REVIEW ARTICLE
Pandemic A(H1N1) 2009 influenza: review of the Southern Hemisphere experience

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SUMMARY

We sought to systematically review the published literature describing the epidemiological aspects of the first wave of pandemic A(H1N1) 2009 influenza in the Southern Hemisphere. Fifteen studies were included in this review, originating from South America, Australia or New Zealand, and Africa. Across the different studies, 16·8–45·3% of the laboratory-confirmed cases were admitted to hospital, and 7·5–26·0% of these cases were admitted to intensive care units (ICUs). The fatality rate was 0·5–1·5% for laboratory-confirmed cases in 6/8 studies reporting specific relevant data, and 14·3–22·2% for cases admitted to ICUs in 5/7 studies, respectively. In 4/5 studies the majority of laboratory-confirmed cases were observed in young and middle-aged adults, the percentage of older adults increased the higher the level of healthcare the cases received (e.g. laboratory confirmation, hospitalization or ICU admission) or for fatal cases. Many of the cases had no prior comorbidity, including conditions identified as risk factors for seasonal influenza. Pregnant women represented 7·4–9·1% and 7·1–9·1% of unselected laboratory-confirmed cases and of those admitted to ICUs, respectively. Obesity and morbid obesity were more commonly reported as the level of healthcare increased.

Key words: Age groups, gravidity, overweight, pandemic influenza, respiratory tract infections, risk factors.

INTRODUCTION

Pandemic A(H1N1) 2009 influenza, caused by a quadruple reassortant virus, emerged in late March 2009, in Mexico, and quickly spread to other countries worldwide [1, 2]. The first pandemic wave in the Northern Hemisphere coincided with the end of the annual influenza season, in contrast with the Southern Hemisphere.

Respiratory infections, have a higher incidence and impact during the cold winter months [3]. The interplay between environmental factors (exposure to cold and dry weather), host factors (alterations in local and systemic immune responses), and social factors (indoor crowding) could account for this phenomenon [3, 4].

In this regard, the experience gained during the 2009 winter season in the Southern Hemisphere could

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best reflect the true impact of the 2009 influenza pandemic. This experience could be useful for evaluating the course of the pandemic in the Northern Hemisphere during the 2009–2010 winter season, and particularly for predicting the nature of future influenza pandemics. We systematically reviewed the published evidence originating from the Southern Hemisphere regarding the epidemiological characteristics of pandemic A(H1N1) 2009 influenza, with a focus on specific risk groups.

METHODS

Data sources

We searched the collection 'Latest H1N1 citations in PubMed', as retrieved on 4 November 2009. The collection of these articles was retrieved using the following combined search terms: '(swine OR H1N1) AND (flu OR influenza OR virus OR outbreak OR pandemic) AND 'last 6 months'[edat]'. The bibliographies of relevant articles of interest were also hand-searched. We selected for inclusion in our review studies that provided original data, obtained in countries of the Southern Hemisphere that referred to the epidemiological characteristics of groups of patients of any age with clinically suspected or laboratory-confirmed pandemic A(H1N1) 2009 influenza. Articles published in languages other than English, Spanish, French, German, or Italian, as well as studies published only as abstracts in scientific conferences, were excluded.

Data extraction

Two author reviewers (P.K.K and E.K.B.) independently performed the literature search, study selection, and data extraction. Data extracted from each of the included studies consisted of the definition of study population, the location and period of study, the criteria used for diagnosis of influenza, as well as the number of total study population and the characteristics and number of different epidemiological subgroups, that were determined according to age, sex, or presence of comorbid conditions, or risk factors for influenza. We extracted specific relevant data for groups of patients with influenza who received different levels of healthcare [e.g. outpatient care, hospitalization, intensive care unit (ICU) admission] and for those with fatal outcome. We excluded information that did not derive from original sources of each study.
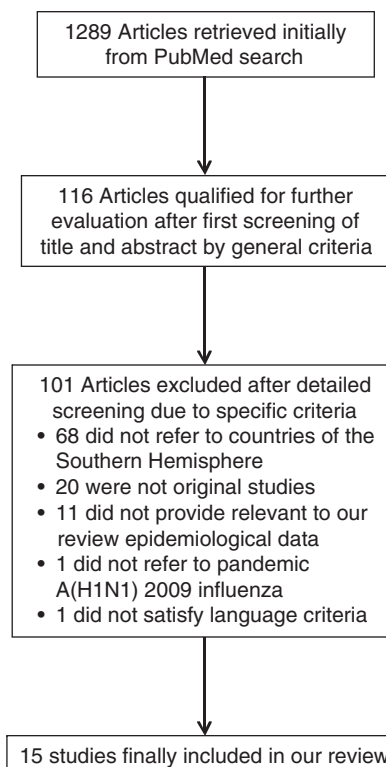

Fig. 1. Flow diagram of the process of selection of articles for inclusion in the review.

RESULTS

Characteristics of the included studies

Among the 1289 citations initially retrieved from PubMed, we finally identified 15 studies as eligible for inclusion in our review [5–19]. The flow chart for the detailed process of selection of the studies to be included in the review is shown in Figure 1.

Table 1 (see also expanded online version of Table 1) presents the data extracted from each of the included studies. Specifically, seven of the 15 studies referred to South American countries [5–11], six to Australia or New Zealand [14–19], and two to Africa [12, 13]. The data reported in the included studies were obtained through various types of influenza surveillance systems in nine of the studies [8, 10–13, 16–19], at multiple hospitals (specifically ICUs) in two studies [14, 15], and at single hospitals in the remaining four studies [5–7, 9].

All but one of the included studies [7], provided data on the characteristics of patients with laboratory-confirmed pandemic A(H1N1) 2009 influenza; the number of this category of patients evaluated in each of the included studies varied widely (median 856, range 20–34 506). It should be mentioned

that three of the 14 studies that reported data on laboratory-confirmed cases did not provide adequate data regarding the exact laboratory methodology used [13, 16, 19]. Four of the 15 included studies additionally provided data on patients with clinically suspected influenza [severe acute respiratory infection or influenza like illness (ILI)] [5, 7, 8, 16]. Seven studies reported data for hospitalized cases of pandemic A(H1N1) 2009 influenza [5, 7, 9, 13, 16, 17, 19], while nine reported data specifically for patients admitted to ICUs [5–7, 13–17, 19].

Laboratory-confirmed cases of pandemic A(H1N1) 2009 influenza

The rate of positivity for pandemic A(H1N1) 2009 influenza in cases tested with RT–PCR was 31·5–53·0% in four studies from Brazil, Argentina, and Australia [5, 8, 9, 18], whereas a lower rate of 12·7% was recorded in a reference laboratory in Bolivia [10]. The percentage of confirmed cases of seasonal influenza in all cases tested for pandemic A(H1N1) 2009 influenza was 8·1% and 8·4% in two studies from Brazil [8, 9], while the percentage of seasonal influenza A, in particular, was 3·3% in cases tested at a general hospital in Argentina [5].

Hospitalized cases

The percentage of cases admitted to hospital was 44·5% and 45·3% in cases of pandemic A(H1N1) 2009 influenza identified in two hospitals in Brazil [9] and Argentina [5], respectively. Among cases of pandemic A(H1N1) 2009 influenza identified through surveillance systems, 16·8–30·6% were admitted to hospital and 3·5–4·4% were admitted to ICUs, as reported by three studies in Australia and New Zealand [16, 17, 19]. The rate of ICU admission in cases hospitalized for pandemic A(H1N1) 2009 influenza varied between 7·5% and 26·0% in five studies that reported specific relevant data [7, 13, 16, 17, 19].

Fatality

The fatality rate among the laboratory-confirmed cases of pandemic A(H1N1) 2009 influenza was between 0·5% and 0·9% in 5/8 studies that reported specific relevant data [11, 12, 16, 17, 19]. A rate of 1·5% was reported for cases identified at a reference laboratory in Bolivia [10], while a higher rate of 3·4% was reported for cases identified at a reference hospital

in Brazil [9], and an even higher rate of 11·2% was recorded for cases identified through Brazil's case notification system [8]. Notably, a case-fatality rate of 4·5% was recorded for all cases of severe acute respiratory infection identified through the latter system.

Among the cases of pandemic A(H1N1) 2009 influenza that were admitted to hospital, the fatality rate varied between 2·4% and 7·6% in the five studies that reported specific relevant data [7, 9, 13, 16, 17]. The fatality rate for the patients admitted to ICUs, in particular, varied between 14·3% and 22·2% in 5/7 studies that reported specific relevant data [7, 14–17]. An additional study from Argentina reported a fatality rate of 50·0% and 22·2% for cases admitted to adult and paediatric ICUs, respectively [5]. The remaining study reported a fatality rate of 50% for cases admitted to a paediatric ICU in Argentina [6].

Epidemiological characteristics of cases

Table 2 presents the percentage of specific epidemiological groups (defined according to age, sex, race, or presence of comorbid conditions) among the cases evaluated in each of the included studies (stratified according to type of diagnosis, level of healthcare received, and outcome).

Age

Among the laboratory-confirmed cases of pandemic A(H1N1) 2009 influenza, the majority were young and middle-aged adults in 4/5 studies reporting specific relevant data. Specifically, the percentage of this age group was between 53·6% and 60% in these four studies [5, 9, 16, 18]. In the remaining study, which reported national surveillance data from Peru, young and middle-aged adults represented 32·7% of the cases, while young children and adolescents accounted for 58·9% of the cases [11]. Seniors aged >60–65 years represented a minority of cases, varying between 0% and 6·4%, in the four studies providing specific relevant data [9, 11, 16, 18]. However, older adults constituted a substantial percentage of the cases admitted to hospital (9·5–16·6%) [7, 16], ICU (13·3–28·5%) [7, 16], or fatal cases (29·2%) [16].

Comorbidity

Cases without any underlying comorbidity constituted the majority of those with severe acute respiratory infection due to ILI (66·7%) and those with laboratory-confirmed pandemic A(H1N1) 2009

Table 1. *Data regarding the epidemiological characteristics of cases of pandemic A(H1N1) 2009 influenza extracted from studies originating in the Southern Hemisphere that were included in our review (only data for the total study population are presented in the printed table below; an expanded version of Table 1 with additional data for specific epidemiological/risk factors groups is available as Supplementary online material)*

Author	Study characteristics (criteria for selection of study population, location, study period, data sources)	Groups of patients according to level of influenza diagnosis and/or level of healthcare received (allocation)				
Raffo *et al.* [5]	Patients with ILI, adult patients with SARI hospitalized in wards (12–17 June 2009) or ICU (7–27 June 2009), paediatric laboratory-confirmed cases with real-time RT–PCR (according to the relevant CDC protocol) of pandemic A(H1N1) 2009 influenza hospitalized in wards (1–27 June 2009), or PICU (1 June to 10 July 2009), at a specific reference general hospital	**Patients with ILI** Laboratory-confirmed cases: 186/411, 45·3%* of hospitalized cases (seasonal influenza: 11/411, 2·7%) 56/133, 42·1%* of outpatients (seasonal influenza A: 7/133, 5·3%)	**Adult patients with SARI hospitalized in wards** $n=110$ Laboratory-confirmed pandemic A(H1N1) 2009 influenza: 21/49, 42·8% of pts specifically examined Fatal cases: 1/110, 0·9% Oseltamivir therapy: all pts	**Paediatric laboratory-confirmed cases hospitalized in wards** $n=49$ Co-infections: RSV: 7/49, 14·3%; influenza B: 2/49, 4%; bacteraemia at admission: 0/49, 0% PICU admission: 6/49, 12·2% Oseltamivir therapy: yes (number not specified)	**Adult patients with SARI admitted in ICU** $n=28$ pts with clinically suspected influenza Laboratory-confirmed pandemic A(H1N1) 2009 influenza: 14/28, 50·0% (14/20, 70% of pts examined) MV: 25/28, 89·3% Fatal cases: 14/28, 50·0% (7/14, 50% of pts with laboratory-confirmed pandemic A(H1N1) 2009 influenza Oseltamivir therapy: 28/28, 100%	**Paediatric laboratory-confirmed cases hospitalized in PICU** $n=27/44$, 61·4% of the pts admitted with SARI Length of PICU-stay, mean (median): 10·7 d (9 d) MV: 25/27, 92·5% (13/27, 48·1% of them were previously healthy) Duration of MV, median (range): 10 (2–30) d Fatal cases: 6/27, 22·2% Causes of death: refractory hypoxaemia: 4/6, 66·7%; cardiogenic shock: 4/6, 66·6%; septic shock: 1/6, 16·6% Oseltamivir therapy: 23/27, 85·1%
Caprotta *et al.* [6]	All patients admitted in the PICU in a Hospital of Argentina from 1 June to 1 August 2009 with pandemic A(H1N1) 2009 influenza confirmed by PCR for influenza A(H1N1) according to the relevant CDC protocol	**PICU-admitted, laboratory-confirmed patients** $n=20/113$, 17·7% of pts admitted for any reason Fatal cases: 10/20, 50·0% Co-infections at admission: RSV 17/113, 15·0%; *Mycoplasma pneumoniae* 6/113, 5·3%; bacteraemia 11/113, 10%; urinary tract infection 6/113, 5·3% Length of PICU stay, mean (range): 18·5 (1–63) d MV: 19/20, 95·0% Duration of MV, mean (range): 15·4 (0–41) d Any complication during PICU hospitalization: 14/20, 70·0% Type of complications: bacterial pneumonia: 9/20, 45·0%; bronchospasm: 6/20, 30·0%; pneumothorax: 5/20, 25·0%; renal insufficiency: 1/20, 5·0%; multi-organ failure: 1/20, 5·0% Oseltamivir therapy: all patients				
Bantar *et al.* [7]	Patients admitted with suspected pandemic A(H1N1) 2009 influenza and moderate or severe acute respiratory disease to a reference, teaching hospital for adults, in Argentina, from 24 June to 8 July 2009 (laboratory confirmation of influenza not specified)	**Hospitalized patients** $n=30$ Oseltamivir therapy: 30/30, 100%	**ICU-admitted patients** $n=7/30$, 23·3% of hospitalized pts MV: 6/7, 85·7% Fatal cases: 1/7, 14·3%			

Table 1 (*cont.*)

Author	Study characteristics (criteria for selection of study population, location, study period, data sources)	Groups of patients according to level of influenza diagnosis and/or level of healthcare received (allocation)	
Oliveira *et al.* [8]	The first cases of ILI with SARI (fever >38 °C, cough, and dyspnoea or death) in Brazil, from 12 April to 16 August 2009, recorded by Brazil's case notification system for influenza-like illness with the pandemic A(H1N1) 2009 influenza virus confirmed with real-time RT–PCR with specific primers for pandemic A(H1N1) 2009 influenza	**ILI with SARI** $n = 34\,506$ Fatal cases: 1567/34 506, 4·5 %	**Laboratory-confirmed cases** 5747/10 838*, 53·0 % (seasonal influenza: 915/10 838, 8·4 %; influenza diagnosis excluded: 4176/10 838, 38·5 %; still under investigation or no specimen: 23 668/34 506, 68·6 %) Fatal cases: 645/5747, 11·2 % Mortality rate: 0·39/100 000 inhabitants
Schout *et al.* [9]	Cases of pandemic A(H1N1) 2009 influenza, confirmed by real-time RT–PCR for novel influenza A(H1N1), in a tertiary-care hospital (specific reference center), in Sao Paolo, Brazil, from 16 June to 18 September 2009	**Laboratory-confirmed patients** $n = 472$ 472/1500, 31·5 % evaluated patients had confirmed pandemic A(H1N1) 2009 influenza 122/1500, 8·1 % had seasonal influenza A 902/1500, 60·1 % had other diagnoses	**Hospitalized patients** 210/472, 44·5 % of pts with pandemic A(H1N1) 2009 influenza *vs.* 53/122, 43·4 % of pts with seasonal influenza A Median length of hospital stay of pts with pandemic A(H1N1) 2009 influenza: 7·4 d Discharged pts with pandemic A(H1N1) 2009 influenza *vs.* discharged pts with seasonal influenza A: 176/210, 83·8 % *vs.* 44/53, 83·0 % Fatal cases with pandemic A(H1N1) 2009 influenza *vs.* fatal cases with seasonal influenza A: 16/210, 7·6 % *vs.* 2/53, 3·8 % Antiviral therapy: directed to all hospitalized influenza cases
Gianella *et al.* [10]	Cases of pandemic A(H1N1) 2009 influenza confirmed by specific real time RT–PCR identified in the National Centre of Tropical Diseases (the only laboratory accredited to perform the test) in Bolivia, from 5 May to 2 August 2009	**Patients with suspected influenza tested by PCR†** $n = 7060$ Antiviral therapy: given to all pts (until 01/08/09)	**Laboratory-confirmed cases** 895/7060, 12·7 % Fatal cases: 13/895, 1·5 %
Munayco *et al.* [11]	Cases of pandemic A(H1N1) 2009 influenza confirmed by RT–PCR (according to the relevant CDC protocol) reported to the National Surveillance Network in Peru from 9 May to 17 July 2009	**Laboratory-confirmed cases** $n = 1771$ Fatal cases: 8/1771, 0·45 % Antiviral therapy: given to all suspected cases (until early July)	

Table 1 (*cont.*)

Author	Study characteristics (criteria for selection of study population, location, study period, data sources)	Groups of patients according to level of influenza diagnosis and/or level of healthcare received (allocation)	
Archer *et al.* [12]	All pandemic A(H1N1) 2009 influenza cases confirmed by real-time PCR (according to relevant CDC protocol) in South Africa through a systematic surveillance system, from 28 April to 12 October 2009	**Laboratory-confirmed cases** $n = 12\,331$ Incidence rate: 25/100 000 population	**Fatal cases** 91/12 331, 0·7 %
Thouillot *et al.* [13]	Hospitalized patients with laboratory-confirmed (method not specified) pandemic A(H1N1) 2009 influenza infection in Reunion Island, Indian Ocean, through a surveillance system of severe and fatal cases related to pandemic A(H1N1) 2009 influenza, from 5 July to 13 September 2009 (method of confirmation not reported)	**Hospitalized patients** $n = 255$ (ICU admitted: 19/255, 7·5 %) Fatal cases: 6/255, 2·3 %	
Webb *et al.* [14]	Patients with pandemic A(H1N1) 2009 influenza, confirmed by virus subtype specific PCR (717 pts) or a specific serological (haemagglutination-inhibition) assay (5 pts), admitted in Australian and New Zealand ICUs, from 1 June to 7 July 2009	**Laboratory-confirmed cases of pandemic A(H1N1) 2009 influenza admitted in ICU** 722/856, 84·3 % of pts admitted in ICU with influenza A (influenza A not subtyped: 97; seasonal influenza: 37) Median ICU-stay: 7 d (IQR: 2·7–13·4) Fatal cases: 103/722, 14·3 % (*vs.* 6/37, 16·2 % of pts with seasonal influenza) Factors significantly associated with mortality: MV at ICU admission, any co-existing condition‡, older age MV: 456/706*, 64·6 % Duration of MV, median (IQR): 8 (4–16) d ECMO: 53/456, 11·6 % Complications: viral pneumonitis or ARDS: 336/689*, 48·8 % Secondary bacterial pneumonia: 140/689*, 20·3 %	
Davies *et al.* [15]	All patients with pandemic A(H1N1) 2009 influenza-associated ARDS in 15 intensive care units (ICUs) in Australia and New Zealand from 1 July to 31 August 2009 Laboratory-confirmed (with PCR or viral culture) pandemic A(H1N1) 2009 influenza: 53 pts; serological evidence of recent influenza A not subtyped: 8 pts	**Suspected cases admitted in ICU treated with ECMO** $n = 61$ pts with laboratory-confirmed pandemic A(H1N1) 2009 influenza or influenza A not subtyped Oseltamivir therapy: 64/68 pts (94 %) of all pts treated with ECMO Estimated incidence of ECMO use due to influenza A: 2·6/million people (95 % CI 2·0–3·2) [due to laboratory-confirmed pandemic A(H1N1) 2009 influenza: 2·0/million people (95 % CI 1·4–2·6)] In the previous winter (1 June to 31 August 2008), only 4 patients received ECMO for ARDS in participating sites (estimated incidence of 0·15 cases/million people) Duration of MV, median (IQR): 18 (9–27) d Length of ICU stay, median (IQR): 22 (13–32) d Fatal cases: 13/61, 21·3 %; Laboratory-confirmed pandemic A(H1N1) 2009 influenza fatal cases: 11/53, 20·8 %	**Suspected cases admitted in ICU who received MV without ECMO** $n = 133$ pts with laboratory-confirmed pandemic A(H1N1) 2009 influenza or influenza A not subtyped Duration of MV, median (IQR): 8 (4–14) d Length of ICU stay, median (IQR): 12 (7–18) d Fatal cases: 17/133, 12·8 %

Table 1 (*cont.*)

Author	Study characteristics (criteria for selection of study population, location, study period, data sources)	Groups of patients according to level of influenza diagnosis and/or level of healthcare received (allocation)			
New South Wales Public Health Network [16]	Suspected or laboratory-confirmed cases of pandemic A(H1N1) 2009 influenza infection in New South Wales (NSW) Australia, from 8 May to 31 August 2009 (reported by laboratories, hospital emergency departments (ED), or ambulance dispatch surveillance system). The methods for laboratory confirmation of pandemic A(H1N1) 2009 influenza were not specified.	**Laboratory-confirmed cases** $n=392$ (8 May to 16 June 2009)	**Emergency department presentations with ILI** $n=7580$ ED presentations with ILI (17 June to 31 August 2009) ED presentation rate: 107·5/100 000 population	**Hospitalized laboratory-confirmed cases** 1214/5106, 23·8 % of all confirmed cases of pandemic A(H1N1) 2009 influenza (8 May to 31 August 2009) Hospitalization rate: 17·2/100 000 population; 95 % CI 16·2–18·2 Median length of hospital stay: 4 d (adults: 4 d; children: 3 d)	**ICU-admitted, laboratory-confirmed cases** 225/1214, 18·5 % of patients hospitalized with confirmed pandemic (H1N1) 2009 influenza ICU admission rate: 3·2/100 000 population Median length of stay in ICU: 7 d (adults: 8 d; children: 4 d) MV: 159/225, 70·6 % invasive MV: 125/225, 55·6 % ECMO: 27/225, 12 % Fatal cases: 48/225, 21·3 % Mortality rate: 0·7/100 000 population
Fielding *et al.* [17]	Cases of pandemic A(H1N1) 2009 influenza confirmed by in-house real time PCR specific for pandemic A(H1N1) 2009 influenza, reported from the two principal surveillance systems in Victoria, Australia, from 27 April to 27 September 2009	**Laboratory-confirmed cases** 3058/6851, 44·6 % of laboratory-confirmed influenza cases of any type (influenza A not further specified: 3340/6895, 48·4 %; 2009 A(H1N1)-negative: 427/6895, 6·2 %; seasonal influenza: 26/6895, 0·4 %)	**Hospitalized patients** 513/3058, 16·8 % (224 ward-based pts, 108 ICU-admitted, 181 with no specific relevant data available) Length of hospital stay, median (range): 3 (1–79) d		**ICU-admitted patients** 108/415*, 26·0 % Length of ICU stay median (range): 10 (1–63) d Fatal cases: 24/108, 22·2 %
Kelly *et al.* 2009§ [18]	Cases of pandemic A(H1N1) 2009 influenza infection confirmed by in-house real time PCR specific for pandemic A(H1N1) 2009 influenza that were reported to the National sentinel surveillance system from a network of 87 General Practitioners (GP) in Victoria, Australia from 27 April to 12 July 2009	**Laboratory-confirmed cases** 223/682, 33 % of patients tested by the sentinel GP network (definitive influenza virus subtyping pending: 69/682, 10·1 %; non-pandemic influenza subtype: 6/682, 0·9 %)			

Table 1 (*cont.*)

Author	Study characteristics (criteria for selection of study population, location, study period, data sources)	Groups of patients according to level of influenza diagnosis and/or level of healthcare received (allocation)	
Baker *et al.* [19]	Cases of pandemic A(H1N1) 2009 influenza infection recorded in New Zealand through a notifiable disease surveillance system for pandemic A(H1N1) 2009 influenza from 25 April to 23 August 2009 (97·8% of these cases were laboratory-confirmed; method not specified)	**Cases of pandemic A(H1N1) 2009 influenza infection** $n = 3179$ cases Incidence rate: 74·5/100 000 population Fatal cases: 16/3179, 0·5%	**Hospitalized patients** 972/3179, 30·6% (ICU admitted: 114/972, 11·7%)

CDC, United States Centers for Disease Control and Prevention; CI, confidence interval; d, days; ECMO, extracorporeal membrane oxygenation; ILI, influenza-like illness; IQR; interquartile range; M, male; MV, mechanical ventilation; (P)ICU, (paediatric) intensive care unit; pts, patients; RSV, respiratory syncytial virus; RT–PCR, reverse transcriptase–polymerase chain reaction; SARI, severe acute respiratory infection.

* Denominators refer to the cases for which specific relevant data were available.

† Suspected case: sudden onset of fever ($\geqslant 38\ ^\circ$C) and respiratory symptoms.

‡ Coexisting conditions: for patients aged $\geqslant 16$ years: any condition defined within the Chronic Health Evaluation component of the APACHE III score; for patients aged < 16 years: prematurity, immune deficiency, cystic fibrosis, congenital heart disease, neuromuscular disorder, or chronic neurological impairment.

§ The population presented in this study may be a subgroup of the population of the Fielding *et al.* [17] study.

influenza (65·4%) that were identified through Brazil's case notification system [8]. However, only 15·5% of the laboratory-confirmed cases evaluated at a Brazilian hospital were considered to have no co-morbidity [9]. Among the cases of pandemic A(H1N1) 2009 influenza that were admitted to hospital, three studies reported that 30·6–53·3% were considered previously healthy [5, 7, 13].

Specifically regarding cases admitted to ICUs, three studies from Argentina (of which two referred to paediatric patients) reported that 48·1–70·0% of the cases were previously healthy [5–7]. In a larger study from Australia and New Zealand the same figure was 31·7% [14], while in another study from Australia 10·2% of the ICU-admitted cases had no underlying risk factor, including obesity or pregnancy [16]. The percentage of cases without any comorbidity was similar for those who died and those who were admitted to ICUs, in two studies that provided specific relevant data [6, 16]. Studies from South America reported a higher percentage (50·1–60·0%) for cases without comorbidity among the fatal cases of pandemic A(H1N1) 2009 influenza [6, 8, 10, 12, 13, 16], compared to studies from Africa or Australia (10·4–21·0%) [12, 13, 16].

Common comorbid conditions in the patients evaluated in the studies included in our review were respiratory disease (asthma, chronic obstructive pulmonary disease), cardiovascular disease, chronic renal insufficiency, diabetes mellitus and other metabolic disorders, immune suppression, and haematological disease (Table 2).

Pregnancy

Across the different studies reporting specific relevant data, pregnant women constituted 5·4–8·1% of the cases with severe acute respiratory infection [5, 8], 7·4–9·1% of the unselected laboratory-confirmed cases with pandemic A(H1N1) 2009 influenza [8, 9], and 0–13% of hospitalized cases [7, 13, 17]. They also constituted 7·1–9·1% of ICU admissions with pandemic A(H1N1) 2009 influenza, in three of the included studies [14, 16, 17], but this figure rose to 11·3% and 17·8%, respectively, in two other studies [5, 15]. Among the fatal laboratory-confirmed cases, pregnant women represented 2·1–4·2% of cases in two studies from Australia [16, 17] but this figure rose to 12·5% and 28·4% in two studies from Brazil [9] and South Africa [12], respectively. In the latter study, many pregnant women were co-infected with HIV or tuberculosis. Regarding women of reproductive age,

pregnant women comprised 20·8% of cases with severe acute respiratory infection due to ILI, 23·3% of laboratory-confirmed cases of pandemic A(H1N1) 2009 influenza [8], 28·6% of ICU admissions [16], and 55·6% of those that died [12].

Obesity

In the studies included in our review, obesity was recorded in 1·5% of patients with severe acute respiratory infection due to ILI [8], 1·8% of unselected laboratory-confirmed cases [8], 1·6–13·3% of hospitalized cases [5, 7, 13], and 28·5–44% of cases admitted to ICUs [7, 14, 16]. Among the fatal cases, obesity was noted in 14·5–21·9% [12, 16]. With regard to different categories of patients evaluated in a single study, obesity appeared to be more frequent in unselected laboratory-confirmed pandemic A(H1N1) 2009 influenza cases compared to cases of severe acute respiratory infection due to ILI [8], in ICU admissions compared to hospitalized cases [5, 7], although it appeared to be less frequent in fatal cases compared to ICU admissions [16]. Morbidly obese represented 13·3% of the obese cases with severe acute respiratory infection due to ILI [8], 16·7% of unselected laboratory-confirmed cases of pandemic A(H1N1) 2009 influenza [8], 33·0% ICU admissions [16], and 57·2% of those that died [16].

DISCUSSION

The evaluation of the published literature included in our review suggests that during the first wave of the pandemic A(H1N1) 2009 influenza in the Southern Hemisphere, the virus was frequently identified in the cases specifically tested with real time RT–PCR, compared to seasonal influenza viruses. Among the laboratory-confirmed cases of pandemic A(H1N1) 2009 influenza, a substantial proportion was admitted to hospital, while many of those hospitalized received ICU care. The fatality rate for the severely ill patients of pandemic A(H1N1) 2009 influenza was considerable.

The age group that accounted for the majority of cases was young and middle-aged adults, followed by older children and adolescents. However, the percentage of elderly individuals increased considerably in the most seriously afflicted and diseased cases. Although relevant findings varied between studies, a considerable proportion of affected cases, even some admitted to ICUs or that died, did not have any

Table 2. *Summary of data from different studies in the Southern Hemisphere regarding the representativeness of different epidemiological groups according to age and underlying condition among the cases of pandemic A(H1N1) 2009 influenza*

Epidemiological groups	% of epidemiological group among category of cases (specification)				
	ILI	Laboratory-confirmed cases	Hospitalized cases	ICU-admitted cases	Fatal cases
Age group					
Young children	10·3% (0–4 yr) [16]	22·7% (0–9 yr) [9] 7% (0–4 yr) [11] 6·6% (0–4 yr) [16] 3·2% (0–4 yr) [18]	85·7% (<5 yr, among paediatric patients) [5] 21·7% (0–4 yr) [16] 11·7% (<1 yr) [13]	7·6% (0–4 yr) [16]	50·0% (0–2 yr) [6] 15·4% (<5 yr) [10] 0·0% (0–4 yr) [16] 12·5% (2–7 yr) [17]
Older children and adolescents	26·6% (5–19 yr) [16]	10·7% (<15 yr) [5] 16·3% (10–19 yr) [9] 58·9% (5–19 yr) [11] 63·5% (<20 yr) [12] 30·5% (5–19 yr) [16] 36·7% (5–19 yr) [18]	14·3% (5–15 yr, among paediatric patients) [5] 14·6% (5–19 yr) [16]	7·6% (5–19 yr) [16]	2·1% (5–19 yr) [16]
Young and middle-aged adults	59·5% (20–64 yr) [16]	53·6% (15–45 yr) [5] 54·6% (20–59 yr) [9] 32·7% (20–59 yr) [11] 60·2% (20–64 yr) [16] 60·2% (20–64 yr) [18]	83·3% (16–64 yr) [7] 54·2% (20–64 yr) [16]	71·4% (16–64 yr) [7] 34·6% (25–49 yr) [14] 71·6% (20–64 yr) [16]	68·8% (20–64 yr) [16]
Older adults	3·6% (≥65 yr) [16]	6·4% (≥60 yr) [9] 1·3% (≥60 yr) [11] 1·0% (>65 yr) [16] 0·0% (>65 yr) [18]	16·6% (≥65 yr) [7] 9·5% (≥65 yr) [16]	28·5% (≥65 yr) [7] 13·3% (≥65 yr) [16]	29·2% (≥65 yr) [16]
Males	42·5% [8] 47·3% [16]	44·6% [5] 43·5% [8] 44·5% [9] 52·6% [10] 47·9% [11] 49·9% [12] 51·1% [16]	46·9% [5] 53·3% [7] 49·8% [16] 54·0% [17]	55·5% [5] 65% [6] 85·7% [7] 47·9% [14] 47·4% (suspected cases) [15] 46·7% [16] 43·5% [17]	60·0% [6] 1/1 [7] 40·1% [12] 66·7% [16] 58·3% [17] 33·3% [13]
Underlying condition					
No comorbidity	66·7% [8]	65·4% [8] 15·5% [9]	30·6% [5] 53·3% [7] 53·3% [13]	48·1% [5] 70·0% [6] 57·1% [7] 31·7% [14] 10·2% [16]	50·1% [8] 60·0% [6] 53·8% [10] 21·1% [12] 10·4% [16] 16·6% [13]
Pregnancy	8·1% [8]	9·1% [8] 7·4% [9]	5·4% (SARI cases) [5] 0% [7] 6·3% [17] 13% [13]	17·8% (SARI cases) [5] 9·1% [14] 11·3% (suspected cases) [15] 7·1% [16] 8·3% [17]	14·3% (SARI cases) [5] 12·5% [9] 28·4% [12] 2·1% [16] 4·2% [17]

Table 2 (*cont.*)

Epidemiological groups	% of epidemiological group among category of cases (specification)				
	ILI	Laboratory-confirmed cases	Hospitalized cases	ICU-admitted cases	Fatal cases
Obesity	1·5% (morbid obesity: 0·2%) [8]	1·8% (morbid obesity: 0·3%) [8]	5·2% (paediatric cases), 7·3% (adult SARI cases) [5] 13·3% [7] 1·6% [13]	17·8% (SARI cases) [5] 28·5% [7] 28·6% [14] 44·0% (morbid obesity: 14·5%) [16]	21·9% [12] 14·5% (morbid obesity: 4/48, 8·3%) [16]
Chronic respiratory disease	9·1% [8]	9·8% [8] 14·6% [9]	32·6% (paediatric cases), 16% (asthma, adult SARI cases), 9% (COPD, adult SARI cases) [5] 0·33% (asthma) [7] 7·8% (COPD), 0·78% (bronchopulmonary dysplasia), 0·4% (cystic fibrosis) [13]	11% [5] 10% [6] 32·7% [14] 27·3% (suspected cases) [15]	10·0% [6] 33·3% (chronic lung disease), 16·7% (asthma) [16]
Cardiovascular disease	5·5% [8]	4·7% [8] 12·3% [9]	4·0% (congenital heart disease, paediatric cases), 4·5% (adult SARI cases) [5] 3·5% (cardiac insufficiency), 1·6% (congenital heart disease) [13]	14·8% (congenital heart disease, paediatric cases) [5] 5·0% [6] 10·5% [14]	10·0% [6] 12·7% [12] 22·9% [16]
Renal disease	1·4% [8]	1·5% [8]	0·4% (nephrotic syndrome) [13]	5·0% [6]	10·0% [6]
Chronic neurological disease			4·0% [5]	7·4% [5] 5·0% [6]	10·0% [6]
Metabolic disorder	5·4% [8]	5·9% [8] 4·7% (including diabetes mellitus) [9]			
Diabetes mellitus	1·6% [8]	1·5% [8]	4·5% (SARI cases) [5] 10% [7] 5·8% [13]	16·0% [14] 16·5% (suspected cases) [15]	15·0% [12]
Immunosuppressive disease	4·2% (immune suppression), 0·5% (HIV/AIDS) [8]	4·4% (immune suppression), 0·4% (HIV/AIDS) [8] 15·3% (immune suppression), 2·1% (transplantation) [9]	4·5% (HIV, SARI cases) [5] 20% [7] 1·6% (immune deficiency) [13]	7·4% (paediatric cases), 7·1% (HIV, adult SARI cases), 7·1% (autoimmune disease, adult SARI cases) [5] 14·3% [7]	100% [7] 53·1% (HIV) [12]
Tuberculosis					10·0% [12]
Malignancy		3·0% (cancer) [9]	6·1% (haematological) [5]		
Haemoglobinopathy	0·8% [8]	0·7% [8]	0·78% (sickle cell anaemia) [13]		
Alcohol abuse				7·1% (SARI cases) [5]	
Smoking		3·2% [9]			
Prematurity			16·3% [5]	18·5% [5] 10·0% [6]	10·0% [6]
Genetic syndrome			4·1% (Down syndrome) [5]	11·1% [5] 5·0% [6]	10·0% [6]

COPD, Chronic obstructive pulmonary disease; ILI, influenza-like illness; SARI, severe acute respiratory infection.

prior comorbidity. Pregnancy and obesity represented particular risk factors for infection with pandemic A(H1N1) 2009 influenza.

Pandemic A(H1N1) 2009 influenza has shown a reversal of the pattern of the age distribution of cases compared to seasonal influenza, which mainly affects elderly individuals and young children [20]. Similar observations have also been made for other recent influenza pandemics [21]. Elderly individuals may have substantial rates of protective antibodies against the novel pandemic virus, presumably due to previous immunological encounters with influenza viruses having antigenic epitopes with high homology to those of the novel strain [22]. Still, elderly individuals may have worse outcome when infected with pandemic A(H1N1) 2009 influenza, because of the frequent presence of underlying comorbidity [23]. It should also be mentioned that young children appear to be the age group primarily affected at the start of a typical influenza outbreak, while elderly individuals may follow in this regard [24].

Pregnant women represent a considerable proportion of the cases affected by pandemic A(H1N1) 2009 influenza. This could partly be attributed to the fact that the majority of the cases were noted in young and middle-aged adults (without major differences between the two sexes). Another explanation for the high incidence of pandemic influenza in pregnant women is that they often have relatively close contact with young children and therefore increased transmission opportunities for influenza. Pregnant women have been identified as a particular risk group for adverse influenza outcome during previous pandemics, and also during seasonal influenza [25]. Immune system alterations, other physiological adaptations of pregnancy, and underlying comorbidity could account for this association [26, 27].

Nevertheless, across the different studies included in our review, the percentage of laboratory-confirmed cases of pandemic A(H1N1) 2009 influenza that were pregnant women, did not appear to substantially increase for the higher level of healthcare that the cases received (i.e. simple laboratory confirmation, hospitalization, ICU admission) or even for fatal cases. This could indicate that the relative risk of requirement for higher level of healthcare or of a fatal outcome might not be considerably different for pregnant women compared to the average cases of pandemic A(H1N1) 2009 influenza receiving the same level of healthcare. In other words, pregnancy might be mostly a risk factor for acquisition of infection with pandemic A(H1N1) 2009 influenza virus, rather than for an adverse outcome.

For example, in three of the studies, the percentage of pregnant women among the fatal cases of pandemic A(H1N1) 2009 influenza was lower than the percentage of pregnant women among ICU-admitted cases (Table 2) [5, 16, 17]. This could be interpreted as a lower relative risk for death for pregnant women admitted to ICUs compared to the average cases of pandemic A(H1N1) 2009 influenza admitted to ICUs. Contrary to the above observations, the percentage of pregnant women among women of reproductive age appeared to increase with higher levels of healthcare.

A substantial proportion of the cases of influenza reported in the studies were obese. Moreover, obese individuals represented an increasing percentage of the cases with higher levels of healthcare than the cases were receiving. This trend was also observed for the percentage of morbidly obese between the obese cases. The above observations could indicate that obesity and particularly morbid obesity is an adverse prognostic factor for pandemic A(H1N1) 2009 influenza.

Although obesity has not generally been listed among the risk factors for seasonal influenza [28], there are studies to suggest that the outcome of bacterial infections is worse for obese patients [29]. Immunological alterations associated with obesity, impaired respiratory function, and associated comorbidity (such as diabetes), along with inadequate antimicrobial drug dosing could be contributory factors to the above association [29, 30]. A question that has not been adequately answered is whether the dosage of oseltamivir must be adjusted for body weight in obese patients.

The statements made above on the potential role of pregnancy and obesity as prognostic factors for infection with pandemic A(H1N1) 2009 influenza should be considered simply as observations made by the authors of this review. Formal statistical analysis to support the above statements cannot be made because the data referring to the cases of influenza receiving different levels of healthcare come from different studies and are not directly comparable. Moreover, an accurate elucidation of the value of the various potential risk factors for pandemic A(H1N1) 2009 influenza would require a multivariate analysis to be made for adjustment for potential confounders.

For example, the use of antiviral agents, including the timing of administration and dosage, as well as the availability of ICU beds, and supportive modalities

like extracorporeal membrane oxygenation, might be important in the determination of the outcome of severe influenza. In this review, we primarily focused on the epidemiology of pandemic A(H1N1) 2009 influenza, particularly with regard to potential differences related to the various baseline characteristics of cases. Other reviews in the literature have addressed the value of the various treatment options [31].

It also should be mentioned that most cases of pandemic influenza have a mild uncomplicated illness and remain unrecognized in the community [32]. Thus, the true impact and characteristics of the 2009 influenza pandemic in the Southern Hemisphere cannot be accurately reflected from the published evidence retrieved herein, as most of the included studies focused on laboratory-confirmed cases. Still, the available data provide useful information for the most seriously affected patients.

An additional limitation in the synthesis of data provided from different studies of the type evaluated in our review, is the heterogeneity regarding the methodology, setting, and period of the study, along with the characteristics of the reference population, healthcare infrastructure, and medical attitudes, worldwide. The above factors, coupled with potential changes in the response measures to the pandemic, the increasing levels of immunity in the population, and, even, the chance for evolution of the virus itself, might preclude the use of the 2009 Southern Hemisphere experience for predicting the course of the current and future influenza pandemics. In addition, the data analysed in the published studies are only a fraction of the information collected for the 2009 influenza pandemic through various relevant surveillance systems, worldwide. Further evaluation of the latter type of data could provide more meaningful conclusions.

CONCLUSION

The synthesis of the available published literature regarding the Southern Hemisphere 2009 experience for the first wave of pandemic A(H1N1) 2009 influenza suggests that pandemic influenza was a common cause of acute respiratory infection, affecting younger patients compared with seasonal influenza, and causing considerable morbidity in those presenting with serious illness, even those without any of the traditional risk factors for seasonal influenza. Pregnant women and obese individuals represented epidemiological groups in which pandemic influenza was relatively frequent and virulent, respectively.

NOTE

Supplementary material accompanies this paper on the Journal's website (http://journals.cambridge.org/hyg).

DECLARATION OF INTEREST

None.

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