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Influenza A (H1N1)pdm09 viral clearance kinetics in hospitalized children☆,☆☆

Cinetica del aclaramiento del virus de la gripe A (H1N1) en niños hospitalizados

Dear Editor:

Children are the main source of transmission and reservoir of influenzavirus. It is believed that control of the virus is poorer in the paediatric population, and that therefore children have longer shedding periods compared to other age groups.[1] The aim of this study was to analyse the influenza A (H1N1)pdm09 virus kinetics and clearance in hospitalized children and to establish their association with different clinical variables.

We conducted a prospective and observational study in the Departments of Paediatrics and Microbiology of 2 hospitals in Valladolid, Spain, and the National Influenza Centre of Valladolid. The study period ranged from week 40 of 2015 to week 20 of 2016, corresponding to the 2015–2016 flu season. We included inpatients aged less than 14 years with laboratory-confirmed influenza A(H1N1)pdm09 virus infection. For the purpose of testing, we collected throat swab samples in patients aged more than 2 years and samples of nasopharyngeal lavage in younger children. The latter allows a more representative sample to be obtained and could overestimate the viral RNA load (VRL) in this group of patients. To analyse the VRL, we collected samples on the day of admission and days 4, 8 and 12 or until negative, if this occurred before day 12. The variables under study included the duration of symptoms from onset, number of long-term excretors (LTE, defined as patients with periods of viral shedding [VS] greater than 8 days from onset), and number of short-term excretors (STE, defined as patients with VS < 8 days). We obtained written informed consent from the legal guardians of every participant.

Influenza A(H1N1)pdm09 virus infection was confirmed by reverse-transcription polymerase chain reaction (RT-PCR) using MAGPIX and NxTAG-RPP reagents (Luminex; Austin, TX, USA). The VRL was measured by quantitative RT-PCR in the influenza-positive samples using a 7500-Fast Real-Time PCR System (Applied Biosystems; Foster City, CA, USA) and LightMix-Kit Influenza A Virus M2 reagents (Roche; Basel, Switzerland). We used the Allplex Respiratory Full Panel (Seegene) reagent kit in every patient, which can detect 19 viral and 7 bacterial targets, including the M2 and H genes of the main endemic strains circulating in Spain. The statistical analysis focused on the comparison of different clinical variables and their relationship with the duration of VS. We used the software SPSS version 20.0 to perform the statistical tests.

We recruited 24 patients (54% male; median age, 17.5 months; age range: 0–120 months) during the study period. Severe asthma and cystic fibrosis were the only comorbidities, detected in two patients (8%), and these were the only patients that received the influenza vaccine. We found the highest VRL in the first sample taken on the day of admission in 87.5% of patients (mean CV_1, 7032.9 copies/mL; 95% confidence interval [CI], 1131.2—16 418.5), with a decrease in the second sample (mean CV_2, 239.5 copies/mL; 95% CI, 51.4–547.9). All patients tested negative in the third timepoint. Fifty percent of patients (12/24) were LTEs. The mean length of stay was 7.4 days (95% CI, 5.1–9.9) in the LTE group, compared to 5.6 days (95% CI, 3.4–8.0) in the STE group, a difference that was not statistically significant (Student *t* test *P* = 0.294) (Table 1).

The VRL became undetectable after 9–12 days from onset in 67% (8/12) of LTEs, between 13 and 16 days in 25% (3/12) and after 12 days in 8% (1/12) (Fig. 1). We found viral or bacterial coinfections with influenza in 58.3% (7/12) of LTEs (5 bacterial and 2 viral). Six patients required admission to the paediatric intensive care unit (PICU), 4 of them were LTEs. The 4 LTEs required respiratory support with non-invasive ventilation (NIV), and none required vasoactive drugs. We detected viral or bacterial coinfection in 45.8% of patients (11/24), bacterial in 54.5% (6/11) (involving *Moraxella catarrhalis, Streptococcus pneumoniae, Staphylococcus aureus* and *Haemophilus influenza*), and viral in 45.5% (5/11) (involving bocavirus, respiratory syncytial virus and adenovirus). We did not find significant differences in the VRL detected in the first (Student *t* test *P* = 0.180) or in the second (Student *t* test *P* = 0.059) between the LTE and STE groups. The approach to treatment was similar in both groups: 100% received symptomatic management,

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Table 1 Demographic and clinical characteristics of the 24 children hospitalized with influenzavirus infection.

Patient ID	Sex	Age(months)	VRL_1(copies/mL)	VRL_2(copies/mL)	Excretion	Coinfection	Days from onset	Length of stay (days)	PICU admission	Treatment
1	F	17	3280	14	LTE	Bacterial *(MC)*	1	5	No	AC
2	F	16	6240	UD	STE	No	4	9	No	AC Oseltamivir
3	M	14	246	2900	LTE	Bacterial *(SP, HI)*	3	5	No	AC
4	F	4	89 200	UD	STE	No	2	2	No	C
5	F	48	11 400	811	LTE	No	21	6	Yes	Not ATB/AV
6	F	7	489	823	LTE	Bacterial *(MC)*	4	7	No	C
7	F	48	781	16	LTE	No	1	6	No	C + V
8	M	26	1330	32	LTE	Viral (B)	5	7	Yes	AZT
9	F	15	27	UD	STE	Viral (A)	1	4	No	C
10	F	0	27	UD	STE	Viral (RSV)	2	13	Yes	AMP + G
11	M	12	41 800	UD	STE	No	2	1	No	Not ATB/AV
12	M	18	53	UD	LTE	Viral (B)	5	1	No	AC
13	M	35	17	UD	STE	No	1	10	No	AC
14	M	18	651	720	LTE	No	8	8	Yes	C + AZT
15	M	48	7540	UD	STE	No	1	5	Yes	Not ATB/AV
16	M	0	749	309	LTE	Bacterial *(MC)*	1	10	No	AC
17	M	0	267	48	LTE	Bacterial *(SA)*	1	15	No	AC
18	M	48	22	UD	LTE	No	7	6	No	Not ATB/AV
19	M	120	3100	UD	STE	No	1	5	No	C Oseltamivir
20	M	13	86	UD	STE	Viral (B, RSV)	7	5	No	AC
21	M	84	359	UD	STE	No	3	3	No	Oseltamivir
22	F	108	832	UD	STE	No	1	9	No	AMP
23	F	48	252	76	LTE	No	6	16	Yes	AMP + C Oseltamivir
24	F	1	42	UD	STE	Bacterial *(MC)*	1	1	No	AC

A, adenovirus; AC, amoxicillin-clavulanic acid; AMP, ampicillin; ATB/AV, antibiotic/antiviral; AZT, azithromycin; B, bocavirus; C, cefotaxime; F, female; G, gentamicin; *HI*, *Haemophilus influenzae*; LTE, long-term excretor; M, male; *MC*, *Moraxella catarrhalis*; PICU, paediatric intensive care unit; RSV, respiratory syncytial virus; *SA*, *Staphylococcus aureus*; *SP*, *Streptococcus pneumoniae*; STE, short-term excretor; UD, undetectable; V, vancomycin; VRL_1, viral RNA load in the first sample; VRL_2, viral RNA load in the second sample.

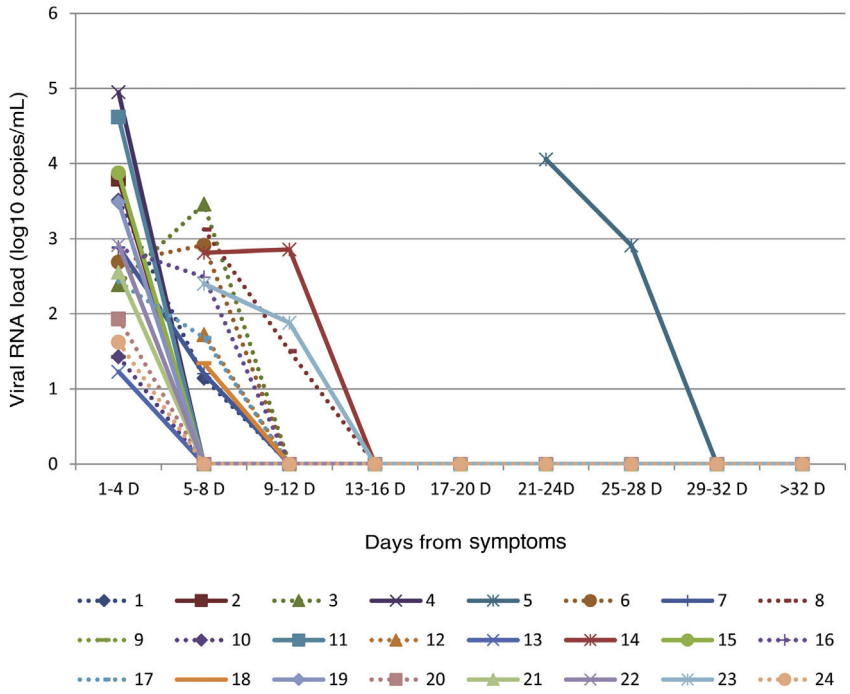

Fig. 1 Relationship between influenza A(H1N1)pdm09 virus viral load and viral clearance time in the 24 hospitalized patients based on the time from onset. Patients with coinfection are represented with a dotted line, and the rest with a solid line.

79% received antibiotherapy (Table 1), 54% bronchodilator therapy, 50% required respiratory support (33% in the form of NIV). Only 4 patients that developed neurologic manifestations received oseltamivir, all of them in the STE group.

Data from our study show that half of the paediatric patients hospitalized on account of a laboratory-confirmed infection of influenza A(H1N1)pdm09 virus had a detectable VRL past day 8 from onset and 17% beyond day 12. Patients with longer duration of disease had longer VS periods, although the length of stay was similar in both groups. This could mean that LTEs have poorer control of viral clearance compared to STEs, which would increase the duration of the respiratory illness, but not their required length of stay.

The paediatric population generally has longer VS periods in influenza infections compared to adults,[2] which can be attributed to the immaturity of their immune systems, a history of immunosuppression, the need for admission to the PICU or infection with antiviral-resistant influenza strains.[3,4] There is also evidence of viral and bacterial coinfections with influenzavirus being common in LTEs, which may increase disease severity and the risk of hospital admission.[5] In our cohort, we found that most patients admitted to the PICU or with bacterial coinfections were LTEs. However, we did not find a significant correlation between LTE status and admission to PICU or bacterial coinfection, probably due to the small sample size.

In conclusion, our findings show that half of paediatric inpatients with laboratory-confirmed influenza A(H1N1)pdm09 virus infection are LTEs, and most of the patients that required intensive care or with bacterial coinfection were LTEs. Monitoring VRL changes in hospitalized paediatric patients could help predict the severity of disease and identify the need of additional microbiological tests.

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Prevalence of congenital heart defects in internationally adopted children☆

Prevalencia de cardiopatías congénitas en niños adoptados internacionalmente

Dear Editor:

Congenital heart defects (CHDs) are the most frequently diagnosed congenital anomalies in children in Europe. The spectrum of disease ranges from complex malformations associated with a high mortality to benign septal defects. Based on data from the European Surveillance of Congenital Anomalies (EUROCAT) network, the prevalence of CHDs in the absence of genetic abnormalities in Europe in the 2000–2018 period was of 0.58% of all live births.[1]

The literature on international adoption shows that congenital anomalies are overrepresented in the population of internationally adopted (IA) children, with differences in prevalence based on the country of origin.[2] The aim of our study was to establish the prevalence of CHDs in a cohort of IA children and analyse differences based in country of origin.

We conducted a retrospective observational study by reviewing the health records of 439 children adopted from another country by Spanish families in the 2000–2018 period and evaluated on arrival to Spain in a specialised adoption clinic. We collected data on the following: age, sex, country of origin, history of corrected CHD, clinical signs or symptoms that led to the cardiac assessment and type of CHD diagnosed by echocardiography.

Of the 439 children (mean age, 29 months; 50.8% male) 300 were adopted from Russia, 35 from China, 32 from Eastern European countries (28 from Ukraine, 2 from Romania and 2 from Moldavia), 22 from Kazakhstan, 16 from the Indian subcontinent (11 from India, 5 from Nepal), 16 from Latin American countries (7 from Colombia, 4 from Bolivia, 2 each from Brazil and Uruguay and 1 from Ecuador), 10 from countries in South East Asia (7 from Vietnam, 3 from Philippines) and 8 from Ethiopia. Two children adopted from Russia had a history of CHD surgically corrected in the country of origin (tetralogy of Fallot in 1 and patent ductus arteriosus in 1). The only clinical sign that prompted performance of a cardiac assessment was detection of a heart murmur in the evaluation performed on arrival to Spain. This occurred in 54 children (12.3% of the total), of who 47 were from Russia, 4 from Ukraine, 1 from Kazakhstan, 1 from Bolivia and 1 from Ethiopia. The echocardiographic evaluation confirmed the presence of CHDs in 18 children (33.3% of the children with a heart murmur).

Table 1 presents the frequency distribution and prevalence of the CHDs identified in IA children compared to the prevalence observed by the EUROCAT surveillance network[2] in infants born alive without genetic abnormalities in the 2000-2018 period. The prevalence of CHDs in the cohort of IA children was 4.55%, 7.8 times higher compared to the prevalence reported by the EUROCAT. The male-to-female ratio was 1.5. Ninety percent of IA children with CHDs had been adopted from Russia. Applying the definitions of the EUROCAT, 80% of CHDs were minor. The most frequent CHDs were atrial septal defect (ASD, 40% of the total) and ventricular septal defect (VSD, 30% of the total).

It is known that CHDs may result from cytogenetic abnormalities, monogenic variants, environmental factors or, most frequently, have a multifactorial aetiology.[3] Increases in maternal exposure to environmental risk factors for CHDs during gestation, such as alcohol, tobacco or drug use, consumption of teratogenic medicines, exposure to organic solvents, viral infection in the first trimester etc, as well as inadequate management of chronic conditions in the mother during gestation (diabetes, obesity, hypertension etc) are among the factors to take into account to explain the high prevalence of CHDs in IA children.[2–4]

The most salient finding of our study was the high prevalence of CHDs in children adopted from Russia. It is known that the frequency of prenatal alcohol exposure (PAE) is high in children residing in orphanages in Russia who are candidates for international adoption.[5] Burd et al.[6] reviewed the literature on the prevalence of CHDs associated with foetal alcohol spectrum disorder (FASD) and found the following: in 12 case series of individuals with FASD, the prevalence of septal defects, other specific CHDs or defects of unspecified type ranged from 33% to 100%; in 14 retrospective studies, the prevalence of septal defects was of 21%, the prevalence of other structural defects 6% and the prevalence of unspecified defects 12%; in 2 case-control studies, the odds of CHD ranged from 1.0 in individuals with FASD to 18.0 in individuals with foetal alcohol syndrome; in 1 prospective study, the odds ratio for a child having both CHD and FASD was 1.0.

To establish the role of PAE as a potential underlying cause of CHDs in the IA children cohort, we reviewed

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