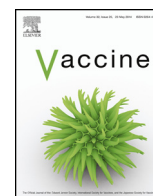




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Influenza epidemiology among hospitalized children in Stockholm, Sweden 1998–2014



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ARTICLE INFO

Article history:

Received 30 November 2015

Received in revised form 22 April 2016

Accepted 26 April 2016

Available online 4 May 2016

Keywords:

Influenza

Children

Epidemiology

Complications

Comorbidity

ABSTRACT

Background: Influenza remains a common reason for the hospitalization of children. There is a need for long term studies that are also population based. We describe the epidemiology of severe influenza in a defined population 1998–2014.

Method: Retrospective study of annually collected data of virologically confirmed influenza in hospitalized children 0–17 years living in the catchment area (230,000 children). We gathered information about comorbidity and complications from case records, and compared Influenza A, B and A(H1N1)pdm09 with respect to these factors.

Results: A total of 922 children with influenza were hospitalized. The mean rate remained unchanged at 22.5–24.2 per 100,000 children per year. There were two major outbreaks: influenza A(H3N2) in 2003–2004 and the A(H1N1) pandemic in 2009–2010. The proportion of children with influenza B increased from 8% during the first half of the study period to 28% during the second half. The highest admission rate was found in children <3 months of age, 169 per 100,000. Children with influenza B were older than those with influenza A. Comorbidity was found in 34%, complications in 41%, and 11% needed intensive care management. The mortality rate was 0.17/100,000 children.

Conclusion: Influenza remains an important reason for the hospitalization of children, especially during the first years of life. The increasing proportion of influenza B may have to be considered when recommending influenza vaccines.

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1. Introduction

Influenza is common among children, especially before 5 years of age [1]. We here describe the influenza A, B and A(H1N1)pdm09 epidemiology in the 0–17-year-old population of northern Stockholm during 17 seasons, 1998/99–2013/14, and its implications for the immunization of children.

In Stockholm, children with certain chronic diseases are eligible for free seasonal influenza immunization. This was introduced in 2004 and originally included children with chronic pulmonary or heart disease, but after the pandemic 2009 was expanded to include also chronic liver or renal diseases, immunosuppression, diabetes mellitus, extreme obesity (body mass index > 40), neuromuscular

disease affecting breathing capacity, and children with multiple dysfunctions/handicaps. During the pandemic, adjuvanted monovalent H1N1 vaccine (Pandemrix[®], GlaxoSmithKline Biologicals, Rixensart, Belgium) was offered to all children from 6 months of age. However, except during the pandemic season, when 60% of all children accepted the offer, the vaccine uptake has been low (<5%), perhaps due to fear of side effects or unawareness of the severity of influenza [2–4].

In order to increase the knowledge base for vaccination recommendations, in addition to data that can be obtained from administrative databases, we here provide population-level influenza burden data based on observed, virologically confirmed hospitalizations.

2. Methods

This is a retrospective study of annually gathered information about influenza in children (<18 years hospitalized at Astrid

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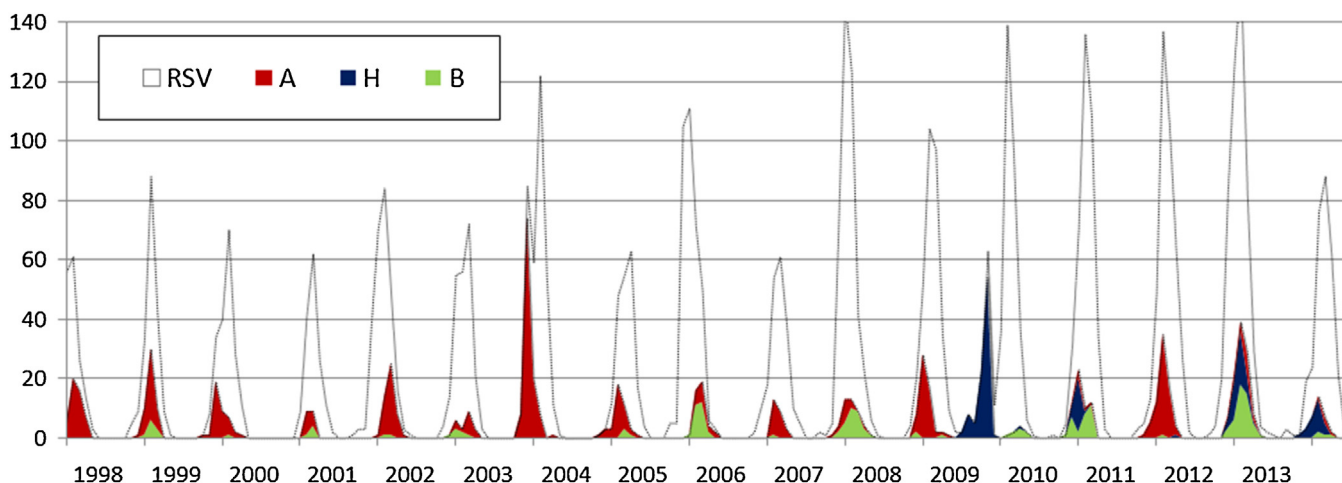


Fig. 1. Number of admitted children per month 1998–2014 with influenza A (A), A(H1N1)pdm09 (H), B (B), and, for comparison, respiratory syncytial virus (RSV).

Lindgren Children's Hospital, Stockholm, Sweden during 1998–2014. The hospital is a tertiary referral center with surgery and a pediatric intensive care unit (PICU) with resources for extracorporeal membrane oxygenation (ECMO), but only children resident in the catchment area were included in the study. We obtained population data from the Stockholm area database at Statistics Sweden (www.scb.se). During the study period, the number of children in the primary catchment area increased by 17%, from 197,945 to 230,877. The number of person years for a specific age group during a certain year was considered equal to the number of children on December 31.

2.1. Patients

We extracted information about risk factors, complications and intensive care management from the hospital charts. From 2009 we have also been able to extract information from the vaccine register in Stockholm County [3]. Risk factors were neuromuscular disease, chronic lung disease, immunosuppression, and chronic conditions such as kidney or liver disease, or inborn errors of metabolism. If a child had both neuromuscular and chronic lung disease, the factor judged most important for the clinical course was counted. Recurrent wheezing/"asthma" in children younger than two years and uncomplicated preterm birth (>30 gestational weeks) were noted but not considered risk factors.

We counted sinusitis, tracheitis and presumed bacterial pneumonia (with or without empyema), but not otitis media as focal complications. Chest x-ray was always performed when pneumonia was suspected. If perihilar infiltrates and/or hyperinflation were present, a diagnosis of bronchitis or bronchiolitis was made. Bacterial and viral pneumonia were differentiated mainly by c-reactive protein (CRP) levels, with a cut-off value of 40 mg/L. Neurologic complications were seizures; either primary or secondary (in children with underlying neurologic disease), and encephalitis confirmed by electroencephalography. Other complications included a few rare conditions such as myocarditis. Dehydration alone was not considered a complication.

2.2. Virology

As a routine, children admitted from our pediatric emergency ward with respiratory symptoms or fever without localizing signs, including febrile convulsions, are examined for viral etiology. During the winter season samples are primarily investigated for respiratory syncytial virus (RSV) and influenza viruses. If they are

found negative, viral investigation is extended to other respiratory viruses (adenovirus, bocavirus, coronavirus, enterovirus, human metapneumovirus, parainfluenza virus 1–3, and rhinovirus) [5].

All cases in this report were virologically confirmed by the laboratory. Influenza virus was detected with immunofluorescence and viral isolation prior to October 2007, when these methods were replaced by real-time polymerase chain reaction (RT-PCR) [5,6]. Before the switch to RT-PCR the diagnostic sensitivity of the three methods was evaluated in 585 samples at our laboratory [5]. The RT-PCR analysis has since then been improved (in 2009 and 2011 by the inclusion of new probes for influenza A(H1N1)pdm09 and in 2014 by the redesign of the influenza B probe).

RSV has since 2009 been diagnosed with a rapid point-of-care test, with negative specimens further investigated for both RSV and influenza with RT-PCR.

The Chi-square test, the Mann–Whitney *U*-test, and exact Clopper–Pearson binomial confidence intervals were employed as appropriate. For multivariate analysis, we used a generalized linear model with the logit function in Statistica® v. 10, with influenza subtype (non-pandemic A or B) as the dependent variable, and age and presence or absence of risk factors and complications as independent variables.

3. Results

There were 922 children (56% male) with confirmed influenza during the study period. 557 had non-pandemic influenza A, 179 had influenza B, and 186 had influenza A(H1N1)pdm09, out of whom 93 belonged to the 2009–2010 pandemic. During all winter seasons there were influenza epidemics with varying severity. All but two influenza epidemics occurred during RSV epidemics after January 1 and there were then always more children with RSV during a given week (Fig. 1). The two largest outbreaks 2003–2004 and 2009–2010 peaked before January 1 and preceded the RSV epidemics. Influenza B was present in all but two seasons and dominated during three seasons, all of which occurred during the second half of the study period. Co-infections (with any simultaneously circulating respiratory virus) were identified in 11% of the patients. This is a minimum figure, since some children, for instance those with a positive point-of-care test for RSV, were not examined for additional viral etiology such as influenza.

When the period comprising the first eight seasons was compared with the second period, excluding the pandemic and thus also comprising eight seasons, there were significantly more cases of influenza B during the latter period ($p < 0.01$). However, the overall

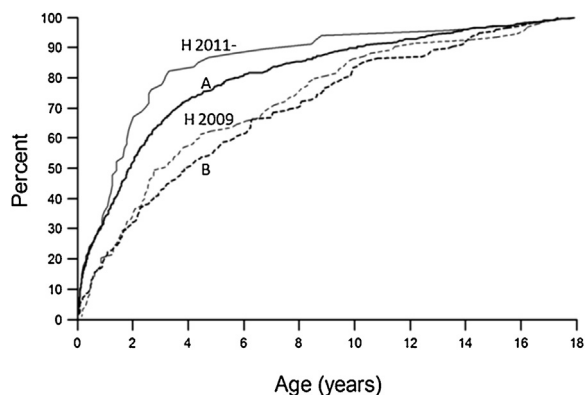


Fig. 2. Age (cumulative percentage) of admitted children with influenza A (A), B (B) or A(H1N1)pdm09 (H): pandemic (2009) or post-pandemic (2011–).

Table 1
Total numbers of tested individuals and influenza subtypes during the studied seasons.

Season	Tested	Influenza subtype		
		A	pdm09	B
1997–1998		49		
1998–1999	319	41		10
1999–2000	266	39		1
2000–2001	331	13		5
2001–2002	379	47		2
2002–2003	478	15		7
2003–2004	618	111		
2004–2005	529	36		4
2005–2006	708	16		26
2006–2007	416	24		1
2007–2008	711	15		30
2008–2009	781	55		3
2009–2010	1303		93	8
2010–2011	838	6	23	29
2011–2012	954	70	3	1
2012–2013	899	16	41	48
2013–2014	900	4	26	4

rate of influenza cases in children <17 years remained unchanged at 22.5 (95% C.I. 20.1–24.9) and 24.2 (21.9–26.5) per 10⁵ person years, respectively.

The cumulative age distribution is shown in Fig. 2. Children with influenza B were older (as also shown in Table 1) than those with influenza A. Influenza A(H1N1)pdm09 is presented separately for the pandemic year 2009–2010 and the post pandemic years, since the pandemic patients were significantly older ($p < 0.001$).

The yearly incidence rates in different age groups varied considerably, with median (range) for children <5 years 59 (19–138), <1 year 99 (52–219), <6 months 144 (69–331), and <3 months 169 (69–463) cases per 10⁵. The highest rates were seen during the influenza A(H3N2) outbreak 2003–2004, followed by the prolonged 2012–2013 season when influenza A, B and A(H1N1)pdm09 were all prevalent.

Table 2
Age, rates of risk factors and complications, and need of pediatric intensive care unit (PICU) management in 922 children hospitalized with influenza.

	N	Age (median)	Risk factors No (%)	Complications No (%)	PICU No (%)
Influenza A	557	1.93	178 (32)	226 (41)	57 (10)
Influenza B	179	3.86 ^a	73 (41)	91 (51)	27 (15)
A(H1N1)pdm09					
Pandemic	93	3.24	32 (34)	30 (32)	8 (9)
Post-pandemic	93	1.74 ^b	29 (31)	33 (36)	13 (14)

^a Comparing influenza A and B, only age remained significantly ($p < 0.001$) different by multivariate analysis including risk factors and complications.

^b Children infected with A(H1N1)pdm09 during the pandemic were significantly older than those admitted during the following seasons ($p < 0.001$).

Previously known risk factors were found in 312/922 (34%, Table 1), the most important being neuromuscular disease (131 cases) and chronic lung disease (40 cases). The frequencies of recurrent wheezing (not included among risk factors) and preterm birth were comparable to their occurrence in the general child population at 6% and 2.6% (24/922), respectively.

Complications were seen in 380/922 (41%). Most were related to the respiratory tract where pneumonia dominated (117) out of which half (58) were considered bacterial in origin. Other bacterial superinfections, such as sinusitis (including periorbital cellulitis) were diagnosed in 22 children. Approximately 50% of the children had a blood culture taken, which was positive in 12 (6 *Streptococcus pneumoniae*, 3 *Staphylococcus aureus*, 2 *Streptococcus pyogenes* and 1 *Neisseria meningitidis*). Neurological complication was the second most common with encephalitis (33) and primary or secondary seizures (104).

Risk factors and complications were more common among children with influenza B than in those with influenza A in the univariate analysis ($p < 0.05$), but when included with age in the multivariate model, only age remained significant ($p < 0.001$, Table 2).

Children with recurrent wheezing had a low rate (1/59) of PICU admission. Their median duration of hospital stay was 2 days, which is equal to that of other children without risk factors.

Intensive care admission was required for 105/922 children (11%); 41/610 (6.7%) without risk factors and 57/171 (33%) with neuromuscular or chronic lung disease ($p < 0.001$). Two children were treated with ECMO. Six children (0.17/10⁵ person years) died, 1 <1 year, 2 1–9 years, and 3 >10 years old. Three of these were previously healthy, whereof two had an influenza B infection. The causes of death were encephalitis, myocarditis and bacterial pneumonia in the previously healthy children, and non-specific complications in the three children with co-morbidity.

4. Discussion

This is a report of children hospitalized for influenza A or B in a defined population in the northern Stockholm area 1998–2014, covering the pre-pandemic period, including the 2003–2004 outbreak, the 2009 pandemic, and four post-pandemic seasons.

There was a strong seasonal variation and the epidemiologic pattern was often in accordance with what has been seen in other countries, such as the large outbreak of A(H3N2) in 2003–2004 [7].

With the exception of the influenza A(H1N1)pdm09 pandemic with a peak in late autumn 2009, the epidemic peaks occurred during winter and coincided with RSV, with co-infections detected in 11%. As we have reported earlier, RSV and influenza co-infections do not have a more severe course or more late wheezing, but tend to follow the expected clinical course of the RSV infection [8].

Most population based long-term studies are from the North American continent, but one study from Finland covers a 16 year period up to 2004 [9]. There have been both single center and multi-center studies [10,11]. Some were population based whereas others represented tertiary centers without a defined population. Many of

these studies have covered the periods before the 2009 pandemic and have later been extended to also include the pandemic year [12,13]. Several studies described the pandemic and a few have included the first post pandemic season [14,15]. No study has like ours covered both pre- and post-pandemic seasons, when the novel influenza A(H1N1)pdm09 continued to circulate.

Our findings are in accordance with these studies, all pointing to the fact that influenza in children is still a problem.

Neuromuscular disease and chronic lung disease were the dominating risk factors. In our setting recurrent wheezing/“asthma” and uncomplicated preterm birth were not important risk factors.

Bacterial superinfection, mostly pneumonia, was the most common complication. In most studies the distinction between bacterial and viral pneumonia has not been discussed. In our study 40% were considered to be viral [16]. Neurologic complications, such as seizures and encephalitis, were the second most common category.

Intensive care was needed for 11% of all children, which is in agreement with most other studies [12,13,17]. The need for intensive care was highest (18%) in children with risk factors.

The case fatality rate noted by us was similar to that reported from other western countries [18].

Our age distribution and incidence rate calculations are similar to, although in the lower range, of what has previously been reported [19]. 30% of the children were below one year and 72% below five years of age, resulting in an incidence of 99/10⁵ and 59/10⁵, respectively. The highest rate, 169/10⁵, was observed among the youngest (<3 months) infants, as in a recent study from the USA [17].

An important part of our study is the comparison of different influenza types. In several studies comparisons have been done between seasonal influenza and (H1N1)pdm09 [14,15]. We studied influenza A(H1N1)pdm09 and the pandemic year separately from the following years, because of the marked difference of age distribution. During the pandemic, children were older in accordance with what has been presented from several other centers [12,15,20]. During the following seasons, however, the average age was actually somewhat lower than in children with other influenza A types. One contributing factor could be the high vaccine coverage (60%) with the adjuvanted vaccine (Pandemrix) during the pandemic in Sweden, which has been shown to give protection for at least two subsequent seasons [3].

In addition to the emergence of pandemic influenza, also the burden of influenza B has come into focus in recent years [21]. We found influenza B especially during the second half of the study period. Previous epidemiologic studies used different methods for estimating the number of influenza cases, such as excess of cases with influenza-like illness during influenza seasons, virus isolation, and rapid methods like immunofluorescence and PCR [22]. At our laboratory immunofluorescence and viral isolation were replaced by the more sensitive PCR in October 2007. To what extent this has contributed to our observed increase of influenza B can be discussed. The initial PCR system had a higher sensitivity for influenza B compared to immunofluorescence and virus isolation, while the sensitivity for influenza A was lower. The influenza A PCR has since then been continually improved, and in a review by Mahoney et al. it is stipulated that well optimized RT-PCR assays have 5–10% higher sensitivity than virus isolation [23].

One limitation of our study is its retrospective nature. However, the same pediatricians have been responsible for the care of the infected children during the entire period. The same level of care has been provided from the PICU with availability of ECMO treatment during the entire period. Furthermore, in our study “retrospective” means yearly reviews and documentation of the previous season as a preparation for planning of the following season. Our study is a summary of these reviews.

Another important factor, as mentioned, is the introduction of new tests that could be more sensitive. On the other hand, the use of rapid tests precluded the detection of coinfections – found in more than 20% in an earlier study from our hospital [8].

The effect of influenza vaccine in children has been the subject of several reviews. In contrast to the known effect of trivalent influenza vaccine (the only one used during the studied period except for the pandemic year) in healthy children >18 months, less is known about its effect in younger children and in those with risk factors.

During the 2009–2010 pandemic when 69% of the Swedish childhood population was vaccinated with a monovalent adjuvanted vaccine an effect of 91% was demonstrated [2]. As also found in an English study, the protective effect was still present in children with comorbidity, albeit smaller than in children without risk factors [24].

Even though the immunization of children with risk factors is free, few parents (<5%) take the opportunity to vaccinate their children. The reason for the low uptake of the vaccine is probably multifactorial. In a recent questionnaire study in the USA two factors were highlighted: fear of side effects and the belief that influenza is not a serious threat to children [4].

In conclusion, our population based study demonstrates that influenza in young individuals is still a major problem, especially but not exclusively in those with risk factors. We hope to be able to use this information to encourage more parents to immunize their children.

There was a significant increase of influenza B during later years, primarily affecting older children with risk factors. The reason for this increase is probably multifactorial, but it points to the need for increased protection against influenza B, e.g. through the development of the quadrivalent vaccine.

It may be important to note that in our study half of the children who died had no risk factors and that influenza B was the cause in 2/6 cases.

Conflicts of interest statement

None.

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