

The healthcare and societal burden associated with influenza in vaccinated and unvaccinated European and Israeli children

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Abstract Few data exist regarding the healthcare and societal burden of culture-confirmed influenza illness in European and Israeli children. The current analysis describes this burden in vaccinated and unvaccinated children 2–17 years of age. Healthcare and societal burden outcomes were prospectively collected for culture-confirmed influenza illness in three previous randomized studies: a study of live attenuated influenza vaccine (LAIV) versus placebo in children aged <48 months attending day care ($N=846-973$), and studies of LAIV versus inactivated influenza vaccine (IIV) in children aged <72 months with recurrent respiratory infections ($N=1,609$) and in children aged 6–17 years with asthma ($N=2,211$). The incidence of each endpoint among enrolled subjects and subjects with influenza was determined by treatment group and by country. Among subjects with influenza, 57–91 % missed school or day care, 45–90 % used non-antibiotic medications, 29–55 % of parents missed work, 17–55 % used antibiotics, 11–62 % had additional provider visits, and 9–20 % had acute otitis media. Where evaluated, rates of outcomes were generally similar between countries. Among all children enrolled, LAIV recipients missed 324–902 and 150 fewer days of day care per 1,000 children than those of placebo and IIV recipients, respectively; parents of LAIV recipients missed 197–340 and 76 fewer days of work per 1,000 children than those of placebo and IIV recipients, respectively. Influenza illness in European and Israeli children

2–17 years of age resulted in a considerable absenteeism and healthcare utilization that was similar across the countries studied. These data underscore the potential benefits of annual vaccination of children against influenza.

Introduction

Influenza is a common illness in children that results in a significant burden on the healthcare system and society in general. Children with influenza illness frequently require medications and visits to healthcare providers (HCPs) [1–15]. Pediatric influenza frequently results in complications, the most common of which is acute otitis media (AOM), which require additional healthcare intervention [16]. From the societal perspective, influenza illness causes significant absenteeism and lost productivity, with children missing school or day care and their parents or guardians missing work [1, 3, 4, 7, 11, 13].

An Ann Arbor strain live attenuated influenza vaccine (LAIV) is approved for eligible children 2–17 years of age in multiple countries, including the European Union and Israel. However, there is ongoing debate in European countries regarding the burden of disease in this population and whether these children should be vaccinated annually against influenza [17].

Multiple studies have demonstrated the country-specific burden of influenza illness in European and Israeli children and their families [1, 3, 4, 7, 11, 13, 18]. In European countries, the incidence of confirmed influenza illness in a single season has been shown to range from 96 to 167 per 1,000 in children ≤ 14 years of age [3, 7]. However, these previous studies were limited to a single country; there are few studies that compare outcomes across multiple European countries using a consistent methodology. Data from prospective, multi-country studies are needed in order to better characterize the

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healthcare and societal burden of influenza in European and Israeli children 2–17 years of age.

Three prospective, multi-country, randomized studies investigated the healthcare and societal burden associated with influenza in children who were vaccinated with LAIV compared with those receiving placebo or inactivated influenza vaccine (IIV) [18–20]. Previous publications of these studies reported the rates of symptomatic influenza illness. However, for the healthcare and societal burden outcomes, only the overall outcome rates were reported, regardless of whether or not the child had culture-confirmed influenza; the rate of health outcomes in children with influenza was not reported. The primary aim of our study was to use data from these studies to describe the overall and country-specific healthcare and societal outcomes associated with culture-confirmed influenza in vaccinated and unvaccinated European and Israeli children 2–17 years of age.

Methods

Data sources

Data for this study were collected from three previous prospective, randomized, controlled studies that evaluated the efficacy and safety of LAIV in children in Europe and Israel. Study 1 by Vesikari et al. [19] was a randomized, controlled trial that examined LAIV versus placebo in 1,784 children 6–35 months of age attending day care in Belgium, Finland, Israel, Spain, and the United Kingdom. Study subjects were followed for two consecutive influenza seasons, between October 2, 2000, and May 31, 2002. LAIV recipients received two doses of LAIV separated by approximately 1 month in year 1 and a single dose in year 2.

Study 2 by Ashkenazi et al. [20] was a randomized, controlled trial that examined LAIV versus IIV in 2,187 children 6–71 months of age with recurrent respiratory tract infections during the 2002–2003 influenza season in Belgium, the Czech Republic, Finland, Germany, Israel, Italy, Poland, Spain, Switzerland, and the United Kingdom. Recurrent respiratory tract infection was defined as two or more practitioner-attended episodes of common colds, AOM, bronchitis, pneumonia, or bronchiolitis in the 12 months before enrollment. Study subjects received two doses of LAIV or IIV separated by approximately 1 month and were followed from October 4, 2002, to June 2, 2003.

Study 3 by Fleming et al. [21] was a randomized, controlled trial that examined LAIV versus IIV in 2,229 children 6–17 years of age with asthma during the 2002–2003 influenza season in Belgium, Finland, Germany, Greece, Israel, Italy, the Netherlands, Norway, Poland, Portugal, Spain, Switzerland, and the United Kingdom. Study subjects received one dose of LAIV or IIV and were followed from October 4, 2002, to May 31, 2003.

Data collection

The studies prospectively evaluated all cases of respiratory illness in enrolled subjects for the presence of influenza using viral culture. Health outcomes were monitored by diary cards or weekly contacts; influenza infection was monitored through regularly scheduled telephone calls, and clinic or home visits. Nasal swab cultures were collected if a child had one or more of the following: AOM (suspected or diagnosed), fever, pneumonia, pulmonary congestion, shortness of breath, or wheezing; or two or more of the following symptoms concurrently: chills, cough, decreased activity, headache, irritability, muscle aches, pharyngitis, rhinorrhea, or vomiting. Healthcare utilization was at the discretion of the parent or guardian and HCP. Aside from vaccination and collection of nasal swabs, there were no study-sponsored healthcare interventions. Investigators were blinded to the nasal swab culture results.

For all cases of respiratory illness, the studies recorded whether the illness resulted in various healthcare and societal outcomes. Healthcare outcomes included the presence of AOM (studies 1 and 2 only), medication use (antibiotic, non-antibiotic), the number of additional unscheduled HCP visits beyond the initial illness visit, and the number of overnight hospitalizations (studies 2 and 3 only). Societal outcomes included child and parental absenteeism. Child absenteeism was measured as the percentage of children who missed day care or school due to influenza and the duration of the absenteeism (in days). Parental absenteeism data were collected only in study 1 and were measured as the percentage of parents (of either sex) who missed paid work to care for the participating child's influenza illness and the duration of this absenteeism (in days). These were the only outcomes systematically collected during the study. To ensure documentation of all sequelae of a particular illness, these outcomes were recorded after illness resolution.

Data analyses

Given differences in the study designs and populations, the data from the three studies were analyzed separately. Analysis was restricted to subjects who were 2 years or older at vaccination. The incidence of culture-confirmed influenza and the total days of missed school or day care (for children) or work (for parents) per 1,000 children per season were calculated for the per-protocol population, consistent with the original study methods [19–21]. Healthcare and societal burden outcomes were evaluated among children with culture-confirmed influenza. All culture-confirmed influenza illnesses were evaluated, regardless of whether the influenza strains matched the strains contained in the vaccines. Data regarding overnight hospitalizations were not analyzed because no influenza-

associated hospitalizations were documented in children 2 years and older. Because of the large number of influenza cases detected in study 1, a by-country analysis of healthcare resource use and absenteeism associated with influenza was conducted. In this analysis, all cases regardless of the study arm were pooled and evaluated. Fisher's exact test was used to test country and treatment group differences for each of these variables. All statistical analyses were conducted using SAS, version 8.2 (SAS Institute, Inc., Cary, NC).

Results

Demographics for all enrolled children 2–17 years of age

In study 1, 846 subjects (LAIV, $n=490$; placebo, $n=356$) were available for analysis in year 1; in year 2, 973 subjects were available (LAIV, $n=570$; placebo, $n=403$). For study 2, there were 1,608 subjects (LAIV, $n=790$; IIV, $n=818$). In study 3, 2,211 subjects were available (LAIV, $n=1,114$; IIV, $n=1,115$). In all studies, the study arms were well balanced for gender and race (Table 1).

Rates of influenza among all enrolled children 2–17 years of age

During the first year of study 1, influenza illness was confirmed in 16 % of placebo recipients ($n=55$) and 2 % of subjects vaccinated with LAIV ($n=11$). During the second year of study 1, influenza illness was confirmed in 31 % of placebo recipients ($n=123$) and 4 % of LAIV recipients ($n=21$). For study 2, 3 % of subjects who received LAIV ($n=23$) experienced confirmed influenza illness compared

with 6 % of subjects vaccinated with IIV ($n=46$). For study 3, 5 % of subjects who received LAIV ($n=50$) experienced confirmed influenza illness compared with 7 % of IIV recipients ($n=73$).

Healthcare and societal outcomes among children 2–17 years of age with influenza

In study 1, healthcare outcomes were frequent among placebo and LAIV recipients with influenza (Fig. 1). Most subjects missed school or day care and received medications. In year 1, the mean number of missed day care days for those children absent due to influenza was 3.1 and 3.2 for LAIV and placebo recipients, respectively. In year 2, the mean durations were 2.6 and 3.6 days, respectively. Approximately one-half of subjects with influenza required a parent to miss work for the child's illness. In years 1 and 2, the mean number of parental missed work days for parents who missed work due to their child's illness was 1.8 and 2.3 for LAIV recipients and 2.8 and 2.7 placebo recipients, respectively. Additional HCP visits after the initial study visit were more frequent in year 1 when subjects were younger. In year 2, the percentages of subjects requiring parental missed work and additional HCP visits were lower in LAIV recipients, but these differences were not statistically significant ($p=0.23$ and $p=0.08$, respectively).

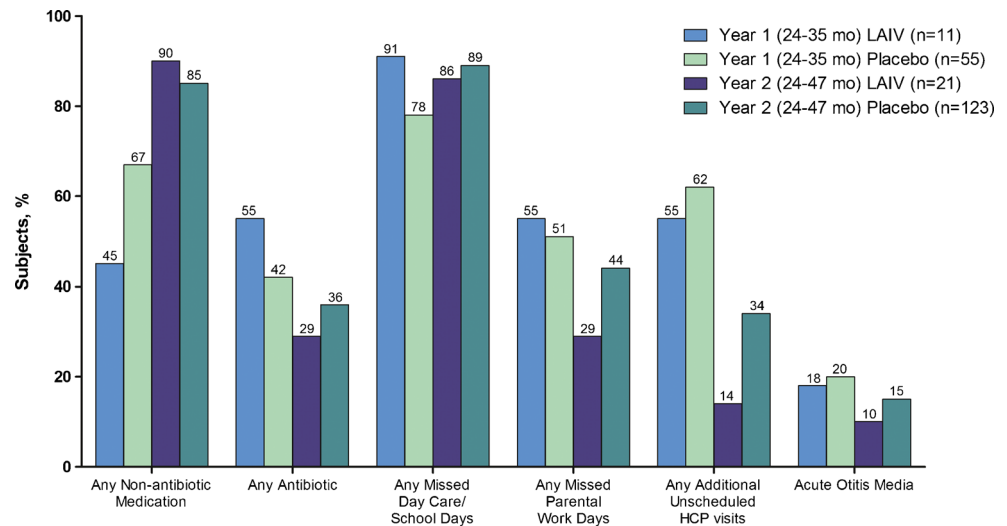
The proportion of influenza-positive subjects with these outcomes was generally similar in each country (Fig. 2). However, non-antibiotic medication use was less common in Finland and Israel than it was in Belgium, Spain, and the United Kingdom. Additionally, parental missed work was less common in Belgium and Spain. These trends were present in both study years and were statistically significant ($p<0.001$) in the

Table 1 Baseline demographics by study and treatment

	Study 1 (24–47 months of age)				Study 2 (24–71 months of age)	Study 3 (6–17 years of age)		
	Year 1		Year 2		LAIV	IIV	LAIV	IIV
	LAIV	Placebo	LAIV	Placebo				
Number of subjects	490	356	570	403	790	818	1114	1115
Gender, n (%)								
Male	264 (53.9)	188 (52.8)	304 (53.3)	195 (48.4)	409 (51.8)	431 (52.7)	694 (62.3)	723 (64.8)
Female	226 (46.1)	168 (47.2)	266 (46.7)	208 (51.6)	381 (48.2)	387 (47.3)	420 (37.7)	392 (35.2)
Race/ethnicity, n (%)								
White	474 (96.7)	344 (96.6)	555 (97.4)	393 (97.5)	769 (97.3)	788 (96.3)	1,091 (97.9)	1,089 (97.7)
Black	4 (0.8)	2 (0.6)	6 (1.1)	2 (0.5)	11 (1.4)	9 (1.1)	9 (0.8)	8 (0.7)
Asian	3 (0.6)	2 (0.6)	4 (0.7)	1 (0.3)	5 (0.6)	13 (1.6)	10 (0.9)	6 (0.5)
Other	9 (1.8)	8 (2.3)	5 (0.9)	7 (1.7)	5 (0.6)	8 (1.0)	4 (0.4)	12 (1.1)
Number of subjects with influenza	11	55	21	123	23	46	50	73

IIV trivalent inactivated influenza vaccine, LAIV live attenuated influenza vaccine

Fig. 1 Healthcare resource use and absenteeism by year and treatment in study 1 among children with confirmed influenza. HCP=healthcare provider; LAIV=live attenuated influenza vaccine



pooled analysis of years 1 and 2. The differences did not appear to be due to differences in the age of subjects with influenza in the countries, because the mean age for influenza cases by country was 28–31 months in year 1 and 34–38 months in year 2.

In studies 2 and 3, child absenteeism and non-antibiotic medication use were the most common outcomes (Fig. 3). In study 2, AOM was reported in 9 % of subjects with confirmed influenza in both treatment groups; AOM was not collected in study 3. In study 2, the mean number of missed school days for those children absent due to influenza was 3.0 and 4.3 days for LAIV and IIV recipients, respectively. In study 3, the mean

number of missed school days for those children absent due to influenza was 3.8 and 3.7 days for LAIV and IIV recipients, respectively.

Influenza-associated absenteeism among all enrolled children 2–17 years of age

Given the potential societal benefits of reductions in influenza-associated absenteeism, the number of days of absenteeism per 1,000 children enrolled was evaluated for each study. In years 1 and 2 of study 1, respectively, LAIV recipients missed 324 and 902 fewer days of day care per 1,000 children than placebo

Fig. 2 Healthcare resource use and absenteeism by country in study 1 (years 1 and 2 combined) among children with confirmed influenza. * $p < 0.001$, p -values were calculated using Fisher's exact test to assess differences among countries. HCP=healthcare provider

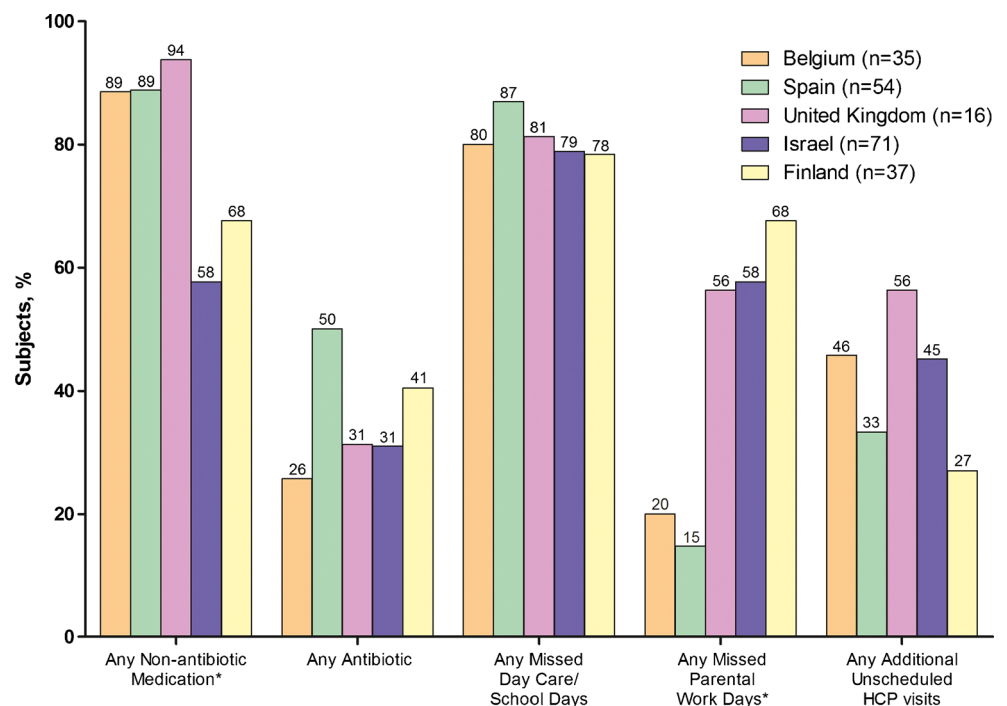
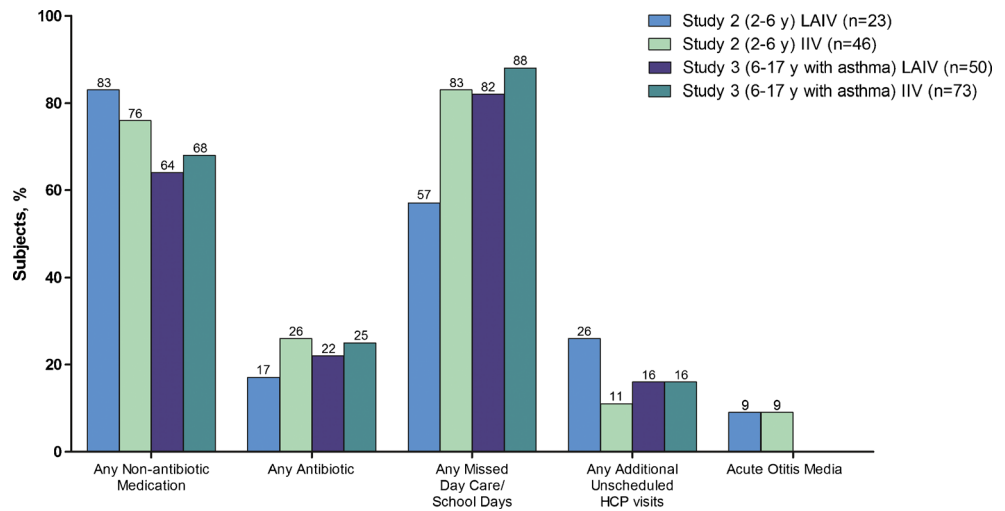


Fig. 3 Healthcare resource use and absenteeism by treatment in studies 2 and 3 among children with confirmed influenza. HCP=healthcare provider; IIV=trivalent inactivated influenza vaccine; LAIV=live attenuated influenza vaccine

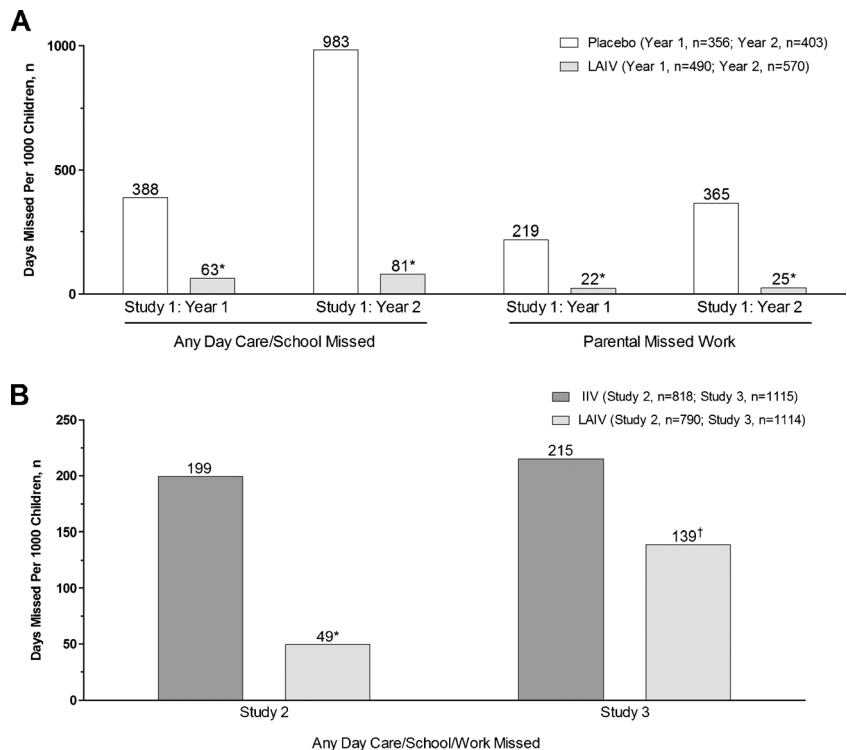


recipients ($p < 0.001$), representing an 84 to 92 % reduction in missed day care days, respectively (Fig. 4a). Parents of LAIV recipients missed 197 (year 1) and 340 (year 2) fewer days of work per 1,000 children compared with parents of placebo recipients ($p < 0.001$), representing a 90 to 93 % reduction, respectively (Fig. 4a). In study 2, LAIV recipients missed 150 fewer days of day care/school due to influenza per 1,000 children compared with IIV recipients ($p < 0.01$), representing a 75 % reduction in missed days of day care/school (Fig. 4b). In study 3, LAIV recipients missed 76 fewer days of school/work per 1,000 children than IIV recipients ($p = 0.02$), representing a 35 % reduction.

Discussion

This analysis of data from three large clinical studies provides additional insight into the vaccine-preventable annual healthcare and societal burden of influenza for children and their families in Europe and Israel. Among children who developed influenza illness, most missed school or day care and required medications, demonstrating that the influenza illness events evaluated in the studies represented clinically and societally meaningful illness. Additionally, in studies 2 and 3, which had similar designs and were conducted during the same influenza season, the rates of the measured outcomes were

Fig. 4 Influenza-associated absenteeism among all children enrolled per 1,000 children per season. **a** Study 1. **b** Studies 2 and 3. IIV=trivalent inactivated influenza vaccine; LAIV=live attenuated influenza vaccine. * $p < 0.001$, LAIV versus comparator; † $p = 0.02$, LAIV versus IIV



similar among younger (2–6 years of age) and older (6–17 years of age) children. Community-based studies among European children have demonstrated a similar healthcare and societal burden of influenza, with 28–43 % of children with confirmed influenza illness receiving antibiotics, 99 % receiving antipyretic medications, 11–41 % developing AOM, and 22–50 % of children requiring a parent to miss work, with an average absenteeism of 2.8–4.5 days [3, 7, 22].

The current analysis provides a valuable multi-country description of healthcare resource use and absenteeism associated with pediatric influenza illness. Few European studies have evaluated with consistent methods the burden of influenza across multiple countries in the same influenza seasons [23]. The current analysis demonstrated that the burden of influenza was generally similar across multiple European countries. However, patients in Finland and Israel used less non-antibiotic medications and parents in Spain and Belgium missed fewer work days than in other countries. These discrepancies may reflect cultural differences in medical practice and child care. Despite these observed differences, the observed outcomes suggest that the healthcare and societal burden of pediatric influenza is generally similar across European countries.

Although multiple European studies have described child and parental absenteeism associated with influenza [1, 3, 4, 7, 11, 13, 22, 24, 25], only a single previous European study has evaluated the incidence rate of child absenteeism in a community-based cohort. In Finland during 2000–2002, 75 % of children with influenza illness missed school or day care, with an average absenteeism of 3.4 days. Additionally, a parent missed at least 1 day of work in 49.4 % of pediatric influenza illnesses, with absenteeism averaging 2.7 days [7]. The current analysis provides valuable estimates of the incidence of absenteeism among children with influenza illness for additional European countries.

Relative to placebo and IIV, LAIV was associated with considerable reductions in the number of missed day care or school days and parental missed work. A previous U.S. study of LAIV relative to placebo also demonstrated that influenza-associated fever, otitis media, missed school or day care days, missed parental work days, and HCP visits decreased by 86 % to 98 % during seasons in which the circulating strains matched [26] and did not match [27] the strains contained in the vaccine. Similarly, in the placebo-controlled study in this analysis, for every ten children attending day care who were vaccinated with LAIV, there were approximately six fewer days of missed school or day care, three fewer days of parental missed work, and one less additional HCP visit beyond the initial influenza illness visit. These data further highlight the potential healthcare and societal benefits of annual influenza vaccination in children and provide reassurance that, by reducing the incidence of influenza illness, LAIV can also reduce the healthcare and societal burden impact of influenza illness.

The primary limitation of the current analysis is that the studies were conducted during three influenza seasons, which may not be representative of the average burden of influenza in Europe and Israel. However, while the absolute incidence of influenza in children can vary considerably by season, vaccine efficacy and the rate of complications and sequelae among those with influenza have been shown to be similar across seasons [3, 7, 22, 28, 29]. Additionally, the studies did not collect the actual costs associated with the healthcare and societal burden outcomes.

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