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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

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

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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, 5five 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 eases, 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 <u>costs.[1]</u> 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 $\frac{age,[2-5]}{age}$ 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].

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 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 Oetober.[15] October [15]. Four other studies covered a time period from May until July,[29, 36]. Two other studies covered a time period from May until July,[29, 36]. Two other studies covered a time period from May until July,[29, 36]. Two other studies covered a time period from May until 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] in 8 of the 35 included studies, of patients admitted iminto the intensive care unit (ICU) ICU in 3-studies,[7, three studies [7, 18, 27] 27], and from fatal cases associated with 2009 H1N1 influenza in 1-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 $\frac{9\%}{93.8\%}$ o and 93.8% in 13 studies that provided relevant $\frac{\text{data.[8, data [8, 10, 11, 13, 14, 19–22, 24, 26, 28, <math>\frac{36}{936}]$. The rate of admission in-into the ICU among the evaluated pandemic influenza cases ranged between $\frac{9\%}{36.4\%}$ o and 36.4% in $\frac{4 \text{ studies.[14, four studies [14, 21, 22, <math>\frac{28}{28}]}{28}$. The rate of admission in-into the ICU among the evaluated pandemic influenza cases ranged between $\frac{9\%}{66.7\%}$ of and $\frac{66.7\%}{9}$ and $\frac{66.7\%}{16}$ in $\frac{6}{5}$ studies.[2, six studies [2, 4, 15, 17, 29, $\frac{32}{32}]$. Specific data are presented in Table 1. The fatality rate among the evaluated pandemic influenza cases was 0% in 13 of the included $\frac{10}{5}$ studies [8–10, 12–14, 16, 19, 20, 24, 26, 28, $\frac{37}{37}]$. However, the respective rates reported from $\frac{5}{5}$ five other studies ranged between $\frac{2\%}{38.5\%}$.[18, 2 and 38.5% [18, 21, 22, 33, $\frac{36}{36}]$. The fatality rate among hospitalized cases ranged between $\frac{9\%}{38.9\%}$ o and $\frac{38.9\%}{38.9\%}$ in $\frac{6}{5}$ six of the included $\frac{5\%}{38.9\%}$.[18, 21, 22, 33, $\frac{36}{36}$]. The fatality rate among hospitalized cases ranged between $\frac{9\%}{38.9\%}$ of $\frac{38.9\%}{38.9\%}$ in $\frac{6}{5}$ six of the included $\frac{5\%}{38.9\%}$.[18, 21, 22, 33, $\frac{36}{36}$]. The fatality rate among hospitalized cases ranged between $\frac{9\%}{38.9\%}$ of $\frac{38.9\%}{38.9\%}$ in $\frac{6}{5}$ six of the included $\frac{5\%}{38.9\%}$.[18, 21, 22, 33, $\frac{36}{36}$]. The fatality rate among hospitalized cases ranged between $\frac{9\%}{38.9\%}$ of $\frac{38.9\%}{38.9\%}$ in $\frac{6}{5}$ six of the included $\frac{5\%}{38.9\%}$.[18, 21, 22, $\frac{37}{31}$].

<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 presence of risk factors or comorbid conditions) among the patients involved in the respective included studies (stratified with regard to 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 between13.2%-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 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 <math>58.8%, [27], 58.8% [27], respectively), whereas the lowest rate was observed for senior patients (3.1%, [7], (3.1%, [7], and <math>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 to 91.7%, according to the data provided from 6-six of the included studies.[27, studies [27, 31, 33–35, 39]Yet, 39]. Yet, substantial percentages ranging from 4.2%-4.2 to 20.7% were observed for seniors.[27, seniors [27, 31, 33–35, 39]Yet, 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]-31]. The respective percentage of hospitalized cases ranged between $\frac{15.8\%-51.2\%}{15.8}$ and 51.2% in 3-three studies providing relevant data,[21, 32, $\frac{37}{37}$], whereas a single study reported a rather low percentage of 6% among ICU eases.[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 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] 37]. Previously healthy cases were represented by percentages of up to 46.8% among ICU cases,[7, cases [7, 27, 29] and up to 42.1% among fatal cases.[2, cases [2, 4, 15, 31, 32] 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]-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] and 5.7% 47.6% 5.7 to 47.6% among hospitalized cases in 3 studies.[2, three studies [2, 4, 29]Obese 29]. Obese patients also constituted 18.8%, [7] and 33.3%, [27] 18.8% [7] and 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% 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]. 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]. 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), 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].

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 $\frac{2006-2008}{2006-2008}$), 2006–2008), the percentages of fatal pandemic cases were lower from those of the respective fatal seasonal cases in the age groups $\frac{0-4}{1829}$ years and >60 years.[34] years [34]. Additionally, another study that compared a total of $\frac{1829}{1829}$ 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].

<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.

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-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].

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-ill, and fatal cases. This finding, along with the evidence provided from studies from the Southern Hemisphe [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 subpopulation as well, 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, 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.

Conflict of interest

None None.

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Tables:

Table 1

Data retrieved from studies originating from European countries regarding specific epidemiological features of pandemic influenza in patients with $\frac{2009(H1N1)}{2009(H1N1)}$ -2009 (H1N1) influenza of different severity^{‡a}

First author Year[ref]Author(s), year	Country Study population Study period Method Country, study	Epidemiological groups	Evaluated	Ho pa
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	population, study period, method of diagnosis			
		Study population Sex		
		Age distribution		
		Previously		
	Spain Spain, 32 ICU cases	healthy		
Rello et al2009[7] al. 2009 [7]	April-August failure, April-August, RT-PCR	Obesity	NA	N
		Pregnancy		
		Respiratory diseases		
		Cardiovascular diseases		
		Diabetes		
		Chronic neurological disease		
		Study population	16/16 (100%)	
		Sex	M: 10/16 (62.5%), F: 6/16 (37.5%)	
			Mean: 32y Median: 29y	
			Age range: 18m- 65y 18m–	

Vaux S. Investigation teams for new New influenza A (IIIN1) in France 2009[8] A(H1N1) investigation teams 2009 [8]	France- France, 16 cases April-May- cases, April– May, RT-PCR	Age distribution Previously healthy	65y (0-9) (0-9) (0-9) (10-19) (10-29) (20-	15
		Respiratory diseases	2/16 (12.5%)	
		diseases Study	1/16 (6.3%) 98/98	┡
		population	(100%)	
		Sex	M: 50/98 (51%), F: 48/98 (49%)	
Surveillance Group for New Influenza A (IIIN1)-A(H1N1) Virus Investigation and Control in Spain 2009[9]	Spain- Spain, 98 cases April-May- cases, April– May, RT-PCR	Age distribution	Mean (SD): 24y (6,3), Median: (6.3), median: 22y, Age age range: 14-55y 14– 55y	NI
		Pregnancy	0/48 (0%)	-
		2008-2009 2008-2009 vaccination	5 /52 5 /52 (9.6%)	
		Study population	252/252 (100%)	
		Sex	M: 134/252 (53%), F: 118/252	

			(47%)	
Health Protection Agency, UK 2009[10] Agency, UK 2009 [10]	United Kingdom Kingdom, 252 cases April-June- cases, April– June NR	Age distribution	Mean: 20y Median: 12y Age range: 0-73y0-73y [0-9y]: [0- 9y]: 73/252 (29%), [10- 19y]: [10- 19y]: [10- 19y]: [20-29y]: 33/252 (13.1%), [20-29y]: 33/252 (13.1%), [20-29y]: 33/252 (13.1%), [20-29y]: [30-39y]: [20-29y]: [30-39y]: [20-29y]: [30-39y]: [20-29y]: [30-39y]: [20-29y]: [30-39y]: [20-29y]: [30-39y]: [20-29y]: [30-39y]: [30-39y]: [30-39y]: [30-39y]: [30-39y]: [30-30]: [30-30]	4/.
Quoilin S. B elgian working group on influenza A (H1N1) virus 2009[11] A	Belgium- Belgium, 43 cases May-June- cases,	Study population Sex	(100%) M: 21/43 (49%), F: 22/43 (51%) Mean: 29y Median: 28y Age range: 8m- 51y8m-51y [0-9y]: [0- 9y]: 1/43 (2.3%), [10-19y]:	1/4

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

Gilsdorf 2009[13] et al. 2009 [13]	Germany 9950 -Germany, 9,950 notified cases April- August -cases, April- August, NR	Sex	5,573/9,950 $(54%), F:$ $4577/9,950$ $(46%)$ Median: 19y Age range: 0-89y0-89y $(-4y]:$ 199/9,950 $(2\%), \frac{15}{-}$ 9y]: 299/9,950 $(2\%), \frac{15}{-}$ 9y]: 299/9,950 $(3\%), \frac{10}{-}$ 299/9,950 $(3\%), \frac{10}{-}$ 299/9,950 $(3\%), \frac{10}{-}$ 299/9,950 $(3\%), \frac{10}{-}$ 299/9,950 $(77\%), \frac{30}{-}$ 59y]: 1,692/9,950 $(17\%), \frac{30}{-}$ (11 $(17\%), \frac{30}{-}$ 100/9,950
		Previously	(1%) 5,690/5,885
		healthy	(96.7%)
		Obesity	BMI>30: 11/5885 (0.2%) 11/5,885 (2.0%)
		Pregnancy	9/4,577 (0.2%)
		Respiratory diseases	87/5885 87/5,885 (1.5%)
		Cardiovascular diseases	29/5885 29/5,885 (0.5%)
		Diabetes mellitus	17/5885 17/5,885 (0.3%)
		Study	115/115

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

Cullen 2009[15] et al. 2009 [15]	Ireland	Ireland, 205 hospitalized cases April- October cases, April- October, NR	Pr he Ol Pr Re dis Ca di Di m NI
	Study	312/312	

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

Yeung 2009[17] et al. 2009 [17]	hospitalized cases June- September cases, June- September, NR	Previously healthy Pregnancy Respiratory diseases Cardiovascular diseases	NA	(2: 24 10 19 NI
		Study population		
	UK 13- United Kingdom,13 critically ill	Sex		
Lister 2009[18] et al. 2009 [18]	children with 2009 influenza A-illchildren with2009 influenzaA (H1N1) VS 58 -vs.58 critically ill children with seasonal influenza (2004- 2007) June- JulyNRillchildren withseasonal influenza	Age distribution	NA	Nź
	(2004–2007),June– July,NR	Previously healthy		
		Respiratory diseases		
		Diabetes mellitus		
		Chronic neurological disease		
		Study population	102/102 (100%) Clinical attack rates	

Smith 2009[19] et al. 2009 [19]	South East England, boarding school 102 EastEngland,boarding school102 ILI ^{***} cases Confirmed (n=63) May- JuneRT- PCR casesconfirmed(n = 63),May–June,RT-PCR	Age distribution	School population: 102/2,132 (4.8%) Students: 101/1,307 (7.7%) [13–14y]: 14/258 (5.4%), [14–15y]: 21/260 (8.1%), [15–16y]: 22/262 (8.4%), [16–17y]: 32/268 (11.9%), [17–18y]: 18/259 (6.9%)	0/.
Awofisayo et al. Health Protection Agency West Midlands H1N1v Investigation Team 2009[20] HealthProtectionAgency WestMidlandsH1N1vInvestigationTeam 2009 [20]	UK, Birmingham 62 pupils (school outbreak) May RT-PCR United Kingdom,Birmingham,62 pupils (schooloutbreak),May,RT- PCR	Study population Sex Age distribution	62/62 (100%) M: 29/62 (46.8%), F: 33/62 (53.2%) Mean: 8.5y Median: 9y Age range: 4 12y4–12y Attack ratesrates: Nursery (4y): 3/58 (5.2%) Reception (5-6y): 5/61 (8.2%) Year 1 (6- 7y): (6-7y): 8/60 (13.4%), Year 2 (7- 8y): (7-8y):	0/(

1			
			5/59
			(8.5%),
			Year 3 (8-
			9y): (8–9y):
			8/59 (13.6),
			(13.6%),
			Year 4 (9-
			10y): (9–
			10y): 10/62
			(16.1%),
			Year 5 (10-
			11y): (10–
			11y): 14/60
			(23.3%),
			Year 6 (11-
			12y): (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

⁺:-^aIn cases where the denominators were <10, percentages (%) were not displayed at-in this table.

§: ^bThe 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 $\frac{2009(H1N1) \text{ influenza}}{2009(H1N1) \text{ influenza}}$ 2009 (H1N1)influenza of different severity $\frac{1}{2}^{a}$

First author Year[ref] Author(s), year	Country Study population Study period Method Country, study population, study period, method of diagnosis	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%)
		Study population	
		Sex	
Louie 2009 [4] et al. 2009 [4]	USA, California 1,088 hospitalized and USA,California,1,088hospitalizedand fatal cases April-August RT- PCR cases,April–August,RT-PCR	Age distribution	
		Previously healthy	
		Obesity	
		Pregnancy	
		Respiratory diseases	
		Cardiovascular diseases	
		Diabetes mellitus	
		Chronic neurological disease	
		Study population	642/642 (100%)

		Sex	M: 302/592 (51%), I (49%)
Dawood 2009[21] et al. 2009 [21]	USA- USA, 642 cases April-May cases, April–May, RT-PCR	Age distribution	Median: 20y Age range: 3m 81y3 [0-23m]: [0-23m]: 1 (2.6%), [2-4y]: 27/53 [5-9y]: 65/532 (12.2 18y]: 212/532 [10-1 (39.8%), [19-50y]: [187/532 (35.2%), ≥£ ≥51y: 27/532 (5.1%)
		Presence of the second se	
		Respiratory diseases	NR
		Cardiovascular diseases	NR
		Chronic neurological disease	NR
		2008-2009- 2008–2009	ND
		vaccination	INK
Jamieson 2009[22]et al. 2009	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) (50%),[30–39y]: 11/ ≥40y: 1/34 (2.9%)
		Respiratory diseases	Asthma: 7/25 (28%)
[22]		Diabetes mellitus	1/34 (2.9%)
		2008-2009- 2008–2009 vaccination	3/22 (13.6%)
		Study population	680/680 (100%)
	USA, Milwaukee, Wisconsin 680 cases April-May RT- PCR USA,Milwaukee,Wisconsin,680 cases,April–May,RT-PCR	Sex	M: 347/680 (51%), l (49%)
Kumar S. 2009[23] et al. 2009 [23]		Age distribution	Mean: 12.2y <2y: 34/680 (5%), [2 5y]: 77/680 (11.3%) 11y]: 311/680 (45.7% 167/680 (24.6%), [1 18y]: 167/680(24.6%) 78/680 (11.5%), [50
			<mark>12/680-</mark> [50–64y]:12/ ≥65y: 1/680 (0.1%)
		Study population	26/26 (100%)
Harriman	USA 26 bealth core personnal	Sex	M: 4/23 (17.4%), F: (82.6%)
Centers for Disease Control	Confirmed (n=18) Probable (n=8) April May RT PCR USA,26 health- carepersonnel,confirmed($n =$	Age distribution	[20-29y]: [20–29y]: [30-39y]: [30–39y]: [40-49y]: (35%),[40

and	18), probable ($n = 8$), April–May, RT-		(15%), ≥50y: 2/20 (
Prevention	PCR	Previously healthy	NR
(CDC) 2009 [24]		2008-2009- 2008–2009	8/16 (50%)
		vaccination	
	Saleeby 2009[25] et al. 2009 [25]	USA, California 7 hospitalized pregnant eases June July NR	USA,California,7 hospitalizedpregnan July,NR
Age distribution		Median: 31y, 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	
		Study population	97/97 (100%)
		Sex	M: 73/97 (75.3%), F (24.7%)
Crum- Cianflone 2009[26] et al. 2009 [26]	USA Military Beneficiaries San Diego County 97 cases April-May RT- PCR USA,MilitaryBeneficiaries,San DiegoCounty,97 cases,April– May,RT-PCR	Age distribution	Median: 21y, IQR: $\frac{1}{25y}$ Age range: $\frac{6m}{78}$ for $\frac{1}{29}$: <2y: 2/97 (2. [2–17y]: 25/97 $\frac{(25.8)}{(25.8\%)}$, [18–2 (44.3%), $\frac{125}{25}$ 49y]: 2 (26.8%), [≥50]: [25–(26.8%), ≥50: 1/97 (
		Pregnancy	4/24 (16.7%)
		Respiratory diseases	17/94 (18.1%)
		Cardiovascular diseases	1/94 (1.1%)(1.1)
		Diabetes mellitus	2/94 (2.1%)
		2008-2009- 2008–2009	62/05(66.20/)
		vaccination	03/93 (00.3%)
		Study population	-
		Sex	
			1

Kumar A. 2009[27]et al. 2009 [27]	Canada-Canada, 168 critically ill patients Confirmed (n = 162) Probable (n = 6) April-August RT- PCR patients, confirmed ($n =$ 162), probable ($n = 6$), April- August, RT-PCR	Age distribution	NA
		Previously healthy	
		Drognonov	
		Pregnancy	
		Respiratory diseases	
		Cardiovascular diseases	1
		Diabetes mellitus	
		Chronic neurological disease	
			1

		2008-2009- 2008–2009 vaccination	
		Study population	41/41 (100%)
Cutler		Sex	M: 21/41 (51.2%), F (48.8%)
2009[28] et al. 2009 [28]	Canada 41 cases April-May RT- PCR Canada,41 cases,April–May,RT- PCR	Age distribution	Mean: 18.2y, Media 17y, Age age range: 46y
		2008-2009- 2008–2009	22/41 (56 10/)
		vaccination	23/41 (56.1%)
		Study population	
		Sex	
O'Riordan 2009[29] et al. 2010 [29]	Canada, Ontario 58 hospitalized children VS 200 hospitalized children with seasonal influenza (2004/2005–2008/2009) May-July RT-PCRCanada,Ontario,58 hospitalizedchildren vs.200hospitalizedchildren withseasonalinfluenza(2004/2005– 2008/2009),May–July,RT-PCR	Age distribution	NA
		Previously healthy	

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

 $\frac{1}{2}$.^aIn cases where the denominators were <10, percentages (%) were not displayed $\frac{1}{at}$ in this table.

⁺.^bIncludes asthma, chronic obstructive pulmonary disorder, bronchopulmonary

dysplasia/respiratory distress syndrome, bronchiolitis obliterans organizing pneumonia, Sjogren syndrome, and Sjögren's syndrome, and obstructive sleep apnea.

 $\frac{1}{1000}$ CIncludes congenital heart disease, atrial fibrillation, status post-aortic post-aortic valve replacement, congestive heart failure, hypertensive heart disease, and coronary artery artery

*: ^dOf 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 originalcase 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

(Delta: Evaluating antipage of the second state of the second s

¢: Excluding asthma.cases

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

^fLogistic 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

^gExcluding 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 of pandemic influenza in patients with $\frac{2009(111N1)}{2009}$ (H1N1) influenza of different severity $\frac{1}{2}a$

Mexico Author (s), year					
Mexico					

		Study population	58/58 (100%)	
		Sex	M: 27/58 (46.6%), F: 31/58 (53.4%)	
			Median: 44y	
Dominguez 2009[31] Domínguez- Cherit et al. 2009 [31]	Mexico 58 Mexico,58 critically ill patients Confirmed (n = 29), Probable (n = 14), Suspected (n = 15) March June RT- PCR ill patients, confirmed (n = 29), probable $(n = 14)$, suspected $(n = 15)$, March–June, RT-PCR	Age distribution	2/24 (8.3%)[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–	58/58 (100%)
			69y]: 1/3, [70–79y]:0/4, [80– 89y]: 0/2	
			Previously healthy	4
			BMI > 30: BMI>30: 21/58	

		Obesity Respiratory diseases	(36.2%), [30< BMI < 40: 13/58 (22.4%), BMI > 40: [30 <bmi<40: 13="" 58(22.4%),<br="">BMI>40: 8/58 (13.8%)] 4/58 (6.9%) Asthma: 2/58 (3.4%), COPD: 2/58 (3.4%)</bmi<40:>	
		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: 1/58 cerebrovascular disease: 1/58 (1.7%), Peripheral-peripheral vascular disease: 3/58 (5.2%)	
		Diabetes mellitus	10/58 (17.2%)	
2008-2009 2008–2009 vaccination	2/58 (3.4%)	NR		
		Mexico 18 hospitalized	Mexico,18 hospitalizedcases	Study population Sex

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

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

Chowell 2009[34] et al. 2009 [34]	2155 cases of severe pneumonia VS 2005-2008 influenza seasons	Mexico,2,155 cases ofseverepneumonia vs.2005– 2008influenzaseasons,March– April2009RT-PCR
	Study	

	RT-PCR	incidence:study period: [25- 44y]: ~28%, 2005-2008 influenza seasons:, [0- 4y]: ~47%[25- 44y]: ~28%, 2005- 2008influenza seasons: [0- 4y]: ~47%		
		Study population Sex	12645/12,645 -12,645/12,645 (100%) NR	-
Fajardo 2009 [35]Fajardo- Dolci et al. 2009 [35]	Mexico 12,645 cases (March-May) and 122 Mexico,12,645 cases (March-May)and122 fatal cases (April-May) RT- PCR cases(April- May),RT-PCR	Age distribution	[0-9y]: 3531/12645	21/122 (17%)

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

WHO Japan 2009[37] 2009 [37]	Japan, Kobe 49 hospitalized eases (school- associated outbreak) April-May RT- PCR Kobe49 hospitalizedcases (school- associatedoutbreak),April– May,RT-PCR	Age distribution Previously healthy Pregnancy Respiratory diseases Cardiovascular diseases Diabetes mellitus 2008–2009 2008–2009 vaccination	NA	17y, Age range: $\frac{5}{60y [0 - 9y]}$ 5-60y[0- 9y]: 1/49 (2%), $\frac{10}{19y]}$: 40/49 (81.6%), ≥ 20y: 8/49 (16.3%) 40/49 (81.6%) 20y: 8/49 (16.3%) 40/49 (81.6%) 0/26 (0%) Asthma: 6/49 (12.2%) 0/49 (0%) 0/49 (0%) 22/43 (51.2%)
Nishiura 2009 [38] et al. 2009 [38]	Japan 361 cases May June NR Japan,361 cases,May– June,NR	Study population Age distribution	361/361 (100%) $\frac{[0-9y]: [0-9y]: 15/361}{(4.2\%), [10 19y]: 287/361} (4.2\%), [20-29y]: [10-19y]: 287/361(79.5\%), [20-29y]: 27/361(7.5\%), [20-29y]: 27/361(7.5\%), [30-39y]: 11/361 (3%), [40-49y]: 11/361 (3%), [40-49y]: [40-49y]: 13/361 (3.6\%), [50-59y]: [50-59y]: 5/361 (1.4\%), ≥60y: 3/361 (0.8\%)$	NR
Worldwide rep	ort	1		. <u> </u>
Vaillant 2009 [39] April- July NR Vailllant et al. 2009 [39]	Canada, USA, Mexico, Europe, Asia 371 USA,Mexico,Europe, Asia,371 fatal cases associated with pandemic H1N1 influenza 2009 casesassociated	Age distribution	NA	NA

withpandemicH1N1 influenza2009,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)

 $\frac{1}{4}$ In cases where the denominators were <10, percentages (%) were not displayed at in this table.

***:^bAs a result of increased patient volumes, many experienced delay in admission to the ICU, and four remained in the emergency department until death

^cAmong 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 a^{a}

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

	(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 & and adolescents [10- 19y] [10–19y]	$\begin{array}{c} (12.5\%)[8], (33.7\%)\\ \hline [10], (14\%)[11], [10-18y]; (16.4\%)[12], \\ \hline [10-29y]; (77\%)[13], \\ \hline (13\%)[14], (39.9\%) \\ \hline [16], [10-18y]; \\ \hline (39.8\%)[21], (12.5\%) \\ \hline [8], (33.7\%) [10], \\ (14\%) [11], [10-18y]; \\ \hline (16.4\%) [12], [10-29y]; (77\%) [13], \\ \hline (13\%) [14], (39.9\%) \\ \hline [16], [10-18y]; \\ \hline (39.8\%) [21], <18y; \\ \hline (14.7\%)[22], (21.3\%) \\ \hline [36], (6.9\%)[31], \\ \hline (79.5\%)[38], [12-18y]; (24.6\%)[23], 13-18y; (8.2\%)[19], [10-12y]; \\ \hline (25.8\%)[26], (33.6\%) \\ \hline [35], (14.7\%) [22], (21.3\%) \\ \hline (25.8\%)[26], (33.6\%) \\ \hline [35], (14.7\%) [22], \\ \hline (21.3\%) [36], (6.9\%) \\ \hline [31], (79.5\%) [38], \\ \hline [12-18y]; (24.6\%) \\ \hline [23], [13-18y]; (8.2\%) \\ \hline [33], [2-17y]; (25.8\%) \\ \hline [33], [2-17y]; (25.8\%) \\ \hline [36], (33.6\%) [35] \end{array}$	(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]	(12.5%) ^[27.] [27]	(3.4%) [27.], (4.2%) [31]; (10%) [39], [11- 15y]; 1/7 [32]; (5.4%) [33], (10%) [39], [11- 15y]; 1/7 [32], (5.4%) [33], (13%) [34], (4.1%) [35], 2/4 [15]	
	[20-59y]: (75%)[8]; [20-59y]: (34.9%) [10], [20-59y]: (83.7%)[11], [19- (55y]: (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]:	[20-59y]:		[20-59y]: [20–59y]: (65.5%) [27.], [20- 59y]: (91.7%) [31], [20- 59y]: (66.3%) [39], [16- 52y]: 5/7	

Adults, young & middle aged [20- 65y] and middle- aged [20–65y]	$\begin{array}{r} (77.6\%)[31], [20\\ 59y]: (15.5\%)[38], \\ \hline (19.64y]: (13.2\%) \\ \hline (23], [20.49y]: (90\%) \\ \hline (24], [20.59y]: (90\%) \\ \hline (24], [20.59y]: (90\%) \\ \hline (24], [20.59y]: (25.8\%) \\ \hline (44.3\%)[33], [25- \\ \hline (44.3\%)[33], [25- \\ \hline (44.3\%)[33], [20- \\ 59y]: (75\%) [8], [20- \\ 59y]: (34.9\%) [10], \\ [20-59y]: (83.7\%) \\ \hline (11], [19-65y]: \\ (69.5\%) [12], [30- \\ 59y]: (17\%) [13], [20- \\ 59y]: (66.1\%) [14], \\ [20-59y]: (66.1\%) [14], \\ [20-59y]: (66.1\%) [14], \\ [20-59y]: (55.8\%) \\ \hline (16], [19-50y]: \\ (35.2\%) [21], [18- \\ 29y]: (50\%) [22], [20- \\ 59y]: (50\%) [22], [20- \\ 59y]: (59.6\%) [36], \\ [20-59y]: (77.6\%) \\ [31], [20-59y]: \\ (15.5\%) [38], [19- \\ 64y]: (13.2\%) [23], \\ [20-49y]: (90\%) [24], \\ [20-59y]: (44.3\%) \\ [33], [25-44y]: ~28\% \\ [34]^b, \frac{18-49y]: \\ (71.1\%)[26], [20- \\ 59y]: (36\%)[35] \\ [18- \\ 49y]: (71.1\%) [26], \\ [20-59y]: (36\%) [35] \\ \hline \end{array}$	(49.3%) [15], [18- (4y]: (15.4%)[2], [16-61y]: (72.2%) [32], [≥ 20y]: (16.3%)[37] [20-59y]: (49.3%) [15], [18- 64y]: (15.4%) [2], [16-61y]: (72.2%) [32], ≥20y: (16.3%) [37]	[20-59y]: [20–59y]: (58.9%) [27:], [18-40y]: (50%)[7] [27], [18– 40y]: (50%) [7]	$\frac{[32], [20-59y]}{(81.1\%)}$ $\frac{(81.1\%)}{[33], [20-64y]}$ $\frac{(60\%)}{[34], [20-59y]}$ $\frac{(74.6\%)}{[35], [50-59y]}$ $\frac{(74.6\%)}{[35], [27], [20-59y]}$ (91.7%) $[31], [20-59y]$ (91.7%) $[32], [20-59y]$ (91.7%) $[32], [20-59y]$ (91.7%) $[33], [20-59y]$ (91.7%) $[33], [20-59y]$ (91.7%) $[33], [20-59y]$ (91.7%) $[33], [20-59y]$ (91.7%) (91.7%) $[32], [20-59y]$ (91.7%) $[33], [20-59y]$ (91.7%) $[34], [20-59y]$ (91.7%) $[35], [50-59y]$ (91.7%) $($
Seniors (elderly) [>65y]	$\frac{[60-69y]: (6.3\%)[8],}{[60-79y]: (2.4\%)[10],}{[260y]: (1\%)[13], [60-69y]: (7.8\%)[14], [60-79y]: (3.3\%)[16], [60-79y]: (4.4\%)[36], [60-89y]: (15.5\%)[31], [200] + (15.5\%)[30] +$	<mark>{≥60y]:</mark> (5.9%)[15], [≥65y]: (5.1%)[2]≥ 60y: (5.9%) [15], ≥65y: (5.1%) [2]	[60-99y]: [60–99y]: (8.3%) ^[27.], (3.1%)[7] [27], (3.1%) [7]	$\frac{[60 - 99y]:}{[60 - 99y]:}$ (20.7%) $\frac{[27.]}{, [60 - 89y]:}$ (4.2%) $\frac{[31], [\geq}{(4.2\%)}$ $\frac{[39], [\geq}{(5.9\%)}$ $\frac{[33], (8\%)}{[33], (8\%)}$ $\frac{[34], [\geq}{(5.7\%)}$ $\frac{[35]}{[27], [60 - 89y]:}$ (4.2%) $[31], \geq$ $60y:$

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

Previously healthy	(75%)[8], (96.7%) [13], (15.5%)[31] (75%) [8], (96.7%) [13], (15.5%) [31]	[37]; (30.8%) [17]; (12.1%)[29] (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]	<pre>(46.8%)[7]; (1.8%)[27]; (8.3%)[29] (42.1%)[15] (46.8%) [7], (1.8%) [27], (8.3%) [29], (42.1%) [15]</pre>	[4], (8.3%) [31], 2/7 [32], 1/5 [18] (42.1%) [15], (31.6%) [2], (24.6%) [4], (8.3%) [31], 2/7 [32], 1/5 [18]	
Pregnancy	(4.5%)[11], (0.2%) [13], 34/34[22], (16.7%)[26](4.5%) [11], (0.2%) [13], 34/34 [22], (16.7%) [26]	<pre>(11.3%) [15], (13.6%)[2], (17.4%)[4], (4.5%)[21], (41.2%) [22], (16.1%)[17] (11.3%) [15], (13.6%) [2], (17.4%) [4], (4.5%) [21], (41.2%) [22], (16.1%) [17]</pre>	(18.2%)[7], (11.5%)[27], (8.8%)[22] (18.2%) [7], (11.5%) [27], (8.8%) [22]	(15.8%) [2], (5.1%)[4], 1/2[21], (2.9%) [22], (15.8%) [2], (5.1%) [4], 1/2 [21], (2.9%) [22], (2.9%) [22], (2.2%) [33]	
Obesity	n			•	
BMI > 30 BMI>30	(0.2%)[13], (36.2%) [31] (0.2%) [13], (36.2%) [31]	(47.6%)[4], (5.7%)[29] (47.6%) [4], (5.7%) [29]	(33.3%)[27], 1/2[29] (33.3%) [27], 1/2 [29]	(39%)[4], 1/7[36] (39%) [4], 1/7 [36]	
30 < BMI < 40 30 <bmi<40< td=""><td>(22.4%)[31](22.4%) [31]</td><td>(29%)[2], (33.2%)[4] (29%) [2], (33.2%) [4]</td><td>(18.8%)[7], 3/7[17] (18.8%) [7], 3/7 [17]</td><td>NR</td><td></td></bmi<40<>	(22.4%)[31] (22.4%) [31]	(29%)[2], (33.2%)[4] (29%) [2], (33.2%) [4]	(18.8%)[7], 3/7[17] (18.8%) [7], 3/7 [17]	NR	
BMI > 40 BMI>40	(13.8%)[31] (13.8%) [31]	(2.2%)[15], (26.0%)[2], (25%)[4] (2.2%) [15], (26.0%) [2], (25%) [4]	(12.5%)[7] (12.5%) [7]	NR	
Comorbidity	r				

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

	(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	(5%)[15], (21%)[2], (10.5%)[4], (4.5%)[21], (17.2%)[29] (5%) [15], (21%) [2], (10.5%) [4], (4.5%) [21], (17.2%) [29]	(3.1%)[7], (15.5%)[27], (38.5%)[18], (16.7%)[29] (3.1%) [7], (15.5%) [27], (38.5%) [18], (16.7%) [29]	(15.3%) [4] (15.3%) [4]	

Abbreviations:-NR: not reported

 $\frac{1}{4}$ A and $\frac{1}{4}$ In cases where the denominators were <10, no percentages were displayed at in this Table. Table

§: ^bPeak incidence.incidence

*: ^cExcluding asthma.asthma

**:-^dObstructive sleep apnea.apnea