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Pandemic influenza A(H1N1)pdm09: An unrecognized cause of mortality in children in Pakistan

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Abstract

The role of influenza virus as a cause of child mortality in South Asia is under-recognized. We aimed to determine the incidence and case fatality rate of influenza A(H1N1)pdm09 infections in hospitalized children in Karachi, Pakistan. Children less than 5 y old admitted with respiratory illnesses to the Aga Khan University Hospital, Karachi, from 17 August 2009 to 16 September 2011, were tested for influenza A(H1N1)pdm09 using a real-time reverse transcriptase polymerase chain reaction. Out of 2650 children less than 5 y old admitted with a respiratory illness during the study period, 812 (31%) were enrolled. Influenza A(H1N1)pdm09 virus was detected in 27 (3.3%) children. There were 4 deaths in children who tested positive for influenza A(H1N1)pdm09 (case fatality rate of 15%). Children with influenza A(H1N1)pdm09 were 5 times more likely to be admitted or transferred to the intensive care unit, 5.5 times more likely to be intubated, and 12.9 times more likely to die as compared to children testing negative for influenza A(H1N1)pdm09.

Keywords

Influenza; children; pneumonia; Pakistan; H1N1

Introduction

The influenza A(H1N1)pdm09 virus caused a global pandemic from June 2009 to August 2010 [1]. The mortality associated with previous influenza pandemics has ranged from 0.03% of the world's population during the 1968 pandemic, to 1–3% of the world's population during the 1918 pandemic [2–4]. The mortality associated with the 2009 pandemic has been challenging to calculate, given that only a few countries reported accurate surveillance data [5]. The World Health Organization (WHO) requested all countries to report deaths associated with laboratory confirmed influenza A(H1N1)pdm09 during the pandemic, with 18,500 such deaths reported [6]. On the other hand, the US Centers for Disease Control and Prevention (CDC) estimates that the mortality burden of

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influenza A(H1N1) pdm09 was about 15 times higher than this reported figure, and most of this burden was probably in Southeast Asia and Africa [5]. The lack of data regarding the attack rate and case fatality rate of influenza A(H1N1)pdm09 from Southeast Asia and Africa has been highlighted as a major limitation in calculating the global mortality burden of influenza A(H1N1)pdm09 accurately [5].

Children accounted for about 15% of the overall mortality associated with influenza A(H1N1)pdm09 [5]. Nair et al. have estimated that case fatality rates for seasonal influenza-associated acute lower respiratory tract infection in children younger than 5 y are 17 times higher in developing countries compared to developed countries [7]. Pakistan is one of 6 countries that account for half of all the global mortality in children less than 5 y of age [8]. However, little influenza A(H1N1)pdm09 was reported from Pakistan, particularly in children [8,9]. Only 262 laboratory confirmed cases with 29 deaths (all ages) were reported as a result of influenza A(H1N1) pdm09 in Pakistan [9]. No study has so far reported the attack rates or case fatality rates of influenza A(H1N1)pdm09 in children in Pakistan. In order to estimate the burden of influenza A(H1N1)pdm09 disease in children in Pakistan, we conducted a 2 y prospective surveillance study to determine the frequency and severity of influenza A(H1N1)pdm09 in children hospitalized with any acute respiratory illness at a tertiary care hospital in Karachi, Pakistan.

Methods

The study was conducted from 17 August 2009 to 16 September 2011 at the Aga Khan University Hospital (AKUH) in Karachi, Pakistan. AKUH is a tertiary care, private sector hospital with 84 general pediatric beds and a state of the art pediatric intensive care unit (ICU). It caters mainly to the population of Karachi and also receives referrals from the rest of Sindh Province. About three-quarters of the patients belong to the middle and lower socioeconomic groups. Financial assistance is available to those who cannot afford the services, and about 25% of the inpatients receive such assistance.

Children less than 5 y old admitted with an acute respiratory illness within the previous 48 h were eligible for this study. A research medical officer reviewed the admission log every day except the weekends and identified potentially eligible patients. After confirming eligibility and receiving informed consent from the parent or guardian, demographic and clinical information about the current illness was recorded. A throat swab was obtained using a commercial flocked swab (Diagnostics Hybrid Inc.) and was immediately transported to the research laboratory in Universal Transport Medium (Diagnostics Hybrid Inc.) for testing of influenza A using a monoplex real-time reverse transcriptase polymerase chain reaction (RT-PCR) assay. RNA was extracted using a QIAamp Viral RNA Mini Kit (Qiagen) in accordance with the manufacturer's instructions. The primers and probes for influenza A and for influenza A(H1N1)pdm09 were in accordance with the CDC protocol for real-time RT-PCR for influenza A(H1N1) [10]. The rRT-PCRs were performed in a 25- μ l reaction volume and thermocycling rRT-PCR conditions were as follows: 50°C for 30 min, Taq activation for 2 min at 95°C, and 45 cycles of 95°C for 15 s, and an annealing–extension step for 55°C for 30 s. Data were collected using a Rotor Gene 6000. All samples were first tested for influenza A, and those testing positive for influenza A were subsequently tested

for influenza A(H1N1)pdm09. Positive and negative controls were used in each run and all influenza A-positive samples were re-confirmed and serotyped at a reference laboratory (North American Medical Research Unit 3, Cairo, Egypt) or in the reference laboratory of the National Institute of Health, Pakistan. After discharge from the hospital, the medical records of all subjects were reviewed and data about the inpatient workup, management, and clinical course were recorded. The study was approved by the Ethics Review Committee of the Aga Khan University.

Results

A total of 2650 children less than 5 y old were admitted to AKUH with an acute respiratory illness during the study period. Of these, 22% had bronchiolitis, 30% had pneumonia, 25% had asthma, and 22% had an upper respiratory tract infection (URTI). A total of 812 (31%) of these 2650 children were enrolled in the study. Major reasons for non-enrollment included unclear diagnosis at the time of admission, lack of surveillance during weekends, early discharge before the family could be approached for enrollment, delay of >48 h in approaching the family for enrollment particularly when the patients were admitted over the weekend, and unavailability or refusal of parents to give consent. The most common admission diagnosis in those enrolled was pneumonia (30%), followed by bronchiolitis (26%), asthma/ reactive airways disease (10%), and URTI (10%). Influenza A(H1N1)pdm09 virus was detected in 27 (3.3%) children. The only other influenza A strain identified during the study period was H3 in 7 children, while 1 influenza A-positive sample could not be typed. The proportion of influenza A(H1N1) pdm09-positive cases in different months varied from 0% to 15%. Most of the influenza A(H1N1) pdm09 cases during the pandemic were seen from October 2009 to January 2010, and a second peak was seen after the pandemic from October 2010 to January 2011. A cluster of cases caused by H3 serotype were identified in the summer of 2011 (Figure 1).

The admission diagnosis of children who had influenza A(H1N1)pdm09 included pneumonia (13/27, 48%), bronchiolitis (4/27, 17%), URTI (3/27, 11%), asthma exacerbation (2/27, 7%), and 1 case each (1/27, 3%) of febrile seizure, urticaria, myocarditis, hemolytic uremic syndrome, and suspected Barter syndrome. Only 4% of all the enrolled children reported receiving influenza vaccine in the previous 1 y. Two (2/27, 7%) of the influenza A(H1N1)pdm09-infected children reported receiving influenza vaccine in the previous year. Most of the children with influenza A(H1N1)pdm09 presented with fever (81%), cough (92%), and nasal congestion (85%) (Table I). While the presenting symptoms were similar in children with and without laboratory confirmed influenza A(H1N1)pdm09, those with confirmed infection were 5 times more likely to be admitted or transferred to the ICU (95% confidence interval (CI) 1.8–13.6), 5.5 times more likely to be intubated (95% CI 2.0–15.0), and 12.9 times more likely to die (95% CI 4.2–39.3) as compared to children who tested negative for influenza A(H1N1)pdm09.

The case fatality rate associated with influenza A(H1N1)pdm09 in this study of hospitalized children was 15% (4/27). One of the children who died with influenza A(H1N1)pdm09 was a previously healthy 6-month-old girl who was admitted with hemolytic uremic syndrome. Her prolonged hospital course in the ICU requiring peritoneal dialysis was complicated by

secondary peritonitis. Another child who died with influenza A(H1N1)pdm09 was a previously healthy 2-y-old boy admitted with acute myocarditis. His hospital course was complicated by secondary acute respiratory distress syndrome, acute renal shutdown, and nosocomial infections. The other 2 children who died with influenza A(H1N1)pdm09 had underlying high-risk conditions. One of them was a 4-month-old girl who was a suspected case of severe combined immune deficiency and presented with acute respiratory distress and pneumonia. The other was a 6-month-old boy with Down's syndrome and complex congenital heart disease who presented with acute respiratory distress and shock. This child received empiric oseltamivir during the admission, the only child among the 4 fatalities in the influenza A(H1N1)pdm09-positive group to have received this antiviral. Of the 23 children who recovered completely from influenza A(H1N1)pdm09, all were previously healthy except 2 who had known cases of reactive airway disease.

Discussion

This study shows that although influenza A(H1N1) pdm09 was responsible for a relatively small proportion of acute respiratory infection-associated hospitalizations in children in Karachi, Pakistan during the pandemic and early post-pandemic period, these infections were associated with high rates of complications including death. Overall, 3% of the children admitted with a respiratory illness had influenza A(H1N1)pdm09, but this proportion was as high as 9% and 15% during the 2009–10 and 2010–11 winter seasons, respectively. Given the high case fatality rate and a population aged <5 y of more than 18 million in Pakistan [11], it is likely that even with the relatively low attack rate, influenza A(H1N1) pdm09 led to a much higher number of pediatric deaths than what has been reported. In that vein, our study supports the speculation of the CDC, that the largest proportion of the influenza A(H1N1)pdm09-associated mortality probably occurred in Southeast Asia and has gone unreported with the high background rates of infant and child mortality masking these excess deaths [5].

The presentation of children with influenza A(H1N1)pdm09 was similar to children who tested negative for this virus. Hence it was not possible to clinically separate children with influenza A(H1N1) pdm09 from other children presenting with respiratory illness at the time of admission. However, the clinical course of children with influenza A(H1N1) pdm09 was more severe compared to children testing negative for this virus. This highlights the importance of diagnostic testing for influenza A(H1N1)pdm09 at the time of presentation for appropriate management during the pandemic season, particularly the use of empiric oseltamivir. Half of the children who died in our study with influenza A(H1N1)pdm09 were previously healthy. This is consistent with the results of studies from other countries, which show that influenza A(H1N1)pdm09 was a severe illness both in immune compromised as well as immune competent children [12,13].

Pakistan is a signatory of the International Health Regulations 2005 (IHR), which mandates prompt global reporting of emerging infectious diseases of global health importance. However, the current national surveillance infrastructure has limited capacity to fulfill the commitments with regards to the reporting of respiratory viruses. A literature review failed to show even a single study on the epidemiology of respiratory viruses in Pakistan using

PCR over the last 20 y [14]. There are only 3 reference laboratories in the entire country capable of diagnosing respiratory viruses using PCR, and the provision for collecting and transporting samples to these laboratories from the field hospitals is very limited [9]. Hence surveillance could be conducted in only a handful of sentinel sites during the pandemic. It is critical for Pakistan to strengthen its surveillance infrastructure to be better able to cope with the next influenza epidemic.

Influenza A(H1N1)pdm09 was almost the exclusive serotype detected in our study until February 2011. This pattern changed in June 2011, when the H3 serotype replaced the novel H1 serotype. Interestingly, while the influenza A(H1N1)pdm09 pandemic global peak was in November–December 2009, our study found the highest proportion of influenza A(H1N1)pdm09-positive cases in January 2011. Potential reasons for this delayed peak could be a less severe initial outbreak, as identified in our study, which left a large proportion of the population unexposed and vulnerable to a second peak, as well as lower rates of influenza vaccination compared to the rest of the world. The influenza vaccine that was available on the private market during the study period covered all the influenza isolates detected in our study, including influenza A(H1N1)pdm09. However, as shown in our study, the uptake of influenza vaccine by the general public was very low during the pandemic, and it continues to be low during the current post-pandemic period. This is primarily because of a lack of data regarding the burden and seasonality of influenza in Pakistan, as well as access to vaccines. There is a need for continuous surveillance to determine the burden and seasonality of influenza outside the pandemic and immediate post-pandemic phase in Pakistan, so evidence-based advocacy for influenza vaccines can be done on a routine basis.

Our study has a few limitations. Since this was a hospital-based study, there is a care-seeking bias and the results may not be a true reflection of the influenza A(H1N1)pdm09 burden in the community. Of all the children admitted with respiratory illnesses during the study period, only 31% were enrolled, which makes the study prone to selection bias. Although the proportion of major respiratory illnesses like bronchiolitis and pneumonia was broadly similar in the eligible and enrolled subjects, a selection bias because of the admission diagnosis, severity of illness, or other unknown factors is possible.

In summary, this study is the first to report the burden of influenza A(H1N1)pdm09 in any population in Pakistan. It suggests that influenza A(H1N1) pdm09 was the cause of a substantial number of pediatric deaths in Pakistan during the pandemic, and almost all of these deaths have gone unreported. Better preparations are needed to promptly diagnose, report, and manage future pandemics of a similar nature, which are bound to come sooner or later.

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Figure 1. Seasonality of influenza A and its relationship with acute respiratory illness-associated hospitalizations at Aga Khan University Hospital, Karachi (17 August 2009 to 16 September 2011).

Table I

Characteristics and outcome of influenza A(H1N1)pdm09 positive and negative children admitted with an acute respiratory illness to the Aga Khan University Hospital (17 August 2009 to 16 September 2011).

	A(H1N1)pdm09 positive (n = 27)	A(H1N1)pdm09 negative (n = 785)	RR (95% CI)	p-Value
Baseline characteristics				
Age, months (median, IQR)	11.2 (6.7–30.1)	9.6 (4–19)		0.13
Male	63%	65%	0.96 (0.71–1.28)	0.83
Birth weight, kg (median, IQR)	3.1 (2.6–3.5)	2.9 (2.5–3.3)		0.33
Months of breast feeding (median, IQR)	8 (3–12)	6 (3–12)		0.79
Day care attendance	3.8%	3.8%	0.99 (0.14–7.01)	1.00
Smokers in the house	61%	71%	0.85 (0.63–1.16)	0.27
Number of household members (median, IQR)	9 (6–13)	7 (5–10)		0.01
Clinical features				
Fever	81%	71%	1.14 (0.95–1.37)	0.28
Cough	92%	87%	1.05 (0.94–1.18)	0.56
Wheezing/noisy breathing	48%	51%	0.94 (0.63–1.40)	0.84
Poor appetite	63%	40%	1.58 (1.17–2.14)	0.02
Shortness of breath	66%	65%	1.02 (0.77–1.34)	1.00
Ear ache	14%	16%	0.92 (0.36–2.31)	1.00
Sore throat	74%	56%	1.31 (1.04–1.66)	0.07
Post-tussive emesis	44%	38%	1.15 (0.74–1.77)	0.55
Nasal congestion	85%	76%	1.12 (0.95–1.31)	0.35
Hospital course				
Intubated	14.8%	2.6%	5.5 (2.0–15.0)	0.007
ICU admission or transfer	14.8%	2.9%	5.0 (1.8–13.6)	0.01
Died during hospitalization	14.8%	1.1%	12.9 (4.2–39.3)	< 0.001

RR, relative risk; CI, confidence interval; IQR, interquartile range; ICU, intensive care unit.