

# The burden of seasonal and pandemic influenza in infants and children

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**Abstract** The burden of influenza is unevenly distributed, with more severe outcomes in children aged <5 years than older children and adults. In spite of this, immunisation policies for young children are far from universal. This article provides an overview of the published evidence on the burden of influenza in children worldwide, with a particular interest in the impact of pandemic influenza in 2009–2010 (caused by the H1N1pdm09 virus). In an average season, up to 9.8 % of 0- to 14-year olds present with influenza, but incidence rates can be markedly higher in younger children. Children aged <5 years have greater rates of hospitalisation and complications than their older counterparts, particularly if the children have co-existing illnesses; historically, this age group have had higher mortality rates from the disease than other children, although during the 2009–2010 pandemic the median age of those who died of influenza was higher than in previous seasons. Admissions to hospital and emergency departments appear to have been more frequent in children with H1N1pdm09 infections than during previous seasonal epidemics, with pneumonia continuing to be a common complication in this setting. Outcomes in children hospitalised with severe disease also seem to have been worse for those infected with H1N1pdm09 viruses compared with seasonal viruses. Studies in children confirm that vaccination reduces the incidence of seasonal influenza and the associated

burden, underlining the importance of targeting this group in national immunisation policies. *Conclusions:* Children aged <5 years are especially vulnerable to influenza, particularly that caused by seasonal viruses, and vaccination in this group can be an effective strategy for reducing disease burden.

**Keywords** Influenza · Children · Burden · Complication · Hospitalisation · Mortality

## Introduction

Influenza is disproportionate in its effect on different age groups. For example, US children aged 0–19 years had a higher risk of being infected with influenza A/H1N1 or A/H3N2 than adults of any age during yearly epidemics between 1977 and 1978 and 1980 and 1981, and in two influenza B epidemics (1976–1977 and 1979–1980), the age group at highest risk of infection was 5- to 14-year olds [77]. In a cohort of 209 US infants monitored weekly from birth until the age of 1 year, 69 (33 %) developed influenza infection [43]. More recent data tell a similar story: in the first 10 months of the 2009–2010 influenza pandemic, the hospitalisation rate in US children under the age of 5 years with laboratory-confirmed influenza was more than double that of any other age group [19], and among 722 patients admitted to intensive care unit (ICU) with confirmed H1N1pdm09 infection in Australia and New Zealand during 2009, the age-specific incidence of admission was higher in infants <1 year old than in any other age group [6]. In Germany, mortality rates in 2009–2010 were highest in children in their first year of life and middle-aged adults (aged 35–59 years) [102].

Since the 2008–2009 influenza season, influenza vaccination has been recommended for children aged 6 months to 18 years in the USA [21]. In addition, the Influenza

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Working Group for the World Health Organisation Strategic Advisory Group of Experts has recommended that children aged 6 months to 5 years be considered as a target group for annual influenza vaccination [100], and the UK Department of Health recently announced a plan to vaccinate children aged 2–17 years annually from 2014 [62]. However, in many other European countries, routine immunisation of children against influenza is not yet recommended. Cost-effectiveness arguments certainly play a part in this, but it is also possible that doubts remain about the burden that influenza poses in children.

This article provides an overview (non-systematic review) of published evidence on this topic. Most of the papers cited in this article came from a search of the PubMed database on 27 April 2012 for articles published at any time in English or German with ‘influenza’ and any of the following words in the title: child, children, schoolchildren, infant (and words with ‘infant’ as root), pediatric(s) or paediatric(s). The search field was restricted to title only to produce a manageable number of papers (1,686) for further searching. The results were searched for publications relevant to our subject headings, with a focus on recently published papers on the impact of the 2009–2010 influenza pandemic (infections with the H1N1pdm09 virus) in children. No formal screening criteria were used, and additional publications not found by the search that contain data pertinent to influenza burden in children are also cited.

## Burden of influenza in children

### Incidence and attack rate

The burden of influenza on communities worldwide is uneven, because the annual disease epidemics vary considerably in severity. Distinguishing the morbidity caused by influenza from that due to influenza-like illness (ILI) caused by other respiratory viruses, such as respiratory syncytial virus (RSV) presents a challenge not only to epidemiologists but also to physicians in relation to diagnosis and treatment. Nevertheless, a systematic review and meta-analysis published in the *Lancet* in 2011 estimated that 90 million cases of influenza occur each year in children aged <5 years around the world; of these, 20 million are associated with acute lower respiratory tract infections (LRTI), one million of which are severe in nature [80]. By modelling surveillance data on all ILI in four countries from 2002 to 2008, the European Paediatric Influenza Analysis project calculated that between 0.3 and 9.8 % of children aged 0–14 years present to a physician with influenza in the average season [89]. These data are in line with the findings of an earlier systematic review, by Bueving et al. [15], of 26 studies from a variety of countries and settings; although the incidence of laboratory-confirmed influenza from

individual studies in that review ranged from 0 to 46 %, two studies that measured incidence over a period at least of 5 years reported estimated incidences of 4.6 % for children and adolescents aged ≤19 years [76] and 9.6 % for children up to 5 years old [84]. Incidence rates could be even higher in the youngest groups of children: during two seasons considered to be milder influenza epidemics, namely 2000–2001 (primarily A/H1N1) and 2001–2002 (primarily A/H3N2), the average annual rate of influenza in Finnish children <3 years old seen as outpatients was 179/1,000 [51]. Surveillance in the USA over three seasons showed that the cumulative rate of influenza-associated acute respiratory illness was nearly twice as high in children aged 0–18 years (median, 6 years) as in elderly adults (20 and 11 %, respectively) [70].

The attack rate, i.e., the probability of people at risk of becoming infected during an influenza outbreak, is often reported as an outcome measure in vaccine efficacy trials. For example, placebo group attack rates in a Japanese study of 6- to 24-month-old children ranged from 7.2 to 12.5 % over the three seasons 2000–2002 [73], and in German and Finnish children aged <6 years, the placebo group attack rates for seasons 2007–2008 and 2008–2009 were 2.4 and 5.2 % [125]. It is also of value for comparing the virulence of infecting viruses from season to season, with clinical attack rates (i.e. infected patients with symptoms) of 12–24 % for seasonal influenza and 20 % for H1N1pdm09 influenza being reported in children up to 14 years old [45, 50] and 3–16 % in infants aged 6–24 months [56]. The statistic should be interpreted with care, however, as attack rates vary by season and geographic location depending on the virulence of the infecting virus. For example, clinical attack rates in a prospective cohort trial in Finnish children were quite similar across the three age groups studied (<3 years; 3–6 years, and 7–13 years) in 2000–2001, when A/H1N1 infections predominated, but in 2001–2002, when A/H3N2 predominated, the attack rate was markedly higher in the youngest children (21.3 %) than the oldest (3.0 %) [51]. In addition, infected individuals do not always develop symptoms [133]; in recent German surveillance, secondary H1N1pdm09 infections in adults were significantly more likely to be asymptomatic than those in children [104]. It is notable that during the 2009 pandemic, H1N1pdm09 seroprevalence rates in Germany were nearly twice as high in 5- to 17-year olds (48 %) as in 1- to 4-year olds (25 %) [127], in agreement with patterns of mortality and hospitalisation rates described in later sections of this article.

### Transmission and infectiousness

Children appear to be more vulnerable to developing infection when influenza is circulating. A study of household

transmission from index cases with laboratory-confirmed influenza found that children aged 0–5 years were significantly more likely to develop clinical influenza than adults (hazard ratio, 1.85; 95 % CI, 1.09–3.26) [126] and in a prophylaxis study, the incidence of laboratory-confirmed influenza in contacts aged 1–12 years receiving expectant treatment was approximately three times as that in those aged >13 years [48]. In 2008–2009, the risk of secondary infections in German households with an influenza-infected index case increased as the age of the household member decreased, but in 2009–2010 (pandemic season), rates in those aged 0–4 years were lower than any other age group, with the highest risk in those aged 5–34 years [103].

Children with influenza contribute to the burden on all age groups because of their high infectiousness [83]. In the French transmission study mentioned above, the risk of developing clinical influenza was significantly higher in contacts exposed to infected children (aged 0–15 years) than infected adults (aged >15 years) [126]. Prolonged viral shedding may play a role in disease transmission. A long duration of shedding was recently demonstrated in children aged <15 years infected with H1N1pdm09 virus by Esposito et al. [35]; at 9 days after influenza onset, 35/74 (47 %) were still shedding virus and 14 (19 %) were still doing so at day 13. Moreover, in households with children shedding virus for at least 9 days, there was significantly more ILI in the 2 weeks after the initial disease compared with children shedding for <9 days [35].

From real-time surveillance of patient visits in a variety of settings, children aged 3–4 years were consistently the earliest age group to make healthcare visits during pneumonia and influenza epidemics, so contributing to disease spread beyond the household [14]. This idea is supported by results of an influenza transmission model based on children in Taipei, suggesting that children aged 4–6 years have the highest transmission potential [24], although other studies have found that older children are a more important age group for transmission than younger children [42, 108, 127], probably because the opportunity for onward spread is greater once children are attending school. As discussed in a later section, vaccinating children can reduce the community infection rate [8, 44, 94].

Influenza illness causes children to lose school time, and their parents to lose work time, causing a socioeconomic as well as a clinical burden. In Finland, influenza infections were estimated to cause 216–274 days of absence from school or day care and 54–195 parental work days lost for every 100 children aged 0–13 years [51]. A US group estimated that 247,000 work days/year were lost nationally by caregivers of children who were taken to emergency departments for influenza infections [13], and an Italian study estimated that, including indirect costs of lost work time, the mean cost of a childhood influenza infection was at

least €130 [34]. A study in Hong Kong found that school absenteeism rates associated with influenza A epidemics from 2003 to 2004 to 2005 to 2006 were much higher in those aged ≤5 years (105–142 days/10,000 population) than in those aged 6–17 years (15–20 days) [25].

#### Mortality rates

The 2011 meta-analysis by Nair and colleagues estimated that between 28,000 and 111,500 children aged <5 years die each year as a result of acute LRTI associated with influenza, and that 99 % of deaths happen in developing countries [80]. Many other studies emphasise the relative vulnerability of younger children with respect to the risk of dying from influenza. In 2004–2007, the US Centres for Disease Control and Prevention (CDC) were notified of 166 influenza deaths in children aged <18 years, with the median age of these children being 5 years [37], and in the survey of seasonal influenza deaths in US children published by Bhat et al. [9], two thirds of deaths occurred in those aged <5 years. In the latter study, the estimated mortality rate associated with influenza was 0.21/100,000 children, but the rates in age groups younger than 2 years old was 0.59 to 0.88/100,000 [9]. In an earlier study by CDC using data from 1990 to 1999, estimated annual rates of underlying respiratory and circulatory deaths associated with influenza per 100,000 were 0.4 in children aged 1–4 years and 0.6 in those aged <1 year [123]. Recent CDC estimates based on a larger time span (1976–2007) suggest that average annual rates for all ages could be 35 % lower than the 2003 estimates, although rates for young children were not calculated [18]. The mortality rate appears to be highest in those aged <1 year for infections caused by either seasonal or pandemic influenza viruses [38, 105]. As would be expected, mortality risk is much higher when the infection follows a more severe course. In H1N1pdm09-infected children with severe illness admitted to ICUs, 81 % of whom underwent mechanical ventilation, death rates were 47 % [124]; many of these children had pre-existing illnesses such as asthma and congenital heart disease, and co-infection with RSV was found to be significantly associated with mortality.

The influenza pandemic of 2009–2010 saw a spike in the number of influenza-associated deaths in children compared with previous seasons in the USA [29]. However, surveys in the USA suggest a change in the age distribution of child deaths during the pandemic. During the early part of the pandemic (April to August 2009), 19 % of reported deaths from H1N1pdm09 influenza in US children were in those aged <5 years [17], yet more recent CDC data showed that after the pandemic, nearly half (46 %) of all child influenza deaths were in this age group [20], similar to the rate calculated for under 5 years who died from seasonal

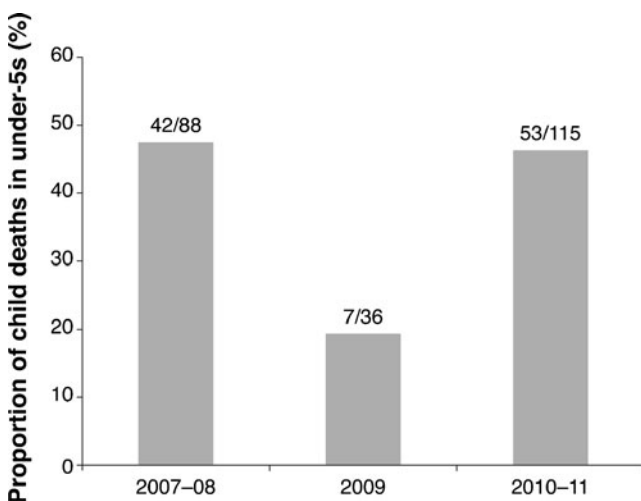
influenza in 2007–2008 (Fig. 1) [92]. This is consistent with a study showing the median age of US children who died from H1N1pdm09 influenza being significantly higher than in those who died in 2007–2009 from seasonal influenza (9.4 and 6.2 years, respectively;  $p < 0.01$ ) (Fig. 2) [29]. However, some of the findings of a recent Dutch study disagree with the US data described above. Using regression modelling, this group estimated that influenza-related mortality in Dutch children aged 0–4 years was much higher during the 2009–2010 pandemic than the average of ten previous seasons [131]; in the 5- to 24-year age group, the estimated pandemic mortality was also higher than the seasonal influenza average.

In more severely ill children, i.e. those requiring admission to an ICU, mortality rate was higher in those with H1N1pdm09 infections than those with influenza A infections during previous seasons [55]. In the context of H1N1pdm09 influenza, children with existing illness appear to have had the highest mortality risk: roughly two thirds of children who died after having H1N1pdm09 infections had co-morbidities [17, 29, 105].

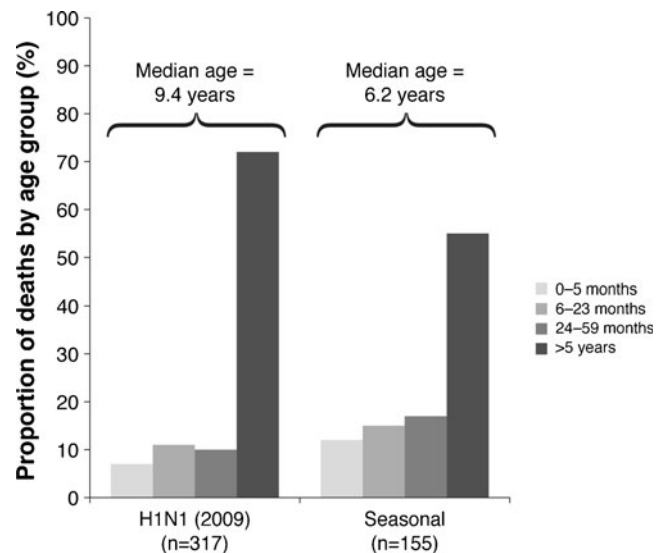
### Clinical manifestations of disease

#### Influenza symptoms

The presenting symptoms of influenza in children do not differ greatly between clinical settings. In children aged <14 years who were treated as outpatients, fever was very common (affecting 95 %), as were cough and rhinitis (77 and 78 % affected, respectively) but headache (39 %) and myalgia (13 %) were less common [114]. An earlier



**Fig. 1** Deaths from influenza in US children <5 years old as a proportion of all child deaths, comparing H1N1pdm09 influenza in summer 2009 with seasonal influenza in 2007–2008 and 2010–2011 [17, 20, 92]



**Fig. 2** Distribution of influenza-related deaths in children by age group, comparing H1N1pdm09 influenza in April 2009–January 2010 with seasonal influenza in October 2007–April 2009. The difference in median ages was statistically significant ( $p < 0.01$ ) [29]

prospective study reported a high prevalence of fever, cough and rhinorrhoea (95–96 %) in influenza-infected outpatients <5 years old [96]. These three symptoms were almost as common in hospital inpatients of the same age, with cough slightly but significantly more common in those >6 months old (94 %) than those up to 5 months old (80 %;  $p = 0.01$ ) [96]. Even in very young hospitalised infants (aged  $\leq 2$  months) with confirmed influenza, fever was the main presenting symptom [101]. Similarly, high rates of fever and cough were reported from a more recent study of hospitalised children and adolescents with H1N1pdm09 influenza [91]. Studies of hospitalised influenza patients also report neurological symptoms, such as febrile convulsions [97, 115, 119], although these are often reported as complications of the disease rather than symptoms (see next section). As well as the neurological system, other non-respiratory systems can be commonly affected in influenza: in some epidemics, up to 50 % of children have presented with gastrointestinal symptoms such as vomiting and diarrhoea, particularly those who are admitted to hospital, and affecting children of all age groups [1, 11, 67, 69, 90, 134]. In a study of children and adolescents hospitalised with laboratory-confirmed influenza, sepsis-like illness was the admission diagnosis for 52 % of those aged <6 months and for up to 16 % of older children [115].

Differentiating influenza from other respiratory infections on the basis of symptoms alone is challenging, and virological testing is necessary to confirm the diagnosis. A Finnish group who used a matched case-control study in children aged  $\leq 13$  years to compare confirmed influenza patients with those who had respiratory symptoms but were influenza-negative found fever to be the only reliable predictor of influenza [54].



## Complications of influenza

Influenza-associated complications contribute significantly to the disease burden in children. Complications are more likely to develop in recognised high-risk groups, including those with co-morbidities [26, 71] and younger children [71].

One of the most common complications of seasonal influenza in children is otitis media, which is associated with excess healthcare visits, antibiotic use and surgical procedures, and can lead to hearing loss. Otitis media affected 28 % of under 5 years presenting as outpatients in the US population-based study by Poehling et al. [96] and occurred in 24 % of young hospitalised children in both a Finnish and a US study [90, 93]. Infants and young children aged under 2 years old, however, appear to be at higher risk of acute otitis media than older children [84], which is consistent with the results of the Finnish prospective cohort study that reported a rate of 40 % in children <3 years old in an outpatient setting [51].

Respiratory tract infections (RTIs) are also frequently encountered as influenza complications. The most important RTI with respect to healthcare burden is pneumonia which is associated with hospitalisation and poorer outcomes. The incidence of pneumonia is high in children admitted to hospital with more severe influenza; in 2,992 hospitalised children and adolescents with seasonal influenza, radiographic evidence of pneumonia was found in 1,072 (36 %) [30], and recently published studies in European and Asian children suggest a similar rate in hospitalised children with H1N1pdm09 influenza, with estimates ranging from 22 to 43 % [11, 69, 91, 111], although two groups found the rate to be higher for H1N1pdm09 infections during 2009 than for influenza A infections in previous seasons [5, 78]. Pneumonia is less common outside the hospital setting: in the Finnish prospective cohort study in outpatients mentioned above, pneumonia was diagnosed in 9 of 370 (2.4 %) children with confirmed influenza, 8 of whom were aged ≤6 years [51]. In a retrospective study of 936 children aged 0–15 years with confirmed influenza seen as hospital outpatients or inpatients, pneumonia was present in 134 (14 %) children, 66 % of whom were <3 years old [65]. As with otitis media, infants aged under 2 years appeared to have a higher risk of LRTI than those aged 2–4 years in a 25-year cohort study, although absolute rates were quite low (annual rates per 1,000 children of 11 and 10 in the first and second years of life, respectively, and 4 for those aged 2–4 years) [84].

Neurological events or disorders are frequently reported as complications of influenza, ranging from febrile convulsions, which typically have a good prognosis, to encephalitis and encephalopathy, which may be fatal.

Japanese and Taiwanese children appear to have a higher vulnerability to CNS complications, although these findings may be the result of more intense surveillance. In 1,000 Japanese patients aged 0–20 years with H1N1pdm09,

neurological complications resulted in hospital admission in 255 (25.5 %) patients; the most common events were febrile convulsions (135 children) whereas encephalopathy, mostly mild, was only seen in 12 [121]. CNS dysfunction occurred in 26 of 84 (31 %) Taiwanese children with seasonal influenza, 60 of whom were aged <5 years; one of the patients had febrile convulsions, but 21 had encephalitis or encephalopathy [128]. In a recent Israeli study, 14 of 74 (19 %) children aged 0–16 years hospitalised with H1N1pdm09 had CNS complications, but these were mainly mild seizures [66].

CNS complications were less common in US studies of seasonal and pandemic influenza. In the earlier survey, 72/842 children hospitalised with seasonal influenza (8.6 %) had CNS complications; 56 had seizures (median age, 1.4 years) and 10 (median age, 3.5 years) had mild encephalopathy [85]. In 307 children aged 1–19 yrs who were hospitalised with H1N1pdm09 infection, 23 (7.5 %) had CNS complications (17 with seizures and 7 with encephalopathy), but 15 patients required monitoring in ICU and three died [64].

Neurological complications appear to be more common in severely ill children. In a French study of 181 children admitted to hospital with H1N1pdm09, 14 (7.7 %) had CNS dysfunction; of the 14 children (median age, 5.1 years), eight had febrile seizures and three had encephalitis or encephalopathy [39]. Twenty-four of the 181 children needed admission to ICU, however, including nine of those with CNS complications (38 % of the ICU cohort). In a study of 20 German children aged 0–15 years (median 7.5 years) who were admitted to ICU with severe seasonal influenza infections, encephalitis or encephalopathy occurred in five cases [120].

Less common complications of influenza include myositis [16, 57, 66, 90] and myocarditis [98, 112].

## Hospitalisation rates in influenza patients

Several studies demonstrate that the burden of hospital admission and emergency department visits in younger children who are infected with influenza is considerable [12, 13, 81, 84, 86]. Younger children are much more likely to be hospitalised as a result of influenza and its complications than their older counterparts. As shown in Table 1, a number of surveys have reported that influenza-associated hospitalisation rates were higher in those aged <5 years than aged ≥5 years. Furthermore, studies consistently report that the highest rates of all are in infants in their first year of life [4, 59, 81, 96, 107, 109, 116].

A 5-year survey of admissions to two children's hospitals in Kiel, Germany, compared incidence rates for types A and B influenza; the cumulative population-based rates per 100,000 children aged 0–5 years were 123 and 30 for influenza A and B, respectively, whereas rates in those aged 6–16 years were 22 and 9, respectively [130]. The authors also

**Table 1** Seasonal influenza-associated hospitalisation rates in children

Location	Period	Hospitalisation rate per 100,000			Reference
		Infants and young children (aged 0–59 months)	Children and adolescents (aged 5–17 years)	Rate ratio (infants to older children)	
Oregon, USA; high-risk children	1967–1973	470	210	2.2	Mullooly and Barker [79]
Oregon, USA; all children	1967–1973	120	40	3	Mullooly and Barker [79]
Tennessee, USA	1973–1993	86–1,038 <sup>a</sup>	41	2.1–25.3	Neuzil et al. [81]
Seattle, USA	1992–1997	100	16	5.6	Izurieta et al. [59]
California, USA	1993–1997	135	19	7.2	Izurieta et al. [59]
Kiel, Germany; influenza A only	1996–2001	123	22	5.6	Weigl et al. [130]
3 US counties	2000–2004	90	–	–	Poehling et al. [96]

<sup>a</sup> Range of rates reported; lowest value is for those aged 36–59 months and highest for those aged <6 months

noted that co-existing cardiac disorders and asthma increased the risk of hospital admission in influenza A patients, in agreement with earlier data from US studies showing that high-risk children, e.g., those with asthma, are more likely to be hospitalised or to have prolonged hospital stays compared with otherwise healthy children [26, 82]. The higher-risk group also have poorer outcomes than low-risk patients after hospitalisation [110], and more than 50 % of the hospital costs of US children aged ≤18 years with an influenza diagnosis was in higher-risk children alone [47].

Recent papers on epidemiology and outcomes in hospitalised children have compared H1N1pdm09 influenza with historical data on seasonal influenza. Some of these studies report a worsening of the disease burden with H1N1pdm09 influenza, either as higher hospitalisation or mortality rates or more severe disease [31, 55, 68, 135] and others report large increases in the hospitalisation rate for ILI during the first months of the pandemic compared with previous seasons [75, 118]. Consistent with the experience from previous pandemics, hospitalised children with H1N1pdm09 infections were significantly older than those hospitalised with seasonal influenza (range of median ages, 2–5 and 0–2 years, respectively) [31, 55, 118, 135]. A study on the impact of H1N1pdm09 influenza in Japan suggested that although infants <1 year old were hospitalised at a higher rate than those aged 12–23 months, agreeing with the historical data for seasonal influenza described above, those in their second year of life had three times the rate of influenza-related complications [122].

## Managing the influenza burden

### Vaccination

A large systematic review of vaccine studies, published in 2012, concluded that live attenuated influenza vaccines

(LAIVs) and inactivated vaccines have similar effectiveness in preventing influenza in children >2 years old (33 and 36 % respectively), but that in children aged ≤2 years, inactivated vaccines (the only type licensed for use in this age group) were no more effective than placebo [61]. Authors of another systematic review and meta-analysis found that vaccine effectiveness in children aged 6–59 months was only significant in three of eight seasons, and concluded that there is a need to improve the effectiveness of current influenza vaccines [87]. A prospective, non-randomised cohort study on trivalent inactivated influenza vaccine (TIV) not included in the Cochrane review showed 66 % effectiveness in preventing infection both in children aged 9 months to 3 years and, notably, in the subgroup of infants aged under 2 years [53]. Adding the oil-in-water adjuvant MF59 to TIV appears to boost vaccine efficacy further, as shown in children aged 6 months to 6 years in a randomised study [125]. Most recently of all, a meta-analysis of eight trials (two-season and single-season) in children 2–17 years old found that intranasal LAIV reduced influenza illness caused by all strains by 79 % compared with placebo and by 48 % compared with TIV [3].

Evidence from several countries suggests that vaccination against seasonal influenza can reduce disease burden. In a randomised placebo-controlled study in Italian children aged 6 months to 14 years, intranasal TIV reduced the mean number of missed school days (5.4 and 13.8 days, respectively) and the mean number of lost work days in household contacts (0.42 and 2.50), although no 95 % CI were reported [32]. A similar single-season study in Sardinia, in younger children (1–6 years old) showed that TIV significantly reduced the rate of ILI compared with no treatment (12.4 and 37.7 %, respectively (risk reduction of 67 %; 95 % CI, 59–74 %)) and the mean duration of absenteeism from day care centres (0.5 and 2.3 days; no 95 % CI given) [28]. Over six consecutive seasons in Japan, a non-randomised community-based study

showed a small but significant difference in the aggregate rate of hospitalisation associated with influenza A infections in children aged 6–59 months who were given two doses of TIV; rates were 0.6 % and 2.0 % in the vaccinated and unvaccinated groups, respectively (71 % risk reduction [95 % CI, 59–80 %]) [63]. In a US study of the 2003–2004 season, two doses of inactivated vaccine reduced the risk of an ILI office visit in infants aged 6–21 months by 69 % (hazard ratio 0.31; 95 % CI, 0.26–0.36 %), although one dose was not effective [2]. In a cost-effectiveness analysis of a 2-year randomised placebo-controlled trial, intranasal LAIV reduced the mean number of ILI fever days per child by 1.2 days in US children aged 15–71 months, although the statistical significance was not reported [72].

As reducing the number of cases in children makes onward transmission in households less likely [58], societal benefits of childhood vaccination are not only predicted by modelling studies [8, 41, 95] but also borne out in practice. Analysis of deaths attributable to pneumonia and influenza in Japan from 1950 to 2000 suggested that the lower rate of excess deaths during the middle three decades was probably due to vaccine-induced herd immunity resulting from the child immunisation programmes that operated from 1962 to 1994 [99], and later statistical analysis of these data, comparing the 1978–1994 and 1995–2006 periods, estimated that the programmes had reduced mortality risk in adults  $\geq 65$  years by 36 % (95 % CI, 17–51 %) after adjusting for virus subtype, population demographics and baseline mortality risk [23]. Lower rates of ILI in other age groups followed vaccination of children in Russia and the USA [40, 94]. Complication rates are also lower in vaccinated children, notably the incidence of otitis media [10, 32, 49, 74, 88] and the rate of respiratory illness in children with asthma [117].

Influenza vaccines cause fever and myalgia, and administration-site-related reactions such as pain and swelling (and nasal congestion for the intranasal vaccine), which are usually mild and temporary. A more serious but rare side-effect is allergic reactions, and adverse reactions such as febrile convulsions [7, 22] and narcolepsy [61] have been reported to be associated with specific vaccine brands.

#### Antiviral agents

The neuraminidase inhibitors oseltamivir and zanamivir are preferred to amantadine and rimantadine as influenza antiviral therapy because of lower rates of drug resistance. Systematic reviews of studies in children showed evidence of their usefulness in shortening influenza duration and reducing the incidence of acute otitis media in paediatric seasonal influenza, although reduction in the incidence of symptomatic influenza after prophylactic use was only modest, and their ability to reduce the incidence of serious

influenza complications has yet to be proved in large trials [113, 129]. A recent Cochrane review that examined regulatory information on neuraminidase inhibitors, principally from trials in adults but including some in children, was unable to reach conclusions about the effect of oseltamivir on complications and transmission [60]. Recent studies report that prompt initiation of oseltamivir treatment can shorten hospital stay in children with severe influenza, whether caused by seasonal virus strains or H1N1pdm09 virus [27, 36]. Seasonal H1N1 viruses developed naturally occurring resistance to oseltamivir, particularly in the 2007–2009 period [33, 106], but H1N1pdm09 viruses that emerged during the 2009 pandemic appear to be mostly sensitive to inhibition [46]. Oseltamivir appears to be very effective for reducing otitis media incidence in children aged 1–3 years, if treatment is started quickly (within 12 h of symptom onset) [52]. WHO guidelines recommend the use of neuraminidase inhibitors in children in high-risk groups and in all children with severe influenza [132], although there are still challenges, e.g. timely diagnosis, when selecting patients who could benefit from therapy.

Children treated with oseltamivir have a significantly higher rate of vomiting compared with placebo, but the adverse event profile of neuraminidase inhibitors is otherwise similar to that of placebo [129]. Neuropsychiatric side-effects have been reported in association with oseltamivir administration, although the significance of this is uncertain given that CNS complications are often reported in untreated influenza patients, as already described.

#### Conclusions

Many of the additional data on influenza in children that have been published in 2009–2012 relate to infections caused by the H1N1pdm09 virus. Some studies report that hospitalisation rates for H1N1pdm09 infections were higher than for seasonal influenza infections, and pneumonia continues to be at least as significant a complication as it was before the arrival of the 2009–2010 pandemic. In contrast, death rates in children under 5 years of age seem to have been lower during the pandemic than they were before and after it and in line with this, there was a difference in the median age of those hospitalised, with pandemic influenza typically affecting children 2–3 years older than those with seasonal influenza. A common theme that does emerge, however, is that young children remain particularly vulnerable to influenza, with greater rates of hospitalisation and complications than their older counterparts, and the burden is worse still in children with co-existing illnesses. The recent data on the effectiveness of vaccines against seasonal influenza supports previous experience, showing that this is a productive strategy for

reducing disease burden in children, although more effective vaccines need to be developed.

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