REVIEW

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 PubMed; 35 studies (14 referred to European countries, eight to the USA, five to Mexico, four to Canada, two to Japan, one to Colombia, and one reviewed relevant data reported worldwide) were included. Considerably high hospitalization, intensive care unit (ICU) admission, and fatality rates (up to 93.8, 36.4, and 38.5%, respectively) among the evaluated cases were reported across studies with available relevant data. Young and middle-aged adults constituted the majority of the evaluated pandemic 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, and morbidly obese patients also constituted substantial percentages of the cases involved in the included 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 perspectives.

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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]. The burden of influenza infection became even more pronounced with the emergence of the recent influenza pandemic. Specifically, the effective management of this global threat necessitated the awareness of the respective epidemiological aspects.

Evidence deriving from studies presenting the experience of countries of the Southern Hemisphere with pandemic influenza, as well as preliminary data from the USA, suggests that 2009 pandemic influenza affects mostly populations of younger age [2–5], a fact that is contradictory to the knowledge regarding seasonal influenza, in which severe disease as well as mortality is observed more frequently in elderly populations [6]. Additionally, patients with comorbidity and, specifically, sub-populations such as pregnant women and obese individuals also appear to suffer more severely 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.

Data sources

The articles to be included in our review were retrieved from searches performed in the PubMed database. The PubMed database was assessed to the end of 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"]", which was provided 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.

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) 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.

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 vaccination). The above-mentioned data were extracted for the whole patient populations involved in each 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 they received (hospitalized patients, patients admitted in the intensive care unit [ICU]), and the outcome of the influenza infection (fatal cases).

Study characteristics

A total of 35 studies were regarded as eligible for inclusion in our review [2, 4, 7–39]. Specifically, 14 of the 35 included studies referred to European countries [7–20],

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

Hospitalization, ICU admission, and fatality rate

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

Table 1 Data retrieved from studies originating from European countries regarding specific epidemiological features of pandemic influenza in patients with 2009 (H1N1) influenza of different severity[a]

Author(s), year	Country, study population, study period, method of diagnosis	Epidemiological groups	Evaluated	Hospitalized patients	ICU patients	Fatal cases
Rello et al. 2009 [7]	Spain, 32 ICU cases with respiratory failure, April–August, RT-PCR	Study population	NA	NA	32/32 (100%)	8/32 (25%)
		Sex			M: 21/32 (73.3%), F: 11/32 (26.7%)	NR
		Age distribution			Mean (SD): 40y (13.9) [18–40y]: 16/32 (50%), <52y: 22/32 (68.7%), >65y: 1/32 (3.1%)	Median: 35y
		Previously healthy			15/32 (46.8%)	NR
		Obesity			30<BMI<40: 6/32 (18.8%), BMI>40: 4/32 (12.5%)	NR
		Pregnancy			2/11 (18.2%)	NR
		Respiratory diseases			9/32 (28.1%) Asthma: 5/32 (15.6%), COPD: 4/32 (12.5%)	NR
		Cardiovascular diseases			1/32 (3.1%)	NR
		Diabetes mellitus			1/32 (3.1%)	NR
		Chronic neurological disease			1/32 (3.1%)	NR
New influenza A(H1N1) investigation teams 2009 [8]	France, 16 cases, April–May, RT-PCR	Study population	16/16 (100%)	15/16 (93.8%)	NR	0/16 (0%)
		Sex	M: 10/16 (62.5%), F: 6/16 (37.5%)			
		Age distribution	Mean: 32y Median: 29y Age range: 18m–65y [0–9 y]: 1/16 (6.3%), [10–19 y]: 2/16 (12.5%), [20–29 y]: 5/16 (31.3%), [30–39 y]: 4/16 (25%), [40–49 y]: 2/16 (12.5%), [50–59 y]: 1/16 (6.3%), [60–69 y]: 1/16 (6.3%)			
		Previously healthy	12/16 (75%)			
		Respiratory diseases	2/16 (12.5%)			
		Cardiovascular diseases	1/16 (6.3%)			
Surveillance Group for New Influenza A(H1N1) Virus Investigation and Control in Spain 2009 [9]	Spain, 98 cases, April–May, RT-PCR	Study population	98/98 (100%)	NR	NR	0/98 (0%)
		Sex	M: 50/98 (51%), F: 48/98 (49%)			
		Age distribution	Mean (SD): 24y (6.3), median: 22y, age range: 14–55y			

Table 1 (continued)

Author(s), year	Country, study population, study period, method of diagnosis	Epidemiological groups	Evaluated	Hospitalized patients	ICU patients	Fatal cases
Health Protection Agency, UK 2009 [10]	United Kingdom, 252 cases, April–June NR	Pregnancy	0/48 (0%)			
		2008–2009 vaccination	5/52 (9.6%)			
		Study population	252/252 (100%)	4/252 (1.6%)	NR	0/252 (0%)
		Sex	M: 134/252 (53%), F: 118/252 (47%)			
		Age distribution	Mean: 20y			
			Median: 12y			
			Age range: 0–73y			
			[0–9y]: 73/252 (29%), [10–19y]: 85/252 (33.7%), [20–29y]: 33/252 (13.1%), [30–39y]: 21/252 (8.3%), [40–49y]: 22/252 (8.7%), [50–59y]: 12/252 (4.8%), [60–69y]: 5/252 (2%), [70–79y]: 1/252 (0.4%)			
Belgian working group on influenza A(H1N1)v 2009 [11]	Belgium, 43 cases, May–June, RT-PCR	Study population	43/43 (100%)	1/43 (2.3%)	NR	NR
		Sex	M: 21/43 (49%), F: 22/43 (51%)			
		Age distribution	Mean: 29y			
			Median: 28y			
			Age range: 8m–51y			
			[0–9y]: 1/43 (29%), [10–19y]: 6/43 (14%), [20–29y]: 16/43 (37.2%), [30–39y]: 10/43 (23.3%), [40–49y]: 9/43 (21%), [50–59y]: 1/43 (2.3%)			
Ciblak et al. 2009 [12]	Turkey, 128 cases, April–May, RT-PCR	Pregnancy	1/22 (4.5%)			
		Study population	128/128 (100%)	NR	NR	0/128 (0%)
		Sex	M: 69/126 (54.8%), F: 57/126 (45.2%)			
		Age distribution	[1–4y]: 6/128 (4.7%), [5–9y]: 10/128 (7.8%), [10–18y]: 21/128 (16.4%), [19–34y]: 66/128 (51.6%), [35–50y]: 13/128 (10.2%), [50–65y]: 10/128 (7.8%)			
Gilsdorf et al. 2009 [13]	Germany, 9,950 notified cases, April–August, NR	2008–2009 vaccination	13/128 (10.2%)			
		Study population	9,950/9,950 (100%)	427/3,630 (11.7%)[b]	NR	0/9,950 (0%)
		Sex	M: 5,573/9,950 (54%), F: 4,577/9,950 (46%)			
		Age distribution	Median: 19y			

Study	Characteristic			
Hahné et al. 2009 [14] — Netherlands, 115 cases, April–June RT-PCR	Age range: 0–89y [0–4y]: 199/9,950 (2%), [5–9y]: 299/9,950 (3%), [10–29y]: 7,662/9,950 (77%), [30–59y]: 1,692/9,950 (17%), >60y: 100/9,950 (1%)			
	Previously healthy	5,690/5,885 (96.7%)		
	Obesity	BMI>30: 11/5,885 (2.0%)		
	Pregnancy	9/4,577 (0.2%)		
	Respiratory diseases	87/5,885 (1.5%)		
	Cardiovascular diseases	29/5,885 (0.5%)		
	Diabetes mellitus	17/5,885 (0.3%)	2/115 (1.7%)	1/115 (0.9%)	0/115 (0%)
	Study population	115/115 (100%)		
	Age distribution	[0–9y]: 16/115 (13.9%), [10–19y]: 15/115 (13%), [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%)		
	2008–2009 vaccination	17/111 (15.3%)		
Cullen et al. 2009 [15] — Ireland, 205 hospitalized cases, April–October, NR	Study population	NA	205/205 (100%)	19/205 (9.3%)	4/205 (2%)
	Sex		M: 99/205 (48.3%), F: 106/205 (51.7%)	NR	M: 1/4, F: 3/4
	Age distribution		Mean: 25y Median: 21y	NR	[5–14y]: 2/4, [50–59y]: 2/4
			Age range: 5m–78y, <35y: 75% [0–9y]: 48/205 (23.4%), [10–19y]: 44/205 (21.5%), [20–29y]: 48/205 (23.4%), [30–39y]: 18/205 (8.8%), [40–49y]: 19/205 (9.3%), [50–59y]: 16/205 (7.8%), [60–69y]: 8/205 (3.9%), ≥70y: 40/205 (1.9%)		
	Previously healthy		91/180 (50.6%)	8/19 (42.1%)	1/4
	Obesity		BMI>40: 4/180 (2.2%)	NR	NR
	Pregnancy		12/106 (11.3%)	NR	NR
	Respiratory diseases		Asthma: 18/180 (10%), chronic respiratory disease: 32/180 (17.8%)	NR	NR
	Cardiovascular diseases		9/180 (5%)	NR	NR
	Diabetes mellitus		8/180 (4.4%)	NR	NR
	Chronic neurological disease		9/180 (5%)	NR	NR

Table 1 (continued)

Author(s), year	Country, study population, study period, method of diagnosis	Epidemiological groups	Evaluated	Hospitalized patients	ICU patients	Fatal cases
Lytras et al. 2009 [16]	Greece, 312 cases, April–July, RT-PCR	Study population	312/312 (100%)	NR	NR	0/312 (0%)
		Sex	M: 170/312 (54.5%), F: 142/312 (45.5%)			
		Age distribution	Mean (SD): Imported : 23.6y (14) Indigenous: 26.4y (13.6) [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%)			
Yeung et al. 2009 [17]	United Kingdom, 78 hospitalized cases, June–September, NR	Study population	NA	78/78 (100%)	7/78 (9%)	1/78 (1.2%)
		Sex		M: 16/78 (20.5%), F: 62/78 (79.5%)	M: 3/7, F: 4/7	
		Age distribution		Median (IQR): 30.5y (23–53)	Median (IQR): 35y (30–48)	
		Previously healthy		24/78 (30.8%)	30<BMI<35: 3/7	
		Pregnancy		10/62 (16.1%)	NR	
		Respiratory diseases		19/78 (24.4%)	2/7	
		Cardiovascular diseases		NR	Ischemic heart disease: 2/7	
Lister et al. 2009 [18]	United Kingdom,13 critically ill children with2009 influenzaA (H1N1) vs.58 critically illchildren with seasonal influenza (2004–2007), June–July,NR	Study population	NA	NA	[13/13 (100%)] vs. [58/58 (100%)]	[5/13 (38.5%)] vs. [9/58 (15.5%)]
		Sex			[M: 7/13 (53.8%), F: 6/13 (46.2%)] vs. [M: 35/58 (56.9%), F: 25/58 (43.1%)]	[M: 1/5, F: 4/5] vs. [NR]
		Age distribution			(median: 9y, age range: 1.3–13y) vs. (median: 2.7y, IQR: 19w–7.6y)	NR
		Previously healthy			[13/13 (100%)] vs. [58/58 (100%)]	[1/5] vs. [NR]
		Respiratory diseases			NR	NR
		Diabetes mellitus			[1/13 (7.7%)] vs. [NR]	NR
		Chronic neurological disease			[5/13 (38.5%)] vs. [12/58 (20.7%)]	NR

Reference						
Smith et al. 2009 [19]	South East England, boarding school 102 ILI cases confirmed (n = 63), May–June, RT-PCR	Study population Age distribution	102/102 (100%) Clinical attack rates 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%)	0/102 (0%)	0/102 (0%)	0/102 (0%)
Health Protection Agency West Midlands H1N1v Investigation Team 2009 [20]	United Kingdom, Birmingham, 62 pupils (school outbreak), 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: 4–12y Attack rates: Nursery (4y): 3/58 (5.2%) Reception (5–6y): 5/61 (8.2%) Year 1 (6–7y): 8/60 (13.4%), Year 2 (7–8y): 5/59 (8.5%), Year 3 (8–9y): 8/59 (13.6%), Year 4 (9–10y): 10/62 (16.1%), Year 5 (10–11y): 14/60 (23.3%), Year 6 (11–12y): 9/60 (15%)	0/62 (0%)	0/62 (0%)	0/62 (0%)

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

a In cases where the denominators were <10, percentages (%) were not displayed in this table

b The proportion of people with risk factors who were hospitalized for influenza was 18.5% (20/108), while the proportion of people without risk factors who were hospitalized for influenza was 7% (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 of different severity[a]

Author(s), year	Country, study population, study period, method of diagnosis	Epidemiological groups	Evaluated	Hospitalized patients	ICU patients	Fatal cases
Jain et al. 2009 [2]	USA, 272 hospitalized cases, April–June, RT-PCR	Study population	NA	272/272 (100%)	67/272 (25%)	19/272 (7%)
		Sex		M: 140/272 (51%), F: 132/272 (49%)		NR
		Age distribution		Median: 21y, age range: 21d–86y [0–23m]: 23/272 (8.5%), [2–4y]: 20/272 (7.4%), [5–9y]: 29/272 (10.7%), [10–17y]: 50/272 (18.4%), [18–49y]: 104/272 (38.2%), [50–64y]: 32/272 (11.8%), ≥14/272 (5.1%)		Median age: 26y, age range 1.3–57y
		Previously healthy		74/272 (27.2%)		6/19 (31.6%)
		Obesity		Adults: 30<BMI<40: 29/100 (29%), BMI>40: 26/100 (26%), children: BMI percentile of 95 to 100: 18/61 (30%)		NR
		Pregnancy		18/132 (13.6%)		3/19 (15.8%)
		Respiratory diseases		Asthma: 76/272 (28%), COPD: 22/272 (8%)		Asthma or COPD: 3/19 (15.8%)
		Cardiovascular diseases		35/272 (13%)		NR
		Diabetes mellitus		40/272 (15%)		NR
		Chronic neurological disease		57/272 (21%)		4/19 (21.1%)
Louie et al. 2009 [4]	USA, California, 1,088 hospitalized and fatal cases, April–August, RT-PCR	Study population	NA	1,088/1,088 (100%)	340/1,088 (31.2%)	0/16 (0%)
		Sex		M: 532/1,088 (48.9%), F: 556/1,088 (51.1%)		M: 59/118 (50%), F: 59/118 (50%)
		Age distribution		Median: 27y, Age range: <1–92y		[0–17y]: 8/118 (6.8%), Median age (range): 6y (<1–14), >18y: 110/118 (93.2%), Median age (range): 46y (18–85)
		Previously healthy		347/1,088 (31.9%)		29/118 (93.2%)
		Obesity		BMI>30: 172/361 (47.6%), Adults (<20y): 30<BMI<34.9: 55/268 (20.5%), 35<BMI<39.9: 34/268 (12.7%), BMI>40: 67/268 (25%)		BMI>30: 46/172 (26.7%)
		Pregnancy		97/556 (17.4%)		6/97 (6.2%)

Study	Variable	Value			
	Respiratory diseases	Asthma: 257/1,088 (23.6%), other/unknown[b]: 146/1,088 (13.4%)			48/403 (11.9%)
	Cardiovascular diseases	167/1,088 (15.3%)[c]			27/167 (16.2%)
	Diabetes mellitus	116/1,088 (10.7%)			20/116 (17.2%)
	Chronic neurological disease	115/1,088 (10.5%)			18/115 (15.7%)
Dawood et al. 2009 [21] USA, 642 cases, April–May, RT-PCR	Study population	642/642 (100%)	36/399(9%)	8/22 (36.4%)	2/36 (5.6%)
	Sex	M: 302/592 (51%), F: 290/592 (49%)	NR		NR
	Age distribution	Median: 20y; Age range: 3m–81y [0–23m]: 14/532 (2.6%), [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%), ≤18y: 60%	NR		NR
	Previously healthy		13/22 (59.1%)		NR
	Pregnancy		1/22 (4.5%)		1/2
	Respiratory diseases		Asthma: 5/22 (22.7%)		NR
	Cardiovascular diseases		2/22 (9.1%)		NR
	Chronic neurological disease		1/22 (4.5%)		1/2
	2008–2009 vaccination		3/19 (15.8%)		NR
Jamieson et al. 2009 [22] USA, 34 pregnant, confirmed (n = 31), probable (n = 3), April–May, RT-PCR	Study population	34/34 (100%)	14/34 (41.2%)	3/34 (8.8%)	1/34 (2.9%)[d]
	Age distribution	<18y: 5/34 (14.7%), [18–29y]: 17/34 (50%), [30–39y]: 11/34 (32.9%), ≥40y: 1/34 (2.9%)			
	Respiratory diseases	Asthma: 7/25 (28%)			
	Diabetes mellitus	1/34 (2.9%)			
	2008–2009 vaccination	3/22 (13.6%)			
Kumar et al. 2009 [23] USA, Milwaukee, Wisconsin, 680 cases, April–May, RT-PCR	Study population	680/680 (100%)	NR	NR	NR
	Sex	M: 347/680 (51%), F: 333/680 (49%)			
	Age distribution	Mean: 12.2y <2y: 34/680 (5%), [2–5y]: 77/680 (11.3%), [5–11y]: 311/680 (45.7%), [12–18y]: 167/680(24.6%), [19–49y]: 78/680 (11.5%), [50–64y]:12/680 (1.8%), ≥65y: (1.8%),			

Table 2 (continued)

Author(s), year	Country, study population, study period, method of diagnosis	Epidemiological groups	Evaluated	Hospitalized patients	ICU patients	Fatal cases
			1/680 (0.1%)			
Centers for Disease Control and Prevention (CDC) 2009 [24]	USA, 26 health-care personnel, confirmed (n = 18), probable (n = 8), April–May, RT-PCR	Study population	26/26 (100%)	2/26 (7.7%)	0/26 (0%)	0/26 (0%)
		Sex	M: 4/23 (17.4%), F: 19/23 (82.6%)	NR		
		Age distribution	[20–29y]: 8/20 (40%), [30–39y]: 7/20 (35%), [40–49y]: 3/20 (15%), ≥50y: 2/20 (10%)	NR		
		Previously healthy	NR	1/2 (50%)		
		2008–2009 vaccination	8/16 (50%)	NR		
Saleeby et al. 2009 [25]	USA, California, 7 hospitalized pregnant cases, June–July, NR	Study population	NA	7/7 — Delivered during the index admission:3/7 (all with Caesarean section due to complications)	4/7 (57.1%)	1/7
		Age distribution		Median: 31y, mean: 29y, age range:18–39y, gestational age at presentation: 18 6/7–38 4/7w		
Crum-Cianflone et al. 2009 [26]	USA, Military Beneficiaries, San Diego County, 97 cases, April–May, RT-PCR	Study population	97/97 (100%)	1/97 (1%)	NR	0/97 (0%)
		Sex	M: 73/97 (75.3%), F: 24/97 (24.7%)			
		Age distribution	Median: 21y, IQR: 15–25y; Age range: 6m–78y; <2y: 2/97 (2.1%), [2–17y]: 25/97 (25.8%),[18–24y]: 43/97 (44.3%), [25–49y]: 26/97(26.8%), ≥50: 1/97 (1%)			
		Pregnancy	4/24 (16.7%)			
		Respiratory diseases	17/94 (18.1%)			
		Cardiovascular diseases	1/94 (1.1%)			
		Diabetes mellitus	2/94 (2.1%)			
		2008–2009 vaccination	63/95 (66.3%)			
Kumar et al. 2009 [27]	Canada, 168 critically ill patients, confirmed (n = 162), probable (n = 6), April–August, RT-PCR	Study population	NA	NA	168/168 (100%)	29/168 (17.3%)
		Sex	M: 55/168 (32.7%), F: 113/168 (67.3%)			M: 8/29 (27.6%), F: 21/29(72.4%)
		Age distribution	Mean (SD): 32.3y (21.4)			Mean age (SD): 42y (21)

Study	Characteristic	Data	
(continued)	Age distribution	[0–9y]: 34/168 (20.2%), [10–19y]: 21/168(12.5%), [20–29y]: 27/168 (16.1%), [30–39y]:20/168 (11.9%), [40–49y]: 25/168 (14.9%),[50–59y]: 27/168 (16.1%), [60–69y]: 7/168(4.2%), [70–79y]: 6/168 (3.6%), [80–89y]:0/168 (0%), [90–99y]: 1/168 (0.6%)	[0–9y]: 3/34 (8.8%), [10–19y]:1/21 (4.8%), [20–29y]: 5/27(18.5%), [30–39y]: 3/20(15%), [40–49y]: 6/25 (24%), [50–59y]: 5/27 (18.5%), [60–69y]: 4/7, [70–79y]: 2/6, [80–89y]: 0/0, [90–99y]: 0/1
	Previously healthy	3/168 (1.8%)	NR
	Obesity	BMI>30: 56/168 (33.3%)	NR
	Pregnancy	13/113 (11.5%)	NR
	Respiratory diseases	69/168 (41.1%)	NR
	Cardiovascular diseases	25/168 (14.9%)	NR
	Diabetes mellitus	35/168 (20.8%)	NR
	Chronic neurological disease	26/168 (15.5%)	NR
	2008–2009 vaccination	10/168 (15.5%)	NR
Cutler et al. 2009 [28] Canada, 41 cases, April–May, RT-PCR	Study population	41/41 (100%)	0/41 (0%) 0/41 (0%) 0/41 (0%)
	Sex	M: 21/41 (51.2%), F: 20/41 (48.8%)	
	Age distribution	Mean: 18.2y, median: 17y, age range: 12–46y	
	2008–2009 vaccination	23/41 (56.1%)	
O'Riordan et al. 2010 [29] Canada, Ontario, 58 hospitalized children vs.200 hospitalized children with seasonal influenza (2004/2005– 2008/2009), May–July, RT-PCR	Study population	NA	
	Sex	[58/58 (100%)] vs. [200/200(100%)] [M: 35/58 (60.3%), F: 23/58 (39.7%)] vs. [M: 108/200 (54%), F: 92/200(46%)]	[12/58 (20.7%)] vs. [28/200 (14%)] NR
	Age distribution	Median (IQR): [6.4y (3.4–10.1)] vs.[3.3y (1.4–7.8)]. <2y: [8/58 (13.8%)] vs. [74/200(37%)], [2–5y]: [13/58 (22.4%)] vs. [54/200 (27%)], >5y: [37/58 (63.8%)]vs. [72/200 (36%)]	Median (IQR): [5.8y (3.2–7.3)] vs.[3.1y (1.4–8.7)]
	Previously healthy	[7/58 (12.1%)] vs. [19/200 (9.5%)]	[1/12 (8.3%)] vs. [4/28 (14.3%)]
	Obesity	[2/35 (5.7%)]e vs. [NR]	1/2e, 2/5e
	Respiratory diseases	Asthmaf: [13/58 (22.4%)] vs. [11/200(5.5%)], chronic lung diseaseg: [2/58(3.4%)] vs. [13/200 (6.5%)]	Asthmaf: [5/12 (41.7%)] vs. [2/28 (7.1%)],chronic lung diseaseg: [0/12 (0%)] vs. [5/28(17.9%)]

Table 2 (continued)

Author(s), year	Country, study population, study period, method of diagnosis	Epidemiological groups	Evaluated	Hospitalized patients	ICU patients	Fatal cases
		Cardiovascular diseases		[4/58 (6.9%)] vs. [20/200 (10%)]	[1/12 (8.3%)] vs. [3/28 (10.7%)]	
		Chronic neurological disease		Neurological impairment: [10/58(17.2%)] vs. [26/200 (13%)]	[2/12 (16.7%)] vs. [6/28 (21.4%)]	
Fisman et al. 2009 [30]	Canada,Ontario,11,560 tested,1,819confirmed, April–June,NR	Study population	1,819/11,560 (15.7%)	NR	NR	NR
		Age distribution	2009 H1N1 vs. seasonal H3N2 vs. seasonalH1N1			
			≤33y: (~24% vs. ~2.3% vs. ~0.5%), [34–41y]:(~9.9% vs. ~2.2% vs. ~1.2%), [42–52y]:(~10.2% vs. ~2.2% vs. ~0.7%), ≥53y: (~3%vs. ~2.5% vs. ~0.3%)			

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

[a] In cases where the denominators were <10, percentages (%) were not displayed in this table

[b] Includes asthma, chronic obstructive pulmonary disorder, bronchopulmonary dysplasia/respiratory distress syndrome, bronchiolitis obliterans organizing pneumonia, Sjögren's syndrome,and obstructive sleep apnea

[c] Includes congenital heart disease, atrial fibrillation, status post-aortic valve replacement, congestive heart failure, hypertensive heart disease, and coronary artery

[d] Of the 45 deaths from pandemic H1N1 virus infection reported to the CDC from April 15 to June 16, 2009, six (13%) were from pregnant women, including one death from the originalcase series of 34 pregnant cases

[e] Data on height and weight were available for 35 of the children with pandemic H1N1 influenza. Two satisfied criteria for obesity, of whom one child, who also had asthma, requiredintensive care. Five of the 23 without height data had weights above the 97th percentile. Two of these five children required intensive care: one child had asthma and the other had seizures

[f] 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); $p = 0.00$

[g] 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[a]

Author(s), year	Country, study population, study period, method of diagnosis	Epidemiological groups	Evaluated	Hospitalized patients	ICU patients	Fatal cases
Mexico						
Dominguez-Cherit et al. 2009 [31]	Mexico,58 critically illpatients, confirmed (n = 29),probable (n = 14),suspected (n = 15), March–June, RT-PCR	Study population	58/58 (100%)	58/58 (100%)	54/58 (93.1%)[b]	24/58 (41.4%)
		Sex	M: 27/58 (46.6%), F: 31/58 (53.4%)			M: 12/24 (50%), F: 12/24(50%)
		Age distribution	Median: 44y Age range: 10–83y			Median age (IQR): 39y (30.5–45.5)
			[10–19y]: 4/58 (6.9%), [20–29y]: 9/58 (15.5%),[30–39y]: 13/58 (22.4%), [40–49y]: 18/58(31%), [50–59y]: 5/58 (8.6%), [60–69y]: 3/58(5.2%), [70–79y]: 4/58 (6.9%), [80–89y]: 2/58(3.4%)			[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
		Previously healthy	9/58 (15.5%)			2/24 (8.3%)
		Obesity	BMI>30: 21/58 (36.2%), [30<BMI<40: 13/58(22.4%), BMI>40: 8/58 (13.8%)]			NR
		Respiratory diseases	4/58 (6.9%) Asthma: 2/58 (3.4%), COPD: 2/58 (3.4%)			NR
		Cardiovascular diseases	12/58 (20.7%) Ischemic heart disease: 1/58 (1.7%),congestive heart failure: 1/58 (1.7%),arrhythmia: 3/58 (5.2%), valvular heartdisease: 3/58 (5.2%), cerebrovascular disease:1/58 (1.7%), peripheral vascular disease: 3/58(5.2%)			NR
		Diabetes mellitus	10/58 (17.2%)			
		2008–2009 vaccination	2/58 (3.4%)			NR
Perez-Padilla et al. 2009 [32]	Mexico, 18 hospitalized cases with pneumonia, March–April, RT-PCR	Study population	NA	18/18 (100%)	12/18 (66.7%)	0/16 (0%)
		Sex		M: 9/18 (50%), F: 9/18 (50%)		M: 5/7, F: 2/7
		Age distribution		Median: 38y Age range: 9m–61y		Median age: 45y Age range: 9–52y
				<5y: 3/18 (16.7%), [5–10y]: 1/18(5.6%), [11–15y]: 1/18 (5.6%), [16–50y]: 11/18 (61.1%), ≥50y: 2/18(11.1%)		<5y: 0/3 (0%), [5–10y]: 1/1,[11–15y]: 1/1, [16–50y]: 4/11,≥50y: 1/2

Table 3 (continued)

Author(s), year	Country, study population, study period, method of diagnosis	Epidemiological groups	Evaluated	Hospitalized patients	ICU patients	Fatal cases
		Previously healthy		10/18 (55.6%)		2/7
		Respiratory diseases		Asthma: 2/18 (11.1%), obstructivesleep apnea: 1/18 (5.6%)		NR
		Diabetes mellitus		3/18 (16.7%)		NR
		2008–2009 vaccination		3/18 (16.7%)		NR
WHO Mexico 2009 [33]	Mexico, 3,734 cases, April–May, RT-PCR	Study population	3,734/3,734 (100%)	NR	NR	74/3,734 (2%)
		Age distribution	[0–9y]: 1,046/3,734 (28%), [10–19y]: 943/3,734(25.3%), [20–29y]: 754/3,734 (20.2%), [30–39y]: 413/3,734 (11.1%), [40–49y]: 306/3,734(8.2%), [50–59y]: 183/3,734 (4.9%), ≥60y:68/3,734 (1.8%), unknown: 21/3,734 (0.6%)			[0–9y]: 6/1,046 (0.6%), [10–19y]: 4/943 (0.4%), [20–29y]:21/754 (2.8%), [30–39y]:17/413 (4.1%), [40–49y]:12/306 (3.9%), [50–59y]:10/183 (5.5%), ≥60y: 4/68(5.9%), unknown: 0/21 (0%)
		Previously healthy	NR			24/45 (53.3%)
		Pregnancy	NR			1/45 (2.2%)
Chowell et al. 2009 [34]	Mexico, 2,155 cases of severe pneumonia vs. 2005–2008 influenza seasons, March–April 2009 RT-PCR	Age distribution	2005–2008 influenza seasons vs. study period[5–59y]: 32% vs. 71% Peak incidence:study period: [25–44y]: ~28%, 2005–2008influenza seasons: [0–4y]: ~47%	NR	NR	2006–2008 influenza seasonsvs. study period (ratio: studyperiod to referent period)[0–4y]: 17% vs. 5% (0.3),[5–9y]: 1% vs. 5% (7.6),[10–14y]: 1% vs. 6% (10.7),[15–19y]: 1% vs. 7% (8.6),[20–24y]: 1% vs. 13% (11.7),[25–29y]: 1% vs. 11% (10.3),[30–34y]: 1% vs. 9% (6.0),[35–39y]: 2% vs. 15% (9.4),[40–44y]: 2% vs. 9% (4.8),[45–49y]: 2% vs. 5% (2.1),[50–54y]: 2% vs. 4% (1.6),[55–59y]: 3% vs. 3% (1.2),[60–64y]: 3% vs. 0% (0.0),[65–69y]: 5% vs. 1% (0.2),[70–74y]: 7% vs. 2% (0.3),[75–79y]: 9% vs. 2% (0.2),≥80y: 42% vs. 3% (0.1)
Fajardo-Dolci et al. 2009 [35]	Mexico,12,645 cases (March–May) and 122 fatal cases (April–May), RT-PCR	Study population	12,645/12,645 (100%)	21/122 (17%)	NR	122/122 (100%)
		Sex	NR			M: 60/122 (49.2%), F: 62/122(50.8%)
		Age distribution	[0–9y]: 3,531/12,645 (27.9%), [10–19y]:4,287/12,645 (33.6%), [20–29y]: 2,132/12,645(16.9%), [30–39y]: 1,146/12,645 (9.1%), [40–49y]: 815/12,645 (6.4%),			[0–9y]: 19/122 (15.6%), [10–19y]: 5/122 (4.1%), [20–29y]:30/122 (24.6%), [30–39y]:25/122 (20.5%), [40–49y]:20/122 (16.4%), [50–59y]:16/122 (13.1%), ≥60y: 7/122(5.7%)

					Mortality rates[c]
		[50–59y]:459/12,645 (3.6%), ≥60y: 189/12,645 (1.5%),not available: 86/12,645 (0.7%)			[0–9y]: 19/1,580 (1.2%), [10–19y]: 5/1,425 (0.3%), [20–29y]: 30/1,092 (2.7%), [30–39y]: 25/592 (4.2%), [40–49y]: 20/438 (4.6%), [50–59y]: 16/255 (6.3%), ≥60y:7/115 (6.1%), total:122/5,563 (2.2%)
Columbia					
Castro-Jiménez et al. 2009 [36]	Study population	183/183 (100%)	26/183 (14.2%)	NR	7/183 (3.8%)
Colombia, 183 cases, May–July, RT-PCR	Sex	M: 96/183 (52.5%), F: 87/183 (47.5%)			M: 2/7, F: 5/7
	Age distribution	Median (IQR): 27y (17–38)[0–9y]: 27/183 (14.8%), [10–19y]: 39/183(21.3%), [20–29y]: 47/183 (25.7%), [30–39y]:33/183 (18%), [40–49y]: 20/183 (10.1%), [50–59y]: 9/183 (4.9%), [60–69y]: 7/183 (3.8%), [70–79y]: 1/183 (0.5%)			NR
	Obesity	NR			BMI>30: 1/7
Japan					
WHO Japan 2009 [37]	Study population	NA	49/49 (100%)	0/49 (0%)	0/49 (0%)
Japan, Kobe 49 hospitalized cases (school-associated outbreak), April–May, RT-PCR	Sex	M: 23/49 (46.9%), F: 26/49 (53.1%)			
	Age distribution		Median: 17y, Age range: 5–60y[0–9y]: 1/49 (2%), [10–19y]: 40/49(81.6%), ≥20y: 8/49 (16.3%)		
	Previously healthy		40/49 (81.6%)		
	Pregnancy		0/26 (0%)		
	Respiratory diseases		Asthma: 6/49 (12.2%)		
	Cardiovascular diseases		0/49 (0%)		
	Diabetes mellitus		0/49 (0%)		
	2008–2009 vaccination		22/43 (51.2%)		
Nishiura et al. 2009 [38]	Study population	361/361 (100%)	NR	NR	NR
Japan, 361 cases, May–June, NR	Age distribution	[0–9y]: 15/361 (4.2%), [10–19y]: 287/361(79.5%), [20–29y]: 27/361 (7.5%), [30–39y]:11/361 (3%), [40–49y]: 13/361 (3.6%), [50–59y]: 5/361 (1.4%), ≥60y: 3/361 (0.8%)			

Table 3 (continued)

Author(s), year	Country, study population, study period, method of diagnosis	Epidemiological groups	Evaluated	Hospitalized patients	ICU patients	Fatal cases
Worldwide report						
Vaillant et al. 2009 [39]	Canada, USA, Mexico, Europe, Asia, 371 fatal cases associated with pandemic H1N1 influenza 2009, April–July, NR	Age distribution	NA	NA	NA	[0–9y]: 42/371 (11.3%), [10–19y]: 37/371 (10%), [20–29y]: 62/371 (16.7%), [30–39y]: 53/371 (14.3%), [40–49y]: 73/371 (19.7%)[50–59y]: 58/371 (15.6%),≥60y: 46/371 (12.4%)

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

[a] In cases where the denominators were <10, percentages (%) were not displayed in this table

[b] As a result of increased patient volumes, many experienced delay in admission to the ICU, and four remained in the emergency department until death

[c] Among a total of 5,563 confirmed cases

Epidemiological characteristics of cases

In Table 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 healthcare they received, and outcome).

Age and sex

Among the evaluated cases of 2009 H1N1 influenza, young and middle-aged adults constituted the majority of the reported cases; the percentages ranged between 13.2 and 83.7% among studies with available relevant data. Older children and adolescents followed, with percentages ranging between 6.3 and 79.5%, and young children with percentages ranging from 2.3 to 62.9%. This observation was consistent regarding the evaluated hospitalized cases. Specific data are presented in Table 4. In two studies with available relevant data, the highest rate of admission into the ICU was observed for young and middle-aged adults (50% [7] and 58.8% [27], respectively), whereas the lowest rate was observed for senior patients (3.1% [7] and 8.3% [27], respectively). Among fatal cases, young and middle-aged adults constituted the majority, with percentages ranging from 65.5 to 91.7%, according to the data provided from six of the included studies [27, 31, 33–35, 39]. Yet, substantial percentages ranging from 4.2 to 20.7% were observed for 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 three studies reporting data for 97 laboratory-confirmed cases [26], 58 hospitalized cases [29], and 32 ICU cases [7]. The respective percentages were 75.3% [26], 60.3% [29], and 73.3% [7].

Seasonal (2008–2009) influenza vaccination

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

Comorbidity

Cases without any comorbidity constituted the majority of the evaluated cases in 2 of the 3 studies that provided

Table 4 Percentage of different epidemiological groups among cases of pandemic influenza with different severity in studies originating from the Northern Hemisphere[a]

Epidemiological groups	Evaluated patient population (ILI or laboratory-confirmed cases) [Specification in case of discrepancies]: (percentage %) [reference]	Hospitalized patients	ICU patients	Fatal cases
Age				
Young children [0–9y]	(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]	(23.4%) [15], (26.5%) [2], [0–10y]: (22.2%) [32], (2.0%) [37]	(20.2%) [27]	(10.3%) [27], (11.3%) [39], [0–10y]: 1/7 [32], (8.1%) [33], (10%) [34], (15.6%) [35], [0–17y]: (6.8%) [4]
Older children and adolescents [10–19y]	(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], <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]	(21.5%) [15], [10–17y]: (18.4%) [2], [11–15y]: (5.6%) [32], (81.6%) [37]	(12.5%) [27]	(3.4%) [27], (4.2%) [31], (10%) [39], [11–15y]: 1/7 [32], (5.4%) [33], (13%) [34], (4.1%) [35], 2/4 [15]
Adults, young and middle-aged [20–65y]	[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][b], [18–49y]: (71.1%) [26], [20–59y]: (36%) [35]	[20–59y]: (49.3%) [15], [18–64y]: (15.4%) [2], [16–61y]: (72.2%) [32], ≥20y: (16.3%) [37]	[20–59y]: (58.9%) [27], [18–40y]: (50%) [7]	[20–59y]: (65.5%) [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]
Seniors (elderly) [>65y]	[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], ≥51y: (5.1%) [21]	≥60y: (5.9%) [15], ≥65y: (5.1%) [2]	[60–99y]: (8.3%) [27], (3.1%) [7]	[60–99y]: (20.7%) [27], [60–89y]: (4.2%) [31], ≥60y: (12.4%) [39], ≥60y: (5.9%) [33], (8%) [34], ≥60y: (5.7%) [35]
Sex				
Males	(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%) [37], (20.5%) [17], (60.3%) [29]	(73.3%) [7], (32.7%) [27], (53.8%) [18]	1/4 [15], (50%) [4], (27.6%) [27], (50%) [31], 5/7 [32], 1/5 [18], 3/7 [17], (49.2%) [35]
Seasonal (2008–2009) influenza vaccination	(9.6%) [9], (10.2%) [12], (15.3%) [14], (56.1%) [28], (13.6%) [22], (3.4%) [31], (50%) [24], (66.3%) [26]	(15.8%) [21], (16.7%) [32], (51.2%) [37]	(6%) [27]	NR
Previously healthy	(75%) [8], (96.7%) [13], (15.5%) [31]	(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]	(46.8%) [7], (1.8%) [27], (8.3%) [29], (42.1%) [15]	(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]	(11.3%) [15], (13.6%) [2], (17.4%) [4], (4.5%) [21], (41.2%) [22], (16.1%) [17]	(18.2%) [7], (11.5%) [27], (8.8%) [22]	(15.8%) [2], (5.1%) [4], 1/2 [21], (2.9%) [22], (2.2%) [33]
Obesity				
BMI>30	(0.2%) [13], (36.2%) [31]	(47.6%) [4], (5.7%) [29]	(33.3%) [27], 1/2 [29]	(39%) [4], 1/7 [36]
30<BMI<40	(22.4%) [31]	(29%) [2], (33.2%) [4]	(18.8%) [7], 3/7 [17]	NR
BMI>40	(13.8%) [31]	(2.2%) [15], (26.0%) [2], (25%) [4]	(12.5%) [7]	NR

Table 4 (continued)

Epidemiological groups	Evaluated patient population (ILI or laboratory-confirmed cases) [Specification in case of discrepancies]: (percentage %) [reference]	Hospitalized patients	ICU patients	Fatal cases
Comorbidity				
Respiratory disease				
Any respiratory disease	(12.5%) [8], (1.5%) [13], (6.9%) [31], (18.1%) [26]	(13.4%) [4][c], (5.6%) [32][d], (24.4%) [17]	(28.1%) [7], (41.1%) [27], (7.7%) [18], 2/7 [17]	(15.8%) [2], (40.7%) [4]
Asthma	(28%) [22], (3.4%) [31]	(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]	NR
COPD	(3.4%) [31]	(17.8%) [15], (8%) [2], (3.4%) [29]	(12.5%) [7], (9.5%) [27]	NR
Cardiovascular disease	(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]	(3.1%) [7], (14.9%) [27], 2/7 [17], (8.3%) [29]	(22.9%) [4]
Diabetes mellitus	(0.3%) [13], (2.9%) [22], (17.2%) [31], (2.1%) [26]	(4.4%) [15], (15%) [2], (10.7%) [4], (16.7%) [32]	(3.1%) [7], (20.8%) [27], (7.7%) [18], 1/7 [17]	(16.9%) [4]
Chronic neurological disease	NR	(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]	(15.3%) [4]

NR: not reported

[a] In cases where the denominators were <10, no percentages were displayed in this Table

[b] Peak incidence

[c] Excluding asthma

[d] Obstructive sleep apnea

relevant data [8, 13]. The respective percentages were 96.7% [13] and 75% [31], respectively. Previously healthy cases were also represented by considerably high percentages ranging from 12.1 to 81.6% in nine studies that reported relevant data for hospitalized 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, 27, 29] and up to 42.1% among fatal cases [2, 4, 15, 31, 32]. Common types of comorbidity, such as respiratory diseases, including asthma and chronic obstructive pulmonary disease, cardiovascular disease, chronic neurological disease, and diabetes mellitus, were reported among the cases involved in the included studies. Specific data are presented in Table 4.

Pregnancy

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

Obesity

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

Morbidly obese patients (BMI>40) in particular, constituted 13.8% of the evaluated cases in a single study [31], whereas their percentages ranged between 2.2 and 26.0% in three studies that provided relevant data for hospitalized cases [2, 4, 15]. In addition, morbidly obese patients constituted 12.5% of the fatal cases recorded in a large study involving a total of 32 ICU patients [7].

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, 29, 34]. Two of

these three studies referred to pediatric populations with 2009 H1N1 infection [18, 29]. Specifically, one of these 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]. No substantial differences were observed regarding sex between the compared children. The median age of children with pandemic influenza was 9 years compared to 2.7 years of children with seasonal 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 and 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 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 and >60 years [34]. Additionally, another study that compared a total of 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 to those that were found to be positive for seasonal H1N1 and H3N2 influenza strains [30].

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, and mortality rate. Specifically, a considerably higher fatality rate was observed in more severely afflicted cases. Young and 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 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, 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], whereas fatal outcome can occur at any 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]. Of note, a similar "epidemiological shift" to younger ages was observed during previous influenza 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]. 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, and fatal cases. This finding, along with the evidence provided from studies from the Southern Hemisphere [5], imply that obesity and morbid obesity may be regarded as risk factors of severe pandemic influenza infection. Many factors may account for this finding. These may include the 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 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]. The fact that obese patients may suffer more severely from pandemic influenza has considerable implications with regard to the treatment of these patients. Specifically, the adjustment of dosing of anti-influenza agents, in particular, for body weight, may prove to be a necessity, as was suggested for the treatment with antimicrobial agents from a recent 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 to which the study referred, as well as the evaluated populations. This hampered our attempts to perform any statistical 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, along with the experience gained from countries of the Southern Hemisphere, may aid considerably in the clarification, at least to some extent, of some of the epidemiological features of pandemic influenza.

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

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