

Estimated incidence of influenza-virus-associated severe pneumonia in children in El Salvador, 2008–2010

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Objective To estimate the incidence of influenza-virus-associated severe pneumonia among Salvadorian children aged < 5 years.

Methods Data on children aged < 5 years admitted with severe pneumonia to a sentinel hospital in the western region were collected weekly. Nasal and oropharyngeal swab specimens were collected from a convenience sample of case patients for respiratory virus testing. A health-care utilization survey was conducted in the hospital catchment area to determine the proportion of residents who sought care at the hospital. The incidence of influenza-virus-associated severe pneumonia among all Salvadorian children aged < 5 years was estimated from surveillance and census data, with adjustment for health-care utilization. Influenza virus strains were characterized by the United States Centers for Disease Control and Prevention to determine their correspondence with northern and southern hemisphere influenza vaccine formulations.

Findings Physicians identified 2554 cases of severe pneumonia. Samples from 608 cases were tested for respiratory viruses and 37 (6%) were positive for influenza virus. The estimated incidence of influenza-virus-associated severe pneumonia was 3.2 cases per 1000 person-years (95% confidence interval, CI: 2.8–3.7) overall, 1.5 cases per 1000 person-years (95% CI: 1.0–2.0) during 2008, 7.6 cases per 1000 person-years (95% CI: 6.5–8.9) during 2009 and 0.6 cases per 1000 person-years (95% CI: 0.3–1.0) during 2010. Northern and southern hemisphere vaccine formulations matched influenza virus strains isolated during 2008 and 2010.

Conclusion Influenza-virus-associated severe pneumonia occurred frequently among young Salvadorian children during 2008–2010. Antigenes in northern and southern hemisphere influenza vaccine formulations corresponded to circulating strains.

Abstracts in [عربي](#), [中文](#), [Français](#), [Русский](#) and [Español](#) at the end of each article.

Introduction

Influenza is a vaccine-preventable disease that annually affects 5–10% of the population worldwide.¹ This burden is well documented in upper-income, temperate countries, where influenza surveillance has been conducted for years, and is being increasingly understood in middle-income countries, where surveillance has substantially improved during recent years. In the United States of America, for example, an annual average of 228 635 hospitalizations for pneumonia and influenza occurred during 1979–2001 and 23 207 deaths were associated with influenza viruses during 1976–2007.^{2,3} In addition, the United States spent an average of 10.4 billion United States dollars annually on the treatment of influenza.⁴ Similarly, in high-income and middle-income countries such as Singapore and Thailand, influenza has substantial disease and economic burdens.^{5,6}

Less is known about the burden of influenza in low-income countries; however, investments in epidemiology and laboratory capacity as a result of efforts to comply with the 2005 International Health Regulations and prepare for influenza pandemics have yielded data about the circulation and burden of influenza in low-income tropical countries. For example, studies now suggest that the rate of influenza-

virus-associated severe acute lower respiratory tract infection is approximately 2 cases per 1000 child-years among children aged < 5 years in low-income countries.⁷ National influenza surveillance data from Bangladesh suggest that approximately 67 000 persons are hospitalized annually as a result of influenza virus infection and that the rate of influenza-virus-associated severe acute lower respiratory infection is 1 case per 1000 child-years among children aged < 5 years.^{8–10} Similar findings have been reported in Guatemala, Kenya, Nicaragua, the Philippines, Thailand and Viet Nam.^{7,11–14}

Although data on the influenza burden are useful to guide investments in influenza prevention and control, these data are not available in many tropical countries in Latin America. In 2004 El Salvador, the smallest and most densely populated country in Central America (293 inhabitants/km²),¹⁵ introduced influenza vaccination among children 6–23 months old, adults > 60 years old and persons with certain pre-existing medical conditions. In 2007 influenza sentinel-hospital surveillance was begun in El Salvador to better guide influenza prevention and control efforts.¹⁶ Although vaccine coverage among children and adults aged > 60 years reached 85–95% during 2010,^{17,18} few data were available about the burden of influenza in El Salvador. These data may help the El Salvador Ministry of Health to better assess the value of influenza vac-

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ination among people vulnerable to severe influenza,¹⁹ adjust vaccination policies and determine the number of influenza vaccine doses to purchase. The primary objective of this study was to estimate the population-based incidence of severe pneumonia associated with influenza virus among children aged < 5 years in El Salvador during 2008–2010 on the basis of findings from sentinel surveillance and a health-care utilization survey. We supplemented these findings with a comparison of the antigenic characteristics of influenza virus strains isolated from case patients with vaccine formulations for the northern and southern hemispheres during the study period.

Methods

Case identification

The San Juan de Dios Hospital in Santa Ana, the largest public hospital in the western region of El Salvador, was the first sentinel surveillance site for severe acute respiratory infection established in the country. For this study, a case patient with severe pneumonia was defined as a patient aged < 5 years hospitalized with cough or difficulty breathing and at least one danger sign (i.e. chest in-drawing, stridor while calm, convulsions, inability to drink, lethargy, unconsciousness or intractable vomiting).^{16,20} Hospital physicians identified all patients with severe pneumonia and collected demographic and clinical data. Nasal and oropharyngeal swab specimens were collected from a convenience sample of 5 or 6 consecutive patients per week. This site was supported by the Influenza Program for the Central American Region of the United States Centers for Disease Control and Prevention (CDC). The hospital regularly provides 35–48% of all respiratory samples tested for influenza virus in the El Salvador national influenza surveillance system.

Sample processing

Respiratory samples were transported in virus-transport medium (i.e. tryptase-phosphate broth) to the hospital's laboratory and tested by indirect immunofluorescence for influenza A and B viruses; respiratory syncytial virus; parainfluenza virus types 1, 2 and 3; and adenovirus. All influenza-virus-positive samples and 10% of influenza-virus-negative samples were sent to the National Influenza Centre at

the El Salvador Ministry of Health (San Salvador) for quality control analysis by immunofluorescence testing. Starting in 2009 approximately 25% of samples that underwent quality control analysis were further tested using real-time reverse-transcription polymerase chain reaction (qRT-PCR).²¹

A convenience sample of influenza-virus-positive specimens was sent to the CDC (Atlanta, United States) every six months for antigenic characterization. There, influenza viruses were isolated in Madin-Darby canine kidney cells and underwent haemagglutination inhibition testing using post-infection ferret antisera.²² Antigenic characteristics of the virus isolates were reported to the National Influenza Centre by the CDC's Influenza Division each year. We classified strains as dominant if they accounted for at least 70% of influenza virus isolates during a particular year and as co-dominant if they accounted for at least 40% but less than 70% (< 70%) of isolates.²³ To determine whether the influenza vaccine formulation used in El Salvador during the study period matched the circulating influenza virus strains, we compared these strains with those used to prepare influenza vaccine formulations for the northern hemisphere (the formulation used in El Salvador until 2010) and the southern hemisphere.

Health-care utilization survey

To estimate the denominator for our incidence calculation, we performed a health-care utilization survey to determine the size of the sentinel hospital's catchment population. During November and December 2009, we used multistage cluster sampling to survey 1663 households in urban and rural locations in five counties of the Santa Ana Department, where 80% of case patients who had severe pneumonia and were admitted to the sentinel hospital lived during 2008 (i.e. the hospital catchment area). For both urban and rural areas, we selected a random sample of census tracts or cantons and then a random sample of households within each of these. Investigators obtained informed consent and surveyed household members to determine who had developed symptoms of and sought care for sudden-onset fever, cough or sore throat (i.e. influenza-like illness) during the preceding month. In addition, the investigators determined where ill individuals had sought care (e.g.

at the sentinel hospital or another facility) and whether they were admitted to hospital for severe pneumonia during the preceding year and, if so, the hospital to which they were admitted. We assumed that the pattern of health-care services use by age group was similar every year.

Statistical analyses

We compared case patients who were tested with those who were not tested for respiratory viruses with respect to age, sex and severity of illness by use of χ^2 and *t* tests (SPSS, version 17.0; SPSS Statistics, New York, United States of America). To estimate the annual incidence of influenza-virus-associated pneumonia, we first used the monthly proportion of case patients who tested positive for influenza virus at San Juan de Dios Hospital to impute the monthly number of case patients who would have tested positive for influenza virus if all had been tested. We then adjusted this estimate by use of census data,²⁴ the proportion of days each year that samples were collected, and the proportion of those surveyed in the catchment area who, in the previous year, developed sudden-onset fever, cough or sore throat and were subsequently admitted to the sentinel site and not to another hospital (Appendix A, available at: <http://xurl.es/pvcvz>).

Results

Case patient characteristics

During 2008–2010, physicians at the sentinel hospital identified 2554 case patients aged < 5 years with severe pneumonia: 495 cases (19%) occurred in 2008, 1367 (54%) occurred in 2009 and 692 (27%) occurred in 2010. Samples from 608 (24%; 153 [31%] in 2008, 217 [16%] in 2009 and 238 [34%] in 2010) were collected and tested for respiratory viruses.

Table 1 summarizes select demographic characteristics among tested and untested case patients. During 2008–2009, the median age and prevalence of male sex among tested and untested case patients were similar. However, during 2010, the median age among tested case patients was significantly less than that among untested case patients (6 versus 11 months; $P < 0.001$). The percentage of tested case patients who died was significantly greater than the percentage of untested case patients who died, both in 2009 (9% versus 0%; $P < 0.001$) and in 2010 (4% versus 0%; $P < 0.001$).

Table 1. Demographic characteristics of children aged < 5 years with severe pneumonia who were or were not tested for influenza virus, San Juan de Dios Hospital, Santa Ana, El Salvador, 2008–2010

Characteristic	2008			2009			2010		
	Tested (n = 153)	Not tested (n = 342)	Overall (n = 495)	Tested (n = 217)	Not tested (n = 1150)	Overall (n = 1367)	Tested (n = 238)	Not tested (n = 454)	Overall (n = 692)
Males, no. (%)	99 (65)	209 (61)	308 (62)	117 (54)	667 (58)	784 (57)	157 (66)	253 (58)	420 (61)
Age in months, median (IQR)	7 (3–12)	7 (3–12)	7 (3–12)	7 (2–12)	8 (3–12)	8 (3–12)	6 (3–12)	11 (5–12)	11 (4–12)
Deceased, no. (%)	0 (0)	4 (1)	4 (1)	20 (9)	2 (0)	22 (2)	9 (4)	0 (0)	9 (1)

IQR, interquartile range.

Table 2. Distribution of severe pneumonia cases overall and of influenza virus positivity among children aged < 5 years with severe pneumonia who underwent testing, by age and month, San Juan de Dios Hospital, Santa Ana, El Salvador, 2008–2010

Characteristic	2008			2009			2010		
	No. of cases	No. positive/ no. tested	Per cent positivity ^a	No. of cases	No. positive/ no. tested	Per cent positivity ^a	No. of cases	No. positive/ no. tested	Per cent positivity ^a
Age (months)									
< 12	347	6/80	8	850	12/121	10	394	2/154	1
12–23	97	3/34	9	344	7/52	13	187	2/58	3
24–59	51	2/39	5	173	2/44	5	111	1/26	4
Month									
Jan	19	0/6	0	45	0/17	0	22	0/22	0
Feb	33	0/4	0	46	1/13	8	38	1/13	8
Mar	29	0/15	0	69	1/17	6	46	1/24	4
Apr	31	0/8	0	99	2/18	11	47	0/26	0
May	45	0/10	0	125	1/19	5	66	0/17	0
Jun	49	3/20	15	259	0/23	0	111	0/16	0
Jul	58	2/14	14	321	8/23	35	89	0/24	0
Aug	44	0/16	0	157	2/23	9	57	3/19	16
Sep	40	4/18	22	99	0/20	0	55	0/16	0
Oct	54	0/13	0	85	0/21	0	50	0/28	0
Nov	57	1/23	4	33	1/10	10	61	0/27	0
Dec	36	1/6	17	29	5/13	38	50	0/6	0

^a Among patients who provided samples for testing.

Of the 608 case patients with severe pneumonia who underwent testing, 113 (19%) tested positive for at least one of the following respiratory viruses: influenza virus, parainfluenza virus, adenovirus and respiratory syncytial virus. Influenza virus was detected in 37 case patients (6%; 95% confidence interval, CI: 4–8) who provided samples for testing. The median age of influenza-virus-positive case patients was 10 months (interquartile range: 4–12 months). The frequency of influenza virus detection among tested case patients aged < 2 years was higher than that among older tested case patients during 2008 and during 2009 but not during 2010 (Table 2).

The proportion of case patients who tested positive for influenza virus was highest each year from June to

September (Table 2). We also observed an increase in influenza-virus-positive cases at the end of December 2009, during the 2009 influenza pandemic, when influenza A virus subtype H1N1pdm (i.e. the pandemic strain) was detected in 17 of 21 patients (81%) with severe pneumonia.

Survey findings

A total of 7683 household members (mean number of members per household: 4.6) were detected during the health-care utilization survey. Participants reported that 464 household members (6%; 95% CI: 4–7) developed influenza-like illness one month before the interview. Of these people, 233 (50%; 95% CI: 45–55) sought medical care. During the year before the interview, 22 household members (0.3%; 95% CI:

0.2–0.4) were hospitalized with a history of influenza-like illness. Among them, 5 of 8 (63%) aged < 5 years were hospitalized at the sentinel hospital.

Overall and annual incidence

Table 3 summarizes the data used to estimate the incidence of influenza-virus-associated severe pneumonia among children aged < 5 years in El Salvador during 2008–2010. The incidence during the study period was estimated to be 3.2 cases per 1000 person-years (95% CI: 2.8–3.7). The greatest annual incidence occurred in 2009, with 7.6 cases per 1000 person-years (95% CI: 6.5–8.9); 6.7 cases per 1000 person-years were attributable to influenza A virus subtype H1N1pdm. Incidence estimates were significantly lower during the other study years: 1.5 cases per 1000 person-

Table 3. Variables used to estimate the incidence of influenza-virus-associated severe pneumonia among children aged < 5 years living in the catchment area of San Juan de Dios Hospital, Santa Ana, El Salvador, 2008–2010

Variable	2008	2009	2010	2008–2010
Case patients identified at San Juan de Dios Hospital, no.	495	1367	692	2554
Case patients tested for respiratory viruses, no.	153	217	238	608
Case patients positive for influenza virus				
Detected no., (%), (95% CI)	11 (7) (3–11)	21 (10) (6–14)	5 (2) (0.2–4)	37 (6) (4–8)
Imputed no.	33	165	14	212
Census population aged < 5 years in catchment area ^a	36 858	37 016	37 205	111 079
Census population that visits the sentinel site when ill, % ^b	63	63	63	63
Days when surveillance was performed, no., (%) ^c	343 (94)	340 (93)	339 (93)	1022 (93)
Adjusted census population (person–years)	21 827	21 688	21 798	65 081

CI, confidence interval.

^a Data are from the National VI Population and V Household Census 2007 of El Salvador.^b Data are from the sentinel site health-care service utilization survey performed in Santa Ana during November–December 2009.^c Percentages represent the proportion of days when surveillance was conducted in one year (365 days) or, for the last column, in three years (1095 days).

years (95% CI: 1.0–2.0) for 2008 and 0.6 cases per 1000 person–years (95% CI: 0.3–1.0) for 2010.

Matching between vaccines and recovered isolates

During 2008–2010, El Salvador used influenza vaccine formulations manufactured for use in the northern hemisphere but haemagglutination inhibition testing showed that the influenza virus strains identified in the study matched antigens from both the northern and southern hemisphere formulations (Table 4). The northern hemisphere formulation seemed to be a better match than the southern hemisphere formulation in 2008 because it included the dominant circulating strain (A/Brisbane/59/2007 [H1N1]-like virus). On the other hand, both formulations were considered best matches to circulating strains in 2010 because both contained the same strains.

Discussion

This study, which is, to our knowledge, the first to estimate the incidence of influenza-virus-associated severe pneumonia among children aged < 5 years in El Salvador, suggests that young children are frequently hospitalized as a result of influenza. If the 2008 incidence of influenza-virus-associated severe pneumonia among children aged < 5 years hospitalized in San Juan de Dios Hospital (1.5 cases per 1000 person–years; 95% CI: 1.0–2.0) was similar throughout El Salvador, we estimate that from 600 to 1100 influenza-virus-associated hos-

pitalizations occurred among children in this age group during 2008 [(1.0–2.0 cases per 1000 person–years) × (555 893 individuals aged < 5 years)]. Almost all cases of influenza-virus-associated severe pneumonia identified during 2009 were attributed to influenza A virus subtype H1N1pdm. Although influenza due to pandemic and seasonal strains had similar clinical manifestations, younger children had higher attack rates during the pandemic year than during 2008 and 2010. This may be explained by the lack of pre-existing immunity against the pandemic influenza strain among children.^{26,27} The incidence of influenza-virus-associated severe pneumonia requiring hospitalization among children in this study was similar to those reported in other low-income and lower-middle-income countries, including Bangladesh, Guatemala, Kenya and the Philippines, but lower than those reported in Nicaragua (3 cases per 1000 person–years), Thailand (5 cases per 1000 person–years) and Viet Nam (9 cases per 1000 person–years).^{7–14}

The incidence of influenza-virus-associated severe pneumonia requiring hospitalization is important because influenza is a vaccine-preventable infection and because respiratory illnesses are among the leading causes of death among children in lower-middle-income countries such as El Salvador.²⁸ During 2008–2010, Ministry of Health hospitals in El Salvador annually admitted approximately 14 000 children aged < 5 years with severe pneumonia. In addition, in El Salvador severe pneu-

monia causes 14% of deaths among children aged < 5 years.¹⁷ Infection with influenza virus also predisposes children to infections with other common pathogens associated with severe illness (e.g. pneumococcal and staphylococcal pneumonia).²⁹ Although our study did not explore the association between influenza and bacterial pneumonia, in 2010 El Salvador initiated a bacterial pneumonia surveillance system and introduced pneumococcal conjugate vaccine.^{30,31}

During the study period, El Salvador used the northern hemisphere influenza vaccine formulation. Our data suggest that both northern and southern hemisphere vaccine formulations matched influenza viruses circulating in El Salvador during 2008 and 2010, with the exception of the pandemic strain. In a similar analysis of unpublished 2003–2010 data, the Ministry of Health concluded that the southern vaccine formulation most often matched influenza viruses identified among Salvadorian patients. As of 2011 the Ministry of Health uses the southern hemisphere vaccine formulation to target children aged < 5 years, elderly people, health-care personnel, pregnant women and people with pre-existing medical conditions during influenza vaccination campaigns starting in March rather than in January, when they were formerly begun. Despite high reported vaccine coverage during 2010, it is unclear how many eligible children receive a second dose of influenza vaccine. It may be useful for the Ministry of Health to verify

Table 4. Match between influenza virus strains isolated from case patients in San Juan de Dios Hospital and influenza vaccine formulations available during 2008–2010, El Salvador

Year	Strain dominance ^a		Formulation		Best match, by hemisphere		
	Strain	Dominance	Southern hemisphere	Northern hemisphere ^b	Southern	Northern	Neither
2008	A/ Brisbane/59/2007- like (H1N1)	Co-dominant	A/Solomon Islands/3/2006 (H1N1)- like virus	A/Brisbane/59/2007 (H1N1)-like virus		X	
	B/Florida/04/2006- like	Co-dominant	A/Brisbane/10/2007 (H3N2)-like virus B/Florida/4/2006-like virus	A/Brisbane/10/2007 (H3N2)-like virus B/Florida/4/2006-like virus			
2009	A/ California/07/2009- like (H1N1)pdm	Dominant	A/Brisbane/59/2007 (H1N1)-like virus A/Brisbane/10/2007 (H3N2)-like virus B/Florida/4/2006-like virus	A/Brisbane/59/2007 (H1N1)-like virus A/Brisbane/10/2007 (H3N2)-like virus B/Brisbane/60/2008-like virus			X
	2010	A/Perth/16/2009 (H3N2) B/ Brisbane/60/2008- like	Co-dominant Co-dominant	A/California/7/2009 (H1N1)-like virus A/Perth/16/2009 (H3N2)- like virus B/Brisbane/60/2008-like virus	A/California/7/2009 (H1N1)- like virus A/Perth/16/2009 (H3N2)- like virus B/Brisbane/60/2008-like virus	X	X

^a Strains were considered dominant if they accounted for $\geq 70\%$ of the annual isolates and were considered co-dominant if they accounted for at least 40% but less than 70% of the annual isolates.

^b Northern hemisphere vaccine compositions are expressed as the year when epidemics start (i.e. 2008 refers to the 2008–2009 season).

Data source: World Health Organization²⁵.

that coverage is high among children and other target groups and to explore strategies to sustain high vaccination coverage. In addition, vaccination coverage among pregnant women and other persons with pre-existing medical conditions remains low, at approximately 33%. Knowledge of rates of influenza-associated hospitalization and other burden of disease data might improve communication of the potential risk of influenza and help mobilize persons and resources in El Salvador for successful influenza vaccine campaigns.

Our findings might also help public health officials in El Salvador to better determine the potential value of empirically treating severe pneumonia in children aged < 5 years with oseltamivir during influenza epidemics. In addition, data on the rates of influenza-associated hospitalization have the potential to help El Salvador explore the potential value of targeted non-pharmaceutical interventions such as hand washing campaigns among groups at high risk of hospitalization as a result of influenza virus infection.

Although there is still little information about influenza seasonality in tropical countries, unpublished data

from 2003–2011 suggest that El Salvador typically has influenza epidemics during June to September (M. Melendez et al., e-mail correspondence, 5 July 2012), concurrent with El Salvador's rainy season, as often occurs in tropical countries in Asia, Africa and South America.^{32–35} Improved understanding of the magnitude and timing of annual influenza activity can help health authorities improve the timing of influenza vaccination campaigns and recommendations to commence empirical antiviral treatment of people with suspected influenza virus infection. In addition, continued surveillance can help determine the best vaccine formulation for El Salvador.

We believe it important for countries like El Salvador to explore sustainable ways to support national laboratories with supplies and reagents for qRT-PCR testing for respiratory viruses; to train clinical and surveillance personnel to identify, register, code and notify all severe pneumonia cases at the sentinel sites; and to use standard case definitions along with standardized operating procedures to avoid selection bias and misclassification. Influenza surveillance can be expensive for low-middle income countries. For example, starting in 2007

the CDC's Central American Regional Office provided El Salvador with approximately US\$ 350 000 in technical and economic assistance to strengthen influenza surveillance. Sustainability should be addressed with long-term strategic planning to promote the rational use of limited resources.

This study has several limitations. First, the collection of samples from patients was not systematic. As a result, 62% of specimens were from children with very severe pneumonia, which might have resulted in selection bias. Second, qRT-PCR was unavailable at El Salvador's National Influenza Centre before 2009 and was performed on approximately 25% of samples obtained during 2009–2010. Therefore, almost all of the respiratory samples in our study underwent immunofluorescence analysis for influenza virus and respiratory syncytial virus, which is less sensitive than qRT-PCR for detecting respiratory viruses.³⁶ In addition, 16% of specimens were collected ≥ 5 days after symptom onset, when immunofluorescence and qRT-PCR testing are both less likely to detect respiratory viruses. Finally, because under-reporting might have arisen, we should have evaluated the

sentinel site's adherence to the severe pneumonia case definition, to better understand the magnitude of bias. These limitations may have yielded conservative estimates of the incidence of influenza-virus-associated severe pneumonia among children who required hospitalization.

Annually, El Salvador has a considerable incidence of influenza-virus-associated pneumonia among children aged <5 years, for whom lower respiratory tract infections are a leading cause of death.¹⁷ An integrated approach to preventing and mitigating childhood pneumonia in El Salvador could include a programme to control and prevent influenza. Our findings suggest

that studies to verify whether influenza vaccine coverage is high among children and other target groups are warranted and that vaccination strategies that have been proven to achieve high coverage should be sustained. The incidence of influenza-virus-associated severe pneumonia in El Salvador may help renew efforts to increase seasonal influenza vaccination coverage among target groups and to expand vaccination coverage among other vulnerable groups (e.g. pregnant women). ■

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ملخص

المعدل المقدر للإصابة بالتهاب الرئوي الحاد المرتبط بفيروس الأنفلونزا لدى الأطفال في السلفادور، 2010-2008
الغرض تقدير معدل الإصابة بالتهاب الرئوي الحاد المرتبط بفيروس الأنفلونزا بين أطفال السلفادور دون سن 5 سنوات. الطريقة تم جمع البيانات الخاصة بالأطفال دون سن 5 سنوات الذين دخلوا بسبب الإصابة بالتهاب الرئوي الحاد إلى مستشفى الرصد في المنطقة الغربية بشكل أسبوعي. وتم جمع عينات أنفية وفموية بلعومية مسحية من عينة ملائمة من مرضى الحالة وذلك لاختبار فيروسات الجهاز التنفسي. وتم إجراء مسح لاستخدام الرعاية الصحية في منطقة خدمة المستشفى لتحديد نسبة المقيمين الذي طلبوا الرعاية في المستشفى. وتم تقدير معدل الإصابة بالتهاب الرئوي الحاد المرتبط بفيروس الأنفلونزا بين كل الأطفال السلفادوريين دون سن 5 سنوات من واقع بيانات الرصد والإحصاء، مع التعديل لاستخدامهما لأغراض الرعاية الصحية. وتم توصيف ذراري فيروس الأنفلونزا من قبل مراكز مكافحة الأمراض والوقاية منها في الولايات المتحدة وذلك لتحديد مدى ملاءمتها مع تركيبات لقاحات الأنفلونزا في نصف الكرة الشمالي والجنوبي.

النتائج حدد الأطباء 2554 حالة من حالات الالتهاب الرئوي الحاد. تم اختبار عينات من 608 حالة للتحقق من وجود فيروسات الجهاز التنفسي وكانت 37 حالة (6%) مصابة بفيروس الأنفلونزا. وبلغ المعدل المقدر للإصابة بالتهاب الرئوي الحاد المرتبط بفيروس الأنفلونزا 3.2 حالة لكل 1000 شخص-سنة (فاصل الثقة 95%: 2.8 - 3.7) إجمالاً، و1.5 حالة لكل 1000 شخص-سنة (فاصل الثقة 95%: 1.0 - 2.0) خلال عام 2008، و7.6 حالة لكل 1000 شخص-سنة (فاصل الثقة 95%: 6.5 - 8.9) خلال عام 2009، و0.6 حالة لكل 1000 شخص-سنة (فاصل الثقة 95%: 0.3 - 0.1) خلال عام 2010. وتطابقت تركيبات اللقاحات في نصف الكرة الشمالي والجنوبي مع ذراري فيروس الأنفلونزا التي تم عزلها خلال عامي 2008 و2010. الاستنتاج تكرر حدوث الإصابة بالتهاب الرئوي الحاد المرتبط بفيروس الأنفلونزا بين الأطفال السلفادوريين الصغار خلال 2008 - 2010. وتطابقت المستضدات في تركيبات لقاحات الأنفلونزا في نصف الكرة الشمالي والجنوبي مع الذراري السارية.

摘要

估算 2008 - 2010 年萨尔瓦多流感病毒相关性重症肺炎在儿童中的发病率

目的 估算萨尔瓦多 5 岁以下儿童中流感病毒相关性重症肺炎的发病率。

方法 每周收集西部地区哨点医院因患重症肺炎入院的 5 岁以下儿童的数据。收集来自病例患者便利样本的鼻、咽拭子样本进行呼吸道病毒检测。在医院辖区进行卫生服务利用的调查，以确定居民入院就医的比例。从监测和普查数据估算萨尔瓦多所有 5 岁以下儿童中流感病毒相关性重症肺炎发病率，同时作出卫生服务利用的调整。流感病毒毒株由美国疾病控制和预防中心鉴定，确定毒株与南北半球流感疫苗配方的对应性。

结果 医生识别出 2554 例重症肺炎。对来自 608 个病例的样本进行了呼吸道病毒检测，37 (6%) 例为流感病

毒阳性。估算的总体流感病毒相关性重症肺炎发病率为 3.2 例/1000 人-年 (95% 置信区间, CI: 2.8 - 3.7)，2008 年期间为 1.5 例/1000 人-年 (95% CI: 1.0 - 2.0)，2009 年期间为 7.6 例/1000 人-年 (95% CI: 6.5 - 8.9)，2010 年期间为 0.6 例/1000 人-年 (95% CI: 0.3 - 1.0)。北半球和南半球疫苗配方与 2008 年和 2010 年期间分离出的流感病毒毒株匹配。

结论 2008 - 2010 年间流感病毒重症肺炎在萨尔瓦多幼儿中发生频繁。南北半球流感疫苗配方中的抗原与流行毒株对应。

Résumé

Incidence estimée des pneumonies sévères associées au virus de l'influenza chez les enfants d'El Salvador, de 2008 à 2010

Objectif Estimer l'incidence des pneumonies graves associées au virus de l'influenza chez les enfants salvadoriens âgés de moins de 5 ans.

Méthodes Les données sur les enfants âgés de moins de 5 ans hospitalisés pour pneumonie grave dans un hôpital sentinelle de la région occidentale ont été recueillies chaque semaine. Des écouvillons nasaux et oropharyngés ont été prélevés auprès d'un échantillon de patients de convenance pour un test des virus respiratoires. Une enquête sur le recours aux soins de santé a été menée dans la zone desservie par l'hôpital afin de déterminer la proportion d'habitants ayant bénéficié de soins hospitaliers. L'incidence de la pneumonie sévère associée au virus de l'influenza chez tous les enfants salvadoriens âgés de moins de 5 ans a été estimée à partir de données d'épidémiologie et de recensement, avec un ajustement pour le recours aux soins de santé. Des souches de virus grippal ont été sélectionnées par les «Centres des États-Unis d'Amérique pour le contrôle et la prévention des maladies» afin de déterminer leur adéquation avec les formulations des vaccins antigrippaux du Nord et du Sud de l'hémisphère.

Résultats Les médecins ont identifié 2554 cas de pneumonie grave. Des échantillons provenant de 608 cas ont été testés pour les virus respiratoires, et 37 d'entre eux (6%) étaient positifs au virus de la grippe. L'incidence estimée des pneumonies graves associées au virus de l'influenza était de 3,2 cas pour 1 000 personnes-années (intervalle de confiance IC de 95%: 2,8 à 3,7) pour l'ensemble de la période, de 1,5 cas pour 1 000 personnes-années (IC de 95%: 1,0 à 2,0) en 2008, de 7,6 cas pour 1 000 personnes-années (IC de 95%: 6,5 à 8,9) en 2009 et de 0,6 cas pour 1 000 personnes-années (IC de 95%: 0,3 à 1,0) en 2010. Les formulations vaccinales des hémisphères Nord et Sud correspondaient aux souches de virus de la grippe isolées au cours des années 2008 et 2010.

Conclusion Les pneumonies graves associées au virus de l'influenza sont fréquemment survenues chez les jeunes enfants salvadoriens au cours de la période 2008-2010. Les antigènes présents dans les formulations des vaccins contre la grippe des hémisphères Nord et Sud correspondaient aux souches en circulation.

Резюме

Расчетный уровень заболеваемости грипп-ассоциированной тяжелой пневмонией детей в Сальвадоре за период с 2008 по 2010 гг.

Цель Оценить уровень заболеваемости грипп-ассоциированной тяжелой пневмонией среди детей Сальвадора в возрасте до пяти лет.

Методы Проводился еженедельный сбор данных по детям в возрасте до пяти лет, поступавших в карантинное учреждение с тяжелой пневмонией в западном регионе. Были собраны назальные и орофарингеальные образцы мазков из нерепрезентативной выборки наблюдаемых пациентов для тестирования на респираторный вирус. Исследование использования ресурсов здравоохранения проводилось в районе, обслуживаемом лечебным учреждением, для определения соотношения жителей, нуждающихся в больничном лечении. Заболеваемость грипп-ассоциированной тяжелой пневмонией среди всех детей в Сальвадоре в возрасте до пяти лет оценивалась по данным наблюдений и переписи, с поправкой на использование ресурсов здравоохранения. Центры по борьбе с болезнями и их профилактике (США) охарактеризовали штаммы вируса гриппа на определение их соответствия составам противогриппозной вакцины Северного и Южного полушарий.

Результаты Врачами выявлено 2554 случаев тяжелой пневмонии. Образцы 608 случаев тестировались на вирусы-возбудители инфекций дыхательных путей, 37 (6%) из которых оказались положительными на вирус гриппа. Расчетный уровень заболеваемости грипп-ассоциированной тяжелой пневмонией в целом составил 3,2 случая на 1000 человеко-лет (95% доверительный интервал, ДИ: 2,8–3,7), 1,5 случая на 1000 человеко-лет (95% ДИ: 1,0–2,0) в течение 2008 г., 7,6 случаев на 1000 человеко-лет (95% ДИ: 6,5–8,9) в течение 2009 г., и 0,6 случаев на 1000 человеко-лет (95% ДИ: 0,3–1,0) в течение 2010 г. Составы противогриппозной вакцины Северного и Южного полушарий соответствуют штаммам вируса гриппа, выделенным в период с 2008 по 2010 гг.

Вывод Грипп-ассоциированная тяжелая пневмония часто встречалась среди детей младшего возраста Сальвадора в течение 2008–2010 гг. Антигены составов противогриппозной вакцины Северного и Южного полушарий соответствуют циркулирующим штаммам.

Resumen

La incidencia estimada de la neumonía grave asociada al virus de la gripe en los niños de El Salvador, 2008-2010

Objetivo Calcular la incidencia de la neumonía grave asociada al virus de la gripe entre los niños salvadoreños con edades inferiores a los cinco años

Métodos Se recogieron de manera semanal los datos de niños menores de cinco años ingresados debido a una neumonía grave en un hospital centinela de la región occidental y frotis nasales y bucofaríngeos de una muestra de conveniencia de pacientes caso para comprobar la presencia de virus respiratorios. En la zona de captación del hospital, se llevó a cabo una encuesta sobre el uso de la atención sanitaria para determinar la proporción de residentes que buscaron atención sanitaria en el hospital. La incidencia de la neumonía grave asociada al virus de la gripe entre todos los niños salvadoreños con edades inferiores a los cinco años se calculó en base a los datos de vigilancia y del censo con el ajuste para el

uso de la atención sanitaria. Los Centros para el Control y Prevención de Enfermedades de los Estados Unidos caracterizaron las cepas del virus de la gripe para determinar su correspondencia con la formulación de la vacuna de la gripe en los hemisferios norte y sur.

Resultados Los médicos identificaron 2554 casos de neumonía grave. Se comprobó la presencia de virus respiratorios en las muestras de 608 casos y 37 de ellas (6%) dieron positivo para el virus de la gripe. La incidencia estimada de la neumonía grave asociada al virus de la gripe fue de 3,2 casos por cada 1000 años–persona (intervalo de confianza del 95%, IC: 2,8–3,7) en total, 1,5 casos por cada 1000 años–persona (IC del 95%: 1,0–2,0) durante el año 2008, 7,6 casos por cada 1000 años–persona (IC del 95%: 6,5–8,9) durante el año 2009 y 0,6 casos por cada 1000 años–persona (IC del 95%: 0,3–1,0) durante el año 2010. La

formulación de la vacuna en los hemisferios norte y sur coincidió con las cepas del virus de la gripe aisladas durante los años 2008 y 2010.

Conclusión La neumonía grave asociada al virus de la gripe tuvo lugar con frecuencia entre los niños pequeños de El Salvador durante los años

2008 y 2012. Los antígenos en las formulaciones de la vacuna contra la gripe de los hemisferios norte y sur se correspondieron con las cepas en circulación.

References

- Nicholson KG, Wood JM, Zambon M. Influenza. *Lancet* 2003;362:1733–45. doi:10.1016/S0140-6736(03)14854-4 PMID:14643124
- Thompson WW, Shay DK, Weintraub E, Brammer L, Bridges CB, Cox NJ et al. Influenza-associated hospitalizations in the United States. *JAMA* 2004;292:1333–40. doi:10.1001/jama.292.11.1333 PMID:15367555
- Centers for Disease Control and Prevention. Estimates of deaths associated with seasonal influenza – United States, 1976–2007 [Internet]. *MMWR Morb Mortal Wkly Rep* 2010;59:1057–62. PMID:20798667
- Molinari NA, Ortega-Sanchez IR, Meisnionier ML, Thompson WW, Wortley PM, Weintraub E et al. The annual impact of seasonal influenza in the US: measuring disease burden and costs. *Vaccine* 2007;25:5086–96. doi:10.1016/j.vaccine.2007.03.046 PMID:17544181
- Simmerman JM, Uyeki TM. The burden of influenza in East and South-East Asia: a review of the English language literature. *Influenza Other Respi Viruses* 2008;2:81–92. doi:10.1111/j.1750-2659.2008.00045.x PMID:19453467
- Simmerman JM, Lertiendumrong J, Dowell SF, Uyeki T, Olsen SJ, Chittaganpitch M et al. The cost of influenza in Thailand. *Vaccine* 2006;24:4417–26. doi:10.1016/j.vaccine.2005.12.060 PMID:16621187
- Nair H, Brooks WA, Katz M, Roca A, Berkley J, 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. doi:10.1016/S0140-6736(11)61051-9 PMID:22078723
- Azziz-Baumgartner E, Alamgir ASM, Rahman M, Homaira N, Sohel BM, Sharker MAY et al. Incidence of influenza-like illness and severe acute respiratory infection during three influenza seasons in Bangladesh, 2008–2010. *Bull World Health Organ* 2012;90:12–9. doi:10.2471/BLT.11.090209 PMID:22271960
- Hasan K, Jolly P, Marquis G, Roy E, Podder G, Alam K et al. Viral etiology of pneumonia in a cohort of newborns till 24 months of age in Rural Mirzapur, Bangladesh. *Scand J Infect Dis* 2006;38:690–5. doi:10.1080/00365540600606473 PMID:16857616
- Brooks WA, Goswami D, Rahman M, Nahar K, Fry A, Balish A et al. Influenza is a major contributor to childhood pneumonia in a tropical developing country. *Pediatr Infect Dis J* 2010;29:216–21. doi:10.1097/INF.0b013e3181bc23fd PMID:20190613
- Lindblade KA, Arvelo W, Gray J, Estevez A, Frenkel G, Reyes L et al. A comparison of the epidemiology and clinical presentation of seasonal influenza A and 2009 pandemic influenza A (H1N1) in Guatemala. *PLoS ONE* 2010;5:e15826. doi:10.1371/journal.pone.0015826 PMID:21209850
- Gordon A, Ortega O, Kuan G, Reingold A, Saborio S, Balmaseda A et al. Prevalence and seasonality of influenza-like illness in children, Nicaragua, 2005–2007. *Emerg Infect Dis* 2009;15:408–14. doi:10.3201/eid1503.080238 PMID:19239753
- Simmerman JM, Tawatsupha P, Kingnate D, Fukuda K, Chaising A, Dowell SF. Influenza in Thailand: a case study for middle income countries. *Vaccine* 2004;23:182–7. doi:10.1016/j.vaccine.2004.05.025 PMID:15531035
- Yoshida LM, Suzuki M, Yamamoto T, Nguyen HA, Nguyen CD, Nguyen AT et al. Viral pathogens associated with acute respiratory infections in central Vietnamese children. *Pediatr Infect Dis J* 2010;29:75–7. doi:10.1097/INF.0b013e3181af61e9 PMID:19907358
- Ndata U [Internet]. El Salvador. New York: United Nation Statistics Division; 2012. Available from: <http://data.un.org/CountryProfile.aspx?crName=EL%20SALVADOR#Summary> [accessed 11 July 2012].
- Pan American Health Organization [Internet]. PAHO-CDC generic protocol for influenza surveillance. Washington: PAHO, Health Surveillance and Disease Management Area; 2006 (Draft No. PAHO/HDM/CD/V/411/06). Available from: <http://www.paho.org/English/AD/DPC/CD/flu-snl-gpis.htm> [accessed 11 July 2012].
- World health statistics 2011*. Geneva: World Health Organization; 2011.
- Pan American Health Organization [Internet]. Seasonal influenza vaccine in the Americas. Washington: PAHO; 2011. Available from: http://new.paho.org/hq/index.php?option=com_content&task=blogcategory&id=4048&Itemid=4210&lang=en [accessed 25 July 2012].
- Centers for Disease Control and Prevention [Internet]. People at high risk of developing flu-related complications. Atlanta: CDC; 2009. Available from: <http://www.cdc.gov/h1n1flu/highrisk.htm> [accessed 11 July 2012].
- World Health Organization [Internet]. Integrated management of childhood illness chart booklet – standard. Geneva: WHO & United Nations Children's Fund; 2008. Available from: http://www.who.int/maternal_child_adolescent/documents/IMCI_chartbooklet/en/index.html [accessed 11 July 2012].
- World Health Organization [Internet]. CDC protocol of realtime RTPCR for influenza A (H1N1). Atlanta: Centers for Disease Control and Prevention; 2009. Available from: http://www.who.int/csr/resources/publications/swineflu/CDCRealtimeRTPCR_SwineH1Assay-2009_20090430.pdf [accessed 11 July 2012].
- Barr IG, McCauley J, Cox N, Daniels R, Engelhardt OG, Fukuda K et al. Epidemiological, antigenic and genetic characteristics of seasonal influenza A(H1N1), A(H3N2) and B influenza viruses: basis for the WHO recommendation on the composition of influenza vaccines for use in the 2009 Northern Hemisphere season. *Vaccine* 2010;28:1156–67. doi:10.1016/j.vaccine.2009.11.043 PMID:20004635
- 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. doi:10.1371/journal.pone.0001296 PMID:18074020
- Dirección General de Estadística y Censos [Internet]. VI Censo de Población y V de Vivienda. San Salvador: Ministerio de Economía; 2007. Spanish. Available from: <http://www.digestyc.gob.sv/> [accessed 11 July 2012].
- World Health Organization [Internet]. WHO recommendations on the composition of influenza virus vaccines, 2012. Available from: <http://www.who.int/influenza/vaccines/virus/recommendations/en/index.html> [accessed 2 August 2012].
- Miller E, Hoschler K, Hardelid P, Stanford E, Andrews N, Zambon M. Incidence of 2009 pandemic influenza A H1N1 infection in England: a cross-sectional serological study. *Lancet* 2010;375:1100–8. doi:10.1016/S0140-6736(09)62126-7 PMID:20096450
- Cowling BJ, Chan KH, Fang VJ, Lau LLH, So HC, Fung ROP et al. Comparative epidemiology of pandemic and seasonal influenza A in households. *N Engl J Med* 2010;362:2175–84. doi:10.1056/NEJMoa0911530 PMID:20558368
- The global burden of disease: 2004 update*. Geneva: World Health Organization; 2008.
- Brooks WA, Goswami D, Rahman M, Nahar K, Fry AM, Balish A et al. Influenza is a major contributor to childhood pneumonia in a tropical developing country. *Pediatr Infect Dis J* 2010;29:216–21. doi:10.1097/INF.0b013e3181bc23fd PMID:20190613
- Pan American Health Organization [Internet]. Informe regional de SIREVA II, 2010. Washington: PAHO; 2011. Spanish. Available from: http://joomla.salumedia.com/index.php?option=com_docman&task=cat_view&gid=809&Itemid=4031&mosmsg=The+file+is+not+available+on+the+server [accessed 11 July 2012].
- World Health Organization [Internet]. Immunization profile – El Salvador. Geneva: WHO; 2011. Available from: http://apps.who.int/immunization_monitoring/en/globalsummary/countryprofilresult.cfm?C=slv [accessed 11 July 2012].
- Viboud C, Alonso WJ, Simonsen L. Influenza in tropical regions. *PLoS Med* 2006;3:e89. doi:10.1371/journal.pmed.0030089 PMID:16509764
- Shek LP, Lee BW. Epidemiology and seasonality of respiratory tract virus infections in the tropics. *Paediatr Respir Rev* 2003;4:105–11. doi:10.1016/S1526-0542(03)00024-1 PMID:12758047
- Chew FT, Dorasingham S, Ling AE, Kumarasinghe G, Lee BW. Seasonal trends of viral respiratory tract infections in the tropics. *Epidemiol Infect* 1998;121:121–8. doi:10.1017/S0950268898008905 PMID:9747763
- Yang L, Wong CM, Chan KP, Chau PY, Ou CQ, Chan KH et al. Seasonal effects of influenza on mortality in a subtropical city. *BMC Infect Dis* 2009;9:133. doi:10.1186/1471-2334-9-133 PMID:19698116
- Harper S, Bradley J, Englund J, File T, Gravenstein S, Hayden F et al. Seasonal influenza in adults and children – diagnosis, treatment, chemoprophylaxis and institutional outbreak management: clinical practice guidelines of the Infectious Diseases Society of America. *Clin Infect Dis* 2009;48:1003–32. doi:10.1086/598513 PMID:19281331