Clinical manifestations, outcomes and prognostic factors of the 2009 pandemic influenza A (H1N1) in children

Manifestações clínicas, desfechos e fatores prognósticos da influenza pandêmica A (H1N1) de 2009 em crianças

Manifestaciones clínicas, desenlaces y factores pronósticos de la influenza pandémica A (H1N1) 2009 en niños

Luana Lenzi[1], Ângela Maron de Mello[2], Lineu Roberto da Silva[3], Mônica Holtz C. Grochocki[4], Roberto Pontarolo[5]

ABSTRACT

Objective: To analyze the pandemic influenza A (H1N1) 2009 in children of the state of Paraná, Southern Brazil, in order to identify clinical features, lethality, and prognostic factors for the infection.

Methods: This was a retrospective observational study. Data were collected from the National Notifiable Disease System (Sinan) from the Brazilian Ministry of Health, from March to December, 2010. Children aged between zero and 12 years-old, with laboratorial confirmation of the infection, were included. Variables related to demographic and clinical characteristics and outcomes were evaluated statistically in order to compare the lethality rates in the presence and absence of these factors. The prognostic factors were identified by logistic regression, being significant $p<0.05$.

Results: 1,307 children were included and 19 of them died. Risk factors for death were heart diseases (OR 7.1; 95%CI 1.5–32.7), immunosuppression (OR 14.9; 95%CI 3.9–56.2), dyspnea (OR 9.5; 95%CI 2.8–32.9), pneumonia (OR 23.8; 95%CI 2.4–239.8), presence of wheezing (OR 11,9; 95%CI 1.4–103.7), and time to start treatment since the onset of symptoms (OR 1.3; 95%CI 1.2–1.5). Early treatment with the antiviral drug oseltamivir was a protective factor for death (OR 0.012; 95%CI 0.003–0.05).

Conclusions: Underlying risk factors had a major role in determining outcomes. Early diagnosis and treatment were important for the reduction of deaths from *influenza* A (H1N1) 2009 in children.

Key-words: Influenza A Virus, H1N1 Subtype; risk factors; lethality; signs and symptoms; child.

RESUMO

Objetivo: Descrever as características clínicas e a letalidade, além de analisar os fatores prognósticos da infecção pela *influenza* pandêmica A (H1N1), em crianças do estado do Paraná.

Métodos: Estudo observacional e retrospectivo. Os dados foram coletados a partir do Sistema Nacional de Agravos de Notificação (Sinan), do Ministério da Saúde, entre março e dezembro de 2010. Foram incluídas as crianças com idade entre zero e 12 anos, com confirmação laboratorial da infecção. As variáveis referentes às características demográficas e clínicas e aos desfechos foram avaliadas estatisticamente a fim de comparar as taxas de letalidade na presença e na ausência desses fatores. Os fatores prognósticos foram identificados por regressão logística. Consideraram-se como significativos os valores de $p<0,05$.

Resultados: Foram incluídas 1.307 crianças, das quais 19 foram a óbito. Os fatores de risco para o óbito foram cardiopatias (OR 7,1; IC95% 1,5–32,7), imunodepressão (OR 14,9; IC95% 3,9–56,2), dispneia (OR 9,5; IC95% 2,8–32,9), pneumonia (OR 23,8; IC95% 2,4–239,8), presença de sibilos (OR 11,9; IC95% 1,4–103,7) e tempo para

Instituição: Universidade Federal do Paraná (UFPR), Curitiba, PR, Brasil

[1]Mestre em Ciências Farmacêuticas pela UFPR, Curitiba, PR, Brasil

[2]Mestre em Ciências Biológicas pela UFPR; Coordenadora do Centro de Informações Estratégicas e Respostas Rápidas da Secretaria Estadual de Saúde, Curitiba, PR, Brasil

[3]Mestre em Ciências Veterinárias pela UFPR; Sanitarista da Secretaria de Estado da Saúde, Curitiba, PR, Brasil

[4]Mestre em Ciências pela UFPR; Diretora Técnica do Consórcio Intergestores Paraná Saúde, Curitiba, PR, Brasil

[5]Doutor em Bioquímica; Professor-Associado do Curso de Graduação em Farmácia da UFPR, Curitiba, PR, Brasil

Endereço para correspondência:
Roberto Pontarolo
Rua Prefeito Lothário Meissner, 632 – Jardim Botânico
CEP 80210-170 – Curitiba/PR
E-mail: pontarolo@ufpr.br

Conflito de interesse: nada a declarar

Recebido em: 14/10/2011
Aprovado em: 22/2/2012

o início do tratamento a partir do início dos sintomas (OR 1,3; IC95% 1,2–1,5). O tratamento precoce com o antiviral oseltamivir foi um fator de proteção ao óbito (OR 0,012; IC95% 0,003–0,05).

Conclusões: Os fatores de risco subjacentes apresentaram papel fundamental na determinação dos desfechos. O diagnóstico e o tratamento precoce foram importantes para a diminuição dos óbitos pela *influenza* A (H1N1) 2009 em crianças.

Palavras-chave: Vírus da Influenza A Subtipo H1N1; fatores de risco; letalidade; sinais e sintomas; criança.

RESUMEN

Objetivo: Describir las características clínicas y la letalidad, además de analizar los factores pronósticos de la infección por la influenza pandémica A (H1N1) en niños de la provincia de Paraná (Brasil).

Métodos: Se trató de un estudio observacional y retrospectivo. Los datos fueron recogidos a partir del Sistema Nacional de Agravos de Notificação (Sinan), del Ministerio de Salud, entre marzo y diciembre de 2010. Se incluyeron a los niños con edad entre cero y 12 años, con confirmación laboratorial de la infección. Las variables referentes a las características demográficas y clínicas y a los desenlaces fueron evaluadas estadísticamente, a fin de comparar las tasas de letalidad en la presencia y ausencia de esos factores. Los factores pronósticos fueron identificados por regresión logística. Se consideraron como significativos los valores de $p<0,05$.

Resultados: Se incluyeron a 1.307 niños, de los que 19 fallecieron. Los factores de riesgo para óbito fueron cardiopatías (OR 7,1; IC95% 1,5-32,7), inmunodepresión (OR 14,9; IC95% 3,9-56,2), disnea (OR 9,5; IC95% 2,8-32,9), neumonía (OR 23,8; IC95% 2,4-239,8), presencia de silbidos (OR 11,9; IC95% 1,4-103,7) y tiempo para el inicio del tratamiento a partir del inicio de los síntomas (OR 1,3; IC95% 1,2-1,5). El tratamiento temprano con el antiviral oseltamavir fue un factor de protección al óbito (OR 0,012; IC95% 0,003-0,05).

Conclusiones: La tasa de letalidad observada en niños fue menor que la encontrada en el grupo que contrajo la enfermedad. Los factores de riesgo subyacentes presentaron un rol fundamental en la determinación de los desenlaces. El diagnóstico y el tratamiento tempranos fueron importantes para la reducción de los óbitos por influenza A (H1N1) 2009 en niños.

Palabras clave: Virus de la Influenza A Subtipo H1N1; factores de riesgo; letalidad; señales y síntomas; niño.

Introduction

The 2009 influenza A (H1N1) pandemic, the first of the 21st Century, originated in Mexico and the United States[1,2]. According to the World Health Organization (WHO), 208 countries reported laboratory-confirmed cases of the disease in 2009, and 12,799 deaths were recorded[3].

Several studies showed that most individuals with that infection had mild symptoms and recovered in a few days[4]. Its pathogenesis, in general, was the same as the one seen in cases of the common flu, and the disease seemed to progress spontaneously to resolution. However, clinical presentations varied widely, from asymptomatic cases to the development of severe or lethal pneumonia[5,6]. Occasionally, clinical conditions deteriorated rapidly (in about five days) into atypical pneumonia, that is, a viral pneumonia with few physical signs, but clearly defined on radiographs, and about half of the patients had acute fulminating respiratory distress[7].

The influenza A (H1N1) virus may produce severe lung infection in young individuals without comorbidities, particularly children, and high hospitalization rates were recorded for this age group[8]. Children are particularly vulnerable to complications during influenza infection, and further studies should be conducted to improve our understanding of determinants and risk factors of deterioration and death in this population. However, few reports have described influenza A among children[9-11]. Because the severity of this disease may change according to geography and seasonality[12], the purpose of this study was to collect data about this disease and its possible risk factors among children infected in the 2009 pandemic in the state of Paraná, Brazil. Moreover, it described the clinical characteristics, lethality and prognostic factors of influenza A (H1N1) infection among children.

Methods

This observational retrospective study was conducted from March to December 2009. Data were collected from structured questionnaires about the 2009 influenza A (H1N1) pandemic stored in the National Reportable Disease System (SINAN) of the Brazilian Ministry of Health.

The study population comprised children aged zero to 12 years living in Paraná, a state in southern Brazil. Cases

were included if confirmed as 2009 pandemic influenza A (H1N1) infection by the results of laboratory tests performed using the reverse-transcriptase polymerase chain reaction (RT-PCR). Suspected cases and those confirmed by clinical and epidemiological criteria, which included fever (>38º C), cough, close contact with an infected person or history of recent (up to ten days) travel to countries with documented cases, with or without other associated signs and symptoms, underwent laboratory tests for confirmation. Samples were analyzed using RT-PCR during the pandemic event, and results were gathered in the beginning of 2010 for a final assessment of the cases and the production of this study. After collection, records were individually checked for inconsistencies or missing information. Patients were excluded if RT-PCR results were negative or data about symptoms, clinical and demographic data, or outcome (hospitalization, cure or death) were missing from their notification forms.

The variables included were: age; presence of known factor of influenza deterioration, entered in the SINAN form (yes or no, separately); use of oseltamivir; hospitalization; results of chest X-ray; and dates of symptom onset, treatment initiation (when treated) and date of death (in case of death).

Statistical analysis compared the lethality of the 2009 influenza A (H1N1) pandemic among children according to the characteristics and variables under study. Descriptive statistics included the calculation of means and standard deviations for continuous variables and absolute numbers and proportions for categorical variables. Risk factors were investigated separately by comparing the distribution of variables according to cure or death. Proportions were compared using the Z score, a chi-square test for categorical variables, the Student *t* test for continuous variables and measures of central tendency. In addition, possible associations between variables and death were analyzed using univariate logistic regression, and results were expressed by odds ratio (OR) and 95% confidence interval (95%CI). Outcomes were used as dependent variables and classified as 0=cure and 1=death. The variables were evaluated using univariate analysis and the forced-entry method, and the constant was included in the models. The Statistical Package for the Social Sciences (SPSS) 17.0 was used for statistical analyses, and the level of significance was set at $p<0.05$.

This study followed the Helsinki Declaration and the applicable Brazilian laws, and was approved by the Ethics in Research Committee of the Health Sciences

Table 1 - Main characteristics of the children that had influenza A (H1N1) during the 2009 pandemic in the state of Paraná, Brazil

Characteristics		Number	%	Cure	%	Death	%	*p*-value	Z score
Sex	Male	694	53.1	683	98.4	11	1.6	0.673	---
	Female	613	46.9	605	98.7	8	1.3		
Skin color/ ethnicity	White	1081	82.7	1066	98.6	15	1.4	0.349	---
	Black	15	1.1	15	100	0	0		---
	Asian	12	0.9	11	91.7	1	8.3		---
	Mixed ethnicity	94	7.2	93	98.9	1	1.1		---
	Native Brazilian	31	2.4	31	100	0	0		---
Comorbidity	With comorbidity	239	18.3	231	96.7	8	3.3	0.007	D>C
	Without comorbidity	1068	81.7	1057	99	11	1		C>D
	Heart disease	23	1.8	21	91.3	2	8.7	0.003	D>C
	Pulmonary disease	148	11.3	144	97.3	4	2.7	0.178	---
	Kidney disease	5	0.4	5	100	0	0	0.786	---
	Blood disease	6	0.5	6	100	0	0	0.766	---
	Immunodepression	19	1.5	16	84.2	3	15.8	0.000	D>C
	Diabetes	6	0.5	6	100	0	0	0.766	---
	Obesity	4	0.3	4	100	0	0	0.808	---
Oseltamivir	Not treated	9	1.6	3	33.3	6	66.7	<0.001	D>C
	Treated	556	98.4	543	97.6	13	2.4		C>D
Hospitalization	Not hospitalized	832	63.7	831	99.9	1	0.1	<0.001	
	Hospitalized	475	36.3	457	96.2	18	3.8		

D: death C: cure

Department of the Universidade Federal do Paraná (UFPR), Curitiba, Brazil.

Results

In our sample, the first case of this disease among children, confirmed by laboratory tests, occurred on June 15, 2009, and the patient was a one-year-old boy. A total of 1,307 children aged zero to 12 years were identified. During the 2009 pandemic, their infection by the influenza A (H1N1) virus was confirmed by laboratory tests using RT-PCR. Mean age was 6.2 (± 3.8) years. A total of 19 deaths were recorded, and lethality was 1.5%, lower than that found for infected individuals in general, which was 5.8% (274/4,740). Mean age of the children that died was 4.7 (± 3) years.

Table 1 shows the main characteristics of our patient sample and their association with the disease outcomes. In this sample, 53.1% were boys and 82.7% were white. A total of 239 children had one or more underlying diseases (comorbidities). The most frequent comorbidities were pulmonary diseases, in 148 (11.3%), heart diseases, in 23 (1.8%), and immunodepression, in19 (1.5%). Only heart diseases and immunodepression had a significant association with outcomes, and the rate of deaths was greater than the rate of cure.

Information about whether children received treatment with the antiviral drug oseltamivir was found in the notification forms of only 565 children. Of those, 556 (98.4%) received antiviral treatment. Mean time from symptom onset to treatment initiation in the group that was cured was two days (zero to 15), whereas in the group that died it was six days (zero to 20) ($p<0.001$). Treatment with oseltamivir was significantly associated with death, and the proportion of deaths was greater among children that did not receive it.

Hospitalization was recorded for 475 (36.3%) of the children. However, death occurred despite drug treatment and intensive care during hospitalization. The proportion of deaths was greater among hospitalized patients than among those that did not require hospitalization. The patients that died stayed about 6.4 days (zero to 21) in the hospital.

Table 2 - Clinical characteristics of the 2009 influenza A (H1N1) pandemic among children of the state of Paraná, Brazil

		n	%	Cure	%	Death	%	p-value	Z score
Signs and Symptoms Clinical presentation	Fever	1282	98.1	1263	98.5	19	1.5	0.540	---
	Cough	1216	93	1198	98.5	18	1.5	0.769	---
	Rhinorrhea	895	68.5	885	98.9	10	1.1	0.134	---
	Sore throat	674	51.6	670	99.4	4	0.6	0.007	C>D
	Chills	565	43.2	558	98.8	7	1.2	0.571	---
	Myalgia	561	42.9	555	98.9	6	1.1	0.314	---
	Dyspnea	478	36.6	462	96.7	16	3.3	<0.001	D>C
	Headache	300	22.9	299	99.7	1	0.3	0.065	---
	Arthralgia	247	18.9	245	99.2	2	0.8	0.348	---
	Vomiting	165	12.6	164	99.4	1	0.6	0.330	---
	Conjunctivitis	150	11.5	150	100	0	0	0.114	---
	Diarrhea	135	10.3	131	97	4	3	0.122	---
	Abdominal pain	36	2.8	34	94.4	2	5.6	0.037	D>C
	Nausea	25	1.9	25	100	0	0	0.540	---
	Wheezing	7	0.5	6	85.7	1	14.3	0.004	D>C
	Chest pain	5	0.4	5	100	0	0	0.786	---
	Pneumonia	4	0.3	3	75	1	25	<0.001	D>C
	Cyanosis	1	0.1	1	100	0	0	---	---
Chest X-ray	Normal	109	30.2	108	30.9	1	9.1	0.002	---
	Interstitial infiltrate	201	55.7	195	55.7	6	54.5		---
	Consolidation	16	4.4	13	3.7	3	27.		D>C
	Mixed findings	13	3.6	12	3.4	1	9.1		---

D: death C: cure

The association of clinical signs of the disease and outcomes is shown in Table 2. The main signs and symptoms were fever, cough, rhinorrhea and sore throat, found in affected over 50% of the children that were examined. Seven patients had wheezing at lung auscultation, and one, cyanosis. Chest X-rays were obtained for 339 children. Of those, 55.7% had interstitial infiltrates and 30.2% had normal results. Dyspnea, abdominal pain, wheezing and pneumonia were significantly associated with the outcomes. The Z score showed that the proportion of deaths was greater than that of cures for children with those clinical signs and symptoms. In addition, of the patient that died, 19 had fever, 18 (94.7%) had cough and 16 (84.2%), dyspnea, which suggests that these are the signs and symptoms most closely associated with disease deterioration.

The variables associated with outcomes and higher number of deaths were analyzed using logistic regression to determine prognostic factors. Among children that had the influenza A (H1N1) viral infection during the 2009 pandemic, risk factors of death were heart disease (OR 7.1; 95%CI 1.5–32.7) and immunodepression (OR 14.9; 95%CI 3.9–56.2), and their presence increased the odds ratio for death. The use of the antiviral drug oseltamivir was a protective factor against death (OR 0.012; 95%CI 0.003–0.05), and not using this medicine resulted in an 83.3 times greater odds ratio for death (95%CI 18.9–333.3). The analysis of oseltamivir use also revealed the importance of treating the patient at an early stage, as each additional day between symptom onset and treatment (measured as a continuous variable) increased the odds ratio for death in 30% (95%CI 20–50).

Among the clinical signs and symptoms of the disease, dyspnea (OR 9.5; 95%CI 2.8–32.9), pneumonia (OR 23.8; 95%CI 2.4–239.8) and wheezing at lung auscultation (OR 11.9; 95%CI 1.4–103.7) were associated with greatest clinical severity and increased odds ratio for death. Abdominal pain was not associated (p=0.056) with risk of death.

Discussion

Lethality in the presence or absence of epidemiological, clinical and therapeutic factors showed that there was a significant association between outcomes and the following factors: comorbidities, use of the antiviral drug oseltamivir, time from symptom onset to treatment initiation and hospitalization. Hospitalization was present in the most severe clinical cases, which explains the higher frequency of death in this subgroup.

The early treatment with the antiviral drug oseltamivir, initiated within two days of symptom onset, has already been reported as a protective factor that decreased the risk of admission to an intensive care unit (ICU) and death for hospitalized patients during the 2009 influenza A (H1N1) pandemic[11,13]. In our study, mean time to treatment initiation after symptoms onset in patients that were cured was two days, differently from those that died, whose treatment started at a mean six days after symptom onset. This result is similar to those reported in other studies, which also suggested that there were benefits for patients treated with oseltamivir when compared with those that did not receive this treatment[13,14]. The rapid progression of the disease in fatal cases was also reported in the United Kingdom[9] and Germany[11], which stresses the importance of prevention against this disease.

The association of heart disease with complications and death due to influenza is likely to be the result of viral replication in cardiac tissue, as demonstrated by other authors[15]. Another possible explanation for the association of its pathogenesis with extra-respiratory complications has been suggested by the connection between acute respiratory distress syndrome (ARDS) and multiple organ dysfunction syndrome (MODS), when the hepatic, renal, central nervous, hematologic, gastrointestinal and cardiac systems are more commonly affected[16].

The MODS pathogenesis has not been fully elucidated, but it seems to involve microcirculation and mitochondrial metabolism, including cytokine released in the circulation[17]. Moreover, during infection by the influenza virus, the myocardium is affected, which may be another possible explanation for the fact that heart diseases is a risk factor of death due to infection[18]. Studies in the United Kingdom showed that 12% of the patients with infection by the influenza virus had elevated levels of cardiac troponin, released when there is a lesion to the heart muscle, which points to possible viral activity in the heart muscle during infection[19]. Ison *et al* reported that a significant proportion of patients in the initial phases of infection by the influenza virus had abnormal electrocardiograms, associated or not with cardiac lesion markers or contractile abnormalities on echocardiograms[20].

Other studies showed that the flu is a known cause of myopericarditis. PCR of biopsy samples confirmed that a mean 45.5% of the patients evaluated had the viral genome in the myocardium[21]. This evidence supports the conclusion that cardiac involvement during acute infection by the influenza virus occurs due to the direct effect of the virus on the myocardium, which exacerbates severity for patients with heart diseases (cardiac insufficiency, myocarditis, etc.).

Another important finding of infection in children was that wheezing was associated with the increase of the odds ratio for death, which may contribute to a rapid diagnosis and early intervention in the most severe cases. Wheezing is defined as a continuous musical long-lasting tone originating in the airways and produced by bronchi obstruction[22]. It may be present in cases of lower airway disorders (bronchi, bronchiole, alveoli and lungs) as a result of complications of the influenza infection[23]. According to the results of our study, in addition of lung auscultation, chest X-rays should help to define disease severity when consolidation and interstitial infiltrates are found.

Our results showed that the lethality of the influenza A (H1N1) pandemic among children aged zero to 12 years in 2009 was 1.45%. Other studies conducted in Canada, Germany, the United Kingdom and Argentina found rates that ranged from 7 to 39%[9,11,24,25] of the patients in ICUs. However, all reports confirmed that lethality was higher than that found for seasonal influenza. Differences in the organization of healthcare, including the criteria for ICU admission, age of the different groups and selection of study sites may partly explain differences between studies.

Our study had several limitations, such as the fact that infection has often been underreported, although this might have been minimized in the 2009 pandemic due to the greatest awareness of the importance of notification during outbreaks. Moreover, patients that were infected may have been left out because they did not seek medical attention. An additional limitation may be associated with the records of patient clinical characteristics and comorbidities, based on the fields of the structured questionnaire, which was prepared according to risk factors and the characteristics of seasonal influenza. Therefore, although there was a field for "other conditions", several items may have been partially omitted because clinical evaluations and data collection were not standardized. Moreover, only children whose infection was confirmed by RT-PCR were included in the study. Also, data were collected according to number of days, which precluded the calculation of time from symptom onset to treatment initiation in hours. Finally, an important limitation of this study was the lack of multiple analysis using logistic regression.

The lethality of the 2009 influenza A (H1N1) pandemic among children aged zero to 12 years was 1.5% of the cases confirmed by RT-PCR. The major symptoms were: fever, cough, rhinorrhea and sore throat. The risk factors of death were: heart disease, immunodepression, dyspnea, pneumonia and wheezing. Early treatment with the antiviral drug oseltamivir was a protective factor against death. Our results stress the role of underlying risk factors, particularly in the progression of the most severe cases, and suggest that early diagnosis and treatment were important to reduce lethality of the 2009 influenza A (H1N1) pandemic among children.

Acknowledgments

We thank the technical team of the Department of Health of the state of Paraná, Brazil, who were responsible for keeping data in the SINAN (DATASUS) electronic system.

References

1. Vaqué Rafart J, Gil Cuesta J, Brotons Agulló M. Main features of the new Influenza virus a pandemic (H1N1). Med Clin (Barc) 2009;133:513-21.
2. Gatherer D. The 2009 H1N1 Influenza outbreak in its historical context. J Clin Virol 2009;45:174-8.
3. World Health Organization [homepage on the Internet]. Pandemic (H1N1) 2009 - update 91 [cited 2010 Jul 14]. Available from: http://www.who.int/csr/don/2010_03_12/en/index.html
4. Hui DS, Lee N, Chan PK. Clinical management of pandemic 2009 influenza A (H1N1) infection. Chest 2010;137:916-25.
5. Gérardin P, El Amrani R, Cyrille B, Gabrièle M, Guillermin P, Boukerrou M *et al*. Low clinical burden of 2009 pandemic influenza A (H1N1) infection during pregnancy on the island of La Réunion. PLoS One 2010;5:e10896.
6. García AH, Sánchez NG, Martí AT. Influenza A (H1N1): clinical manifestations and prophylactic and therapeutic indications. Arch Bronconeumol 2010;46 (Suppl 2):19-23.
7. Ho TS, Wang SM, Liu CC. Historical review of pandemic Influenza A in Taiwan, 2009. Pediatr Neonatol 2010;51:83-8.
8. Restrepo MI, Mazo M, Anzueto A. Influenza A (H1N1). Experience in the United States. Arch Bronconeumol 2010;46 (Suppl 2):13-8.
9. Lister P, Reynolds F, Parslow R, Chan A, Cooper M, Plunkett A *et al*. Swine-origin influenza virus H1N1, seasonal influenza virus, and critical illness in children. Lancet 2009;374:605-7.
10. Van Zwol A, Witteveen R, Markhorst D, Geukers VG. Clinical features of a Dutch cohort of critically ill children due to the 2009 new influenza A H1N1 pandemic. Clin Pediatr (Phila) 2011;50:69-72.
11. Altmann M, Fiebig L, Soyka J, von Kries R, Dehnert M, Haas W. Severe cases of pandemic (H1N1) 2009 in children, Germany. Emerg Infect Dis 2011; 17:186-92.
12. Peiris JS, Poon LL, Guan Y. Emergence of a novel swine-origin Influenza A virus (S-OIV) H1N1 virus in humans. J Clin Virol 2009;45:169-73.
13. Jain S, Kamimoto L, Bramley AM, Schmitz AM, Benoit SR, Louie J *et al*. Hospitalized patients with 2009 H1N1 influenza in the United States, April-June 2009. N Engl J Med 2009;12;361:1935-44.
14. Domínguez-Cherit G, Lapinsky SE, Macias AE, Pinto R, Espinosa-Perez L, de la Torre A *et al*. Critically ill patients with 2009 influenza A (H1N1) in Mexico. JAMA 2009;302:1880-7.
15. Cioc AM, Nuovo GJ. Histologic and *In Situ* viral findings in the myocardium in cases of Sudden, unexpected death. Mod Pathol 2002;15:914-22.

16. Dorinsky PM, Gadek JE. Multiple organ failure. Clin Chest Med 1990;11:581-91.
17. Kuiken T, Taubenberger JK. Pathology of human Influenza revisited. Vaccine 2008;26 (Suppl 4):D59-66.
18. Mamas AM, Fraser D, Neyses L. Cardiovascular manifestations associated with influenza virus infection. Int J Cardiol 2008;130:304-9.
19. Greaves K, Oxford JS, Price CP, Clarke GH, Crake T. The prevalence of myocarditis and skeletal muscle injury during acute viral infection in adults: measurement of cardiac troponins I and T in 152 patients with acute Influenza infection. Arch Intern Med 2003;163:165-8.
20. Ison MG, Campbell V, Rembold C, Dent J, Hayden FG. Cardiac findings during uncomplicated acute influenza in ambulatory adults. Clin Infect Dis 2005;40:415-22.
21. Bowles NE, Ni J, Kearney DL, Pauschinger M, Schultheiss HP, McCarthy R *et al*. Detection of viruses in myocardial tissues by polymerase chain reaction. evidence of adenovirus as a common cause of myocarditis in children and adults. J Am Coll Cardiol 2003;42:466-72.
22. Brussee JE, Smit HA, Koopman LP, Wijga AH, Kerkhof M, Corver K *et al*. Interrupter resistance and wheezing phenotypes at 4 years of age. Am J Respir Crit Care Med 2004;169:209-13.
23. Martinez FD, Wright AL, Taussig LM, Holberg CJ, Halonen M, Morgan WJ. Asthma and wheezing in the first six years of life. The Group Health Medical Associates. N Engl J Med 1995;332:133-8.
24. Jouvet P, Hutchison J, Pinto R, Menon K, Rodin R, Choong K *et al*. Critical illness in children with influenza A/pH1N1 2009 infection in Canada. Pediatr Crit Care Med 2010;11:603-9.
25. Farias JA, Fernández A, Monteverde E, Vidal N, Arias P, Montes MJ *et al*. Critically ill infants and children with influenza A (H1N1) in pediatric intensive care units in Argentina. Intensive Care Med 2010;36:1015-22.