



Review

Influenza in Latin America: A report from the Global Influenza Initiative (GII)



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ABSTRACT

The Global Influenza Initiative (GII) is a global expert group that aims to raise acceptance and uptake of influenza vaccines globally and provides recommendations and strategies to address challenges at local, national, regional, and global levels. This article provides a consolidated estimation of disease burden in Latin America, currently lacking in published literature, and delivers the GII recommendations specific to Latin America that provide guidance to combat existing vaccination challenges.

While many countries worldwide, especially in the tropics and subtropics, do not have a seasonal influenza policy, 90% of Latin American countries have a seasonal influenza policy in place. Local governments in the Latin American countries and The Pan American Health Organization's Technical Advisory Group on Vaccine-preventable Diseases play a major role in improving the vaccination coverage and reducing the overall disease burden. Influenza seasonality poses the biggest challenge in deciding on optimal timing for vaccination in Latin America, as in temperate climates seasonal influenza activity peaks during the winter months (November–February and May–October) in the northern and southern hemispheres, respectively, while in the tropics and subtropical regions it usually occurs throughout the year, but especially during the rainy season. Besides this, vaccine mismatch with circulating strains, misconception concerning influenza vaccine effectiveness, and poor disease and vaccine awareness among the public are also key challenges that need to be overcome. Standardization of clinical case definitions is important across all Latin American countries. Surveillance (mostly passive) has improved substantially in the Latin American countries over the past decade, but more is still required to better understand the disease burden and help inform policies.

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Abbreviations: EW, epidemiology week; GII, Global Influenza Initiative; GISRS, Global Influenza Surveillance and Response System; HCW, healthcare worker; ILI, influenza-like illness; PAHO, Pan American Health Organization; QIV, quadrivalent influenza vaccine; SARI, severe acute respiratory illness; TAG, Technical Advisory Group on Vaccine-preventable Diseases; TIV, trivalent inactivated influenza vaccine; WHO, World Health Organization.

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1. Introduction

Influenza is an important vaccine-preventable human respiratory disease, predominantly caused by influenza types A and B, and transmitted through droplets or aerosols originating from the respiratory secretions of infected individuals and also by contracting the virus-infected fomites [1,2]. Influenza type C is less predominant and generally causes mild illness [3]. The classification (type A, B, and C) of influenza viruses is based on their nucleoprotein [1]. The high mutation rates of influenza viruses often leads to seasonal influenza outbreaks during inter-pandemic years [1]. Two distinct influenza B virus lineages (Victoria and Yamagata) have been reported in many countries [1]. Globally, the annual attack rate of influenza is estimated at 5–10% in adults, while in children it is 20–30% [1]. Both influenza A and B types can cause seasonal epidemics, with illnesses ranging from mild to severe to fatal [4]. In temperate climates, influenza mostly occurs during winter months; in tropical climates, it can occur throughout the year [5]. However, the effects of influenza epidemics in developing countries—including those of Latin America—are not well documented, but estimates show that 99% of influenza-related deaths in children <5 years old are found in developing countries [6]. Reports suggest that mortality from influenza in most of Latin America decreased gradually between 1998 and 2008 but increased in 2009, which was possibly due to the H1N1 2009 pandemic [7].

In a recent World Health Organization (WHO) survey, Latin American countries have been shown to make fast decisions to adopt and implement influenza vaccination recommendations [8]. In 2004, there were only 13 countries in the Americas that had a seasonal influenza vaccination policy; this number increased to 35 countries by the end of 2008. Recent data suggest that a high percentage of countries in Latin America and the Caribbean have a seasonal vaccination policy in place, which compares with other countries in the tropics and subtropics, [8,9]. The respective Latin American governments' roles in financing routine immunization programs and maintaining constantly high technical performance led them to achieve ownership of such programs and ultimately to enact new vaccine laws [10]. Reports suggest that countries with vaccine laws spend more on purchasing vaccines than those that do not [10]. The Technical Advisory Group on Vaccine-preventable Diseases (TAG) of the Pan American Health Organization (PAHO) has a larger role in the expansion of influenza vaccination programs in the Americas. For example, in 2004, the TAG expanded its recommendations for Latin America to include yearly seasonal vaccination for those ≥ 60 years old, chronically ill patients, healthcare workers (HCWs), and pregnant women, and further expanded them in 2006 to include children 6–23 months old [9]. For the countries, considering initiation or expansion of the seasonal influenza vaccination programs, WHO has recommended prioritizing pregnant women over other risk groups. Other recommended groups, in no order of priority, are children (6–59 months old), the elderly (≥ 65 years old), individuals with chronic medical conditions, and HCWs [1]. For interna-

tional travelers belonging to any of these risk groups, seasonal influenza vaccination has been recommended to be part of their routine immunization schedule [1]. Other factors influencing vaccine legislation in Latin American countries include a fear of an impending influenza pandemic, an increased use of influenza vaccine in the private sector (by public demand), and the actions taken by neighboring countries [9]. Moreover, PAHO's ProVac Initiative has provided a platform for countries with the goal of strengthening national technical capacity to make evidence-based decisions on new vaccine introduction, focusing on economic evaluations [9]. However, a strong need for standardization of influenza data collection and evaluation methods for both direct and indirect cost components in low- and middle-income countries (LMICs) has been documented [11]. Despite increased number of countries with influenza policies in most Latin American countries, there are several challenges in influenza immunization in these countries, especially tropical and sub-tropical countries. These include influenza seasonality, vaccine mismatch, lack of vaccine surveillance and cost-effectiveness data, lack of vaccine awareness, and others that have been discussed in detail later in this article.

This article summarizes the epidemiology, surveillance, vaccination policy and programs, and obstacles to vaccination in Latin American countries, with the aim of better understanding and then informing people of the current influenza situation in this region. This article therefore fills the general gap in publicly available and collated information of the Latin American region.

2. Epidemiology and surveillance of influenza in the Latin America region

2.1. Burden of disease in Latin America

In a recent (2018) study, the total number of seasonal influenza-associated respiratory deaths globally was estimated as 291,243–645,832 (4.0–8.8 per 100,000 individuals) with the highest mortality rate among the elderly (≥ 75 years old) (51.3–99.4 per 100,000 individuals) [12]. In Latin America, a lack of good-quality accessible data makes estimating the burden of influenza difficult. Influenza-related mortality and morbidity information is also scarce and may be due to underreporting [13]. A recent (2017) study compared the influenza surveillance systems and assessed the prevalence of influenza A and B viruses in 10 Latin American countries (Argentina, Brazil, Chile, Costa Rica, Ecuador, El Salvador, Guatemala, Honduras, Nicaragua, and Panama); among 37,087 influenza cases reported from 2004 to 2012, they found that influenza A and B accounted for 86.6% and 13.4% of cases, respectively [14]. Of these, Chile contributed the most cases (28.2%) [14]. In a recent modeling study, the annual mean influenza-associated mortality rate, calculated using both respiratory and circulatory mortality data in 35 PAHO countries (including Latin American countries), was estimated as 2.1, 31.9, and 161.8 per 100,000 among those aged <65, 65–74, and ≥ 75 years, respectively [15]. It was also estimated that 40,880–160,270 individuals die of influenza annually in the PAHO

region [15]. Another modelling study estimated overall 17,500 respiratory deaths in all age groups associated with the 2009 pandemic influenza A H1N1 during the first 12 months of the virus circulation in the WHO Americas region [16]. Influenza-associated events may not be causally associated; therefore, the vaccine-preventable disease is a challenge to estimate and may be different.

Table 1
Influenza (and ILI) incidences and mortality in Latin America [18,21–25].

Countries	Climate	Overall incidence	Overall hCFR
Argentina	Subtropical and temperate	ILI: 2462.9 of 100,000 (2017) SARI: 137.8 of 100,000 (2017)	176.62 of 100,000 (deaths by influenza among SARI cases)
Brazil	Tropical, subtropical, and temperate	N/A	2213.43 of 100,000 (hCFR; hospitalized deaths by influenza among SARI cases) (2017)
Chile	Temperate	8800 of 100,000 (2012–2014)	832.3 of 100,000 (deaths by influenza among SARI cases, 2012–14)
Paraguay	Tropical and subtropical	9876 of 100,000 (2017)	482.27 of 100,000 (hCFR; deaths by influenza among SARI cases, 2017, only in sentinel centers)

hCFR, hospitalized case fatality rate; ILI, influenza-like illness; N/A, data not available; SARI, severe acute respiratory illness.

Note: On Table 1 Countries reported in-hospital case fatality ratio (hCFR), the proportion of SARI hospitalized cases that are fatal (hCFR = deaths/SARICases X100).

A recent study suggests that, in the WHO Americas region, the estimated total number of annual seasonal influenza-associated respiratory deaths was 41,007–71,710 [12]. A study in selected Central American countries (using influenza surveillance virology data from 2009 to 2012) revealed highest influenza-associated mortality among children 0–4 years old in Guatemala (2.26 per 100,000 persons in 2012), and among adults >65 years old in Costa Rica (11.39 per 100,000 persons in 2012) [17]. In Argentina, 1,096,074 cases of influenza-like illness (ILI) were reported until epidemiology week (EW) 52 of 2017; the peak was observed during EW24 and EW25, after which the number of cases decreased markedly until recently [18,19]. In Mexico, the rates of laboratory-confirmed influenza A/H1N1 hospitalizations and deaths were shown to be significantly higher ($p < 0.001$) among those aged 30–59 years old during the 2013–2014 winter influenza season compared with the previous A/H1N1 season in 2011–2012 [20]. Available influenza incidence and mortality data in Latin American countries are presented in Table 1.

In a recent study assessing the prevalence of influenza A and B viruses in 10 Latin American countries, a total of 37,087 laboratory-confirmed influenza cases were identified from the available data for 2003–2014 where influenza A(H1N1), A(H1N1) pdm2009, and A(H3N2) were detected in 2.4%, 48.3%, and 20.8% of cases, respectively [14]. Influenza B Victoria and Yamagata were found in 0.9% and 1.2% cases, respectively, while in 11.3% cases, the influenza B strain was not characterized [14]. Fig. 1 depicts the circulation of influenza virus by types and subtypes in the PAHO regions between 2012 and 2017.

Influenza B has increased in the United States and Europe in recent years [26]. Data suggest that among pediatric influenza-related deaths in the United States between 2004 and 2011 (excluding the 2009–2010 pandemic), 22–44% of deaths were due to influenza B [26]. Circulation of the B strain in Latin America varies according to season and country, and even among regions within the same country [27].

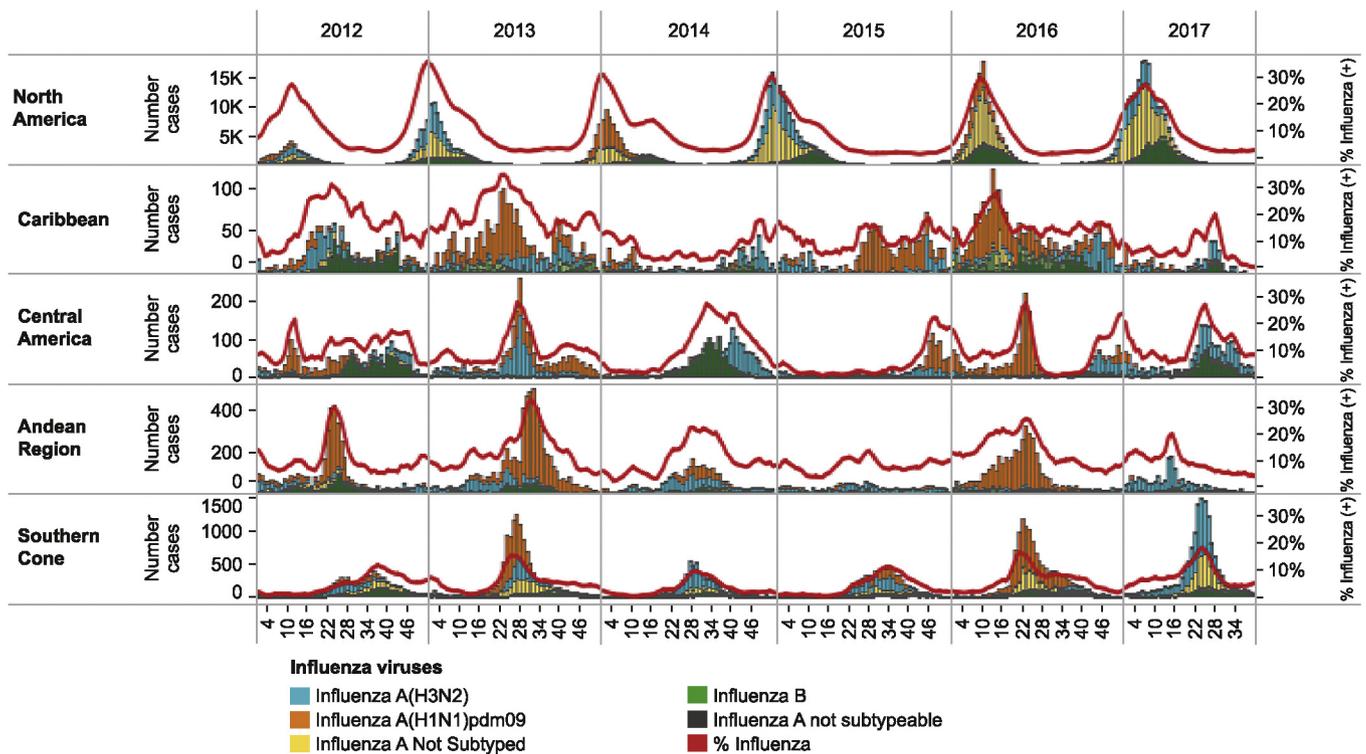


Fig. 1. Influenza circulation by region, PAHO, 2012–2017 [65].

2.2. Influenza seasonality

In temperate climates, seasonal influenza activity peaks occur during the winter months (November–February and May–October in the northern and southern hemispheres, respectively), while the seasonality pattern in the tropical and subtropical regions is more complex and usually occurs throughout the year, but especially during the rainy season [5,28]. Influenza seasonality patterns in the tropics and subtropics could be a critical challenge to vaccine delivery [5]. In Latin America, Argentina, Brazil, and Chile (south and southeast) showed a primary peak during June–September, while Costa Rica, Ecuador, El Salvador [29], Guatemala, Honduras, Nicaragua, and Panama showed varied timings in peaks (Table 2) [5,14].

2.3. Influenza surveillance in Latin America

After the 2009 influenza A(H1N1) pandemic, surveillance in many Latin American countries has improved, although more is needed to inform policy [14]. In a hospital-based sentinel surveillance system in Colombia, between January 2007 and December 2012, 2039 patients with respiratory illness were enrolled; of 1040 laboratory-diagnosed samples, 737 tested positive for ≥ 1 respiratory viruses [31]. Of those, 57.8% had influenza A or B [31]. A prospective surveillance study in Ecuador between 2006 and 2010 revealed that out of 1702 ILI cases, 597 patients were detected with nine viral agents [32]. Influenza was shown to be a common cause of ILI in Ecuador, leading to more than one outbreak per year [32]. In another study, conducted on 1756 patients in El Salvador, Honduras, and Nicaragua between August 2006 and April 2009, influenza A virus was detected in 7.4% and influenza B virus in 2.7% of cases [33]. A hospital-based surveillance study in São Paulo, Brazil, was conducted in different patient groups between 2001 and 2013. Of 2992 respiratory samples collected, 3.8% were positive for influenza B and it was more frequently detected in teenagers [34].

Between June 2006 and May 2008, 6835 patients with respiratory illnesses were enrolled in an ILI sentinel surveillance system in Peru; of 2688 positive samples, 25.1% and 9.7% were positive

for influenza A and B, respectively [35]. An additional study found that South and North America reported influenza-positive respiratory samples (2.8 and 9.0/10,000 persons/year, respectively) to the Global Influenza Surveillance and Response System (GISRS) during 2002–2013, while Central America reported influenza-positive samples of 2.4/10,000 persons/year to GISRS during 2006–2013 [36]. Table 3 presents the surveillance systems in place in selected Latin American countries. We note that these countries have either national or sentinel surveillance systems for either severe acute respiratory illness (SARI), ILI, or influenza, and report to the global influenza monitoring authorities [37]. These countries also usually follow the WHO-defined clinical definitions for the respective respiratory illnesses and have a specific influenza pandemic preparedness plan ready [37].

In addition to national surveillance, some major global initiatives monitor influenza activities and work toward its prevention. The Global Influenza B Study, launched in 2012, focuses on influenza B incidence in 30 countries worldwide [14]. FluNet, launched in 1997, is a global Web-based platform for influenza virologic surveillance, and receives data from 143 national influenza centers in 113 countries and other national influenza reference laboratories that collaborate with the GISRS [5,41]. The WHO-funded GLAMOR project is an international collaborative initiative designed to make conservative estimates of influenza mortality (based on respiratory mortality) for different WHO regions, and age groups [42]. Other than these, FluID is a global data-sharing platform that maintains regional influenza epidemiologic data in a single database and facilitates tracking of global trends, transmission, intensity, and impact of influenza globally [43].

3. Influenza vaccines and vaccination policies in Latin America

Trivalent inactivated influenza vaccines (TIVs) containing two influenza A strains and one influenza B strain are mostly used as a seasonal influenza vaccine; however, a quadrivalent live-attenuated influenza vaccine was licensed in the United States in 2012 [1]. The antigenic composition of the vaccines is revised twice yearly with the aim of providing optimal efficacy against the prevailing strains circulating in both northern and southern

Table 2

Timing and amplitude of primary and secondary seasonal influenza peaks in Latin American countries, 2003–2014 [14].

Regions/countries	Availability of data ^a	Climate	Primary peak		Secondary peak		Predominant influenza virus strain ^a
			Timing (month)	Amplitude (%)	Timing (month)	Amplitude (%)	
Argentina	2016–2017 [18] 2003–2012	Temperate	June–July August	N/A 102.9	N/A —	N/A 0.0	A(H3N2), influenza B (Victoria)
Brazil North	2007–2012	Tropical	April	63.5	August	20.0	Influenza A (not subtyped)
Brazil Northeast	2004–2012	Tropical	April	61.3	September	7.6	Influenza A (not subtyped) and influenza B (not characterized)
Brazil Midwest	2006–2012	Tropical	October	73.8	July	53.7	Influenza A (not subtyped) and influenza B (not characterized)
Brazil South	2004–2012	Temperate	July	95.7	November	17.2	Influenza A (not subtyped) and influenza B (not characterized)
Brazil Southeast	2004–2012	Temperate	June	80.5	November	27.3	Influenza A (not subtyped)
Chile	2013–2017 [30]	Temperate	July	104.5	—	0.0	A(H3N2), influenza B (Yamagata)
Costa Rica	2009–2012	Tropical	November	88.6	July	53.0	A(H3N2)
Ecuador	2011–2014	Tropical	August	86.2	January	75.1	A(H3N2)
El Salvador	2007–2012	Tropical	July	99.4	February	8.5	Influenza A (not subtyped) and influenza B (not characterized)
Guatemala	2007–2012	Tropical	March	91.7	July	82.9	A(H3N2), influenza A (not subtyped) and influenza B (not characterized)
Honduras	2009–2012	Tropical	August	96.8	April	54.7	A(H3N2), influenza A (not subtyped)
Nicaragua	2008–2012	Tropical	November	110.1	June	72.8	A(H3N2), influenza B (not characterized)
Panama	2008–2013	Tropical	July	107.8	November	21.5	Influenza A (not subtyped) and influenza B (not characterized)

N/A, not available.

^a A(H1N1)pdm2009 data were not included.

Table 3
Influenza surveillance in selected Latin American countries [37–40].

Countries	Surveillance strategy	Reports to (FluID/ FluNet)	WHO case definition used	Year surveillance introduced	Influenza pandemic preparedness plan available	Number of health facilities/hospitals involved
Argentina	Sentinel (SARI, ILI)	FluNet: ✓ FluID: In progress	Yes	1997	Yes	3 SARI hospitals 3 ILI centers 3 national influenza centers
Brazil	National (SARI, deaths) Sentinel (SARI, ILI)	FluNet: ✓ FluID: ✓	Yes	2000	Yes	National: all hospitals Sentinel: 115 SARI hospitals; 145 ILI sites
Chile	National (SARI, ILI, respiratory viruses)	FluNet: ✓ FluID: ✓	Yes	1968	Yes	6 SARI hospitals 42 ILI primary centers 31 hospitals (respiratory virus surveillance)
Paraguay	Sentinel (SARI, ILI)	FluNet: ✓ FluID: ✓	No	1997 (virologic), 2004 (epidemiologic)	Yes	10 SARI hospitals 5 ILI centers
Peru	Sentinel (SARI, ILI)	FluNet: ✓ FluID: In progress	Yes	2006	Yes	7 SARI hospitals 21 sentinel ILI sites

ILI, influenza-like illness; N/A, not available; SARI, severe acute respiratory illness; WHO, World Health Organization.

hemispheres [1]. TIVs are licensed for use in children <2 years old, but not for infants <6 months old, individuals ≥ 50 years old, or pregnant women [1]. In one study, MF59-adjuvanted TIV was shown to confer protection against mismatched and frequently co-circulating influenza B strains [44]. Quadrivalent influenza vaccines (QIVs), including both influenza B lineages, provide a broader protection compared to TIVs when there is a mismatch of B strain [45]. It has been reported that in 2013, QIVs would have reduced influenza B cases in Brazil and Colombia by 22% and 13%, respectively [45]. However, QIVs are costlier than TIVs and may not be a cost-effective option for many LMICs [46].

Influenza vaccine effectiveness depends mostly on the age and immunocompetence of the vaccine recipient, as well as the degree of match between virus strains in the vaccine and those prevailing in the circulation [47]. It has been reported that for a close match between the vaccine and the circulating influenza strains, TIV efficacy for healthy individuals aged <65 years can vary based on study design, outcome(s) measured, population studied and the season in which the flu vaccine was studied [47]. The WHO recommends that countries willing to initiate or expand seasonal influenza vaccination programs should consider pregnant women as the highest priority, followed (with no specific order of priority) by children aged 6–59 months, the elderly, individuals with specific chronic medical conditions, and HCWs. Countries that have an influenza immunization program in place should also include pregnant women in their programs [1]. The majority (90%) of Latin America countries have seasonal influenza vaccination policies in place [8]. In 2013, 67% of Latin American countries had influenza vaccination recommendations for children, 89% for the elderly, 87% for HCWs, and 56% for pregnant women [48]. To increase the influenza pandemic preparedness and improve vaccine supply, both Brazil and Argentina have partnered with international vaccine manufacturers for technology transfer to build dedicated influenza vaccine production plants in their respective countries [49,50]. Information on the use of seasonal influenza vaccines in Latin American countries is summarized in Table 4.

The age group recommendations for influenza vaccination vary in most countries. Globally, around 50% of countries target children aged 6 months to 2 years for influenza vaccination, while one third of all countries include children aged 2–5 years in their immunization programs as a priority group [8]. Most Latin American countries recommend vaccination for children aged 6–23 months [48]. A recent study suggests that pregnant women in LMICs were at a 66% increased risk of influenza-associated severe outcomes than other patients with influenza [55]. However, 48% of Latin American countries have recommendations for seasonal influenza vaccina-

tion for pregnant women, and most have included them as a priority group for immunization after the 2009 pandemic [8]. Importantly, influenza vaccination coverage among pregnant women in Latin America is currently increasing [56].

Influenza remains a major contributor to mortality in the elderly [1]. A survey in 2009 found that 32 of 35 Latin American and Caribbean countries immunized HCWs with an influenza vaccine through local public systems [8]. However, there are challenges to vaccination, which often involve concerns over vaccine effectiveness and safety, medical contraindications, and religious beliefs; efforts to overcome such challenges are required to improve vaccination coverage. Although influenza vaccination coverage has improved substantially in Latin American countries, very few reports on vaccine effectiveness from the regions are available, making it difficult to sustain or expand vaccination programs to specific target groups. Thus, a systematic and annual evaluation on vaccine performance is required [57]. TAG emphasizes Latin American countries, especially tropical countries, continue generating evidence on disease burden, seasonality, and vaccine effectiveness. It also recommends large countries undertake subregional seasonality analysis stratified by microclimates to inform vaccine use as required. It recommends intensive vaccination coverage prior to the primary peak through a single campaign. The influenza vaccine should then be available to those unvaccinated through routine health programs, while the influenza season lasts [57].

4. Challenges

One of the key challenges in Latin American countries (especially Brazil, which has a large latitudinal spread) is the two peaks of seasonal influenza activity, and deciding when to vaccinate for optimal protection [8]. In northern Brazil, the peak occurs in March–April, while it occurs in May–June in the south [8]. The Southern Hemisphere vaccine becomes available in April, so by the time it is implemented it is often too late to have an optimal protective effect as the influenza activity in northern Brazil is almost at an end [8]. These seasonal timing discrepancies may lead to misconceptions about vaccine effectiveness.

In most Latin American countries, mismatch between influenza vaccine virus and the circulating virus was often observed [8]. New seasonal influenza vaccines with a good match to the circulating virus types/strains are thus required. Despite having influenza immunization policies in place in most Latin American countries, surveillance data stratified by vaccine target groups are still lacking

Table 4
Seasonal influenza vaccines used in selected Latin American countries [45,51–53].

Country	Year of vaccine introduction	Vaccines available (public market)	Target groups for vaccination	Vaccine formulation used
Argentina	1993	TIV	<ul style="list-style-type: none"> • Children (6–23 months) • The elderly (≥ 65 years) • Pregnant women • Post-partum until discharge from maternity (maximum 10 days) who have not received the vaccine during pregnancy. • HCWs • Persons 2–64 years with chronic conditions (respiratory disease, heart disease, congenital or acquired immunodeficiencies [non-oncohematologic], oncohematologic, and transplant patients, as well as others groups such as obese with a BMI > 40, diabetics, patients with chronic renal failure on dialysis or with expectations of dialysis in the next 6 months, severe maturational delay in children under 18 years, genetic syndromes, neuromuscular diseases with respiratory compromise and severe congenital malformations, co-survivors of oncohematologic patients, premature survivors under 1500 g • Security and essential services personnel 	SH
Brazil	1999	TIV	<ul style="list-style-type: none"> • Children (6–59 months) • The elderly (≥ 60 years) • Pregnant or post-partum (up to 45 days) women • HCWs • Persons in prison including adolescents and young adults (12–21 years) in special prison • Prison workers • Teachers in public and private schools • Persons with chronic diseases 	SH
Chile	1975	TIV	<ul style="list-style-type: none"> • Indigenous population • Children (6–71 months) [54] • The elderly (≥ 65 years) • Pregnant women • HCWs • Persons with chronic conditions • Poultry workers • Pig farm workers 	SH
Colombia	2005	TIV	<ul style="list-style-type: none"> • Children (6–23 months) • The elderly (≥ 60 years) • Pregnant women • HCWs • Persons with chronic diseases 	NH until 2006, changed to SH in 2007
Panama	2005	TIV	<ul style="list-style-type: none"> • Children (6–59 months) • The elderly (≥ 60 years) • Pregnant women • HCWs • Persons with chronic diseases • Poultry workers 	SH
Paraguay	2005	TIV	<ul style="list-style-type: none"> • Children (6–35 months) • The elderly (≥ 60 years) • Pregnant women • HCWs • Persons with chronic diseases • Poultry workers 	SH

BMI, body mass index; HCW, healthcare worker; NH, Northern Hemisphere; SH, Southern Hemisphere; TIV, trivalent inactivated influenza vaccine.

[58]. Surveillance systems need to be strengthened to allow a better understanding of the epidemiology and seasonality of influenza, and to inform decisions on when and whom to vaccinate [8]. Estimation of vaccination coverage among different target groups is complicated by the lack of standard definitions of groups. For instance, some countries define HCWs as only those who provide direct patient care, while others include all health professionals [56]. Other obstacles to vaccine uptake include a lack of knowledge on vaccinations, a lack of awareness of immunization recommendations, and a perception among patients and physicians that influenza is not an important disease. Lack of adequate vaccine cost-effectiveness data are also considered a challenge in informing policy. Introduction of new vaccines with higher dose volumes requires increased cold chain capacity. Thus, consideration of the capacity of immunization systems, delivery mechanisms, product presentation, and packaging parameters at an early stage will be beneficial and save additional costs of reformulation later [59]. The gap in vaccine availability in temperate countries with prolonged or atypical influenza seasons due to fixed expiration dates is also an important issue [59]. Lack of access to vaccines for logis-

tical/travel reasons for older and disabled adults and a fear of injections are some of the other barriers to vaccination in Latin America.

5. The Global Influenza Initiative (GII)

The GII was initiated in 2012 with the aim of raising acceptance and uptake of influenza vaccines globally and to gather the most recent data to ensure that the epidemiology of influenza is well understood. The GII continues to work on its mission:

- To prevent seasonal influenza worldwide through the promotion of vaccine recommendations, vaccine deployment, increased vaccine uptake, education, and international cooperation, as informed by virologic, epidemiologic, public health, and health-economic data
- To encourage and develop strategies for improving seasonal vaccines, increasing the duration of effect, improving efficacy, understanding reasons for failure, improving delivery, and countering vaccine hesitancy [60].

Table 5
GII recommendations for Latin American countries.

Background	Recommendation
1. In Latin America, countries with a temperate climate showed a primary influenza activity peak in June–September, while countries with a tropical climate showed smaller primary peaks at different times of the year with often detectable secondary peaks [14]. Most Latin American countries use the SH formulation, except Ecuador and the Bolivarian Republic of Venezuela, which use the NH vaccine formulation [8]	Latin American countries with tropical climates should decide on the optimum time to vaccinate, depending on the primary peaks usually observed in that country. More surveillance data in these countries are needed to optimize the time to vaccinate
2. Most Latin American countries now have an influenza vaccination policy in place. Surveillance in this region is mostly passive and hospital- or laboratory-based, and can be further improved in some specific risk groups. As per WHO global influenza surveillance standards, an effective surveillance system should include collection, reporting, and consolidation of data; data analysis and interpretation; updating decision makers with the interpreted data; providing feedback to those who have provided the data; detection and analysis of any unusual patterns; and maintaining adequate quality [61]	The GII recommends more research on surveillance methods
3. In Latin America, availability of good-quality accessible data on influenza mortality and morbidity is scarce, which makes estimating the burden of influenza difficult [13]	The GII recommends standardization of reporting systems and case definitions used across Latin America to compare data from different countries. This would help better understand the situation and to make informed decisions
4. Interestingly, it has been documented that influenza virus strains identified during an epidemic in South America generally become predominant during subsequent epidemics in Central and North America, and vice versa. Sharing timely data between countries would have helped design an influenza vaccine that could reduce the chances of virus mismatch [36]	The GII recommends that Latin American countries should share timely influenza virologic and epidemiologic data with one another, and to report this information to the WHO Collaborating Centers
5. Lack of knowledge on vaccination, awareness of recommendations, and a trend among both patients and physicians of not considering influenza as an important disease are obstacles to vaccine uptake	The GII recommends more vaccine advocacy among physicians, HCWs, patients, and healthy individuals to alleviate potential misconceptions and improve vaccine uptake
6. The existing seasonal influenza vaccines present lower effectiveness, even when there is a good antigenic match [62]. With the emergence of new viral strains, these vaccines fail to provide adequate protection [63]. Development of a universal influenza vaccine provides broader protection, regardless of circulating influenza viruses [64]	The GII recommends development of a new universal influenza vaccine for broader protection and increased effectiveness

GII, Global Influenza Initiative; HCW, healthcare worker; NH, Northern Hemisphere; SH, Southern Hemisphere; WHO, World Health Organization.

To achieve these goals, the GII convenes global and regional roundtable meetings of experts in influenza, healthcare, policy implementation, and health economics. These specialists work together to achieve a consensus of recommendations and strategies to address challenges at local, national, regional, and global levels. The 5th GII Global Roundtable Meeting was held on August 23–24, 2016, in Chicago, IL, USA, and the speakers presented on various current topics on influenza and shared information on current influenza situations and challenges to vaccination in the Americas. The recommendations for Latin American countries from GII are summarized in Table 5.

6. Summary and conclusion

While the majority of countries worldwide do not have influenza vaccination in their immunization programs, most Latin American countries do have policies in place [8]. The overall vaccination coverage is increasing in Latin America—most notably among pregnant women [56]. However, active influenza surveillance is still heterogeneous and needs to be improved to understand the current situation in Latin America and to inform healthcare decision makers on the optimal use of resources [37].

The present influenza situation, as depicted in this article, provides a consolidated estimation of disease burden in the region, which is currently lacking in the published literature. The GII recommendations specific to Latin America are of great importance as they provide guidance to combat existing vaccination challenges.

The current situation shows that influenza is an important contributor to mortality and morbidity, particularly in children, thus requiring greater global attention to alleviating the disease. Undoubtedly, improvements in influenza vaccination coverage have been made in the Latin American countries, but more is needed to reduce the disease burden.

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Conflict of interest

The authors are Steering Committee members of the GII, which is funded by an educational grant from Sanofi Pasteur. The GII is not influenced in any way by Sanofi Pasteur. GII members hold the full right to determine meeting agenda items and to lead the discussions and outputs. Sanofi Pasteur representatives might have attended the meetings, but as observers only, and they do not influence the findings of the group. NB was a member of the Advisory Board and presented in symposia organized by Sanofi Pasteur. JPT presented in a symposium organized by Sanofi Pasteur. The other authors do not have any conflict of interest. All authors had full access to the study data and take full ownership for the integrity of the data and the accuracy of the data analysis. All authors agreed to submit this manuscript for publication.

Author contributions

All authors have contributed original content, reviewed, and revised the manuscript, and approved the final version.

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References

- [1] World Health Organization. Vaccines against influenza WHO position paper – November 2012. *Wkly Epidemiol Rec* 2012;87:461–76.
- [2] Kraay ANM, Hayashi MAL, Hernandez-Ceron N, Spicknall IH, Eisenberg MC, Meza R, et al. Fomite-mediated transmission as a sufficient pathway: a comparative analysis across three viral pathogens. *BMC Infect Dis* 2018;18:540.
- [3] Centers for disease control and prevention. Types of influenza viruses, <<https://www.cdc.gov/flu/about/viruses/types.htm> 2017> [accessed January 24, 2018].
- [4] World Health Organization. WHO influenza (seasonal) fact sheet, November 2018, <<http://www.who.int/mediacentre/factsheets/fs211/en/> 2018> [accessed March 28, 2019].
- [5] Hirve S, Newman LP, Paget J, Azziz-Baumgartner E, Fitzner J, Bhat N, et al. Influenza seasonality in the tropics and subtropics – when to vaccinate? *PLoS ONE* 2016;11:e0153003.
- [6] Nair H, Brooks WA, Katz M, Roca A, Berkley JA, Madhi SA, et al. Global burden of respiratory infections due to seasonal influenza in young children: a systematic review and meta-analysis. *Lancet* 2011;378:1917–30.
- [7] de Souza MdFM, Widdowson MA, Alencar AP, Gawryszewski VP, Azziz-Baumgartner E, Palekar R, et al. Trends in mortality from respiratory disease in Latin America since 1998 and the impact of the 2009 influenza pandemic. *Bull World Health Organ* 2013;91:525–32.
- [8] World Health Organization. WHO seasonal influenza vaccine use in low and middle income countries in the tropics and subtropics – a systematic review, <http://apps.who.int/iris/bitstream/10665/119789241565097_eng.pdf?ua=1 2015> [accessed November 21, 2017].
- [9] Ropero-Alvarez AM, Kurtis HJ, Danovaro-Holliday MC, Ruiz-Matus C, Andrus JK. Expansion of seasonal influenza vaccination in the Americas. *BMC Public Health* 2009;9:361.
- [10] McQuestion M, Garcia AG, Janusz C, Andrus JK. National legislation and spending on vaccines in Latin America and the Caribbean. *J Public Health Policy* 2017;38:3–15.
- [11] de Francisco Shapovalova N, Donadel M, Jit M, Hutubessy R. A systematic review of the social and economic burden of influenza in low- and middle-income countries. *Vaccine* 2015;33:6537–44.
- [12] Iuliano AD, Roguski KM, Chang HH, Muscatello DJ, Palekar R, Tempia S, et al. Estimates of global seasonal influenza-associated respiratory mortality: a modelling study. *Lancet* 2018;391:1285–300.
- [13] Savy V, Ciapponi A, Bardach A, Glujovsky D, Aruj P, Mazzoni A, et al. Burden of influenza in Latin America and the Caribbean: a systematic review and meta-analysis. *Influenza Other Respir Viruses* 2013;7:1017–32.
- [14] Caini S, Alonso WJ, Balmaseda A, Bruno A, Bustos P, Castillo L, et al. Characteristics of seasonal influenza A and B in Latin America: Influenza surveillance data from ten countries. *PLoS ONE* 2017;12:e0174592.
- [15] Cheng PY, Palekar R, Azziz-Baumgartner E, Iuliano D, Alencar AP, Bresee J, et al. Burden of influenza-associated deaths in the Americas, 2002–2008. *Influenza Other Respir Viruses* 2015;9(Suppl 1):13–21.
- [16] Dawood FS, Iuliano AD, Reed C, Meltzer MI, Shay DK, Cheng PY, et al. Estimated global mortality associated with the first 12 months of 2009 pandemic influenza A H1N1 virus circulation: a modelling study. *Lancet Infect Dis* 2012;12:687–95.
- [17] Descalzo MA, Clara W, Guzman G, Mena R, Armero J, Lara B, et al. Estimating the burden of influenza-associated hospitalizations and deaths in Central America. *Influenza Other Respir Viruses* 2016;10:340–5.
- [18] Ministry of Health –Argentina. Boletín Integrado de Vigilancia, SE 06, 2018–Argentina, <http://www.msal.gob.ar/images/stories/boletines/BIV_398_SE06.pdf 2018> [accessed April 2, 2018].
- [19] Pan American Health Organization. Influenza and ORV country cumulative analysis – Argentina, <http://ais.paho.org/hiph/viz/ed_flu.asp 2018> [accessed April 2, 2018].
- [20] Davila-Torres J, Chowell G, Borja-Aburto VH, Viboud C, Grajales-Muniz C, Miller MA. Intense seasonal A/H1N1 influenza in Mexico, winter 2013–2014. *Arch Med Res* 2015;46:63–70.
- [21] Ministry of Health – Brazil. Influenza epidemiology situation, <<http://portalmis.saude.gov.br/saude-de-a-z/influenza/situacao-epidemiologica-dados> 2018> [accessed February 14, 2018].
- [22] Ministry of Health – Paraguay. Epidemiology bulletin, Paraguay; 2017. <http://vigisalud.gov.py/boletines/17_01_2018_11_49_39_Boletin-Epidemiologico_SE-52.pdf 2017> [accessed February 16, 2018].
- [23] Sotomayor V, Fasce RA, Vergara N, De la Fuente F, Loayza S, Palekar R. Estimating the burden of influenza-associated hospitalizations and deaths in Chile during 2012–2014. *Influenza Other Respir Viruses* 2018;12:138–45.
- [24] Ministry of Health – Paraguay. Epidemiological updates-2018, <http://www.vigisalud.gov.py/paginas/pag/Actualizaciones-Epidemiologicas> 2018 [accessed April 3, 2018].
- [25] World Health Organization. A manual for estimating disease burden associated with seasonal influenza, http://apps.who.int/iris/bitstream/handle/10665/178801/9789241549301_eng.pdf?sequence=1 2015 [accessed November 28, 2018].
- [26] Paul Glezen W, Schmier JK, Kuehn KM, Ryan KJ, Oxford J. The burden of influenza B: a structured literature review. *Am J Public Health* 2013;103:e43–51.
- [27] Falleiros Arlant LH, Bricks LF. Influenza B burden in Latin America and potential benefits of the new quadrivalent vaccines. *J Pediatric Infect Dis Soc* 2016;5:1–2.
- [28] World Health Organization. Influenza seasonality: timing and formulation of vaccines, <http://www.who.int/bulletin/volumes/92/5/14-139428/en/> 2014 [accessed October 25, 2017].
- [29] Newman LP, Bhat N, Fleming JA, Neuzil KM. Global influenza seasonality to inform country-level vaccine programs: an analysis of WHO FluNet influenza surveillance data between 2011 and 2016. *PLoS ONE* 2018;13:e0193263.
- [30] Ministry of Health – Chile. Situación de influenza y virus respiratorios informe 2017 (SE 1-52), <http://epi.minsal.cl/wp-content/uploads/2018/02/InformeInfluenzaRespiratoriasSE52.pdf> [accessed June 12, 2018].
- [31] Arango AE, Jaramillo S, Perez J, Ampuero JS, Espinal D, Donado J, et al. Influenza-like illness sentinel surveillance in one hospital in Medellín, Colombia, 2007–2012. *Influenza Other Respir Viruses* 2015;9(1):1.
- [32] Douce RW, Aleman W, Chicaiza-Ayala W, Madrid C, Sovero M, Delgado F, et al. Sentinel surveillance of influenza-like-illness in two cities of the tropical country of Ecuador: 2006–2010. *PLoS ONE* 2011;6:e22206.
- [33] Laguna-Torres VA, Sanchez-Largaespada JF, Lorenzana I, Forshey B, Aguilar P, Jimenez M, et al. Influenza and other respiratory viruses in three Central American countries. *Influenza Other Respir Viruses* 2011;5:123–34.
- [34] Perosa AH, Granato C, Bellei N. Detection of influenza B lineages from 2001 to 2013 in a tertiary hospital in the city of Sao Paulo, Brazil. *Mem Inst Oswaldo Cruz* 2015;110:606–10.
- [35] Laguna-Torres VA, Gomez J, Ocana V, Aguilar P, Saldarriaga T, Chavez E, et al. Influenza-like illness sentinel surveillance in Peru. *PLoS ONE* 2009;4:e6118.
- [36] Azziz-Baumgartner E, Garten RJ, Palekar R, Cerpa M, Mirza S, Ropero AM, et al. Determination of predominance of influenza virus strains in the Americas. *Emerg Infect Dis* 2015;21:1209–12.
- [37] Pan American Health Organization. PAHO influenza and other respiratory virus surveillance systems in the Americas, http://www.paho.org/hq/index.php?option=com_content&view=article&id=3352%3Ainfluenza-situation-report&catid=2407%3Ainfluenza-respiratory-viruses&Itemid=2469&lang=en 2018 [accessed January 18, 2018].
- [38] Ministry of Health – Paraguay. Operational guide for ILI sentinel surveillance and national surveillance of Serious Acute Respiratory Infection (SARI), http://vigisalud.gov.py/documentos/30_06_2016_20_48_34_Guia-operativa-ETI-IRAG-13-06-12.pdf 2018 [accessed April 3, 2018].
- [39] Institute of Public Health – Chile. Vigilancia de virus respiratorios, www.ispch.cl/virusrespiratorios 2018 [accessed June 12, 2018].
- [40] Institute of Public Health – Chile. Informe de circulación de virus respiratorios, <http://www.ispch.cl/sites/default/files/documento/2018/06/Informe%20Circulaci%C3%B3n%20virus%20respiratorios%20SE22%2005-06-2018.pdf> 2018 [accessed June 12, 2018].
- [41] World Health Organization. WHO FluNet, http://www.who.int/influenza/gisrs_laboratory/fluNet/en/ 2019 [accessed March 28, 2019].
- [42] Netherlands Institute for Health Services Research. The epidemiological signature of seasonal influenza-related mortality- WHO-funded GLAMOR project, http://eswi.org/influenzaconferences/wp-content/uploads/sites/13/2017/09/Paget-et-al_GLAMOR.pdf 2017 [accessed February 9, 2018].
- [43] World Health Organization. WHO FluID, http://www.who.int/influenza/surveillance_monitoring/fluID/en/ 2019 [accessed March 28, 2019].
- [44] Camilloni B, Neri M, Lepri E, Iorio AM. Cross-reactive antibodies in middle-aged and elderly volunteers after MF59-adjuncted subunit trivalent influenza vaccine against B viruses of the B/Victoria or B/Yamagata lineages. *Vaccine* 2009;27:4099–103.
- [45] Jamotte A, Clay E, Macabeo B, Caicedo A, Lopez JG, Bricks L, et al. Public health impact and economic benefits of quadrivalent influenza vaccine in Latin America. *Hum Vaccin Immunother* 2017;13:877–88.
- [46] Hendriks J, Hutubessy RCW, Grohmann G, Torelli G, Friede M, Kiemy MP. Quadrivalent influenza vaccines in low and middle income countries: cost-effectiveness, affordability and availability. *Vaccine* 2018;36:3993–7.
- [47] Fiore AE, Uyeki TM, Broder K, Finelli L, Euler GL, Singleton JA, et al. Prevention and control of influenza with vaccines: recommendations of the Advisory Committee on Immunization Practices (ACIP), 2010. *MMWR Recomm Rep* 2010;59:1–62.
- [48] Falleiros Arlant LH, Ferro Bricks L. Toward improved influenza control through vaccination. *Rev Chilena Infectol* 2015;32:198–210.
- [49] Miyaki C, Meros M, Precioso AR, Raw I. Influenza vaccine production for Brazil: a classic example of successful North-South bilateral technology transfer. *Vaccine* 2011;29(Suppl 1):A12–5.
- [50] Independent Accountability Panel. 2018 Report. Private sector: Who is accountable? for women's, children's and adolescents' health, http://iapreport.org/img/pdf/IAP18001_REPORT_B_020_WEB.pdf 2018 [accessed December 4, 2018].
- [51] Argentinean and Brazilian Influenza Vaccine Working Group. Epidemiology and prevention of influenza in children in Argentina and Brazil. *Rev Panam Salud Publica* 2017;41:e76.
- [52] El Omeiri N, Azziz-Baumgartner E, Thompson MG, Clara W, Cerpa M, Palekar R, et al. Seasonal influenza vaccine effectiveness against laboratory-confirmed influenza hospitalizations – Latin America, 2013. *Vaccine* 2018;36:3555–66.
- [53] Ministry of Health – Argentina. Influenza vaccination; 2018, http://www.msal.gob.ar/images/stories/bes/graficos/0000001137cnt-2018-03_it_vacunagripe-2018.pdf 2018 [accessed November 28, 2018].
- [54] Ministry of Health – Chile. Campaña de Vacunación contra la Influenza 2018, [accessed December 18, 2018].
- [55] Coleman BL, Fadel SA, Fitzpatrick T, Thomas SM. Risk factors for serious outcomes associated with influenza illness in high- versus low- and middle-

- income countries: systematic literature review and meta-analysis. *Influenza Other Respir Viruses* 2018;12:22–9.
- [56] Ropero-Alvarez AM, El Omeiri N, Kurtis HJ, Danovaro-Holliday MC, Ruiz-Matus C. Influenza vaccination in the Americas: progress and challenges after the 2009 A(H1N1) influenza pandemic. *Hum Vaccin Immunother* 2016;12:2206–14.
- [57] Technical Advisory Group on Vaccine-preventable Diseases (TAG). XXIII Meeting, Cuba; 2015, <https://www.paho.org/hq/dmdocuments/2015/vaccine-preventable-diseases-tag23-2015-FinalReport-Eng.pdf> 2015 [accessed November 9, 2018].
- [58] Ropero-Alvarez AM, Whittombury A, Kurtis HJ, dos Santos T, Danovaro-Holliday MC, Ruiz-Matus C. Pandemic influenza vaccination: lessons learned from Latin America and the Caribbean. *Vaccine* 2012;30:916–21.
- [59] World Health Organization. WHO preferred product characteristics for next-generation influenza vaccines, <http://apps.who.int/iris/bitstream/handle/10665/258767/9789241512466eng.pdf;jsessionid=4E4CD9A49CAD521F6910F4DCA08F9A8F?sequence=1> 2017 [accessed November 14, 2018].
- [60] Global Influenza Initiative. The global influenza initiative, <https://www.globalinfluenzainitiative.org> 2019 [accessed March 28, 2019].
- [61] World Health Organization. WHO global epidemiological surveillance standards for influenza, http://www.who.int/influenza/resources/documents/WHO_Epidemiological_Influenza_Surveillance_Standards_2014.pdf?ua=1 2013 [accessed January 9, 2018].
- [62] Lewnard JA, Cobey S. Immune history and influenza vaccine effectiveness. *Vaccines (Basel)* 2018;6:E28.
- [63] Keshavarz M, Mirzaei H, Salemi M, Momeni F, Mousavi MJ, Sadeghalvad M, et al. Influenza vaccine: where are we and where do we go? *Rev Med Virol* 2019;29:e2014.
- [64] European centre for disease prevention and control. New influenza vaccine developments; 2018, <https://ecdc.europa.eu/en/seasonal-influenza/prevention-and-control/vaccines/vaccine-developments> [accessed November 29, 2018].
- [65] Pan American Health Organization. Influenza report EW 40, PAHO, http://www.paho.org/hq/index.php?option=com_docman&task=doc_view&Itemid=270&gid=42602&lang=en 2017 [accessed October 24, 2017].