DOI:10.1111/irv.12036
www.influenzajournal.com

Review Article

Burden of influenza in Latin America and the Caribbean: a systematic review and meta-analysis

Vilma Savy,[a] Agustín Ciapponi,[b] Ariel Bardach,[b] Demián Glujovsky,[b] Patricia Aruj,[b] Agustina Mazzoni,[b] Luz Gibbons,[b] Eduardo Ortega-Barría,[c] Rómulo E. Colindres[c]

[a]Instituto Nacional de Enfermedades Infecciosas, ANLIS "Dr. Carlos G. Malbran", Buenos Aires, Argentina. [b]Institute for Clinical Effectiveness and Health Policy (IECS), Buenos Aires, Argentina. [c]GlaxoSmithKline Biologicals, Rio de Janeiro, Brazil.
Correspondence: Vilma Savy, Av. Vélez Sársfield 563 (1261), Buenos Aires, Argentina.
E-mail: vsavy@anlis.gov.ar

Accepted 25 September 2012. Published Online 05 December 2012.

Objective Influenza causes severe morbidity and mortality. This systematic review aimed to assess the incidence, etiology, and resource usage for influenza in Latin America and the Caribbean.

Design Meta-analytic systematic review. Arcsine transformations and DerSimonian Laird random effects model were used for meta-analyses.

Setting A literature search from 1980 to 2008 in MEDLINE, Cochrane Library, EMBASE, LILACS, Ministries of Health, PAHO, proceedings, reference lists, and consulting experts.

Sample We identified 1092 references, of which 31 were finally included, in addition to influenza surveillance reports. We also used information from the 10 reports from the collaborative group for epidemiological surveillance of influenza and other respiratory virus (GROG), and information retrieved from the WHO global flu database FLUNET.

Main outcome measures Incidence, percentage of influenza specimens out of the total received by influenza centers and resource-use outcomes.

Results A total of 483 130 specimens of patients with influenza were analyzed. Meta-analysis showed an annual rate of 36 080 (95%CI 28 550 43 610) influenza-like illness per 100 000 persons-years. The percentage of influenza out of total specimens received by influenza centers ranged between 4.66% and 15.42%, with type A the most prevalent, and A subtype H3 predominating. The mean length of stay at hospital due to influenza ranged between 5.8 12.9 days, total workdays lost due to influenza-like illnesses were 17150 days, and the mean direct cost of hospitalization was US$575 per laboratory-confirmed influenza case.

Conclusions Our data show that seasonal influenza imposes a high morbidity and economic burden to the region. However, the vaccine-uptake rate has been low in this region. Population-based cohort studies are required to improve the knowledge about incidence and resource utilization, which would inform healthcare authorities for decision making.

Keywords Burden of disease, costs, epidemiology, influenza, influenza-like illness, Latin America & Caribbean, use of resources.

Please cite this paper as: Savy *et al.* (2013) Burden of influenza in Latin America and the Caribbean: a systematic review and meta-analysis. Influenza and Other Respiratory Viruses 7(6), 1017–1032.

Introduction

Influenza virus is a highly contagious etiological agent that spreads rapidly and causes an acute respiratory illness, mostly characterized by sudden onset of high fever, myalgia, headache, sore throat, and inflammation.[1,2] It is usually self-limited, and the patient recovers within 1 or 2 weeks. However, in some cases it may lead to serious complications such as pneumonia, bronchitis, and sometimes death, particularly in young children (6–23 months), the elderly (>65 years), and people with underlying chronic health problems.[3,4]

The knowledge of influenza incidence by country and region is an important public health topic that helps taking measures to organize health care services during peaks of circulation. About 10–20% of the general population is usually affected during the cold season. In the United States (US), influenza-related consultations vary from 6 to 29 per 100 children annually;[3,5–7] the rate of hospitalization in children aged <5 years varies from 500 (high-risk) to 100 (healthy) per 100 000 children.[8–14] Studies conducted in the temperate regions of Europe have revealed influenza-related hospitalization rates ranging from 11 to 237 per 100 000 children,[12,15–18] while higher rates have been reported in Hong Kong.[19] During the influenza season, H1N1 and H3N2 influenza A and influenza B viruses usually circulate according to different patterns: either two types/subtypes can circulate at the same time or sequentially, or one type/subtype can replace the previous one.

These different patterns can impact with a different burden.[20] Besides, influenza A (H1N1) has emerged as a new strain responsible for the influenza pandemic in 2009, which has so far resulted in more than 182 000 laboratory-confirmed cases and 1799 deaths in 177 countries.[21]

In the region of Latin America and the Caribbean (LA&C), scarce information on influenza mortality and morbidity is available, most likely due to underreporting.[22–25] The poor quality of accessible data makes the estimation of the burden of disease difficult. The actual impact of influenza in LA&C is often obscured by the lack of usage of specific diagnostic methods by physicians to confirm etiology, as most reported data come from clinical diagnoses of influenza-like illnesses (ILI).[3] This was particularly the case before the 2009 flu pandemic. The lack of laboratory confirmation in the diagnosis of co-circulating pathogens and the occurrence of diseases clinically similar to influenza act as major barriers for estimating the true incidence.

We conducted a systematic review and meta-analysis of the available epidemiological and virological data to assess the incidence, etiology, and use of healthcare resources in people with influenza in LA&C. The results of this analysis will help inform public health decision makers.

Methods

We performed a meta-analysis of observational studies following guidelines the Meta-analysis Of Observational Studies in Epidemiology (MOOSE)[26] and the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA).[27,28]

Search strategy and selection criteria

We conducted a systematic search of the following electronic databases: Cochrane CENTRAL register and specialized register of the Cochrane Acute Respiratory Infections Group, MEDLINE, EMBASE, and LILACS, between January 1980 and September 2008 (Appendix S1). We also performed a generic and academic Internet search and meta-search. An annotated search strategy for 'gray literature' was included to retrieve information from relevant sources like regional Ministries of Health, PAHO, hospital reports, databases containing regional proceedings or congresses' annals and doctoral theses, reference lists of included studies, and consultations with expert and institutions related to the topic. Authors were contacted to obtain missing or extra information when needed. Other sources searched were SLIPE (Latin-American Society of Pediatric Infectious Diseases) for annals and proceedings from international congresses and the World Health Organization (WHO)'s FluNet. This is a global tool for influenza virological surveillance. Data entered into FluNet are publically available. Data are provided remotely by National Influenza Centres (NICs) of the Global Influenza Surveillance and Response System (GISRS) and other national influenza reference laboratories collaborating actively with GISRS or are uploaded from WHO regional databases.[29] In the WHO Region of the Americas, the majority of specimens are from children.[30]

We included the control arms of controlled trials, cohort studies, case–control studies, case series, surveillance, and cross-sectional studies without language restriction. Systematic reviews and meta-analyses with original data were also included for qualitative synthesis of the data. Studies were included only if at least 20 cases of ILI or laboratory-confirmed influenza were reported. We included studies enrolling patients of any age since 1995.

We included studies in which influenza diagnosis was confirmed by viral isolation, detection of viral protein or viral RNA in nasal, throat, or respiratory tract secretion samples, rapid diagnostic tests, and seroconversion (defined as greater than fourfold increase in antibody titers in 2 weeks).

We included studies that assessed at least one of the following outcomes in the context of ILI: incidence of clinical and laboratory-confirmed cases of influenza, mortality and pneumonia due to influenza, mixed pneumonia, secondary bacterial pneumonia, lower respiratory tract complications, exacerbations of chronic obstructive pulmonary disease, central nervous system complications, myocarditis and pericarditis, toxic shock syndrome, and influenza-related admissions. We assessed the proportion of influenza among all specimens reported to the FluNet, proportion of type A in influenza-positive specimens, and proportion of subtypes H1 and H3 in type A-positive specimens. We also evaluated viral subtype etiology distribution and use of healthcare resources in terms of laboratory tests, treatment methods, absenteeism from school and work, number of physician visits, and overall impact on economy.

Selection of eligible articles and data abstraction

Two reviewers independently screened titles and abstracts of all identified citations and selected all potentially eligible studies. Full-text versions of these articles were independently assessed by two reviewers to evaluate whether they met the inclusion criteria. Disagreements were solved by consensus in both phases. Data were abstracted using a previously piloted electronic chart.

Quality assessment of included studies

The methodological quality of all included studies was independently assessed by three reviewers (AB, AC, DG), based on the checklist of essential items stated in Strengthening the Reporting of Observational studies in Epidemiology (STROBE),[31] the results of a systematic review evaluating tools for assessing quality and susceptibility to bias in observational studies,[32] and the guidelines for appraising medical research published by Fowkes *et al.*[33] We used an algorithm

(Appendix S2) to estimate an overall risk of bias taking into account five potential sources of bias: methods for selecting study participants, methods for measuring exposure and outcome variables, methods to control confounding, design-specific sources of bias, and statistical methods. Disagreements were solved by consensus.

Statistical analyses

A proportion meta-analysis was performed. We applied an arcsine transformation to stabilize the variance of proportions (Freeman–Tukey variant of the arcsine square root of transformed proportions method).[34] The pooled proportion was calculated as the back-transformation of the weighed mean of the transformed proportions, using inverse arcsine variance weights for the fixed and random effects model. The estimates and its 95% confidence interval (CI) were calculated using the DerSimonian–Laird weights for the random effects model where heterogeneity between studies was found.[35] We calculated the I^2 statistic as a measure of the proportion of the overall variation that was attributable to between-study heterogeneity.[36] Stats-direct (StatsDirect Ltd, Altrincham, Cheshire, UK) and STATA 9.0 (StataCorp LP, College Station, TX, USA) were used for all analyses.

We expressed incidence as the number of patients with at least one episode of influenza (ILI or laboratory confirmed) per 100 000 person, years. We calculated proportions (percentages) of total specimens remitted to influenza centers or of influenza-positive specimens. Subgroup analyses by age and by country were performed. We used maps to represent the yearly proportion of influenza-positive samples among total specimens analyzed and among rates reported in FluNet. When data were missing from FluNet, we complemented it with data from the Collaborative Group For Epidemiological Surveillance Of Influenza and Other Respiratory Viruses in Argentina (GROG). Cutoff points for categories were selected according to the quartiles of proportions observed for all countries in the period 1999–2008. Country proportion was represented only if the total number of samples reported for a given year for that country was ≥100. Maps also reflect the distribution of influenza types and A-subtypes in 1999 and 2008. The distribution of influenza subtypes was reported for a particular year and country if the total number of influenza-positive samples was ≥30. The denominator for the subtype pie charts presented in the maps is the reported number of influenza-positive samples.

To estimate the burden of ILI in the region for year 2008—before the H1N1 influenza pandemic—we used the upper and lower limits of the 95% CI of incidence obtained from the meta-analysis of the prospective studies reporting incidence. We also projected the total number of confirmed influenza cases and influenza A and B cases for the year 2008 applying the influenza incidence obtained from prospective studies to the countries' populations, and pooled type proportion rates obtained from the FluNet.

Results

The study selection process is shown in Figure 1. The literature search retrieved 1092 potential articles. Of these, 95 full-text articles, one book, 10 GROG reports for Argentina, and a database were included for detailed assessment. A total of 64 articles were excluded due to inability to meet the inclusion criteria, irrelevant information, or data duplication. Finally, 31 articles, 10 GROG reports for Argentina (1999–2008), and 75 sub-studies from FluNet (1999–2008) were included for analyses. These sources encompassed a total of 483 130 samples from patients diagnosed with influenza or ILI. Seven studies were excluded due to duplication of information with the FluNet,[37–39] GROG,[40–42] or due to the recruitment date being prior to 1995.[43]

Table 1 describes the included studies' characteristics. Most data were from Argentina (36·6%), Brazil (22·0%), Chile (17·1%), Cuba (4·9%), and Mexico (4·9%). Most were surveillance studies (39·0%) or case series (39·0%). The majority (82·9%) of the cases reported in these studies were laboratory-confirmed influenza, 75·6% had the influenza type reported, 58·5% were low respiratory tract infections (LRTI), and 41·5% were ILI.

The overall risk of bias was high in 71·0% (22/31), medium in 3·0% (1/31), and low in 26·0% (8/31) of the studies (Appendix S2).

Cases and deaths

We estimated that about 164 and 251 million ILI cases occurred in LA&C in 2008 (Table 2), including the estimated total number of Influenza A and B cases. For this period, considering theses estimations, Chile presented the highest

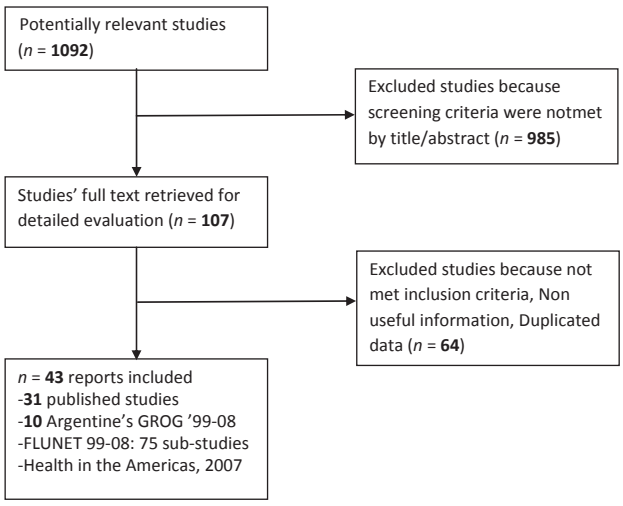

Figure 1. Flow diagram for study selection.

Table 1. Characteristics and Influenza detection of included studies

ID (Author, reporting date)	Country	Date for recruitment		Follow-up (m)	No influenza seasons	Design	Complexity level hospital	Setting (in/ outpatient)	Cohort sample size	Median age (m)	Mean age (m)	Lower age (m)	Upper age (m)	*N* with ILI	Inpatients with LRTI	Confirmed influenza (*N*)	H1	H3	A (H1 + H3 + Not typed)	B
		Start	End																	
Arg GROG 1999[62,106]	Argentina	Jan-99	Nov-99	11	1	Surveillance	High	Both				All ages			16 297	972			893	79
Arg GROG 2000[63]	Argentina	Jan-00	Nov-00	11	1	Surveillance	High	Both				All ages			21 116	454			398	56
Arg GROG 2001[64]	Argentina	Jan-01	Nov-01	11	1	Surveillance	High	Both				All ages		796	20 356	869			795	74
Arg GROG 2002[65]	Argentina	Jan-02	Nov-02	11	1	Surveillance	High	Both				All ages		678	18 041	425			182	243
Arg GROG 2003[66]	Argentina	Jan-03	Nov-03	11	1	Surveillance	High	Both				All ages		1499	26 577	1323			1304	19
Arg GROG 2004[67]	Argentina	Jan-04	Nov-04	11	1	Surveillance	High	Both				All ages		1675	28 918	1130			990	140
Arg GROG 2005[68]	Argentina	Jan-05	Nov-05	11	1	Surveillance	High	Both				All ages		2990	26 029	894			779	115
Arg GROG 2006[69]	Argentina	Jan-06	Nov-06	11	1	Surveillance	High	Both				All ages		2351	26 570	716			560	156
Arg GROG 2007[70]	Argentina	Jan-07	Nov-07	11	1	Surveillance	High	Both				All ages		1917	28 928	986			953	33
Arg GROG 2008[107]	Argentina	Jan-08	Jul-08	6	0·5	Surveillance	High	Both				All ages		N/A	18 628	781			448	333
Canas 2000[108]	Argentina	Jan-97	Dec-98	24	2	Surveillance	High	N/A				N/A	N/A			27			26	1
Lopez 2008[71]	Argentina	Mar-05	Sep-05	6	1	Case series	High	Inpatient				0	24		633	43			37	6
Parra 2005[78]	Argentina	Jan-98	Dec-98	12	1	Case series	High	Inpatient			18	N/A	N/A		388	61				
Parra 2005[109]	Argentina	Jan-02	Dec-02	12	1	Case series	High	Inpatient			16·4	N/A	N/A		565	13				
Viegas 2004[77]	Argentina	Jan-98	Dec-02	47	5	Retrospective Case series	High	Inpatient				0	60		18 561	523			508	13
Bellei 2007[58]	Brazil	Jun-01	Dec-01	7	1	Case series	High	Outpatient				216	Older	412		83			47	36
Coelho 2007[2]	Brazil	Jan-96	Dec-01	72	5	Retrospective case series	High	Inpatient				0	24		1033	45			31	14
Costa 2006[110]	Brazil	Jan-01	Dec-04	48	5	Case series	High	Inpatient				0	60			36				
De Freitas Souza 2003[49]	Brazil	May-96	Apr-97	12	1	Case series	Low	Outpatient	138			0	24			8			7	1
Diniz 2005[72]	Brazil	Nov-00	Sep-02	23	2	Cross-sectional	High	Inpatient		4 days		0	1		78	11			11	0
Mixeu 2002[111]	Brazil	Mar-97	Oct-97	7	1	RCT	Low	Outpatient	299	34		216	768	203						
Straliotto 2002[75]	Brazil	May-90	Dec-92	24	3	Prospective Case series	High	N/A				0	60		862	17	0	22	22	17
Thomazelli 2007[76]	Brazil	Jan-03	Jan-04	12	1	Prospective Case series	High	Inpatient		5		0	60		336	17			17	
Tsuchiya 2005[56]	Brazil	Jan-00	Jan-03	36	4	Cross-sectional	High	Both				0	840	273	1348	125			97	28
Avendaño 1999[83]	Chile	Mar-98	Sep-98	6	1	Surveillance	High	Inpatient				0	60		500					
Avendaño 1996-2006[83]	Chile	Jan-96	Dec-06	120	10	Cross-sectional	High	Inpatient				0	60		3672	118				
Delpiano 2003[84]	Chile	May-99	Sep-99	5	1	Prospective cohort study	High	Inpatient			14	0	60		175				166	9
Perret Perez 2004[73]	Chile	Jun-04	Jul-04	1	N/A	Case series	High	Inpatient		9		0	780		3053	892				
Rabagliati 2004[74]	Chile	May-04	Jun-04	2	1	Case series	High	Inpatient				816	180		163	55			59	2
Rabagliati 2006[82]	Chile	May-04	Jul-04	3	1	Retrospective Case series	High	Inpatient			68	180	1212		83	61			40	21
Sotomayor 2008[112]	Chile	Jan-08	Nov-08	10	1	Surveillance	N/A	N/A				N/A	N/A	509		56			53	3
Duque 2001[113]	Colombia	Mar-97	Aug-97	6	1	RCT	High	Outpatient	246			18	60	225						
Herrera 2008[80]	Colombia	Sep-03	Dec-03	3	1	Surveillance	High	Inpatient				0	Older		64	8		7	7	1
Morales 2004[1]	Colombia	Oct-00	May-01	8	1	Prospective cohort study	N/A	Outpatient	335		32	216	780	158						
Cancio 2000[81]	Cuba	Jan-95	Dec-98	36	3	Case series	High	Inpatient				0	Older		301	195			129	66
Oropesa Fernandez 1998[54]	Cuba	Jan-92	Dec-95	48	4	Case series	High	N/A				N/A	N/A	148		136	47	51	98	38
Canas 2000[108]	Ecuador	Jan-97	Dec-98	24	2	Surveillance	High	N/A				N/A	N/A			4			3	1
Jackson 2004[57]	Jamaica	Jan-03	Feb-04	13	1	Cross-sectional	High	Inpatient				N/A	N/A	318		70	4	48	52	
Cabello 2006[48]	Mexico	Jan-97	Feb-98	13	1	Prospective cohort study	Low	Outpatient	290		35	0	60			86			60	26
Talavera 2007[55]	México	Dec-99	Dec-02	36	3	Prospective Case series	N/A	N/A			32·6	0	60	98		28		28	28	
Gordon 2009[47]	Nicaragua	Jan-06	Jan-07	12	1	Community-based cohort	Low	Outpatient	3999			24	144	1156						
Canas 2000[108]	Peru	Jan-97	Dec-98	24	2	Surveillance	High	N/A				N/A	N/A			48			41	7

ILI, influenza-like illnesses.

Table 2. Projection of annual number of ILI, confirmed Influenza, Influenza A and B cases for 2008

Country	ILI cases		Confirmed Influenza cases		Influenza A cases		Influenza B cases	
	Lower 95%CI	Upper 95%CI	Lower 95%CI	Upper 95%CI	Lower 95%CI	Upper 95%CI	Lower 95%CI	Upper 95%CI
Argentina*	11 386 597	17 392 976	477 098	728 766	256 727	443 527	186 736	285 239
Brazil*	54 808 006	83 718 989	4 170 889	6 371 015	2 121 731	3 976 151	1 567 837	2 394 865
Chile*	4 797 542	7 328 224	163 596	249 892	149 936	238 472	7476	11 420
Mexico*	4 797 542	7 328 224	746 918	1 140 914	599 028	1 056 030	55 571	84 884
Panama*	970 415	1 482 304	84 135	128 516	57 136	111 307	11 266	17 208
All LA&C*	164 487 970	251 254 654	7 665 139	11 708 467	5 988 007	9 969 760	1 138 273	1 738 707

*Countries with available data to obtain specific estimations. Note: Estimations based on the 46 countries of LA&C and global proportions from meta-analysis.
ILI, influenza-like illnesses.

testing rate (using number of tests registered in the FluNet as nominator, and the 95% CI lower and upper bounds of estimated ILI cases as denominator) between 0·275% and 0·419%, while Brazil showed the lowest one (0·005–0·007%).

Influenza-specific mortality was often unavailable, and countries reported 'influenza and pneumonia' (I&P) combined mortality to PAHO. I&P-related mortality was the highest in the youngest and eldest age groups in most of the countries. In Latin America, in children under 5 years of age, I&P deaths were the highest in Ecuador representing 14·4% of all deaths (for the year 2003), 13·5% in Brazil (2004), 4·8% in Paraguay (2001–2003), and 4·0% in Argentina (2004). In the Caribbean, the highest I&P death rate was recorded in Barbados (85·0%) in 2002 for the ≥65, year age group. Across all age groups, I&P were responsible for 2·1% of total deaths in Bermuda (2001–2002), 5·6% in the Cayman Islands (1998–2000), 5·8% in Haiti (2003), 3·5% in Puerto Rico (2004), 7·0% in St. Kitts & Nevis (2002–2004), 14·7% in Guatemala (2001–2003), and 4·3% in Honduras (2003).

Further details can be found in the supplemental material (Appendix S3).[44] In Chile, a country that uses population-based nationwide Sentinel Units to record data, the influenza-specific mortality rate was 0·4 per 100 000 population, and 2633 cases of influenza occurred per 100 000 population in 2001.

Incidence

Information on ILI incidence was provided by four studies (two randomized controlled trials, one prospective study, and one cohort study).[1,45–47] Incidence of influenza-related acute respiratory infections (ARI) in children of 5 years of age and younger was described in a prospective study conducted in Mexico,[48] while influenza-related LRTIs incidences were described in a longitudinal prospective study conducted in Brazil[49] in children attending day care center and aged between 0 and 2 years. The ages of patients included ranged from 18 months to 65 years. The median duration of follow-up in the above-mentioned four studies was 12 months. The random effect meta-analysis of the ILI incidence showed an annual incidence rate of 36 080 (95% CI: 28 550–43 610) episodes per 100 000 person, years, with the highest annual incidence rate recorded in the <5, year age group (45 730 per 100 000 person, years; 95% CI: 39 760–51 710). The incidence of influenza-related ARI[48] in children <5 years of age was the highest in the 3- to 4, year age group (57 500 per 100 000 person, years; 95% CI: 34 000–81 000) and lowest in the 1 to 2, year age group (15 090 per 100 000 person, years; 95% CI: 7700–22 490).

LRTI incidence was 5800 per 100 000 person, years (95% CI: 1780–9810) in children aged 0–2 years.[49] Incidence rates across all age groups are presented in Table 3, Figure 2.

Proportion of confirmed influenza, influenza types, and subtypes among total influenza specimens processed at national reference laboratories

In the meta-analysis performed to estimate the proportion of influenza-positive specimens among total respiratory specimens received at influenza centers, the pooled percentage of specimens positive for influenza (all types) ranged between 4·7% and 15·4% per year, with an overall percentage of 8·2% (95% CI: 7·3–9·3) between 1999 and 2008 (Table 4). During the same period, meta-analyses of influenza types and subtypes showed that the pooled percentage of influenza-positive type A samples ranged between 60·2% and 96·2%, and the pooled percentage of type B samples ranged between 3·7% and 39·8%. The pooled percentage of influenza type A samples that were H1 subtyped was 9·3%, and H3 subtyped was 19·3% (Table 5).

The proportion of influenza (all types), influenza types, and subtypes is presented by year (1999–2008) and by

Table 3. Incidence of ILI, ARI, and LRTI

Incidence	Study and age group	Events/ Persons, years	Incidence per 100 000 persons-years (95% CI)	Annual mean rate per 100 000 persons-years (95% CI)
ILI (meta-analyzed data)	Duque 2001[50] (18 months–5 years)	225/492	45 730 (39 760–51 710)	36 080 (28 550–43 610)
	Morales 2004[1] (18–65 years)	158/503	31 410 (26 510–36 310)	
	Mixeu 2002[51] (21–58 years)	203/513	39 570 (34 130–45 010)	
	Gordon 2009[52] (2–12 years)	1156/3999	28 910 (27 240–30 570)	
ARI	Cabello 2006[53] (0–1 year)	13/29	44 830 (20 460–69 200)	–
	Cabello 2006[53] (1–2 years)	16/106	15 090 (7700–22 490)	
	Cabello 2006[53] (2–3 years)	14/53	26 420 (12 580–40 250)	
	Cabello 2006[53] (3–4 years)	23/40	57 500 (34 000–81 000)	
	Cabello 2006[53] (4–5 years)	20/39	51 280 (28 810–73 760)	
LRTI	De Freitas Souza 2003[54] (0–2 years)	8/138	5800 (1780–9810)	–

ILI, influenza-like illnesses.

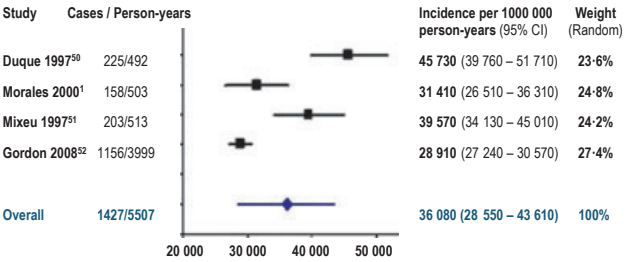

Figure 2. Incidence of Influenza-like illness.

country in Tables 6 and 7. Initial and final maps are shown in Figure 3. In Appendix S4, the proportion forest plot and the entire map series are shown. The highest percentage of influenza among countries under surveillance was recorded in Peru (69·5%; 95% CI: 66·4–72·5) in 2002 followed by Uruguay (42·6%; 95% CI: 36·6–48·6) in 2005.

ILI and LRTI rates

The ILI rate was reported in four countries: Argentina (2644·9 per 100 000 persons -2005-), Chile (633 per 100 000 persons -2005-), Dominica (605 per 100 000 persons -2003-), and Panama (cases increased from 6250 to 9822 per 100 000 persons -1995–2004-). This large increase of ILI burden in Panama may have been attributed to the influenza epidemic in 1999 that resulted in an annual ILI rate of 46 262 per 100 000 persons.[44]

Information from the Ministries of Health and viral surveillance centers of Argentina and Brazil was available on ILI and LRTI. In Argentina, a median of 874 809 ILI cases and 48 728 LRTI were notified between 2003 and 2007.[50]

Table 4. Percentage of influenza among all specimens analyzed at influenza centers

Year	Number of sub-studies	*N**	Percentage of influenza % (95% CI)
1999	2	3021	10·13 (4·52–17·66)
2000	4	28 084	8·42 (1·90–18·95)
2001	4	22 818	10·95 (4·26–20·23)
2002	7	41 442	15·42 (7·64–25·29)
2003	8	70 280	11·39 (5·99–18·24)
2004	10	63 676	8·35 (5·92–11·15)
2005	8	61 781	10·62 (7·12–14·73)
2006	9	65 662	6·13 (4·64–7·83)
2007	10	70 461	5·13 (3·82–6·62)
2008**	12	55 905	4·66 (3·45–6·04)
All	74	483 130	8·23 (7·25–9·28)

*Number of specimens received for analysis at all influenza centers.
**Argentinean GROG 2008[107] was not analyzed because complete influenza season's data were not available.

The rate of ILI notification until August 2007 was 2264·19 per 100 000 persons in adults and 6062·38 per 100 000 persons in children <5 years of age.[51] Between 2000 and 2008, the influenza surveillance system in Brazil revealed that ILI led to a total of 4·39–16·92% of hospital consultations.[52]

Influenza-like illnesses activity in LA&C for the period 1999–2008 is presented in Appendix S4 (data taken from the FluNet). Each national influenza center defines the geographical spread of influenza based on the WHO global

Table 5. Percentage of influenza types (A and B*) and subtypes (H1, H3, and NT**)***

Year	Number of sub-studies	*N*	Percentage of type A % (95% CI)	Percentage of type B % (95% CI)
1999	4	429	85·49 (82·03–88·65)	14·51 (11·35–17·97)
2000	5	1448	96·25 (91·61–99·08)	3·75 (0·92–8·39)
2001	5	2503	76·96 (63·20–88·27)	23·04 (11·73–36·80)
2002	9	1952	60·16 (42·08–76·91)	39·84 (23·09–57·92)
2003	8	3298	95·19 (89·56–98·72)	4·81 (1·28–10·44)
2004	8	3051	75·51 (66·86–83·22)	24·49 (16·78–33·14)
2005	8	2875	84·88 (78·46–90·34)	15·12 (9·66–21·54)
2006	8	2048	82·44 (71·59–91·11)	17·56 (8·89–28·41)
2007	8	2495	83·63 (73·36–91·78)	16·37 (8·22–26·64)
2008†	8	2206	72·67 (56·31–86·37)	27·33 (13·63–43·69)
All	71	22 305	81·77 (78·12–85·15)	18·23 (14·85–21·88)

Number of studies	*N*‡	Type A subtype	Percentage % (95% CI)
63	18 586	H1	9·27 (5·68–13·62)
		H3	19·32 (13·77–25·55)
		NT§	63·85 (58·22–69·30)

*Number of cases with influenza.
**Not typed.
***The percentages do not add up to 100% because each one is a different meta-analysis with a different subset of studies.
†Argentinean GROG 2008[107] was not analyzed because complete FLU season's data were not available.
‡Number of cases with influenza type A.
§NT, Not subtyped.

influenza surveillance system as follows: Region, No report, No activity, Sporadic, Local outbreak, Regional activity, and Widespread activity.[53]

In the meta-analysis of ILI by age, we included six studies and the Argentinean GROG reports 2001–2007.[54–70] The proportion of confirmed influenza in ILI cases was high in children aged 5–14 years, while in children younger than 5 years and older than 14 years the proportion of confirmed influenza in ILI cases was low. Meta-analysis of the proportion of confirmed influenza in LRTI reported in 16 studies[2,55,60–83] showed that the highest proportion occurred in the adolescent population. Type A was more prevalent than type B in confirmed cases of ILI and LRTI (Table 8).

Use of resources

The impact of influenza, ILI, LRTI, and ARI on healthcare resources was reported in eight studies.[1,2,45,46,71,72,74,84] A meta-analysis on the use of healthcare resources was not performed due to the heterogeneity of the designs and included populations.

Many of the influenza cases were severe and led to hospitalization. The mean duration of stay in hospitals ranged between 5·8 and 12·9 days in non-intensive care units (ICU);[2,71,72] for patients who were admitted to ICU, the median duration of stay (one study) was 32 days,[71] although it ranged between 5·9 and 13·6 days in another study.[84]

The use of antibiotic and/or neuraminidase inhibitors in the treatment of patients with influenza was reported in three studies.[2,71,72] Oseltamivir resistance of influenza A (H1N1) 2009 virus was reported in two studies in Argentina.[85,86]

Influenza-like illnesses also resulted in absenteeism and workdays lost, being the total number of work days lost (in unvaccinated population) of 17,[1] 102,[45] and 150 days[45] in the three analyzed studies, respectively.

Hospitalization due to influenza or ILI led to several direct (e.g., hospitalization, diagnosis, and treatment) and indirect costs (domestic help, transportation, loss of productivity due to absenteeism). The mean direct cost at the time of discharge from hospitals was US$575 per laboratory-confirmed influenza case, US$473 for other respiratory diseases, and US$657 for subjects who tested negative for all viral pathogens. Overall, societal cost at discharge, which takes into account direct and indirect costs, was US$620 per laboratory-confirmed influenza case, US$453 for other respiratory viruses, and US$669 for subjects who were negative for all viral pathogens.[71]

Table 6. Percentage of influenza of all specimens analyzed at influenza centers, and its Type A, and Type B percentage by country and year

Country	Year	Influenza			*N*	Percentage* % (95% CI)	Percentage type A** % (95% CI)	Percentage type B** % (95% CI)
		All	Type A	Type B				
Argentina	1999	186	154	32	2616	7·11 (6·15–8·16)	82·80 (76·59–87·92)	17·20 (12·08–23·41)
	2000	454	398	56	21 116	2·15 (1·96–2·35)	87·67 (84·28–90·55)	12·33 (9·45–15·72)
	2001	869	795	74	21 152	4·11 (3·84–4·38)	91·48 (89·43–93·25)	8·52 (6·75–10·57)
	2002	425	182	243	18 719	2·27 (2·06–2·49)	42·82 (38·07–47·68)	57·18 (52·32–61·93)
	2003	1323	1304	19	28 076	4·71 (4·47–4·97)	98·56 (97·77–99·13)	1·44 (0·87–2·23)
	2004	1130	990	140	30 593	3·69 (3·49–3·91)	87·61 (85·55–89·48)	12·39 (10·52–14·45)
	2005	894	779	115	29 019	3·08 (2·88–3·29)	87·14 (84·76–89·26)	12·86 (10·74–15·24)
	2006	716	560	156	28 921	2·48 (2·30–2·66)	78·21 (75·01–81·18)	21·79 (18·82–24·99)
	2007	986	953	33	30 845	3·20 (3·00–3·40)	96·65 (95·33–97·69)	3·35 (2·31–4·67)
	2008	781	448	333	18 628	4·19 (3·91–4·49)	57·36 (53·81–60·86)	42·64 (39·14–46·19)
Brazil	1999	–	47	6	–	–	88·68 (76·97–95·73)	11·32 (4·27–23·03)
	2001	–	16	20	–	–	44·44 (27·94–61·90)	55·56 (38·10–72·06)
	2002	–	12	31	–	–	27·91 (15·33–43·67)	72·09 (56·33–84·67)
	2003	101	97	4	1080	9·35 (7·68–11·25)	96·04 (90·17–98·91)	3·96 (1·09–9·83)
	2004	157	126	31	1939	8·10 (6·92–9·40)	80·25 (73·16–86·17)	19·75 (13·83–26·84)
	2005	99	57	42	2350	4·21 (3·44–5·11)	57·58 (47·23–67·45)	42·42 (32·55–52·77)
	2006	239	187	52	3131	7·63 (6·73–8·62)	78·24 (72·47–83·30)	21·76 (16·70–27·53)
	2007	58	39	19	4457	1·30 (0·99–1·68)	67·24 (53·66–78·99)	32·76 (21·01–46·34)
	2008	298	169	129	3918	7·61 (6·79–8·48)	56·71 (50·87–62·41)	43·29 (37·59–49·13)
Chile	1999		113	21		–	84·33 (77·05–90·03)	15·67 (9·97–22·95)
	2000	356	347	9	2749	12·95 (11·72–14·26)	97·47 (95·26–98·84)	2·53 (1·16–4·74)
	2001	585	1206	218	19 232	3·04 (2·80–3·29)	84·69 (82·71–86·52)	15·31 (13·48–17·29)
	2002	554	536	49	19 912	2·78 (2·56–3·02)	91·62 (89·08–93·74)	8·38 (6·26–10·92)
	2003	1037	553	1	24 137	4·30 (4·04–4·56)	99·82 (99·00–100·00)	0·18 (0·00–1·00)
	2004	914	873	164	23 626	3·87 (3·63–4·12)	84·19 (81·82–86·35)	15·81 (13·65–18·18)
	2005	710	744	170	24 858	2·86 (2·65–3·07)	81·40 (78·72–83·87)	18·60 (16·13–21·28)
	2006	799	676	34	24 029	3·33 (3·10–3·56)	95·21 (93·37–96·66)	4·79 (3·34–6·63)
	2007	686	618	181	20 125	3·41 (3·16–3·67)	77·35 (74·28–80·21)	22·65 (19·79–25·72)
	2008	56	643	43	405	13·83 (10·62–17·58)	93·73 (91·65–95·43)	6·27 (4·57–8·35)
Colombia	1999	32	53	3	488	6·56 (4·53–9·13)	94·64 (85·13–98·88)	5·36 (1·12–14·87)
	2000	21	32	0	414	5·07 (3·17–7·65)	100·00 (89·11–100·00)	0·00 (0·00–10·89)
	2002	31	22	9	517	6·00 (4·11–8·40)	70·97 (51·96–85·78)	29·03 (14·22–48·04)
	2003	67	66	1	381	17·59 (13·90–21·79)	98·51 (91·96–99·96)	1·49 (0·04–8·04)
	2004	67	22	45	712	9·41 (7·37–11·80)	32·84 (21·85–45·40)	67·16 (54·60–78·15)
	2005	77	70	7	972	7·92 (6·30–9·80)	90·91 (82·16–96·27)	9·09 (3·73–17·84)
	2006	49	47	2	617	7·94 (5·93–10·36)	95·92 (86·02–99·50)	4·08 (0·50–13·98)
Costa Rica	2008	–	–	–	2482	0·97 (0·62–1·44)	–	–
Ecuador	2007	–	40	2	–	–	95·24 (83·84–99·42)	4·76 (0·58–16·16)
El Salvador	2006	22	–	–	398	5·53 (3·50–8·25)	–	–
	2008	24	–	—	369	6·50 (4·21–9·52)	–	–
French Guiana	2002	72	68	4	273	26·37 (21·25–32·02)	94·44 (86·38–98·47)	5·56 (1·53–13·62)
	2008		27	6		–	81·82 (64·54–93·02)	18·18 (6·98–35·46)
Honduras	2007	5	–	–	139	3·60 (1·18–8·19)	–	–
	2008	6	–	–	256	2·34 (0·86–5·03)	—	–
México	2000	568	546	22	3731	15·22 (14·09–16·42)	96·13 (94·19–97·56)	3·87 (2·44–5·81)
	2001	83	81	2	991	8·38 (6·73–10·28)	97·59 (91·57–99·71)	2·41 (0·29–8·43)
	2002	108	61	47	1655	6·53 (5·38–7·82)	56·48 (46·60–66·00)	43·52 (34·00–53·40)
	2003	376	357	19	3098	12·14 (11·01–13·34)	94·95 (92·22–96·93)	5·05 (3·07–7·78)
	2004	61	27	34	2375	2·57 (1·97–3·29)	44·26 (31·55–57·55)	55·74 (42·45–68·45)
	2005	297	274	23	2721	10·92 (9·77–12·15)	92·26 (88·61–95·03)	7·74 (4·97–11·39)
	2006	97	49	48	4189	2·32 (1·88–2·82)	50·52 (40·17–60·83)	49·48 (39·17–59·83)
	2007	389	351	38	5497	7·08 (6·41–7·79)	90·23 (86·84–92·99)	9·77 (7·01–13·16)
	2008	126	110	16	5232	2·41 (2·01–2·86)	87·30 (80·20–92·56)	12·70 (7·44–19·80)
Panama	2007	71	52	19	612	11·60 (9·17–14·41)	73·24 (61·41–83·06)	26·76 (16·94–38·59)
	2008	83	65	18	957	8·67 (6·97–10·64)	78·31 (67·91–86·61)	21·69 (13·39–32·09)
Paraguay	2000		38	0		–	100·00 (90·75–100·00)	0·00 (0·00–9·25)
	2001	91	39	52	261	34·87 (29·09–40·99)	42·86 (32·53–53·66)	57·14 (46·34–67·47)
	2002	31	15	16	150	20·67 (14·49–28·03)	48·39 (30·15–66·94)	51·61 (33·06–69·85)
	2003	37	31	6	15 516	0·24 (0·17–0·33)	83·78 (67·99–93·81)	16·22 (6·19–32·01)
	2004	118	111	7	1317	8·96 (7·47–10·63)	94·07 (88·16–97·58)	5·93 (2·42–11·84)
	2005	83	75	8	1089	7·62 (6·12–9·36)	90·36 (81·89–95·75)	9·64 (4·25–18·11)
	2008	17	–	–	936	1·82 (1·06–2·89)	–	–

Table 6. (Continued)

Country	Year	Influenza			*N*	Percentage* % (95% CI)	Percentage type A** % (95% CI)	Percentage type B** % (95% CI)
		All	Type A	Type B?				
Peru	2002	623	377	246	896	69·53 (66·40–72·53)	60·51 (56·55–64·37)	39·49 (35·63–43·45)
	2003	757	637	120	1912	39·59 (37·39–41·82)	84·15 (81·35–86·68)	15·85 (13·32–18·65)
	2004	435	350	85	1874	23·21 (21·32–25·19)	80·46 (76·42–84·08)	19·54 (15·92–23·58)
	2005	394	374	20	1729	22·79 (20·83–24·84)	94·92 (92·27–96·87)	5·08 (3·13–7·73)
	2006	131	114	17	2610	5·02 (4·21–5·93)	87·02 (80·04–92·26)	12·98 (7·74–19·96)
	2007	84	59	25	2370	3·54 (2·84–4·37)	70·24 (59·27–79·73)	29·76 (20·27–40·73)
	2008	119	86	33	2184	5·45 (4·53–6·48)	72·27 (63·32–80·08)	27·73 (19·92–36·68)
Uruguay	2002		10	24		–	29·41 (15·10–47·48)	70·59 (52·52–84·90)
	2003	83	80	3	305	27·21 (22·30–32·58)	96·39 (89·80–99·25)	3·61 (0·75–10·20)
	2004	46	36	10	432	10·65 (7·90–13·95)	78·26 (63·64–89·05)	21·74 (10·95–36·36)
	2005	117	86	31	275	42·55 (36·63–48·62)	73·50 (64·55–81·23)	26·50 (18·77–35·45)
	2006	54	52	2	151	35·76 (28·14–43·96)	96·30 (87·25–99·55)	3·70 (0·45–12·75)
	2007	66	58	8	516	12·79 (10·03–15·98)	87·88 (77·51–94·62)	12·12 (5·38–22·49)
	2008	80	35	45	376	21·28 (17·25–25·76)	43·75 (32·68–55·30)	56·25 (44·70–67·32)
Venezuela	2004	12	–	–	186	6·45 (3·38–11·00)	–	–
	2006	52	32	20	787	6·61 (4·97–8·57)	61·54 (47·02–74·70)	38·46 (25·30–52·98)

*The denominator is the number of specimens received by influenza centers.
**The denominator is the number of specimens positive for influenza.

Discussion

Influenza virus has an unparalleled potential to cause epidemics and global pandemics.[87] The disease affects millions of people all over the world and leads to fatal complications in approximately 1 million people every year.[88] In LA&C, seasonal influenza has been the major cause of respiratory infection-associated morbidity and mortality in older adults and younger children.[89,90]

In this systematic review, 31 articles, 75 sub-studies from the FluNet database, the book *Health in the Americas 2007 Edition,* and 10 reports from collaborative groups were analyzed. We included information mostly derived from surveillance systems, case series, and cross-sectional studies, which were based on samples from patients who attended healthcare centers or specific sub-populations. The annual incidence rate of ILI per 1000 person, years was found to be 36 080 per 100 000 person, years. Meta-analysis was performed on four prospective studies with the highest incidence observed in the <5, year age group. It is important to acknowledge that there may have been underreporting of ILI cases in these studies and thus the rates calculated here may be lower than the true value, highlighting the need of alternative methods, as presented in this report, to estimate the real burden of influenza.

The burden of influenza was high, with increased risk of morbidity and mortality in children under 5 years of age and in the elderly population having underlying medical problems. Consequently, these patients also contributed significantly to the economic burden of the country in terms of hospitalization, treatment, and other resource costs. The rate of hospitalization due to respiratory diseases in children in the United States aged <5 years varied from 100 to 500 per 100 000 children in different reports.[8–14] Studies in temperate regions in Europe show similar figs.[12,16–18] In Hong Kong, where the epidemiological pattern is similar to the tropical zone, higher hospitalization rates (2093–2882 per 100 000) were reported.[19]

No meaningful conclusions could be drawn on influenza-related mortality since Chile was the only country with available mortality data attributable to influenza (overall 0·4 per 100 000 persons; 4·1 per 100 000 persons in ≥65, year age group). Influenza and all-cause pneumonia deaths are reported together for the majority of LA&C official MOH databases.[44,91] While these deaths were originated both from laboratory-confirmed and ILI cases, and from bacterial pneumonia cases, they still provide a broad complementary perspective of the upper limit of influenza burden. Chilean data were in line with previous studies demonstrating that influenza-related mortality rate was the highest in the <5, year and >65, year age groups.[92,93] One study in the United States used a regression model to attribute an annual average of 41 400 deaths (95% CI: 27 100–55 700) to influenza between 1979 and 2001.[94] Other studies in the United States and England have also shown that influenza infections were seldom fatal in younger adults, but led to deaths (range: 0·8–6·7 per 100 000 persons) in the <5, year age group.[95,96]

Meta-analysis of the proportion of influenza-positive specimens among all specimens received by influenza

Table 7 Percentage of subtype H1, H3, and NT out of Type A strains by country and year

Country	Year	Subtype H1	Subtype H3	Subtype non-specified	N	Percentage subtype H1 % (95% CI)	Percentage subtype H3 % (95% CI)	Percentage subtype NT[b] % (95% CI)
Argentina	1999	8	45	101	154	5·19 (2·27–9·98)	29·22 (22·18–37·08)	65·58 (57·51–73·04)
	2000	117	10	281	398	29·40 (24·96–34·14)	0·00 (0·00–0·92)	70·60 (65·86–75·04)
	2001	1	417	377	2795	0·13 (0·00–0·70)	52·45 (48·91–55·97)	47·42 (43·90–50·96)
	2002	23	10	149	182	12·64 (8·18–18·36)	5·49 (2·67–9·87)	81·87 (75·49–87·18)
	2003	263	249	792	1304	20·17 (18·02–22·45)	19·10 (17·00–21·34)	60·74 (58·03–63·40)
	2004	0	483	507	990	0·00 (0·00–0·37)	48·79 (45·63–51·95)	51·21 (48·05–54·37)
	2005	0	453	326	779	0·00 (0·00–0·47)	58·15 (54·60–61·64)	41·85 (38·36–45·40)
	2006	265	26	269	560	47·32 (43·12–51·55)	4·64 (3·06–6·73)	48·04 (43·83–52·26)
	2007	0	321	632	953	0·00 (0·00–0·39)	33·68 (30·68–36·78)	66·32 (63·22–69·32)
	2008	20	0	428	448	4·46 (2·75–6·81)	0·00 (0·00–0·82)	95·54 (93·19–97·25)
Brazil	1999	0	1	46	47	0·00 (0·00–7·55)	2·13 (0·05–11·29)	97·87 (88·71–99·95)
	2003	25	26	46	97	25·77 (17·42–35·65)	26·80 (18·32–36·76)	47·42 (37·19–57·82)
	2004	4	34	88	126	3·17 (0·87–7·93)	26·98 (19·47–35·62)	69·84 (61·03–77·69)
	2005	3	3	51	57	5·26 (1·10–14·62)	5·26 (1·10–14·62)	89·47 (78·48–96·04)
	2006	41	26	120	187	21·93 (16·22–28·55)	13·90 (9·29–19·71)	64·17 (56·85–71·04)
	2007	4	12	23	39	10·26 (2·87–24·22)	30·77 (17·02–47·57)	58·97 (42·10–74·43)
	2008	96	0	73	169	56·80 (48·98–64·39)	0·00 (0·00–2·16)	43·20 (35·61–51·02)
Chile	1999	1	33	79	113	0·89 (0·02–4·83)	29·20 (21·03–38·50)	69·91 (60·57–78·18)
	2000	2151	3	193	347	43·52 (38·23–48·91)	0·86 (0·18–2·51)	55·62 (50·22–60·92)
	2001	4	245	957	1206	0·33 (0·09–0·85)	20·32 (18·08–22·70)	79·35 (76·96–81·61)
	2002	105	0	431	536	19·59 (16·31–23·21)	0·00 (0·00–0·69)	80·41 (76·79–83·69)
	2003	2	316	235	553	0·36 (0·04–1·30)	57·14 (52·90–61·31)	42·50 (38·33–46·74)
	2004	0	478	395	873	0·00 (0·00–0·42)	54·75 (51·38–58·09)	45·25 (41·91–48·62)
	2005	0	468	276	744	0·00 (0·00–0·49)	62·90 (59·32–66·38)	37·10 (33·62–40·68)
	2006	151	192	333	676	22·34 (19·25–25·67)	28·40 (25·03–31·97)	49·26 (45·43–53·10)
	2007	7	310	301	3618	1·13 (0·46–2·32)	50·16 (46·15–54·18)	48·71 (44·70–52·73)
	2008	393	0	250	643	61·12 (57·23–64·91)	0·00 (0·00–0·57)	38·88 (35·09–42·77)
Colombia	1999	0	43	10	53	0·00 (0·00–6·72)	81·13 (68·03–90·56)	18·87 (9·44–31·97)
	2000	22	5	5	32	68·75 (49·99–83·88)	15·63 (5·28–32·79)	15·63 (5·28–32·79)
	2003	1	57	8	66	1·52 (0·04–8·16)	86·36 (75·69–93·57)	12·12 (5·38–22·49)
	2005	0	2	68	70	0·00 (0·00–5·13)	2·86 (0·35–9·94)	97·14 (90·06–99·65)
	2006	0	0	47	47	0·00 (0·00–7·55)	0·00 (0·00–7·55)	100·00 (92·45–100·00)
Ecuador	2007	38	0	2	40	95·00 (83·08–99·39)	0·00 (0·00–8·81)	5·00 (0·61–16·92)
French Guiana	2002	0	59	9	68	0·00 (0·00–5·28)	86·76 (76·36–93·77)	13·24 (6·23–23·64)
México	2000	4	23	519	546	0·73 (0·20–1·87)	4·21 (2·69–6·25)	95·05 (92·89–96·72)
	2001	9	6	66	781	11·11 (5·21–20·05)	7·41 (2·77–15·43)	81·48 (71·30–89·25)
	2002	3	6	52	61	4·92 (1·03–13·71)	9·84 (3·70–20·19)	85·25 (73·83–93·02)
	2003	24	79	254	357	6·72 (4·35–9·84)	22·13 (17·93–26·80)	71·15 (66·15–75·80)
	2005	26	94	154	274	9·49 (6·29–13·59)	34·31 (28·70–40·26)	56·20 (50·11–62·17)
	2006	83	14	32	49	6·12 (1·28–16·87)	28·57 (16·58–43·26)	65·31 (50·36–78·33)
	2007	76	95	180	351	21·65 (17·46–26·33)	27·07 (22·49–32·04)	51·28 (45·92–56·62)
	2008	16	63	31	110	14·55 (8·55–22·54)	57·27 (47·48–66·66)	28·18 (20·02–37·56)
Panama	2007	0	0	52	52	0·00 (0·00–6·85)	0·00 (0·00–6·85)	100·00 (93·15–100·00)
	2008	0	0	65	65	0·00 (0·00–5·52)	0·00 (0·00–5·52)	100·00 (94·48–100·00)
Paraguay	2000	0	0	38	38	0·00 (0·00–9·25)	0·00 (0·00–9·25)	100·00 (90·75–100·00)
	2001	0	0	39	39	0·00 (0·00–9·03)	0·00 (0·00–9·03)	100·00 (90·97–100·00)
	2003	0	15	16	31	0·00 (0·00–11·22)	48·39 (30·15–66·94)	51·61 (33·06–69·85)
	2004	0	51	60	111	0·00 (0·00–3·27)	45·95 (36·45–55·67)	54·05 (44·33–63·55)
	2005	2	27	46	75	2·67 (0·32–9·30)	36·00 (25·23–47·91)	61·33 (49·38–72·36)
Peru	2002	90	222	65	377	23·87 (19·66–28·50)	58·89 (53·73–63·90)	17·24 (13·57–21·44)
	2003	47	85	505	637	7·38 (5·47–9·69)	13·34 (10·80–16·23)	79·28 (75·92–82·36)
	2004	78	66	206	350	22·29 (18·03–27·01)	18·86 (14·89–23·36)	58·86 (53·50–64·06)
	2005	145	42	187	374	38·77 (33·80–43·91)	11·23 (8·21–14·88)	50·00 (44·82–55·18)
	2006	2	1	111	114	1·75 (0·21–6·19)	0·88 (0·02–4·79)	97·37 (92·50–99·45)
	2007	0	0	59	59	0·00 (0·00–6·06)	0·00 (0·00–6·06)	100·00 (93·94–100·00)
	2008	2	0	84	86	2·33 (0·28–8·15)	0·00 (0·00–4·20)	97·67 (91·85–99·72)
Uruguay	2003	16	37	27	80	20·00 (11·89–30·44)	46·25 (35·03–57·76)	33·75 (23·55–45·19)
	2004	0	5	31	36	0·00 (0·00–9·74)	13·89 (4·67–29·50)	86·11 (70·50–95·33)
	2005	2	26	58	86	2·33 (0·28–8·15)	30·23 (20·79–41·08)	67·44 (56·48–77·16)
	2006	10	0	42	52	19·23 (9·63–32·53)	0·00 (0·00–6·85)	80·77 (67·47–90·37)
	2007	0	32	26	58	0·00 (0·00–6·16)	55·17 (41·54–68·26)	44·83 (31·74–58·46)
	2008	25	0	10	35	71·43 (53·70–85·36)	0·00 (0·00–10·00)	28·57 (14·64–46·30)
Venezuela	2006	18	14	0	32	56·25 (37·66–73·64)	43·75 (26·36–62·34)	0·00 (0·00–10·89)

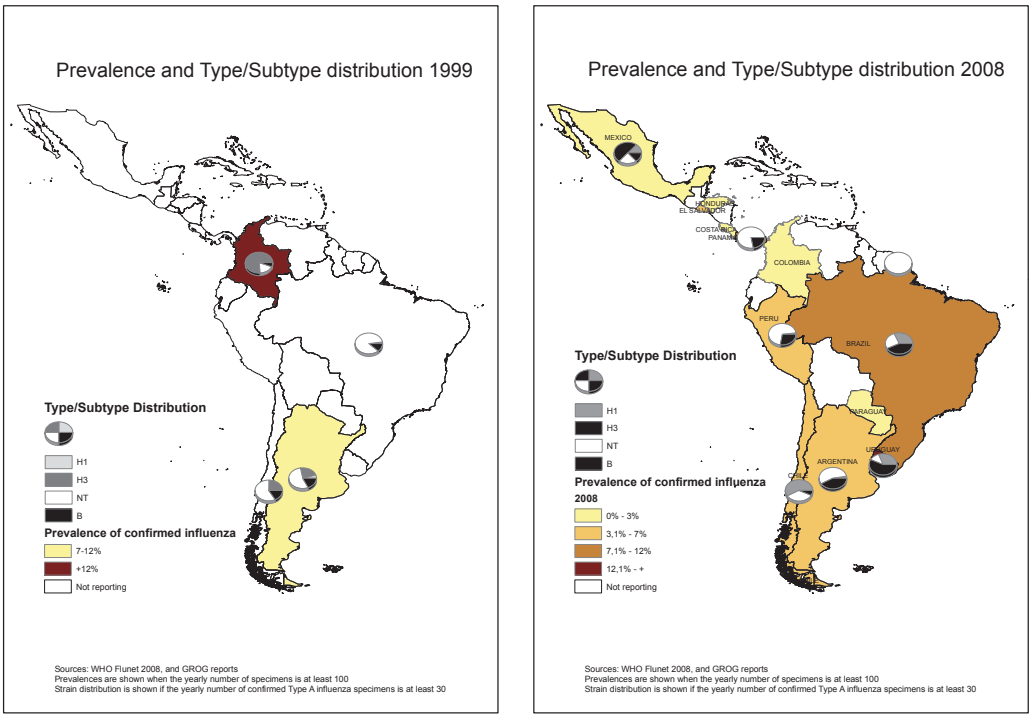

Figure 3. Percentage of influenza in samples by country and year: initial (1999) and final (2008) reports.

Table 8 Percentage of confirmed influenza in ILI and LRTI by age groups

	Age groups	Number of studies	*N*	Influenza Percentage % (95% CI)	Number of studies	*N*	Percentage Type A % (95% CI)	Percentage Type B % (95% CI)
Confirmed influenza in ILI	0–5 years	5	1513	24·53 (16·94–33·01)	5	390	94·29 (83·05–99·66)	5·71 (0·34–16·95)
	5–14 years	4	1193	29·98 (23·19–37·25)	4	382	83·36 (45·88–99·98)	16·64 (0·02–54·12)
	14–59 years	4	1891	19·21 (15·59–23·12)	4	352	84·01 (60·02–98·10)	15·99 (1·90–39·98)
	60 or more	3	149	18·55 (12·79–25·10)	3	27	83·89 (50·73–99·77)	16·11 (0·23–49·27)
	Any age*	7	12 584	16·32 (10·41–23·26)	7	1898	85·62 (73·84–94·30)	14·38 (5·70–26·16)
	NR	3	975	41·57 (5·09–85·05)	3	262	80·86 (65·07–92·72)	19·14 (7·28–34·93)
Confirmed influenza in LRTI	0–2 years	18	6716	4·48 (3·07–6·14)	7	223	83·53 (69·70–93·74)	16·46 (6·26–30·30)
	0–5 years	16	142 149	3·00 (2·20–3·91)	15	4078	87·12 (79·31–93·29)	12·88 (6·71–20·69)
	5 to 14/16 years	10	6856	11·35 (5·06–19·73)	9	796	76·16 (57·11–90·92)	23·84 (9·08–42·89)
	14/16 to ≥59 years	5	2303	19·38 (16·47–22·47)	5	435	79·20 (55·22–95·48)	20·80 (4·52–44·78)
	≥60 years	4	457	6·66 (4·57–9·11)	4	29	92·25 (80·87–98·76)	7·75 (1·24–19·13)
	All ages*	18	217 784	2·98 (2·91–3·06)	18	7111	79·22 (70·25–86·94)	20·78 (13·06–29·75)
	NR	3	1271	11·79 (2·04–28·01)	–	–	–	–

*Studies without a specific age range.
ILI, influenza-like illnesses.

centers over a 10, year period (1999–2008) showed a range of 4·7–5·4%. Of all influenza-positive specimens analyzed during the period of study, type A was more frequent than type B, accounting for 81·8% and 18·2% of influenza-positive samples, respectively. The percentages of laboratory-confirmed influenza appeared to fluctuate within the period studied, probably due to the severity of annual epidemics. Assessment of the percentage of influenza-positive

specimens per country demonstrated diverse rates between different countries. This could be due to the sampling of patients with different case definitions. Additionally, each country used different baseline and epidemic curves to determine the situation at a given moment, so comparison of the percentages of influenza clinical specimens between countries was not possible. When all studies were grouped, influenza type A predominated in all the years assessed. However, when analyzed by country and year, influenza B was the most prevalent type in Argentina, Brazil, and Uruguay in 2002, Colombia and Mexico in 2004, and Paraguay in 2001. With respect to the proportion of type A-positive samples accounted for by the different influenza subtypes, H3 influenza viruses were found to be more frequent, although a high proportion of viruses were not subtyped.

As a limitation, substantial heterogeneity was observed; however, the use of a random effect model provided conservative estimations (e.g., on the proportion of influenza cases meta-analyses).

When conducting seasonal influenza circulation studies using specimens collected at international reference centers, it was generally considered sufficient to analyze only a minimal proportion of isolates to determine the influenza strain in circulation. The circulation of H3 or H1 subtypes did not appear to show a definite trend when analyzed by season or by country. Some calendar years were characterized by the circulation of one unique subtype, while in others there was co-circulation of H3 and H1.

While sentinel surveillance is not adequate for capturing ILI incidence, it is still useful to learn about flu yearly seasonality patterns and to obtain information related with flu types and subtypes, genetic changes, and the emergence of antiviral resistance. Different surveillance systems coexist in the region and even in a country: virological surveillance, sentinel sites or units, population-based studies, outbreak investigations. In general, it is not possible to estimate what proportion of the ILI cases has been confirmed as influenza cases because the mentioned systems do not circumscribe a definite population, except for Chilean data where samples are provided by hospitals attending a restricted population. Important underreporting could have arisen from mild episodes that may have not sought medical attention, and also due to the passive nature of the surveillance in LAC countries.

Respiratory syncytial virus (RSV) is the most frequent viral agent causing severe acute LRTI, needing hospitalization in infant and young children worldwide.[97–99] The diagnosis of viral respiratory infections improved in the last years, and currently comprises 21 national influenza centers in the region, including detection of RSV, adenovirus, and para-influenza viruses. Weekly information on the circulation of respiratory viruses started to be organized by PAHO in 2009. Besides, epidemiological data on bronchiolitis notifications started to be analyzed at the Ministries of Health of several countries. In Argentina, bronchiolitis notifications started in 2004.

The emergence of the H1N1 2009 pandemic virus triggered a number of new investigations, some of them reflecting ILI incidence data in previously non-studied regions,[100] in an active population-based surveillance in 2008–2009 in the Amazon Basin, Peru, estimated an age-adjusted incidence of ILI of 46·7 episodes/1000 person-years and an age-adjusted incidence rate of 16·5 symptomatic influenza virus infections/1000 person, years.

Besides, different testing methods have been employed in the literature analyzed with marked differences in sensitivity and specificity for detection of influenza virus and co-circulating viruses of relevance as RSV. In general, virological influenza surveillance before H1N1 2009 pandemics has been performed by immunofluorescence as well as for etiological studies. Special facilities proportionate new etiological approaches as in the studies by Laguna Torres *et al.* in Peru[101–103] or Douce *et al.* in Ecuador.[104] Even though, most of them are biased by the selection of the population or the recruitment sites.

Laboratory-confirmed influenza hospitalizations and deaths underestimate influenza burden because influenza rarely appears on medical records, and death can occur after secondary bacterial infection or exacerbation of comorbidities several weeks after the primary viral infection has subsided. Charu *et al.*[105] estimate influenza-related mortality rates for interpandemic and pandemic seasons during 2000–2010, applying Serfling cyclical regression models to monthly death rates due to I&P, respiratory causes, cardiac causes, and all-cause mortality, with data obtained from the vital statistics at the Mexican Ministry of Health.[24] Results obtained estimate that the excess pandemic mortality was 0·6–2·6 times higher than the seasonal mean excess mortality.

Conclusion

We critically reviewed data collected over the last decade on the circulation of the influenza virus and of its types and subtypes in LA&C. Although we could not draw solid conclusions on incidence and use of resources due to heterogeneity between populations, sampling methods, and definitions used, this review could be informative for decision makers in adopting measures to control the disease.

Although there has been a considerable improvement in the influenza surveillance systems in the region, the ILI notification rate is still unsatisfactory. Limited conclusions can be drawn from trends identified in the circulation of different influenza types or subtypes, or their geographical distribution and spread. In LA&C, pneumonia and influenza are placed together between the first and eighth leading causes of death in men and women alike. The highest rates of pneumonia and influenza-related deaths are seen in the <5, year

and ≥60, year age groups. To improve our knowledge about incidence and resource use for influenza in LA&C, more data from population-based cohort studies are needed.

Acknowledgements

The authors express their gratitude to the librarian Daniel Comandé for his crucial contribution to this study; Geetha Subramanyam and Juliette Gray for medical writing, Camilo Moreno and Jessica Mattos for editorial assistance and coordination of this publication (all four employees or on behalf of GSK).

Conflict of interest

IECS authors and Vilma Savy declare no conflicts of interest. Eduardo Ortega-Barría and Rómulo E. Colindres are employees of GlaxoSmithKline Biologicals.

Funding

This work was supported by GlaxoSmithKline Biologicals and by the Institute for Clinical Effectiveness and Health Policy.

References

1 Morales A, Martinez MM, Tasset-Tisseau A, Rey E, Baron-Papillon F, Follet A. Costs and benefits of influenza vaccination and work productivity in a Colombian company from the employer's perspective. Value Health 2004; 7:433–441.

2 Coelho MC, Tsuchiya LRRV, Nogueira MB *et al.* Impact of respiratory infections by influenza viruses A and B in pediatrics patients from Federal University of Parana, Brazil. Braz J Infect Dis 2007; 11:220–223.

3 Neuzil KM, Zhu Y, Griffin MR *et al.* Burden of interpandemic influenza in children younger than 5 years: a 25, year prospective study. J Infect Dis 2002; 185:147–152.

4 Dayan GH, Nguyen VH, Debbag R, Gomez R, Wood SC. Cost-effectiveness of influenza vaccination in high-risk children in Argentina. Vaccine 2001; 19:4204–4213.

5 Glezen WP, Taber LH, Frank AL, Gruber WC, Piedra PA. Influenza virus infections in infants. Pediatr Infect Dis J 1997; 16:1065–1068.

6 Principi N, Esposito S, Gasparini R, Marchisio P, Crovari P. Burden of influenza in healthy children and their households. Arch Dis Child 2004; 89:1002–1007.

7 Poehling KA, Edwards KM, Weinberg GA *et al.* The underrecognized burden of influenza in young children. N Engl J Med 2006; 355:31–40.

8 Fiore AE, Shay DK, Haber P *et al.* Prevention and control of influenza. Recommendations of the advisory committee on immunization practices (ACIP), 2007. MMWR Recomm Rep 2007; 56:1–54.

9 Glezen WP, Decker M, Perrotta DM. Survey of underlying conditions of persons hospitalized with acute respiratory disease during influenza epidemics in Houston, 1978–1981. Am Rev Respir Dis 1987; 136:550–555.

10 Iwane MK, Edwards KM, Szilagyi PG *et al.* Population-based surveillance for hospitalizations associated with respiratory syncytial virus, influenza virus, and parainfluenza viruses among young children. Pediatrics 2004; 113:1758–1764.

11 Izurieta HS, Thompson WW, Kramarz P *et al.* Influenza and the rates of hospitalization for respiratory disease among infants and young children. N Engl J Med 2000; 342:232–239.

12 Ploin D, Gillet Y, Morfin F *et al.* Influenza burden in febrile infants and young children in a pediatric emergency department. Pediatr Infect Dis J 2007; 26:142–147.

13 Neuzil KM, Mellen BG, Wright PF, Mitchel EF Jr, Griffin MR. The effect of influenza on hospitalizations, outpatient visits, and courses of antibiotics in children. N Engl J Med 2000; 342:225–231.

14 American Academy of Pediatrics Committee on Infectious Diseases. Recommendations for influenza immunization of children. Pediatrics 2004; 113:1441–1447.

15 Ploin D, Liberas S, Thouvenot D *et al.* Influenza burden in children newborn to eleven months of age in a pediatric emergency department during the peak of an influenza epidemic. Pediatr Infect Dis J 2003; 22(10 Suppl):S218–S222.

16 Nicholson KG, McNally T, Silverman M, Simons P, Stockton JD, Zambon MC. Rates of hospitalisation for influenza, respiratory syncytial virus and human metapneumovirus among infants and young children. Vaccine 2006; 24:102–108.

17 Weigl JA, Puppe W, Schmitt HJ. The incidence of influenza-associated hospitalizations in children in Germany. Epidemiol Infect 2002; 129:525–533.

18 Rojo JC, Ruiz-Contreras J, Fernandez MB, Marin MA, Folgueira L. Influenza-related hospitalizations in children younger than three years of age. Pediatr Infect Dis J 2006; 25:596–601.

19 Chiu SS, Lau YL, Chan KH, Wong WH, Peiris JS. Influenza-related hospitalizations among children in Hong Kong. N Engl J Med 2002; 347:2097–2103.

20 Stamboulian D, Bonvehi PE, Nacinovich FM, Cox N. Influenza. Infect Dis Clin North Am 2000; 14:141–166.

21 WHO. Pandemic (H1N1) 2009 – update 62. 2009. Available at http://www.who.int/csr/don/2009_08_21/en/index.html (Accessed 21 August 2009).

22 DATASUS. Morbidade Hospitalar. 2007. [cited; Available at http://w3.datasus.gov.br/datasus/datasus.php?area=359A1B624C4D0E0F359G104H0I1Jd4L24M0N&VInclude=../site/infsaude1.php&lista=op1 (Accessed 21 August 2009).

23 DEIS. Dirección de Estadísticas e Información de Salud Argentina. Indicadores de natalidad y mortalidad. 2007. Available at http://www.deis.gov.ar (Accessed 31 August 2009).

24 MEXICO. SINAIS. Sistema Nacional de Información en Salud. Estadísticas por tema. Available at http://www.sinais.salud.gob.mx/acercade/index.html (Accessed 17 May 2011).

25 WHO. WHO mortality database: tables 2009. 2009. Available at http://wwwwhoint/healthinfo/morttables/en/ (Accessed 25 August 2009).

26 Stroup DF, Berlin JA, Morton SC *et al.* Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis of observational studies in epidemiology (MOOSE) group. JAMA 2000; 283:2008–2012.

27 Liberati A, Altman DG, Tetzlaff J *et al.* The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. PLoS Med 2009; 6:e1000100.

28 Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med 2009; 6:e1000097.

29 World Health Organization. World Health Organization FluNet. Available at http://www.who.int/influenza/gisrs_laboratory/flunet/en/ (Accessed 12 June 2008).

30 Brief summary of analyses of the 2007 survey on the capacity of National Influenza Centres. Wkly Epidemiol Rec 2008; 83:133–144.

31 von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP. The strengthening the reporting of observational studies in epidemiology (STROBE) statement: guidelines for reporting observational studies. Lancet 2007; 370:1453–1457.

32 Sanderson S, Tatt ID, Higgins JP. Tools for assessing quality and susceptibility to bias in observational studies in epidemiology: a systematic review and annotated bibliography. Int J Epidemiol 2007; 36:666–676.

33 Fowkes FG, Fulton PM. Critical appraisal of published research: introductory guidelines. BMJ 1991; 302:1136–1140.

34 Freeman MF, Tukey JW. Transformations related to the angular and the square root. Ann Math Stat 1950; 21:607–611.

35 DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials 1986; 7:177–188.

36 Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ 2003; 327:557–560.

37 Finkelman BS, Viboud C, Koelle K, Ferrari MJ, Bharti N, Grenfell BT. Global patterns in seasonal activity of influenza A/H3N2, A/H1N1, and B from 1997 to 2005: viral coexistence and latitudinal gradients. PLoS ONE 2007; 2:e1296.

38 Ayora-Talavera G, Gongora-Biachi RA, Lopez-Martinez I *et al.* Detection of human influenza virus in Yucatan, Mexico. Rev Invest Clin 2002; 54:410–414.

39 De Paiva TM, Ishida MA, Goncalves MG, Benega MA, De Souza MCO, Cruz AS. Occurrence of influenza B/Hong Kong-like strains in Brazil, during 2002. Rev Inst Med Trop Sao Paulo 2003; 45: 51–52.

40 Pontoriero AV, Baumeister EG, Campos AM, Savy VL, Lin YP, Hay A. Antigenic and genomic relation between human influenza viruses that circulated in Argentina in the period 1995–1999 and the corresponding vaccine components. J Clin Virol 2003; 28:130–140.

41 Imaz MS, Eimann M, Poyard E, Savy V. Exceso de mortalidad asociada a influenza en Argentina: 1992–2002. Rev chil infectol 2006; 23:297–306.

42 Kusznierz GF, Imaz MS, Zerbini EV, Savy V, Knez V, Sequeira MD. Effect of influenza epidemics on mortality in Santa Fe, Argentina, during 1992–1999. [Spanish]. Rev Panam Salud Publica 2002; 12:26–36.

43 Carballal G, Videla CM, Espinosa MA *et al.* Multicentered study of viral acute lower respiratory infections in children from four cities of Argentina, 1993–1994. J Med Virol 2001; 64:167–174.

44 PAHO. Health in the Americas, Volume II–Countries, 2007 edn. PAHO Publications Catalog, Northwest Washington, D.C., USA: Pan American Health Organization (PAHO), 2007.

45 Mesa Duque SS, Pérez Moreno A, Hurtado G, Arbeláez Montoya MP. [Effectiveness of an influenza vaccine in a working population in Colombia]. Rev Pan Salud Pública. 2001; 10:232–239. (Accessed 31 August 2009).

46 Mixeu MSAG, Vespa GNR, Forleo-neto E, Toniolo-Neto J, Alves PM. Impact of influenza vaccination on civilian aircrew illness and absenteeism. Aviat Space Environ Med 2002; 73:876–880.

47 Gordon A, Ortega O, Kuan G *et al.* Prevalence and seasonality of influenza-like illness in children, Nicaragua, 2005–2007. Emerg Infect Dis 2009; 15:408–414.

48 Cabello C, Manjarrez ME, Olvera R, Villalba J, Valle L, Paramo I. Frequency of viruses associated with acute respiratory infections in children younger than five years of age at a locality of Mexico City. Mem Inst Oswaldo Cruz 2006; 101:21–24.

49 De Freitas Souza LS, Goncalves Ramos EA, Carvalho FM *et al.* Viral respiratory infections in young children attending day care in urban Northeast Brazil. Pediatr Pulmonol 2003; 35: 184–191.

50 Ministrio de Salud de Argentina. COFESA. Vigilancia Epidemiologica de las enfermedades respiratorias. 2008. Available at http://www.msal.gov.ar/htm/site/pdf/confesa_2008/acta_confesa_%2009-07/anexos/anexo_VI_sistema_de_vigilancia_de_influenza.pdf (Accessed 31 August 2009).

51 Ministerio de Salud de Argentina. Dirección de Epidemiología. Vigilancia de la morbilidad -Infecciones Respiratorias Altas. 2007. [updated 15/09/2007]; Available at http://www.msal.gov.ar/htm/site/sala_situacion/PANELES/Panel_Tematico/Vigilancia_epidemiologica_IRA.pps (Accesed 29 January 2009).

52 SIH/SUS HISotNHS. Admissions for Influenza Related Causes. 2008. Brasil: SIH/SUS HISotNHS.

53 Paget W. Flu season in Europe starts off at very low levels. 2001. Available at http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=2047 (accessed 31 August 2009).

54 Oropesa Fernandez S, Rodriguez Peralta D, Goyenechea Hernandez A *et al.* [Fast detection and characterization of influenza A and B viruses in nasopharyngeal secretions by the immunoperoxidase method]. Rev Cubana Med Trop 1998; 50:36–41.

55 Talavera GA, Mezquita NE. Human metapneumovirus in children with influenza-like illness in Yucatan, Mexico. Am J Trop Med Hyg 2007; 76:182–183.

56 Tsuchiya LRRV, Costa LMD, Raboni SM *et al.* Viral respiratory infection in Curitiba, Southern Brazil. J Infect 2005; 51:401–407.

57 Jackson ST, Dowe G, Smikle MF. Influenza activity in Jamaica, 2003–2004: detection of the newly emerged influenza A/Fujian/411/2002(H3N2). West Indian Med J 2004; 53:258–259.

58 Bellei N, Carraro E, Perosa A, Granato C. Patterns of influenza infections among different risk groups in Brazil. Braz J Infect Dis 2007; 11:399–402.

59 Sotomayor V. Informe de Vigilancia de Influenza, Vol. 1. Gobierno de Chile: Departamento de Epidemiología D-M, editor, 2008.

60 Savy V, Baumeister E. Boletín GROG. San Isidro: Grupo Colaborativo de Vigilancia Epidemiológica de Gripe y Otras Virosis Respiratorias en Argentina, 1997; 1–17.

61 Savy V, Baumeister E. Boletín GROG. San Isidro: Grupo Colaborativo de Vigilancia Epidemiológica de Gripe y Otras Virosis Respiratorias en Argentina, 1998; 1–30.

62 Savy V, Baumeister E. Boletín GROG. San Isidro: Grupo Colaborativo de Vigilancia Epidemiológica de Gripe y Otras Virosis Respiratorias en Argentina, 1999; 1–39.

63 Savy V, Baumeister E, Uez O. Boletín GROG. San Isidro: Grupo Colaborativo de Vigilancia Epidemiológica de Gripe y Otras Virosis Respiratorias en Argentina, 2000; 1–42.

64 Savy V, Baumeister E, Uez O. Boletín GROG. San Isidro: Grupo Colaborativo de Vigilancia Epidemiológica de Gripe y Otras Virosis Respiratorias en Argentina, 2001; 1–40.

65 Savy V, Baumeister E, Uez O. Boletín GROG. San Isidro: Grupo Colaborativo de Vigilancia Epidemiológica de Gripe y Otras Virosis Respiratorias en Argentina, 2002; 1–40.

66 Savy V, Baumeister E, Uez O. Boletín GROG. San Isidro: Grupo Colaborativo de Vigilancia Epidemiológica de Gripe y Otras Virosis Respiratorias en Argentina, 2003; 1–44.

67 Savy V, Baumeister E, Uez O. Boletín GROG. San Isidro: Grupo Colaborativo de Vigilancia Epidemiológica de Gripe y Otras Virosis Respiratorias en Argentina, 2004; 1–30.

68 Savy V, Baumeister E, Uez O. Boletín GROG. San Isidro: Grupo Colaborativo de Vigilancia Epidemiológica de Gripe y Otras Virosis Respiratorias en Argentina, 2005.

69 Savy V, Baumeister E, Uez O. Boletín GROG. San Isidro: Grupo Colaborativo de Vigilancia Epidemiológica de Gripe y Otras Virosis Respiratorias en Argentina, 2006; 1–40.

70 Savy V, Baumeister E, Uez O. Boletín GROG. 1 computer file ed. San Isidro: Grupo Colaborativo de Vigilancia Epidemiológica de Gripe y Otras Virosis Respiratorias en Argentina, 2007.

71 Lopez E, Bologna R, Savy V *et al.* Disease burden and economic impact of influenza on hospitalizations of children under two years old in two pediatric hospital in Buenos Aires, Argentina. Unpublished material. With permission of the authors. Peliminary report presented at 12th ICID – June 15–18, 2006, Lisbon, Portugal 2008.

72 Diniz EMDA, Vieira RA, Ceccon MEJ, Ishida MA, Vaz FAC. Incidence of respiratory viruses in preterm infants submitted to mechanical ventilation. Rev Inst Med Trop Sao Paulo 2005; 47:37–44.

73 Perret Pérez C. Vigilancia de virus respiratorios: temporada 2004. Cuad med-soc (Santiago de Chile). Cuad Med Soc (Santiago de Chile) 2004; 44:139–143.

74 Rabagliati BR, Benítez GR, Fernández MA *et al.* Reconocimiento de influenza-A como etiología de síndrome febril e insuficiencia respiratoria en adultos hospitalizados durante brote en la comunidad. Rev Med Chile 2004; 132:317–324.

75 Straliotto SM, Siqueira MM, Muller RL, Fischer GB, Cunha MLT, Nestor SM. Viral etiology of acute respiratory infections among children in Porto Alegre, RS, Brazil. Rev Soc Bras Med Trop 2002; 35:283–291.

76 Thomazelli LM, Vieira S, Leal AL *et al.* Surveillance of eight respiratory viruses in clinical samples of pediatric patients in Southeast Brazil. [Portuguese, English]. J Pediatr 2007; 83:422–428.

77 Viegas M, Barrero PR, Maffey AF, Mistchenko AS. Respiratory viruses seasonality in children under five years of age in Buenos Aires, Argentina. A five-year analysis. J Infect 2004; 49:222–228.

78 Parra A, Pellegrino P, Viale DSIyMHdPDJPGBAA, eds. Infecciones respiratorias virales (IRV) en niños hospitalizados. 2005. XI Congreso Latinoamericano de Infectología Pediátrica; Veracruz, México.

79 Parra A, Viale D, Pellegrino P, Casimir L, Rocco C, Bologna R. Hospitalizing influenza in children in buenos aires: morbidity and mortality risk factors. 2004. Poster Presentation 42nd Annual Meeting of IDSA; Sep 30–Oct 3, 2004; Boston, USA 2-10.

80 Herrera D, de la Hoz F, Velandia M. Severe respiratory disease and its relationship with respiratory viruses in Colombia. Int J Infect Dis 2008; 12:139–142.

81 Cancio R, Savón C, Oropeza S *et al.* Diagnóstico rápido de los principales virus respiratorios en Ciudad de la Habana, 1995–97. Rev Argent Microbiol 2000; 32:21–26.

82 Rabagliati BR, Serri VM, Perret PC *et al.* Perfil clínico-epidemiológico de las infecciones por virus respiratorios en adultos hospitalizados durante la estación de influenza 2004. Rev chil infectol 2006; 23:111–117.

83 Avendano L. Annual adenovirus (ADV), respiratory syncytial virus (RSV), influenza (FLU) and parainfluenza (PIV) viral detection in infants and young children hospitalized for ALRI in a Children's Hospital. Santiago of Chile, January 1996 to December 2006. Unpublished material with permission of the author.

84 Delpiano ML, Guillen BB, Casado FMC. Comportamiento clínico-epidemiológico de la influenza en niños hospitalizados. Rev chil infectol 2003; 20:159–165.

85 Valinotto LE, Diez RA, Barrero PR, Farias JA, Lopez EL, Mistchenko AS. Emergence of intratreatment resistance to oseltamivir in pandemic influenza A H1N1 2009 virus. Antivir Ther [Case Reports Research Support, Non-U.S. Gov't] 2010; 15:923–927.

86 Cane A, Casanueva E, Iolster T *et al.* First isolation of a oseltamivir-resistant influenza A (H1N1) strain in Argentina. Pediatr Infect Dis J [Case Reports Letter] 2010; 29:384.

87 Cox NJ, Subbarao K. Influenza. Lancet 1999; 354:1277–1282.

88 Organization WH. Global Burden of Disease 2002 Estimates (Web page). Available at http://www.who.int/ healthinfo/bodgbd2002/en/index.html (Accessed 19 September 2006).

89 PAHO. Influenza vaccination among risk groups in costa rica: an evidence-based decision. EPI Newsl. 2004;26:32–34. Available at http://www.paho.org/english/ad/fch/im/sne2603.pdf (Accessed 15 September 2006).

90 Pan American Health Organization. Influenza control in El Salvador. Immunization Newsl 2006; 28:2. Available at http://www.paho.org/english/ad/fch/im/sne2802.pdf (Accessed 15 September 2006).

91 PAHO. Health in the Americas. Volume I–Regional. 2007 edn. Pan American Health Organization (PAHO) 2007.

92 Fry AM, Shay DK, Holman Rc Curns AT, Anderson LJ. Trends in hospitalizations for pneumonia among persons aged 65 years or older in the United States, 1988–2002. JAMA 2005; 294:2712–2719.

93 Neuzil KM, Reed GW, Mitchel EF Jr, Griffin MR. Influenza-associated morbidity and mortality in young and middle-aged women. JAMA 1999; 281:901–907.

94 Dushoff J, Plotkin JB, Viboud C, Earn DJD, Simonsen L. Mortality due to Influenza in the United States – an annualized regression approach using multiple-cause mortality data. Am J Epidemiol 2006; 163:181–187.

95 Thompson WW, Shay DK, Weintraub E *et al.* Mortality associated with influenza and respiratory syncytial virus in the United States. JAMA 2003; 289:179–186.

96 Fleming DM, Pannell RS, Cross KW. Mortality in children from influenza and respiratory syncytial virus. J Epidemiol Community Health 2005; 59:586–590.

97 Leader S, Kohlhase K. Recent trends in severe respiratory syncytial virus (RSV) among US infants, 1997 to 2000. J Pediatr 2003; 5(Suppl):S127–S132.

98 Tregoning JS, Schwarze J. Respiratory viral infections in infants: causes, clinical symptoms, virology, and immunology. Clin Microbiol Rev [Review] 2010; 23:74–98.

99 Djelantik AA, Kunst AE, van der Wal MF, Smit HA, Vrijkotte TG. Contribution of overweight and obesity to the occurrence of adverse pregnancy outcomes in a multi-ethnic cohort: population attributive fractions for Amsterdam. BJOG [Research Support, Non-U.S. Gov't] 2012; 119:283–290.

100 Forshey BM, Laguna-Torres VA, Vilcarromero S *et al.* Epidemiology of influenza-like illness in the Amazon Basin of Peru, 2008–2009. Influenza Other Respir Viruses [Research Support, U.S. Gov't, Non-P.H.S.] 2010; 4:235–243.

101 Laguna-Torres VA, Gomez J, Aguilar PV *et al.* Changes in the viral distribution pattern after the appearance of the novel influenza A H1N1 (pH1N1) virus in influenza-like illness patients in Peru. PLoS ONE [Research Support, Non-U.S. Gov't Research Support, U.S. Gov't, Non-P.H.S.] 2010; 5:e11719.

102 Laguna-Torres VA, Gomez J, Ocana V *et al.* Influenza-like illness sentinel surveillance in Peru. PLoS ONE [Research Support, U.S. Gov't, Non-P.H.S.] 2009; 4:e6118.

103 Laguna-Torres VA, Sanchez-Largaespada JF, Lorenzana I *et al.* Influenza and other respiratory viruses in three Central American countries. Influenza Other Respir Viruses 2011; 5:123–134.

104 Douce RW, Aleman W, Chicaiza-Ayala W *et al.* Sentinel surveillance of influenza-like-illness in two cities of the tropical country of Ecuador: 2006–2010. PLoS ONE [Research Support, U.S. Gov't, Non-P.H.S.] 2011; 6:e22206.

105 Charu V, Chowell G, Palacio Mejia LS *et al.* Mortality burden of the A/H1N1 pandemic in Mexico: a comparison of deaths and years of life lost to seasonal influenza. Clin Infect Dis [Research Support,

U.S. Gov't, Non-P.H.S. Research Support, U.S. Gov't, P.H.S.] 2011; 53:985–993.

106 Savy V, Baumeister E, Uez O. GROG REPORT Argentina. Grupo colaborativo de Vigilancia Epidemiologica de Gripe y otras virosis. Argentina. Available at http://www.grog-argentina.org/ (Accessed 27 November 2012).

107 Savy V, Baumeister E, Uez O. Boletín GROG. 1 computer file ed. San Isidro: Grupo Colaborativo de Vigilancia Epidemiológica de Gripe y Otras Virosis Respiratorias en Argentina, 2008.

108 Canas LC, Lohman K, Pavlin JA *et al.* The department of defense laboratory-based global influenza surveillance system. Mil Med 2000; 7(Suppl 2):52–56.

109 Parra A. Influenza in hospitalized children. Mortality Risk Factors. SLIPE Congress. 2005.

110 Costa L, Yokosawa J, Mantese O *et al.* Respiratory viruses in children younger than five years old with acute respiratory disease from 2001 to 2004 in Uberlândia, MG, Brazil. Mem Inst Oswaldo Cruz 2006; 101:301–306.

111 Mixeu M, Vespa G, Forleo-Neto E, J T-N. Impact of influenza vaccination on civilian aircrew illness and absenteeism. Aviat Space Environ Med 2002; 73:876–880.

112 Sotomayor V. Informe de Vigilancia de Influenza, Vol. 1. Gobierno de Chile: Departamento de Epidemiología D-M, editor, 2008.

113 Duque SSM, Moreno AP, Hurtado G, Montoya MPA. Effectiveness of an influenza vaccine in a working population in Colombia. [Spanish]. Rev Panam Salud Publica 2001; 10:232–239.

Supporting Information

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

Appendix S1. Search strategy in electronic databases.

Appendix S2. Tool for assessing susceptibility to bias in observational studies.

Appendix S3. Country-wise reports on national health situations on influenza and ARI.

Appendix S4. Prevalence of influenza by country and year.

Appendix S5. Yearly ILI activity report 1999–2008 by country in LA&C[#] (FLUNET reports).

Map S1. Prevalence and Type/Subtype distribution 1999.

Map S2. Prevalence and Type/Subtype distribution 2000.

Map S3. Prevalence and Type/Subtype distribution 2001.

Map S4. Prevalence and Type/Subtype distribution 2002.

Map S5. Prevalence and Type/Subtype distribution 2003.

Map S6. Prevalence and Type/Subtype distribution 2004.

Map S7. Prevalence and Type/Subtype distribution 2005.

Map S8. Prevalence and Type/Subtype distribution 2006.

Map S9. Prevalence and Type/Subtype distribution 2007.

Map S10. Prevalence and Type/Subtype distribution 2008.