, 31]~~ data [9, 12, 14, 22, 24, 26, 28, 31]. The respective percentage of hospitalized cases ranged between ~~15.8%–51.2%~~ 15.8 and 51.2% in ~~3~~ three studies providing relevant ~~data, [21, data [21, 32, 37]~~ data [21, 32, 37], whereas a single study reported a rather low percentage of 6% among ICU ~~cases, [27]~~ cases [27]. No relevant data were available regarding fatal cases.

## <H2>. Comorbidity

Cases without any comorbidity constituted the majority of the evaluated cases in 2 of the 3 studies that provided relevant ~~data, [8, 13]~~ data [8, 13]. The respective percentages were ~~96.7%, [13]~~ 96.7% [13] and ~~75%, [31]~~ 75% [31], respectively. Previously healthy cases were also ~~represented~~ represented, with considerably high percentages ranging from ~~12.1%–12.1~~ 12.1 to 81.6% in ~~9~~ nine studies that reported relevant data for hospitalized ~~cases, [2, cases [2, 4, 15, 17, 21, 24, 29, 32, 37]~~ cases [2, 4, 15, 17, 21, 24, 29, 32, 37]. Previously healthy cases were represented by percentages of up to 46.8% among ICU ~~cases, [7, cases [7, 27, 29]~~ cases [7, 27, 29] and up to 42.1% among fatal ~~cases, [2, cases [2, 4, 15, 31, 32]~~ cases [2, 4, 15, 31, 32]. Common types of ~~comorbidity~~ comorbidity, such as respiratory diseases, including asthma and chronic obstructive pulmonary disease, cardiovascular disease, chronic neurological disease, and diabetes ~~mellitus~~ mellitus, were reported among the cases involved in the included studies. Specific data are presented in Table 4.

## <H2>. Pregnancy

Two of the studies included in our review involved exclusively pregnant cases with H1N1 ~~infection, [22, 25]~~ infection [22, 25]. Specifically, 34 pregnant women (31 with ~~laboratory confirmed~~ laboratory-confirmed infection and ~~3~~ three with probable infection) were included in the one ~~study, [22]~~ study [22]. Fourteen (41.2%) of these 34 pregnant cases were hospitalized, 3 (8.8%) were included in the ICU, and 1 (2.9%) ~~died, [22]~~ died [22]. The other study recorded ~~7~~ seven hospitalized pregnant ~~cases, [25]~~ cases [25]. Regarding the remaining studies, pregnant women constituted ~~0.2%–16.7%~~ 0.2 to 16.7% among the evaluated cases in ~~3~~ studies. [11, three studies [11, 13, 26] 26]. Pregnant women constituted ~~the 4.5%–17.4%~~ 4.5 to 17.4% among the hospitalized cases in ~~5~~ five studies that provided relevant ~~data, [2, data [2, 4, 15, 17, 21]~~ data [2, 4, 15, 17, 21]. Among ICU cases, pregnant women were represented by percentages of ~~11.5%, [27]~~ 11.5% [27] and ~~18.2%, [7]~~ 18.2% [7] in ~~2~~ two other studies that provided relevant data. Among fatal cases, pregnant women were represented by percentages ranging from ~~2.2%–15.8%~~ 2.2 to 15.8% in ~~3~~ studies. [33] three studies [33].

## <H2>. Obesity

Obesity was recorded in ~~0.2%–36.2%~~ 0.2 to 36.2% among the evaluated cases in ~~2~~ two of the included studies that provided relevant ~~data, [13, data [13, 31]~~ data [13, 31] and ~~5.7%–47.6%~~ 5.7 to 47.6% among hospitalized cases in ~~3~~ studies. [2, three studies [2, 4, 29] 29]. Obese patients also constituted ~~18.8%, [7]~~ 18.8% [7] and ~~33.3%, [27]~~ 33.3% [27] of the evaluated ICU cases reported in the respective ~~2~~ studies. [7, 27] Among two studies [7, 27]. Among fatal cases, obese patients constituted ~~the 39%~~ 39% in a large study involving a total of ~~1088~~ 1,088 patients and recorded a total of 118 deaths.

Morbidly obese patients (~~BMI > 40~~) (BMI>40) in particular, constituted ~~the~~ 13.8% of the

evaluated cases in a single ~~study,[31]~~ study [31], whereas their ~~percentage-percentages~~ ranged between ~~2.2%-26.0%-2.2~~ and 26.0% in ~~3~~ three studies that provided relevant data for hospitalized ~~cases.[2, cases [2, 4, 15]-15]~~ cases [2, 4, 15]–15]. In addition, morbidly obese patients constituted ~~the~~ 12.5% of the fatal cases recorded in a large study involving a total of 32 ICU ~~patients.[7]~~ patients [7].

## <H2>. Comparisons between pandemic and seasonal influenza

Three of the 35 included studies provided comparative data regarding a specific period of pandemic influenza and previous seasonal influenza ~~periods.[18, periods [18, 29, 34]-34]~~ periods [18, 29, 34]–34]. Two of these ~~3~~ three studies referred to pediatric populations with 2009 H1N1 ~~infection.[18, 29]~~ infection [18, 29]. Specifically, ~~1~~ one of these ~~2~~ two studies provided comparative data regarding 13 critically ill pediatric cases of pandemic influenza versus 58 critically ill pediatric cases with seasonal influenza (reported during seasons ~~2004-2007).[18]-2004-2007)~~ [18]. No substantial differences were observed regarding sex between the compared children. ~~Median~~ The median age of children with pandemic influenza was 9 years compared to 2.7 years of children with seasonal ~~influenza.[18]~~ influenza [18]. Regarding the other pediatric study that compared 58 hospitalized children with pandemic influenza with 200 hospitalized children with seasonal influenza (seasons ~~2004-2005, 2004-2005 and 2008-2009), 2008-2009)~~, the median age of children with pandemic influenza was 6.4 years compared to 3.3 years of children with seasonal ~~influenza.[29]~~ influenza [29].

According to another study that also provided comparative data regarding the age distribution of fatal cases of pandemic influenza versus fatal cases of seasonal influenza (seasons ~~2006-2008), 2006-2008)~~, the percentages of fatal pandemic cases were lower from those of the respective fatal seasonal cases in the age groups ~~0-4 years, 0-4 years~~ and >60 ~~years.[34]~~ years [34]. Additionally, another study that compared a total of ~~1829~~ 1,829 confirmed pandemic cases with cases that were found to be negative for H1N1v reported that patients <53 years of age had an increased risk of infection from pandemic influenza in comparison ~~with~~ to those that were found to be positive for seasonal H1N1 and H3N2 influenza ~~strains.[30]~~ strains [30].

## <H1>. Discussion

The evaluation of contemporary published evidence regarding the experience of countries of the Northern Hemisphere with 2009 pandemic (H1N1) influenza suggests that pandemic influenza is an infection with a considerable hospitalization, ICU ~~admission-admission~~, and mortality rate. Specifically, a considerably higher fatality rate was observed in more severely afflicted cases. Young and ~~middle aged-middle-aged~~ adults constituted the majority of the evaluated cases, followed by older children and adolescents. Yet, considerable percentages of elderly patients were reported among more severely afflicted cases. Men constituted the majority in only ~~3~~ three of the evaluated studies involving cases with different disease severity. Despite the fact that considerable percentages of patients without any underlying conditions were observed among the total of the cases involved in the herein reviewed studies, as well as among hospitalized, critically ~~ill~~ ill, and fatal cases, pregnancy and obesity appear to represent particular risk factors for pandemic (H1N1) 2009 influenza infection, as well as for severe pandemic influenza infection.

Our findings are in accordance with evidence derived from studies focused on the experience gained during the 2009 winter season from countries of the Southern Hemisphere. Specifically, these studies suggest that 2009 pandemic influenza occurs more frequently in younger ~~populations.[3-5]~~ populations [3–5], whereas fatal outcome can occur at any ~~age.[4]~~ age [4]. The observed “epidemiological shift” to younger ages appears to be contradictory to the current knowledge regarding seasonal influenza that mostly affects younger children and elderly frail ~~individuals.[40]~~ individuals [40]. Of note, a similar “epidemiological shift” to younger ages was observed during previous influenza ~~pandemics.[41]~~ pandemics [41]. A possible explanation may be the fact that elderly individuals that were infected with previous influenza strains that have antigenic similarities with 2009 H1N1v may have already developed a substantial antibody response to this new pandemic

influenza virus. However, the considerable percentages of elderly individuals among critically ill and fatal cases observed in the herein reviewed studies imply that elderly individuals do suffer severely from pandemic influenza. This might be due to the presence of serious comorbidity and inadequate immune response mechanisms in elderly individuals.

Pregnant women constituted a considerable percentage among the total of the evaluated pandemic cases reported in the included studies, as well as among the evaluated hospitalized, critically ~~ill~~, and fatal cases. This finding is in accordance with the findings of relevant studies from the Southern Hemisphere. However, pregnancy has already been regarded as a risk factor for severe influenza infection, as well as for an adverse outcome of influenza infection, based on the experience from seasonal ~~influenza~~.~~[42, 43]~~influenza [42, 43]. A possible explanation for this may be the alterations to the immune response system, as well as psychological alterations that may occur during pregnancy. Notably, a recent review suggests there is a significant relationship between psychosocial factors and the onset or the progression of acute respiratory tract ~~illness~~.~~[44]~~illness [44].

Obese and morbidly obese patients also constituted a considerable proportion of the evaluated cases with pandemic influenza infection of different severity. Specifically, obese and morbidly obese patients represented considerably high percentages among hospitalized, critically ~~ill~~, and fatal cases. This finding, along with the evidence provided from studies from the Southern ~~Hemisphere~~, ~~[5]~~Hemisphere [5], imply that obesity and morbid obesity may be regarded as a risk factor of severe pandemic influenza infection. Many factors may account for this finding. Some of these are inadequate immune response mechanisms in obese patients and the common presence of serious comorbidity. The role of psychological factors should not be underestimated in this specific sub-population ~~as well as either~~. Recent reviews have also suggested that obese and morbid obese individuals are more likely than people with normal body weight to develop infections of various types of infections, as well to develop serious complications of common infections, such as respiratory ~~infections~~.~~[45, 46]~~infections [45, 46]. The fact that obese patients may suffer more severely from pandemic influenza has considerable implications in regard to the treatment of these patients. Specifically, ~~the~~ adjustment of dosing of anti-influenza ~~agents~~ agents, in particular, for ~~bodyweight~~ body weight, may prove to be a necessity, as was suggested for the treatment with antimicrobial agents from a recent ~~review~~.~~[47]~~review [47].

Our study has limitations that should be taken into consideration before extrapolation of the findings. Firstly, considerable heterogeneity was observed among the included studies regarding the methodology used to identify and present the pandemic cases, the clinical settings, the period ~~in to~~ which the study ~~referred to~~, referred, as well as the evaluated populations. This hampered our attempts to perform any statistical ~~analysis, and consequently~~ analysis and, consequently, the establishment of firm conclusions based on a pooled evaluation of the extracted data. Moreover, the retrospective nature of the collection and presentation of the data regarding the pandemic cases that was used in the majority of the included studies may also induce a bias. However, the herein reviewed ~~data~~ data, along with the experience gained from countries of the Southern ~~Hemisphere~~ Hemisphere, may aid considerably in the clarification, at least to some ~~extent~~ extent, of some of the epidemiological features of pandemic influenza.

In conclusion, the evaluation of the currently available published literature regarding the experience of the Northern Hemisphere with the pandemic 2009 A(H1N1) influenza suggests that pandemic influenza affects younger patients compared with seasonal influenza. Pandemic influenza ~~seems~~ also seems to be associated with considerable morbidity in the patients that present with serious illness, even in otherwise healthy individuals. Pregnancy and obesity may also be regarded as risk factors for both ~~infection~~, infection as well as severe pandemic influenza infection.

Funding

~~None~~None.

Conflict of interest

~~None~~None.

## References

1. Molinari ~~NA~~NA, Ortega-Sanchez IR, Messonnier ML, Thompson WW, Wortley PM, Weintraub E et al (2007) The annual impact of seasonal influenza in the US: measuring disease burden and costs. *Vaccine* 25(27):5086–5096
2. Jain ~~S~~S, Kamimoto L, Bramley AM, Schmitz AM, Benoit SR, Louie J et al (2009) Hospitalized patients with 2009 H1N1 influenza in the United States, ~~April–June~~ April–June 2009. *N Engl J Med* 361(20):1935–1944
3. Kelly ~~HK~~H, Grant K (2009) ~~Grant~~ Interim analysis of pandemic influenza (H1N1) 2009 in Australia: surveillance trends, age of infection and effectiveness of seasonal vaccination. *Euro Surveill* ~~14(31)~~14(31). pii:19288
4. Louie ~~JK~~JK, Acosta M, Winter K, Jean C, Gavali S, Schechter R et al (2009) Factors associated with death or hospitalization due to pandemic 2009 influenza A(H1N1) infection in California. *JAMA* 302(17):1896–1902
5. Webb ~~SA~~SA, Pettilä V, Seppelt I, Bellomo R, Bailey M, Cooper DJ et al (2009) Critical care services and 2009 H1N1 influenza in Australia and New Zealand. *N Engl J Med* 361(20):1925–1934
6. Thompson WW, Comanor L, Shay DK (2006) Epidemiology of seasonal influenza: use of surveillance data and statistical models to estimate the burden of disease. *J Infect Dis* 194(Suppl 2):S82–S91
7. Rello ~~J et al~~J, Rodríguez A, Ibañez P, Socias L, Cebrian J, Marques A (2009) Intensive care adult patients with severe respiratory failure caused by Influenza A (H1N1)v in Spain. *Crit Care* 13(5):R148
8. New influenza A(H1N1) investigation teams (2009) New influenza A(H1N1) virus infections in France, ~~April–May 2009 (2009)~~ April–May 2009. *Euro Surveill* ~~14(21)~~14(21). pii:19221
9. Surveillance Group for New Influenza A(H1N1) Virus Investigation and Control in Spain (2009) New influenza A(H1N1) virus infections in Spain, ~~April–May 2009 (2009)~~ April–May 2009. *Euro Surveill* ~~14(19)~~14(19). pii:19209
10. Health Protection Agency; Health Protection Scotland; National Public Health Service for Wales; HPA Northern Ireland Swine influenza investigation teams (2009) Epidemiology of new influenza A (H1N1) virus infection, United Kingdom, ~~April–June 2009 (2009)~~ April–June 2009. *Euro Surveill* ~~14(22)~~14(22). pii:19232
11. Belgian working group on influenza A(H1N1)v (2009) Influenza ~~A (H1N1) v~~ A(H1N1)v virus infections in Belgium, ~~May–June 2009 (2009)~~ May–June 2009. *Euro Surveill* ~~14(28)~~14(28). pii:19270
12. Ciblak ~~MA~~MA, Albayrak N, Odabas Y, Basak Altas A, Kanturvardar M, Hasoksuz M et al (2009) Cases of influenza A(H1N1)v reported in Turkey, ~~May–July 2009 (2009)~~ May–July 2009. *Euro Surveill* ~~14(32)~~14(32). pii:19304
13. Gilsdorf A, Poggensee ~~G~~G; Working Group Pandemic Influenza A(H1N1)v (2009) Influenza A (H1N1)v in Germany: the first 10,000 cases. *Euro Surveill* ~~14(34)~~14(34). pii:19318
14. ~~Hahné S~~Hahné S, Donker T, Meijer A, Timen A, van Steenbergen J, Osterhaus A et al (2009) Epidemiology and control of influenza A(H1N1)v in the Netherlands: the first 115 cases. *Euro*



- Surveill ~~14(27)~~14(27). pii:19267
15. Cullen ~~G-G~~, Martin J, O'Donnell J, Boland M, Canny M, Keane E et al (2009) Surveillance of the first 205 confirmed hospitalised cases of pandemic H1N1 influenza in Ireland, 28 ~~April-3~~ ~~April-3~~ April–3 October 2009. Euro Surveill ~~14(44)~~14(44). pii:19389
  16. Lytras ~~F et al~~T, Theocharopoulos G, Tsiodras S, Mentis A, Panagiotopoulos T, Bonovas S (2009) Enhanced surveillance of influenza A(H1N1)v in Greece during the containment phase. Euro Surveill ~~14(29)~~14(29). pii:19275
  17. Yeung ~~JH et al~~JH, Bailey M, Perkins GD, Smith FG (2009) Presentation and management of critically ill patients with influenza A (H1N1): a UK perspective. Crit Care 13(6):426
  18. Lister ~~P-P~~, Reynolds F, Parslow R, Chan A, Cooper M, Plunkett A et al (2009) Swine-origin influenza virus H1N1, seasonal influenza virus, and critical illness in children. Lancet 374 (9690):605–607
  19. Smith ~~A et al~~A, Coles S, Johnson S, Saldana L, Ihekweazu C, O'Moore E (2009) An outbreak of influenza A(H1N1)v in a boarding school in South East England, ~~May-June~~ ~~May-June~~ May–June 2009. Euro Surveill ~~14(27)~~14(27). pii:19263
  20. Health Protection Agency West Midlands H1N1v Investigation Team (2009) Preliminary descriptive epidemiology of a large school outbreak of influenza A(H1N1)v in the West Midlands, United Kingdom, May ~~2009-(2009)~~2009. Euro Surveill ~~14(27)~~14(27). pii:19264
  21. Dawood ~~FS-FS~~, Jain S, Finelli L, Shaw MW, Lindstrom S, Garten RJ et al (2009) Emergence of a novel swine-origin influenza A (H1N1) virus in humans. N Engl J Med 360(25):2605–2615
  22. Jamieson ~~DJ et al~~DJ, Honein MA, Rasmussen SA, Williams JL, Swerdlow DL, Biggerstaff MS (2009) H1N1 2009 influenza virus infection during pregnancy in the USA. Lancet 374 (9688):451–458
  23. Kumar ~~S-S~~, Chusid MJ, Willoughby RE, Havens PL, Kehl SC, Ledebor NA et al (2009) Introduction of a ~~Novel Swine Origin Influenza~~ ~~novel swine-origin influenza A (H1N1)~~ ~~Virus~~ virus into Milwaukee, Wisconsin in 2009. Viruses 1(1):72–83
  24. Centers for Disease Control and Prevention (CDC) (2009) Novel influenza A (H1N1) virus infections among health-care ~~personnel—United~~ ~~personnel—United~~ States, ~~April-May 2009~~ ~~(2009)~~ April–May 2009. MMWR Morb Mortal Wkly Rep ~~58(23):641-645~~58(23):641–645
  25. Saleeby ~~E et al~~E, Chapman J, Morse J, Bryant A (2009) H1N1 influenza in pregnancy: cause for concern. Obstet Gynecol 114(4):885–891
  26. Crum-Cianflone ~~NE-NF~~, Blair PJ, Faix D, Arnold J, Echols S, Sherman SS et al (2009) Clinical and epidemiologic characteristics of an outbreak of novel H1N1 (swine origin) influenza A virus among United States military beneficiaries. Clin Infect Dis 49(12):1801–1810
  27. Kumar ~~A-A~~, Zarychanski R, Pinto R, Cook DJ, Marshall J, Lacroix J et al (2009) Critically ill patients with 2009 influenza A(H1N1) infection in Canada. JAMA 302(17):1872–1879
  28. Cutler ~~J-J~~, Schleihau E, Hachette TF, Billard B, Watson-Creed G, Davidson R et al (2009) Investigation of the first cases of human-to-human infection with the new swine-origin influenza A (H1N1) virus in Canada. CMAJ 181(3–4):159–163
  29. O'Riordan ~~S et al (2009)~~S, Barton M, Yau Y, Read SE, Allen U, Tran D (2010) Risk factors and outcomes among children admitted to hospital with pandemic H1N1 influenza. CMAJ ~~182~~ ~~(1):39-44~~ (1):39–44
  30. Fisman ~~DN et al~~DN, Savage R, Gubbay J, Achonu C, Akwar H, Farrell DJ (2009) Older age and a reduced likelihood of 2009 H1N1 virus infection. N Engl J Med 361(20):2000–2001
  31. ~~Dominguez-Cherit G~~ Domínguez-Cherit G, Lapinsky SE, Macias AE, Pinto R, Espinosa-Perez L, de la Torre A et al (2009) Critically Ill patients with 2009 influenza A(H1N1) in Mexico. JAMA 302(17):1880–1887
  32. Perez-Padilla ~~R-R~~, de la Rosa-Zamboni D, Ponce de Leon S, Hernandez M, Quiñones-Falconi F, Bautista E et al (2009) Pneumonia and respiratory failure from swine-origin influenza A (H1N1) in Mexico. N Engl J Med 361(7):680–689

33. [No authors listed] (2009) Human infection with new influenza A (H1N1) virus: clinical observations from Mexico and other affected countries, May ~~2009 (2009)~~ 2009. Wkly Epidemiol Rec ~~84(21):185–189~~ 84(21):185–189
34. Chowell ~~G~~ G, Bertozzi SM, Colchero MA, Lopez-Gatell H, Alpuche-Aranda C, Hernandez M et al (2009) Severe respiratory disease concurrent with the circulation of H1N1 influenza. N Engl J Med 361(7):674–679
35. Fajardo-Dolci ~~GE~~ GE, Hernández-Torres F, Santacruz-Varela J, Rodríguez-Suárez J, Lamy P, Arboleya-Casanova H et al (2009) Epidemiological profile of mortality due to human influenza A (H1N1) in Mexico. Salud Pública Méx 51(5):361–371
36. ~~Castro Jimenez MA~~ Castro-Jiménez MA, Castillo-Pabón JO, Rey-Benito GJ, Pulido-Domínguez PA, Barbosa-Ramírez J, Velandia-Rodríguez DA et al (2009) Epidemiologic analysis of the laboratory-confirmed cases of influenza A(H1N1)v in Colombia. Euro Surveill 14(30):19284
37. [No authors listed] (2009) Human infection with new influenza A (H1N1) virus: clinical observations from a school-associated outbreak in Kobe, Japan, May ~~2009 (2009)~~ 2009. Wkly Epidemiol Rec ~~84(24):237–244~~ 84(24):237–244
38. Nishiura ~~H et al~~ H, Castillo-Chavez C, Safan M, Chowell G (2009) Transmission potential of the new influenza A(H1N1) virus and its age-specificity in Japan. Euro Surveill ~~14(22)~~ 14(22). pii:19227
39. Vaillant ~~L et al~~ L, La Ruche G, Tarantola A, Barboza P (2009) Epidemiology of fatal cases associated with pandemic H1N1 influenza 2009. Euro Surveill ~~14(33)~~ 14(33). pii:19309
40. Thompson ~~WW~~ WW, Shay DK, Weintraub E, Brammer L, Cox N, Anderson LJ et al (2003) Mortality associated with influenza and respiratory syncytial virus in the United States. JAMA 289(2):179–186
41. Simonsen ~~L et al~~ L, Clarke MJ, Schonberger LB, Arden NH, Cox NJ, Fukuda K (1998) Pandemic versus epidemic influenza mortality: a pattern of changing age distribution. J Infect Dis 178(1):53–60
42. Dodds ~~L~~ L, McNeil SA, Fell DB, Allen VM, Coombs A, Scott J et al (2007) Impact of influenza exposure on rates of hospital admissions and physician visits because of respiratory illness among pregnant women. CMAJ 176(4):463–468
43. Schanzer DL, Langley JM, Tam TW (2007) Influenza-attributed hospitalization rates among pregnant women in Canada ~~1994–2000~~. 1994–2000. J Obstet Gynaecol Can 29(8):622–629
44. Falagas ~~M et al~~ M, Karamanidou C, Kastoris AC, Karlis G, Rafailidis PI (2009) Psychosocial factors and ~~susceptibility/outcome to/of~~ susceptibility to or outcome of acute respiratory tract ~~infections (in press)~~. infections. Int J Tuberc Lung Dis 14(2):141–148
45. Falagas ~~ME et al~~ ME, Athanasoulia AP, Peppas G, Karageorgopoulos DE (2009) Effect of body mass index on the outcome of infections: a systematic review. Obes Rev 10(3):280–289
46. Falagas ME, Kompoti M (2006) Obesity and infection. Lancet Infect Dis 6(7):438–446
47. Falagas ME, ~~DE~~ Karageorgopoulos ~~(2009)~~ DE (2010) Adjustment of dosing of antimicrobial agents for bodyweight in adults. Lancet 375(9710):248–251

Tables:

Table 1

Data retrieved from studies originating from European countries regarding specific epidemiological features of pandemic influenza in patients with ~~2009(H1N1)~~ 2009 (H1N1) influenza of different severity<sup>†a</sup>

<del>First author</del> <del>Year[ref]</del> Author(s), year	<del>Country</del> Study population Study period Method Country, study	Epidemiological groups	Evaluated	Hc pa
--	--	------------------------	-----------	-------

	population, study period, method of diagnosis			
<p>Rello et al. 2009 [7]</p>	<p><del>Spain</del> Spain, 32 ICU cases with respiratory failure April–August failure, April–August, RT-PCR</p>	<p>Study population</p> <p>Sex</p> <p>Age distribution</p> <p>Previously healthy</p> <p>Obesity</p> <p>Pregnancy</p> <p>Respiratory diseases</p> <p>Cardiovascular diseases</p> <p>Diabetes mellitus</p> <p>Chronic neurological disease</p>	<p>NA</p>	<p>N<sub>2</sub></p>
		<p>Study population</p> <p>Sex</p> <p>Mean: 32y</p> <p>Median: 29y</p> <p>Age range: <del>18m–65y</del> 18m–</p>	<p>16/16 (100%)</p> <p>M: 10/16 (62.5%), F: 6/16 (37.5%)</p>	

<p><del>Vaux S. Investigation teams for new New influenza A (H1N1) in France 2009 [8]</del> A(H1N1) investigation teams 2009 [8]</p>	<p><del>France</del> France, 16 cases April–May cases, April–May, RT-PCR</p>	<p>Age distribution</p>	<p>65y  <del>[0–9</del> [0–9 y]: 1/16 (6.3%),  <del>[10–19</del> [10–19 y]: 2/16 (12.5%),  <del>[20–29</del> [20–29 y]: 5/16 (31.3%),  <del>[30–39</del> [30–39 y]: 4/16 (25%),  <del>[40–49</del> [40–49 y]: 2/16 (12.5%),  <del>[50–59</del> [50–59 y]: 1/16 (6.3%),  <del>[60–69</del> [60–69 y]: 1/16 (6.3%)</p>	<p>15</p>
<p>Surveillance Group for New Influenza A (H1N1) A(H1N1) Virus Investigation and Control in Spain <del>2009 [9]</del> 2009 [9]</p>	<p><del>Spain</del> Spain, 98 cases April–May cases, April–May, RT-PCR</p>	<p>Study population</p> <p>Sex</p> <p>Age distribution</p> <p>Pregnancy</p> <p><del>2008–2009</del> 2008–2009 vaccination</p>	<p>98/98 (100%)</p> <p>M: 50/98 (51%), F: 48/98 (49%)</p> <p>Mean (SD): 24y (<del>6.3</del>),  <del>Median:</del> (6.3),                  median: 22y, <del>Age</del> age range: <del>14–55y</del> 14–55y</p> <p>0/48 (0%)</p> <p>5/52 5/52 (9.6%)</p>	<p>NI</p>
		<p>Study population</p> <p>Sex</p>	<p>252/252 (100%)</p> <p>M: 134/252 (53%), F: 118/252</p>	

<p>Health Protection Agency, UK 2009 [10] Agency, UK 2009 [10]</p>	<p>United Kingdom, 252 cases April-June cases, April-June NR</p>	<p>Age distribution</p>	<p>(47%)                  Mean: 20y                  Median: 12y                  Age range: <del>0-73y</del> 0-73y  <del>[0-9y]:</del> [0-9y]: 73/252 (29%), <del>[10-19y]:</del> [10-19y]: 85/252 (33.7%), <del>[20-29y]:</del> [20-29y]: 33/252 (13.1%), <del>[30-39y]:</del> [30-39y]: 21/252 (8.3%), <del>[40-49y]:</del> [40-49y]: 22/252 (8.7%), <del>[50-59y]:</del> [50-59y]: 12/252 (4.8%), <del>[60-69y]:</del> [60-69y]: 5/252 (2%), <del>[70-79y]:</del> [70-79y]: 1/252 (0.4%)</p>	<p>4/2</p>
<p><del>Quoclin S.</del> Belgian working group on influenza A (H1N1) virus 2009 [11] A</p>	<p><del>Belgium</del> Belgium, 43 cases May-June cases,</p>	<p>Study population                  Sex                  Mean: 29y                  Median: 28y                  Age range: <del>8m</del> 8m-51y  <del>[0-9y]:</del> [0-9y]: 1/43 (2.3%), <del>[10-19y]:</del></p>	<p>43/43 (100%)                  M: 21/43 (49%), F: 22/43 (51%)</p>	<p>1/2</p>

<p>(H1N1)v 2009 [11]</p>	<p>May–June, RT-PCR</p>	<p>Age distribution</p>	<p>(29%), [10–19y]: 6/43 (14%), <del>[20–29y]:</del> [20–29y]: 16/43 (37.2%), <del>[30–39y]:</del> [30–39y]: 10/43 (23.3%), <del>[40–49y]:</del> [40–49y]: 9/43 (21%), <del>[50–59y]:</del> [50–59y]: 1/43 (2.3%)</p>	
<p>Ciblak <del>2009</del>[12] et al. 2009 [12]</p>	<p><del>Turkey</del> Turkey, 128 cases April–May cases, April–May, RT-PCR</p>	<p>Study population</p> <p>Sex</p> <p>Age distribution</p> <p><del>2008–2009</del> 2008–2009 vaccination</p>	<p>1/22 (4.5%)</p> <p>128/128 (100%)</p> <p>M: 69/126 (54.8%), F: 57/126 (45.2%)</p> <p><del>[1–4y]:</del> [1–4y]: 6/128 (4.7%), <del>[5–9y]:</del> [5–9y]: 10/128 (7.8%), <del>[10–18y]:</del> [10–18y]: 21/128 (16.4%), <del>[19–34y]:</del> [19–34y]: 66/128 (51.6%), <del>[35–50y]:</del> [35–50y]: 13/128 (10.2%), <del>[50–65y]:</del> [50–65y]: 10/128 (7.8%)</p> <p>13/128 (10.2%)</p>	<p>NI</p>
		<p>Study population</p>	<p><del>9950/9950</del> 9,950/9,950 (100%)</p> <p>M: <del>5373/9950</del></p>	

Gilsdorf <del>2009</del> [13] et al. 2009 [13]	Germany <del>9950</del> Germany, 9,950 notified cases April–August, NR	Sex	5,573/9,950 (54%), F: <del>4,577/9,950</del> 4,577/9,950 (46%)		
		Age distribution	Median:	19y	
			Age range:	<del>0–89y</del> 0–89y	
			<del>[0–4y]:</del>	<del>199/9,950</del>	
			[0–4y]:	199/9,950 (2%), <del>[5–9y]:</del>	
			<del>299/9,950</del>		
			[5–9y]:	299/9,950 (3%), <del>[10–29y]:</del>	
			<del>7,662/9,950</del>		
			[10–29y]:	7,662/9,950 (77%), <del>[30–59y]:</del>	42
		<del>1,692/9,950</del>		42	
[30–59y]:	1,692/9,950 (17%), >60y:	(1)			
		<del>100/9,950</del>			
		100/9,950 (1%)			
		Previously healthy	5,690/5,885 (96.7%)		
		Obesity	BMI>30: <del>11/5,885</del> (0.2%) 11/5,885 (2.0%)		
		Pregnancy	9/4,577 (0.2%)		
		Respiratory diseases	<del>87/5,885</del> 87/5,885 (1.5%)		
		Cardiovascular diseases	<del>29/5,885</del> 29/5,885 (0.5%)		
		Diabetes mellitus	<del>17/5,885</del> 17/5,885 (0.3%)		
		Study	115/115		

<p><del>Hahné 2009</del>[14] Hahné et al. 2009 [14]</p>	<p><del>Netherlands</del> Netherlands, 115 cases April–June RT-PCR</p>	<p>population Age distribution <del>2008–2009</del> 2008–2009 vaccination</p>	<p>(100%) [0–9y]: 16/115 (13.9%), <del>[10–19y]:</del> [10–19y]: 15/115 (13%), <del>[20–29y]:</del> [20–29y]: 30/115 (26.1%), <del>[30–39y]:</del> [30–39y]: 24/115 (20.9%), <del>[40–49y]:</del> [40–49y]: 11/115 (9.6%), <del>[50–59y]:</del> [50–59y]: 11/115 (9.6%), <del>[60–69y]:</del> [60–69y]: 9/115 (7.8%) 17/111 (15.3%)</p>	<p>2/</p>
				<p>Stu po Se</p>



	<p>Cullen <del>2009</del>[15] et al. 2009 [15]</p>	<p>Ireland</p>	<p>Ireland, 205 hospitalized cases April–October, NR</p>	<p>Pr he Ot Pr Re dis Ca dis Di me NI</p>
	<p>Chronic neurological disease</p>	<p>Study</p>	<p>9/180 (5%) 312/312</p>	

<p>Lytras <del>2009</del>[16] et al. 2009 [16]</p>	<p><del>Greece</del> Greece, 312 cases  <del>April-July</del> cases, April-July, RT-PCR</p>	<p>population (100%)</p> <p>Sex                  M: 170/312 (54.5%), F: 142/312 (45.5%)</p> <p>Mean (SD):  <del>Imported:</del>                  Imported : 23.6y (14)</p> <p>Indigenous: 26.4y (13.6)</p> <p><del>[0-9y]: 27/301 (9%), [10-19y]: 104/301 (34.6%), [20-29y]: 32/301 (10.6%), [30-39y]: 18/301 (6%), [40-49y]: 14/301 (4.7%), [50-59y]: 8/301 (2.7%), [60-69y]: 2/301 (0.7%)</del>                  [0-9y]: 27/301 (9%), [10-19y]: 96/301 (31.9%), [20-29y]: 104/301 (34.6%), [30-39y]: 32/301 (10.6%), [40-49y]: 18/301 (6%), [50-59y]: 14/301 (4.7%), [60-69y]: 8/301 (2.7%), [70-79y]: 2/301 (0.7%)</p>	<p>NI</p>
	<p><del>UK</del> United Kingdom, 78</p>	<p>Study population</p> <p>Sex</p> <p>Age distribution</p>	<p>78</p> <p>M</p> <p>(26)</p> <p>62</p> <p>M</p> <p>30</p>

<p>Yeung <del>2009</del>[17] et al. 2009 [17]</p>	<p>hospitalized <del>cases June–September cases, June–September, NR</del></p>	<p>Previously healthy Pregnancy Respiratory diseases Cardiovascular diseases</p>	<p>NA</p>	<p>(2. 24 10 19 NI</p>
<p>Lister <del>2009</del>[18] et al. 2009 [18]</p>	<p><del>UK 13</del> United Kingdom, 13 critically ill children with 2009 influenza A (H1N1) <del>vs 58</del> vs. 58 critically ill children with seasonal influenza (2004–2007) June–July NR ill children with seasonal influenza (2004–2007), June–July, NR</p>	<p>Study population Sex Age distribution Previously healthy Respiratory diseases Diabetes mellitus Chronic neurological disease</p>	<p>NA</p>	<p>N<sub>2</sub></p>
		<p>Study population</p>	<p>102/102 (100%)</p>	<p>Clinical attack rates</p>

<p>Smith <del>2009</del>[19] et al. 2009 [19]</p>	<p>South <del>East England,</del> boarding school 102 EastEngland,boarding school102 ILI**cases <del>Confirmed (n=63) May</del> <del>June</del>RT- PCRcasesconfirmed(n = 63),May–June,RT-PCR</p>	<p>Age distribution</p>	<p>School population: 102/2,132 (4.8%) Students: 101/1,307 (7.7%) <del>[13–14y]:</del> [13–14y]: 14/258 (5.4%), <del>[14–15y]:</del> [14–15y]: 21/260 (8.1%), <del>[15–16y]:</del> [15–16y]: 22/262 (8.4%), <del>[16–17y]:</del> [16–17y]: 32/268 (11.9%), <del>[17–18y]:</del> [17–18y]: 18/259 (6.9%)</p>	<p>0/</p>
<p><del>Awofisayo et al. Health Protection Agency West Midlands H1N1v Investigation Team 2009</del>[20] HealthProtectionAgency WestMidlandsH1N1vInvestigationTeam 2009 [20]</p>	<p><del>UK, Birmingham 62</del> pupils (school outbreak) May RT-PCRUnited Kingdom,Birmingham,62 pupils (schooloutbreak),May,RT- PCR</p>	<p>Study population</p> <p>Sex</p> <p>Age distribution</p>	<p>62/62 (100%) M: 29/62 (46.8%), F: 33/62 (53.2%) Mean: 8.5y Median: 9y Age range: <del>4–12y</del>4–12y Attack rates: Nursery (4y): 3/58 (5.2%) Reception <del>(5–6y):</del> (5– 6y): 5/61 (8.2%) Year 1 <del>(6– 7y):</del> (6–7y): 8/60 (13.4%), Year 2 <del>(7– 8y):</del> (7–8y):</p>	<p>0/t</p>

		5/59 (8.5%), Year 3 <del>(8-9y):</del> (8-9y): 8/59 <del>(13.6):</del> (13.6%), Year 4 <del>(9-10y):</del> (9-10y): 10/62 (16.1%), Year 5 <del>(10-11y):</del> (10-11y): 14/60 (23.3%), Year 6 <del>(11-12y):</del> (11-12y): 9/60 (15%)
--	--	---

~~Abbreviations:~~ NA: not ~~applicable,~~ applicable; NR: not ~~reported,~~ reported; SD: standard ~~deviation,~~ deviation; IQR: interquartile ~~range,~~ range; w: ~~weeks,~~ weeks; y: ~~year(s),~~ year(s); m: ~~month(s),~~ month (s); d: ~~day(s)-day(s)~~; ILI: influenza-like illness

~~‡:~~ <sup>a</sup>In cases where the denominators were <10, percentages (%) were not displayed ~~at~~ in this ~~table.~~ table

~~§:~~ <sup>b</sup>The proportion of people with risk factors who were ~~hospitalised~~ hospitalized for influenza was 18.5% (20/108), while the proportion of people without risk factors ~~that who~~ were ~~hospitalised~~ hospitalized for ~~influenza was~~ influenzawas 7% ~~(220/3,162).~~ (220/3,162)

Table 2  
 Data retrieved from studies originating from ~~the~~ USA and Canada regarding specific epidemiological features of pandemic influenza in patients with ~~2009(H1N1) influenza~~ 2009 (H1N1)influenza of different severity<sup>‡a</sup>

<del>First author</del> <del>Year[ref]</del> Author(s), year	<del>Country</del> <del>Study population</del> <del>Study period</del> <del>Method</del> <del>Country, study population, study period, method of diagnosis</del>	Epidemiological groups	Evaluated

Jain ~~2009~~[2] et al. 2009 [2]

~~USA 272 hospitalized cases  
April June RT-PCR~~

USA,272hospitalize  
June,RT-PCR

		Diabetes mellitus	40/272 (15%)
		Chronic neurological disease	57/272 (21%)
<p>Louie 2009 [4] et al. 2009 [4]</p> <p><del>USA, California 1,088 hospitalized and fatal cases April–August RT-PCR cases, April–August, RT-PCR</del></p> <p>USA, California, 1,088 hospitalized and fatal cases April–August RT-PCR cases, April–August, RT-PCR</p>		Study population	
		Sex	
		Age distribution	
		Previously healthy	
		Obesity	
		Pregnancy	
		Respiratory diseases	
		Cardiovascular diseases	
		Diabetes mellitus	
		Chronic neurological disease	
		Study population	642/642 (100%)

Dawood 2009[21]etal. 2009 [21]	USA, 642 cases April–May cases, April–May, RT-PCR	Sex	M: 302/592 (51%), 1 (49%)
		Age distribution	Median: 20y
			Age range: 3m–81y3
			[0–23m]: [0–23m]: 1 (2.6%), [2–4y]: 27/532 (5.1%)
			[5–9y]: [2–4y]: 27/532 (5.1%)
			[5–9y]: 65/532 (12.2%)
		[10–18y]: 212/532 (39.8%), [19–50y]: 187/532 (35.2%), ≥51y: 27/532 (5.1%)	
		Previously healthy	NR
		Pregnancy	NR
Respiratory diseases	NR		
Cardiovascular diseases	NR		
Chronic neurological disease	NR		
2008–2009–2008–2009 vaccination	NR		
Jamieson 2009[22]etal. 2009 [22]	USA, 34 pregnant Confirmed (n=31) Probable (n=3) April–May RT-PCR USA, 34 pregnant, confirmed (n=31), probable (n=3), April–May, RT-PCR	Study population	34/34 (100%)
		Age distribution	<18y: 5/34 (14.7%), [18–29y]: 17/34 (50%), [30–39y]: 11/34 (32.4%), ≥40y: 1/34 (2.9%)
		Respiratory diseases	Asthma: 7/25 (28%)
		Diabetes mellitus	1/34 (2.9%)
		2008–2009–2008–2009 vaccination	3/22 (13.6%)
Kumar S. 2009[23]etal. 2009 [23]	USA, Milwaukee, Wisconsin 680 cases April–May RT-PCR USA, Milwaukee, Wisconsin, 680 cases, April–May, RT-PCR	Study population	680/680 (100%)
		Sex	M: 347/680 (51%), 1 (49%)
		Age distribution	Mean: 12.2y <2y: 34/680 (5%), [2–4y]: 77/680 (11.3%), [5–9y]: 311/680 (45.7%), [10–17y]: 167/680 (24.6%), [18–29y]: 167/680 (24.6%), [30–39y]: 78/680 (11.5%), [40–49y]: 12/680 (1.8%), [50–64y]: 12/680 (1.8%), ≥65y: 1/680 (0.1%)
Harriman 2009[24]Centers for Disease Control	USA, 26 health-care personnel Confirmed (n=18) Probable (n=8) April–May RT-PCR USA, 26 health-care personnel, confirmed (n=	Study population	26/26 (100%)
		Sex	M: 4/23 (17.4%), F: 19/23 (82.6%)
		Age distribution	[20–29y]: [20–29y]: [30–39y]: [30–39y]: [40–49y]: (35%), [40–49y]:



and Prevention (CDC) 2009 [24]	18),probable (n = 8),April–May,RT-PCR		(15%), ≥50y: 2/20 (
		Previously healthy	NR
		<del>2008–2009</del> 2008–2009 vaccination	8/16 (50%)
	Saleeby <del>2009</del> [25] et al. 2009 [25]	<del>USA, California 7 hospitalized pregnant cases June–July NR</del>	USA,California,7 hospitalizedpregnant July,NR
Age distribution		Median: 31y, <del>Mean: mean: 29y, Age range: 18–39y, Gestational age at presentation: range:18–39y, gestational age atpresentation: 18 6/7–38 6/7–38 4/7w</del>	
Crum-Cianflone <del>2009</del> [26] et al. 2009 [26]	<del>USA Military Beneficiaries San Diego County 97 cases April–May RT-PCR</del> USA, Military Beneficiaries, San Diego County, 97 cases, April–May, RT-PCR	Study population	97/97 (100%)
		Sex	M: 73/97 (75.3%), F (24.7%)
		Age distribution	Median: 21y, IQR: <del>4 25y</del>
			Age range: <del>6m–786r</del>
			<del>[&lt;2y]: &lt;2y: 2/97 (2.1%), [2–17y]: 25/97 (25.8%), [18–24y]: (25.8%), [25–49y]: 2 (26.8%), [≥50]: [25–(26.8%), ≥50: 1/97 (</del>
		Pregnancy	4/24 (16.7%)
		Respiratory diseases	17/94 (18.1%)
		Cardiovascular diseases	1/94 ( <del>1.1%</del> )(1.1)
Diabetes mellitus	2/94 (2.1%)		
		<del>2008–2009</del> 2008–2009 vaccination	63/95 (66.3%)
		Study population	
		Sex	

<p>Kumar A. 2009[27] et al. 2009 [27]</p>	<p><del>Canada</del> Canada, 168 critically ill patients Confirmed (<math>n = 162</math>) Probable (<math>n = 6</math>) April–August RT-PCR patients, confirmed (<math>n = 162</math>), probable (<math>n = 6</math>), April–August, RT-PCR</p>	<p>Age distribution</p> <p>NA</p> <p>Previously healthy</p> <p>Obesity</p> <p>Pregnancy</p> <p>Respiratory diseases</p> <p>Cardiovascular diseases</p> <p>Diabetes mellitus</p> <p>Chronic neurological disease</p>
---	---	---

		<del>2008-2009</del> 2008-2009 vaccination	
Cutler <del>2009</del> [28]et al. 2009 [28]	<del>Canada 41 cases April-May RT-PCR</del> Canada,41 cases, April-May, RT-PCR	Study population	41/41 (100%)
		Sex	M: 21/41 (51.2%), F (48.8%)
		Age distribution	Mean: 18.2y, <del>Media</del> 17y, <del>Age</del> age range: 4-6y
		<del>2008-2009</del> 2008-2009 vaccination	23/41 (56.1%)
O’Riordan <del>2009</del> [29]et al. 2010 [29]	<del>Canada, Ontario 58 hospitalized children VS 200 hospitalized children with seasonal influenza (2004/2005-2008/2009) May-July</del> RT-PCR Canada, Ontario, 58 hospitalized children vs. 200 hospitalized children with seasonal influenza (2004/2005-2008/2009), May-July, RT-PCR	Study population	NA
		Sex	
		Age distribution	
		Previously healthy	

		Obesity	
		Respiratory diseases	
		Cardiovascular diseases	
		Chronic neurological disease	
			Study population
	<del>Canada, Ontario 11,560 tested 1,819 confirmed April June NR</del>		
Fisman <del>2009</del> [30]et al. 2009 [30]		Canada, Ontario, 11,560 tested, 1,819 confirmed, April– June, NR	Age distribution

--	--	--	--

~~Abbreviations: NA: not applicable, applicable; NR: not reported, reported; SD: standard deviation, deviation; IQR: interquartile range, range; w: weeks, weeks; y: year(s), year(s); m: month(s), month (s); d: day(s).day(s); ILI: influenza-like illness~~

~~‡: <sup>a</sup>In cases where the denominators were <10, percentages (%) were not displayed at in this table.~~

~~‡: <sup>b</sup>Includes asthma, chronic obstructive pulmonary disorder, bronchopulmonary dysplasia/respiratory distress syndrome, bronchiolitis obliterans organizing pneumonia, Sjogren syndrome, and Sjögren’s syndrome, and obstructive sleep apnea.~~

~~⊖: <sup>c</sup>Includes congenital heart disease, atrial fibrillation, status post-aortic valve replacement, congestive heart failure, hypertensive heart disease, and coronary artery~~

~~\*: <sup>d</sup>Of the 45 deaths from pandemic H1N1 virus infection reported to the CDC from April 15 to June 16, 2009, six (13%) were in from pregnant women, including one death from the original case series of 34 pregnant cases.~~

~~#: As a result of increased patient volumes, many experienced delay in admission to the ICU, and 4 remained in the emergency department until death.~~

~~\*\* : Influenza like illness.~~

~~⊙: Logistic regression analysis, with age as a continuous variable, showed an age-adjusted odds ratio for asthma of 4.38 (95% confidence interval 1.81–10.60);  $p = 0.001$ .~~

~~⊘: Excluding asthma cases~~

~~⊚: <sup>e</sup>Data on height and weight were available for 35 of the children with pandemic H1N1 influenza. Two satisfied criteria for obesity, of whom 1-one child, who also had asthma, required intensive care. Five of the 23 without height data had weights above the 97th percentile. Two of these 5-five children required intensive care: 1-one child had asthma, and the other had seizures.~~

~~<sup>f</sup>Logistic regression analysis, with age as a continuous variable, showed an age-adjusted odds ratio for asthma of 4.38 (95% confidence interval 1.81–10.60);  $p = 0.00$~~

~~<sup>g</sup>Excluding asthma~~

Table 3

Data retrieved from studies originating from countries of the rest of the world (except for the USA and Canada) regarding specific epidemiological features of pandemic influenza in patients with 2009(H1N1) influenza of different severity<sup>‡a</sup>

<del>Mexico</del> Author (s), year				
<del>Mexico</del>				

<p><del>Mexico 58</del> Mexico, 58 critically ill patients                  Confirmed (<math>n = 29</math>), Probable (<math>n = 14</math>), Suspected (<math>n = 15</math>)  <del>March–June RT-PCR</del> ill patients, confirmed (<math>n = 29</math>), probable (<math>n = 14</math>), suspected (<math>n = 15</math>), March–June, RT-PCR</p> <p>Dominguez 2009 [31]                  Domínguez-Cherit et al. 2009 [31]</p>	<p>Study population</p>	<p>58/58 (100%)</p>	<p>58/58 (100%)</p>
	<p>Sex</p>	<p>M: 27/58 (46.6%), F: 31/58 (53.4%)</p>	
	<p>Age distribution</p>	<p>Median: 44y</p>	
	<p>Age distribution</p>	<p><del>2/24 (8.3%)</del> [10–19y]: 1/4, [20–29y]: 5/9, [30–39y]: 8/13 (61.5%), [40–49y]: 8/18 (44.4%), [50–59y]: 1/5, [60–69y]: 1/3, [70–79y]: 0/4, [80–89y]: 0/2</p>	
	<p>Age distribution</p>	<p>Previously healthy</p>	
<p>Age distribution</p>	<p><del>BMI &gt; 30</del> BMI &gt; 30: 21/58</p>	<p></p>	

		Obesity	(36.2%), [ <del>30&lt;BMI&lt;40: 13/58 (22.4%), BMI &gt; 40:</del> [30<BMI<40: 13/58(22.4%), BMI>40: 8/58 (13.8%)]
		Respiratory diseases	4/58 (6.9%) Asthma: 2/58 (3.4%), COPD: 2/58 (3.4%)
		Cardiovascular diseases	12/58 (20.7%) Ischemic heart disease: 1/58 (1.7%), Congestive (1.7%), congestive heart failure: 1/58 (1.7%), Arrhythmia: (1.7%), arrhythmia: 3/58 (5.2%), Valvular heart disease: valvular heart disease: 3/58 (5.2%), Cerebrovascular disease: 1/58 cerebrovascular disease: 1/58 (1.7%), Peripheral peripheral vascular disease: <del>3/58 (5.2%)</del>
		Diabetes mellitus	10/58 (17.2%)
<del>2008-2009</del> 2008-2009 vaccination	2/58 (3.4%)	NR	
			Study population
			Sex
		<del>Mexico 18 hospitalized</del>	Mexico, 18 hospitalized cases

<p><del>Perez 2009 [32]</del></p>	<p>Perez-Padilla et al. 2009 [32]</p>	<p><del>cases with pneumonia March–April RT-PCR</del></p>	<p>with pneumonia, March–April, RT-PCR</p>	
	<p>Diabetes mellitus</p>		<p>3/18 (16.7%)</p>	<p>NR</p>
<p><del>2008–2009</del> 2008–2009 vaccination</p>	<p>3/18 (16.7%)</p>	<p>NR</p>		
	<p>WHO Mexico 2009 [33] 2009 [33]</p>	<p><del>Mexico 3,734 cases April–May RT-PCR</del></p>	<p>Mexico, 3,734 cases, April–May, RT-PCR</p>	<p>Age distribution</p>



				Previously healthy
	Pregnancy		NR	1/45 (2.2%)
		Mexico		

<p>Chowell <del>2009</del>[34] et al. 2009 [34]</p>	<p><del>2155 cases of severe pneumonia VS 2005-2008 influenza seasons</del></p>	<p>Mexico, 2,155 cases of severe pneumonia vs. 2005–2008 influenza seasons, March–April 2009 RT-PCR</p>
<p><del>March–April 2009</del></p>	<p>Peak incidence:</p>	
	<p>Study</p>	

	<p><del>RT-PCR</del></p>	<p>incidence:study period: [<del>25-44y</del>]: <del>~28%</del>, <del>2005-2008</del> influenza seasons:; [0-4y]: <del>~47%</del> [25-44y]: ~28%, 2005-2008influenza seasons: [0-4y]: ~47%</p>		
<p><del>Fajardo 2009 [35]</del> Fajardo-Dolci et al. 2009 [35]</p>	<p><del>Mexico 12,645 cases (March-May) and 122</del> Mexico, 12,645 cases (March-May) and 122 fatal cases (April-May) RT-PCR cases (April-May), RT-PCR</p>	<p>Study population</p> <p>Sex</p> <p>Age distribution</p>	<p><del>12645/12645</del> 12,645/12,645 (100%)</p> <p>NR</p> <p><del>[0-9y]: 3531/12645</del></p>	<p>21/122 (17%)</p>

<del>Colombia</del> Colombia				
<p><del>Castro 2009 [36]</del>Castro-Jiménez et al. 2009 [36]</p>	<p><del>Colombia 183 cases May-July RT-PCR</del>Colombia,183 cases,May-July,RT-PCR</p>	Study population	183/183 (100%)	26/183 (14.2%)
		Sex	M: 96/183 (52.5%), F: 87/183 (47.5%)	
		Age distribution	Median (IQR): 27y ( <del>17-38</del> ) <del>[0-9y]: (17-38)</del> [0-9y]: 27/183 (14.8%), <del>[10-19y]: 39/183 (21.3%), [20-29y]: 39/183</del> (21.3%), [20-29y]: 47/183 (25.7%), <del>[30-39y]: 33/183</del> [30-39y]:33/183 (18%), <del>[40-49y]: 20/183</del> (10.1%), <del>[50-59y]: 9/183 (4.9%), [60-69y]: 7/183 (3.8%), [70-79y]: 1/183 (0.5%)</del>	
		Obesity	NR	
Japan				
		Study population		49/49 (100%)
		Sex		M: 23/49 (46.9%), F 26/49 (53.1%)
				Median:

<p>WHO Japan 2009 [37] 2009 [37]</p>	<p>Japan, <del>Kobe 49 hospitalized cases (school-associated outbreak)</del> April-May RT-PCR Kobe 49 hospitalized cases (school-associated outbreak), April-May, RT-PCR</p>	<p>Age distribution</p> <p>Previously healthy</p> <p>Pregnancy</p> <p>Respiratory diseases</p> <p>Cardiovascular diseases</p> <p>Diabetes mellitus</p> <p><del>2008-2009</del> 2008-2009 vaccination</p>	<p>NA</p>	<p>17y, Age range: <del>5-60y</del> [0-9y]: 5-60y [0-9y]: 1/49 (2%), <del>[10-19y]: 40/49 (81.6%)</del>, [10-19y]: 40/49 (81.6%), ≥ 20y: 8/49 (16.3%)</p> <p>40/49 (81.6%)</p> <p>0/26 (0%)</p> <p>Asthma: 6/49 (12.2%)</p> <p>0/49 (0%)</p> <p>0/49 (0%)</p> <p>22/43 (51.2%)</p>
<p>Nishiura 2009 [38] et al. 2009 [38]</p>	<p>Japan 361 cases May-June NR Japan, 361 cases, May-June, NR</p>	<p>Study population</p> <p>Age distribution</p>	<p>361/361 (100%)</p> <p><del>[0-9y]:</del> [0-9y]: 15/361 (4.2%), <del>[10-19y]: 287/361 (79.5%)</del>, [10-19y]: 287/361 (79.5%), [20-29y]: 27/361 (7.5%), <del>[30-39y]: 11/361</del> [30-39y]: 11/361 (3%), <del>[40-49y]:</del> [40-49y]: 13/361 (3.6%), <del>[50-59y]:</del> [50-59y]: 5/361 (1.4%), ≥60y: 3/361 (0.8%)</p>	<p>NR</p>
<p><del>Worldwide report</del></p>				
<p><del>Vaillant 2009 [39] April-July</del> NR Vaillant et al. 2009 [39]</p>	<p>Canada, <del>USA, Mexico, Europe, Asia</del> 371 USA, Mexico, Europe, Asia, 371 fatal cases associated with pandemic H1N1 influenza 2009 cases associated</p>	<p>Age distribution</p>	<p>NA</p>	<p>NA</p>

	with pandemic H1N1 influenza 2009, April–July, NR				
--	---	--	--	--	--

~~Abbreviations:~~ NA: not ~~applicable, applicable~~; NR: not ~~reported, reported~~; SD: standard ~~deviation, deviation~~; IQR: interquartile ~~range, range~~; w: ~~weeks, weeks~~; y: ~~year(s), year(s)~~; m: ~~month(s), month(s)~~; d: ~~day(s), day(s)~~

~~†:~~<sup>a</sup> In cases where the denominators were <10, percentages (%) were not displayed ~~at~~ in this ~~table, table~~

~~\*\*\*:~~<sup>b</sup> As a result of increased patient volumes, many experienced delay in admission to the ICU, and four remained in the emergency department until death

<sup>c</sup> Among a total of 5,563 confirmed ~~cases, cases~~

Table 4  
Percentage of different epidemiological groups among cases of pandemic influenza with different severity in studies originating from the Northern Hemisphere<sup>†a</sup>

	Epidemiological groups	Evaluated patient population (ILI or <del>laboratory confirmed, laboratory-confirmed</del> cases)	Hospitalized patients	ICU patients	Fatal cases
					[Specification in case of discrepancies]: (percentage %) <del>reference</del> [reference]
Age					
Young children <del>[0–9y]</del> [0–9y]	<del>(6.3%) [8], (29%) [10], (2.3%) [11], (12.5%) [12], (5.1%) [13], (13.9%) [14], (9%) [16], (19.9%) [21], (14.8%) [36], (4.2%) [38], 0–11y: (62.1%) [23], (62.9%) [20], (28%) [33], (27.9%) [35]</del> (6.3%) [8], (29%) [10], (2.3%) [11], (12.5%) [12], (5.1%) [13], (13.9%) [14], (9%) [16], (19.9%) [21], (14.8%) [36], (4.2%) [38], 0–11y: (62.1%) [23], (62.9%) [20], (28%) [33], (27.9%) [35]	<del>(23.4%) [15], (26.5%) [2], (22.2%) [32], (2.0%) [37]</del> (23.4%) [15], (26.5%) [2], (22.2%) [32], (2.0%) [37]	<del>(20.2%) <sup>†27</sup> [27]</del> (20.2%) <sup>†27</sup> [27]	<del>(10.3%) [27], (11.3%) [39], [0–10y]: 1/7 [32], (8.1%) [33], (10%) [34], (15.6%) [35] [0–17y]: (6.8%) [4]</del> (10.3%) [27], (11.3%) [39], [0–10y]: 1/7 [32], (8.1%) [33], (10%) [34], (15.6%) [35] [0–17y]: (6.8%) [4]	

	(9%) [16], (19.9%) [21], (14.8%) [36], (4.2%) [38], [0–11y]: (62.1%) [23], (62.9%) [20], (28%) [33], (27.9%) [35]	(22.2%) [32], (2.0%) [37]		10y]: 1/7 [32], (8.1%) [33], (10%) [34], (15.6%) [35], [0–17y]: (6.8%) [4]
Older children & adolescents <del>[10–19y]</del> [10–19y]	<del>(12.5%)[8], (33.7%) [10], (14%) [11], [10–18y]: (16.4%) [12], [10–29y]: (77%) [13], (13%) [14], (39.9%) [16], [10–18y]: (39.8%) [21], (12.5%) [8], (33.7%) [10], (14%) [11], [10–18y]: (16.4%) [12], [10–29y]: (77%) [13], (13%) [14], (39.9%) [16], [10–18y]: (39.8%) [21], &lt;18y: (14.7%) [22], (21.3%) [36], (6.9%) [31], (79.5%) [38], [12–18y]: (24.6%) [23], 13–18y: (8.2%) [19], [10–12y]: (37.1%) [20], (25.3%) [33], [2–17y]: (25.8%) [26], (33.6%) [35] (14.7%) [22], (21.3%) [36], (6.9%) [31], (79.5%) [38], [12–18y]: (24.6%) [23], [13–18y]: (8.2%) [19], [10–12y]: (37.1%) [20], (25.3%) [33], [2–17y]: (25.8%) [26], (33.6%) [35]</del>	<del>(21.5%) [15], [10–17y]: (18.4%) [2], [11–15y]: (5.6%) [32], (81.6%) [37] (21.5%) [15], [10–17y]: (18.4%) [2], [11–15y]: (5.6%) [32], (81.6%) [37]</del>	(12.5%) <del>[27]</del> [27]	(3.4%) <del>[27]</del> , (4.2%) [31], (10%) [39], [11–15y]: 1/7 [32], (5.4%) [33], (13%) [34], (4.1%) [35] 2/4 [15] [27], (4.2%) [31], (10%) [39], [11–15y]: 1/7 [32], (5.4%) [33], (13%) [34], (4.1%) [35] 2/4 [15]
	<del>[20–59y]: (75%) [8], [20–59y]: (34.9%) [10], [20–59y]: (83.7%) [11], [19–65y]: (69.5%) [12], [30–59y]: (17%) [13], [20–59y]: (66.1%) [14], [20–59y]: (55.8%) [16], [19–50y]: (35.2%) [21], [18–29y]: (50%) [22], [20–59y]: (59.6%) [36], [20–59y]:</del>	<del>[20–59y]:</del>		<del>[20–59y]: [20–59y]: (65.5%) [27], [20–59y]: (91.7%) [31], [20–59y]: (66.3%) [39], [16–52y]: 5/7</del>

<p>Adults, young &amp; middle aged [20-65y] and middle-aged [20-65y]</p>	<p><del>(77.6%)[31], [20-59y]: (15.5%)[38], [19-64y]: (13.2%)[23], [20-49y]: (90%)[24], [20-59y]: (44.3%)[33], [25-44y]: ~28%[34]<sup>s</sup>[20-59y]: (75%) [8], [20-59y]: (34.9%) [10], [20-59y]: (83.7%) [11], [19-65y]: (69.5%) [12], [30-59y]: (17%) [13], [20-59y]: (66.1%) [14], [20-59y]: (55.8%) [16], [19-50y]: (35.2%) [21], [18-29y]: (50%) [22], [20-59y]: (59.6%) [36], [20-59y]: (77.6%) [31], [20-59y]: (15.5%) [38], [19-64y]: (13.2%) [23], [20-49y]: (90%) [24], [20-59y]: (44.3%) [33], [25-44y]: ~28% [34]<sup>b</sup>, [18-49y]: (71.1%)[26], [20-59y]: (36%)[35][18-49y]: (71.1%) [26], [20-59y]: (36%) [35]</del></p>	<p><del>(49.3%) [15], [18-64y]: (15.4%)[2], [16-61y]: (72.2%) [32], [20-20y]: (16.3%)[37]</del>          [20-59y]: (49.3%) [15], [18-64y]: (15.4%) [2], [16-61y]: (72.2%) [32], ≥20y: (16.3%) [37]</p>	<p><del>[32], [20-59y]: (81.1%)[33], [20-64y]: (69%)[34], [20-59y]: (74.6%)[35][50-59y]: 2/4 [15][27], [20-59y]: (91.7%) [31], [20-59y]: (66.3%) [39], [16-52y]: 5/7 [32], [20-59y]: (81.1%) [33], [20-64y]: (69%)[34], [20-59y]: (74.6%)[35], [50-59y]: 2/4 [15]</del>          [20-59y]: (58.9%)<sup>[27]</sup>, [18-40y]: (50%)[7]          [27], [18-40y]: (50%) [7]</p>	<p><del>[32], [20-59y]: (81.1%)[33], [20-64y]: (69%)[34], [20-59y]: (74.6%)[35], [50-59y]: 2/4 [15]</del>          [60-99y]: (20.7%)<sup>[27]</sup>, [60-89y]: (4.2%) [31], ≥60y: (12.4%) [39], ≥60y: (5.9%) [33], (8%) [34], ≥60y: (5.7%) [35][27], [60-89y]: (4.2%) [31], ≥60y:</p>
<p>Seniors (elderly) [&gt;65y]</p>	<p><del>[60-69y]: (6.3%)[8], [60-79y]: (2.4%)[10], [≥60y]: (1%)[13], [60-69y]: (7.8%)[14], [60-79y]: (3.3%)[16], [60-79y]: (4.4%)[36], [60-89y]: (15.5%)[31], [≥60y]: (0.8%)[38], [≥65y]: (0.1%)[23], [≥60y]: (1.8%)[33], (1%)[26], [≥60y]: (1.5%)[35], [60-69y]: (6.3%) [8], [60-79y]: (2.4%) [10], ≥60y: (1%) [13], [60-69y]: (7.8%) [14], [60-79y]: (3.3%) [16], [60-79y]: (4.4%) [36], [60-89y]:</del>          [≥60y]: (5.9%)[15], [≥65y]: (5.1%)[2]≥60y: (5.9%) [15], ≥65y: (5.1%) [2]</p>	<p><del>[60-99y]: (20.7%) [27], [60-89y]: (4.2%) [31], ≥60y: (12.4%) [39], [60y]: (5.9%) [33], (8%) [34], ≥60y: (5.7%) [35][27], [60-89y]: (4.2%) [31], ≥60y:</del>          [60-99y]: (8.3%)<sup>[27]</sup>, [60-99y]: (3.1%)[7]          [27], (3.1%) [7]</p>	<p><del>[60-99y]: (20.7%) [27], [60-89y]: (4.2%) [31], ≥60y: (12.4%) [39], [60y]: (5.9%) [33], (8%) [34], ≥60y: (5.7%) [35][27], [60-89y]: (4.2%) [31], ≥60y:</del>          [60-99y]: (8.3%)<sup>[27]</sup>, [60-99y]: (3.1%)[7]          [27], (3.1%) [7]</p>	<p><del>[60-99y]: (20.7%) [27], [60-89y]: (4.2%) [31], ≥60y: (12.4%) [39], [60y]: (5.9%) [33], (8%) [34], ≥60y: (5.7%) [35][27], [60-89y]: (4.2%) [31], ≥60y:</del>          [60-99y]: (20.7%) [27], [60-89y]: (4.2%) [31], ≥60y: (12.4%) [39], [60y]: (5.9%) [33], (8%) [34], ≥60y: (5.7%) [35][27], [60-89y]: (4.2%) [31], ≥60y:</p>



	(15.5%) [31], ≥60y: (0.8%) [38], ≥65y: (0.1%) [23], ≥60y: (1.8%) [33], (1%) [26], ≥60y: (1.5%) [35], ≥51y: <del>(5.1%)</del> <del>[21]</del> (5.1%) [21]			(12.4%) [39], ≥ 60y: (5.9%) [33], (8%) [34], ≥ 60y: (5.7%) [35]
<b>Sex</b>				
Males	<del>(62.5%)</del> [8], <del>(51%)</del> [9], <del>(53%)</del> [10], <del>(49%)</del> [11], <del>(54.8%)</del> [12], (54%) [13], <del>(54.5%)</del> [16], <del>(51.2%)</del> [28], (51%) [21], <del>(52.5%)</del> [36], <del>(46.6%)</del> [31], (51%) [23], (17.4%) [24], <del>(46.8%)</del> [20], <del>(75.3%)</del> <del>[26]</del> (62.5%) [8], (51%) [9], (53%) [10], (49%) [11], (54.8%) [12], (54%) [13], (54.5%) [16], (51.2%) [28], (51%) [21], (52.5%) [36], (46.6%) [31], (51%) [23], (17.4%) [24], (46.8%) [20], (75.3%) [26]	<del>(48.3%)</del> [15], (51%) [2] (48.9%) [4], (50%) [32] <del>(46.9%)</del> [37], (20.5%) [17], <del>(60.3%)</del> [29] (48.3%) [15], (51%) [2], (48.9%) [4], (50%) [32], (46.9%) [37], (20.5%) [17], (60.3%) [29]	<del>(73.3%)</del> [7], <del>(32.7%)</del> [27], <del>(53.8%)</del> [18] (73.3%) [7], (32.7%) [27], (53.8%) [18]	<del>1/4</del> [15], <del>(50%)</del> [4], <del>(27.6%)</del> [27], <del>(50%)</del> [31], 5/7 <del>[32]</del> , 1/5 [18], 3/7 [17], <del>(49.2%)</del> <del>[35]</del> 1/4 [15], (50%) [4], (27.6%) [27], (50%) [31], 5/7 [32], 1/5 [18], 3/7 [17], (49.2%) [35]
Seasonal <del>(2008-2009) influenza vaccination</del> (2008-2009) influenzavaccination	<del>(9.6%)</del> [9], <del>(10.2%)</del> [12], <del>(15.3%)</del> [14], <del>(56.1%)</del> [28], (9.6%) [9], (10.2%) [12], (15.3%) [14], (56.1%) [28], (13.6%) [22], <del>(3.4%)</del> [31], <del>(50%)</del> <del>[24]</del> , <del>(66.3%)</del> [26] (3.4%) [31], (50%) [24], (66.3%) [26]	<del>(15.8%)</del> [21], <del>(16.7%)</del> [32], <del>(51.2%)</del> [37] (15.8%) [21], (16.7%) [32], (51.2%) [37]	<del>(6%)</del> [27] (6%) [27]	NR
		<del>(50.6%)</del> [15], <del>(27.2%)</del> [2], <del>(31.9%)</del> [4], <del>(59.1%)</del> [21], <del>(55.6%)</del> [32], (50%) [24], <del>(81.6%)</del>		<del>(42.1%)</del> [15], <del>(31.6%)</del> [2], <del>(24.6%)</del>

<p>Previously healthy</p>	<p><del>(75%)[8], (96.7%)[13], (15.5%)[31]</del>                  (75%) [8], (96.7%) [13], (15.5%) [31]</p>	<p><del>[37], (30.8%) [17], (12.1%)[29]</del>                  (50.6%) [15], (27.2%) [2], (31.9%) [4], (59.1%) [21], (55.6%) [32], (50%) [24], (81.6%) [37], (30.8%) [17], (12.1%) [29]</p>	<p><del>(46.8%)[7], (1.8%)[27], (8.3%)[29]</del>                  (46.8%) [7], (1.8%) [27], (8.3%) [29], (42.1%) [15]</p>	<p><del>[4], (8.3%) [31], 2/7 [32], 1/5 [18]</del>                  (42.1%) [15], (31.6%) [2], (24.6%) [4], (8.3%) [31], 2/7 [32], 1/5 [18]</p>
<p>Pregnancy</p>	<p><del>(4.5%)[11], (0.2%)[13], 34/34[22], (16.7%)[26]</del>                  (4.5%) [11], (0.2%) [13], 34/34 [22], (16.7%) [26]</p>	<p><del>(11.3%) [15], (13.6%)[2], (17.4%)[4], (4.5%)[21], (41.2%) [22], (16.1%)[17]</del>                  (11.3%) [15], (13.6%) [2], (17.4%) [4], (4.5%) [21], (41.2%) [22], (16.1%) [17]</p>	<p><del>(18.2%)[7], (11.5%)[27], (8.8%)[22]</del>                  (18.2%) [7], (11.5%) [27], (8.8%) [22]</p>	<p><del>(15.8%) [2], (5.1%)[4], 1/2[21], (2.9%) [22], (2.2%) [33]</del>                  (15.8%) [2], (5.1%) [4], 1/2 [21], (2.9%) [22], (2.2%) [33]</p>
<p>Obesity</p>				
<p><del>BMI &gt; 30</del> BMI&gt;30</p>	<p><del>(0.2%)[13], (36.2%)[31]</del>                  (0.2%) [13], (36.2%) [31]</p>	<p><del>(47.6%)[4], (5.7%)[29]</del>                  (47.6%) [4], (5.7%) [29]</p>	<p><del>(33.3%)[27], 1/2[29]</del>                  (33.3%) [27], 1/2 [29]</p>	<p><del>(39%)[4], 1/7[36]</del>                  (39%) [4], 1/7 [36]</p>
<p><del>30 &lt; BMI &lt; 40</del> 30&lt;BMI&lt;40</p>	<p><del>(22.4%)[31]</del>                  (22.4%) [31]</p>	<p><del>(29%)[2], (33.2%)[4]</del>                  (29%) [2], (33.2%) [4]</p>	<p><del>(18.8%)[7], 3/7[17]</del>                  (18.8%) [7], 3/7 [17]</p>	<p>NR</p>
<p><del>BMI &gt; 40</del> BMI&gt;40</p>	<p><del>(13.8%)[31]</del>                  (13.8%) [31]</p>	<p><del>(2.2%)[15], (26.0%)[2], (25%)[4]</del>                  (2.2%) [15], (26.0%) [2], (25%) [4]</p>	<p><del>(12.5%)[7]</del>                  (12.5%) [7]</p>	<p>NR</p>
<p>Comorbidity</p>				

		Respiratory disease		
Any respiratory disease	<del>(12.5%)</del> [8], (1.5%) [13], (6.9%) [31], (18.1%) [26] (12.5%) [8], (1.5%) [13], (6.9%) [31], (18.1%) [26]	<del>(13.4%)</del> [4] <sup>*</sup> , (13.4%) [4] <sup>c</sup> , <del>(5.6%)</del> [32] <sup>**</sup> , (5.6%) [32] <sup>d</sup> , <del>(24.4%)</del> [17] (24.4%) [17]	<del>(28.1%)</del> [7], (41.1%) [27], (7.7%) [18], 2/7 [17], (28.1%) [7], (41.1%) [27], (7.7%) [18], 2/7 [17]	<del>(15.8%)</del> [2], (40.7%) [4] (15.8%) [2], (40.7%) [4]
Asthma	<del>(28%)</del> [22], (3.4%) [31] (28%) [22], (3.4%) [31]	<del>(10%)</del> [15], (28%) [2], (23.6%) [4], (22.7%) [21], (11.1%) [32], (12.2%) [37], (22.4%) [29], (10%) [15], (28%) [2], (23.6%) [4], (22.7%) [21], (11.1%) [32], (12.2%) [37], (22.4%) [29]	(15.6%) [7], (22.6%) [27], (41.7%) [29] (15.6%) [7], (22.6%) [27], (41.7%) [29]	NR
COPD	<del>(3.4%)</del> [31] (3.4%) [31]	<del>(17.8%)</del> [15], (8%) [2], (3.4%) [29] (17.8%) [15], (8%) [2], (3.4%) [29]	<del>(12.5%)</del> [7], (9.5%) [27] (12.5%) [7], (9.5%) [27]	NR
Cardiovascular disease	<del>(6.3%)</del> [8], (0.5%) [13], (20.7%) [31], (1.1%) [26] (6.3%) [8], (0.5%) [13], (20.7%) [31], (1.1%) [26]	<del>(5%)</del> [15], (13%) [2], (15.3%) [4], (9.1%) [21], (6.9%) [29] (5%) [15], (13%) [2], (15.3%) [4], (9.1%) [21], (6.9%) [29]	<del>(3.1%)</del> [7], (14.9%) [27], 2/7 [17], (8.3%) [29] (3.1%) [7], (14.9%) [27], 2/7 [17], (8.3%) [29]	<del>(22.9%)</del> [4] (22.9%) [4]
Diabetes mellitus	<del>(0.3%)</del> [13], (2.9%) [22], (17.2%) [31], (2.1%) [26] (0.3%) [13], (2.9%) [22],	<del>(4.4%)</del> [15], (15%) [2], (10.7%) [4], (16.7%) [32] (4.4%) [15],	<del>(3.1%)</del> [7], (20.8%) [27], (7.7%) [18], 1/7 [17] (3.1%) [7],	<del>(16.9%)</del> [4] (16.9%) [4]

	(17.2%) [31], (2.1%) [26]	(15%) [2], (10.7%) [4], (16.7%) [32]	(20.8%) [27], (7.7%) [18], 1/7 [17]	[4]
Chronic neurological disease	NR	<del>(5%) [15], (21%) [2], (10.5%) [4], (4.5%) [21], (17.2%) [29]</del> (5%) [15], (21%) [2], (10.5%) [4], (4.5%) [21], (17.2%) [29]	<del>(3.1%) [7], (15.5%) [27], (38.5%) [18], (16.7%) [29]</del> (3.1%) [7], (15.5%) [27], (38.5%) [18], (16.7%) [29]	<del>(15.3%) [4]</del> (15.3%) [4]

**Abbreviations:** NR: not reported

~~‡~~<sup>a</sup> In cases where the denominators were <10, no percentages were displayed ~~at~~ in this ~~Table~~. Table

~~§~~<sup>b</sup> Peak ~~incidence~~. incidence

~~\*~~<sup>c</sup> Excluding ~~asthma~~. asthma

~~\*\*~~<sup>d</sup> Obstructive sleep ~~apnea~~. apnea