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Vaccine effectiveness against severe laboratory-confirmed influenza in children: Results of two consecutive seasons in Italy

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ABSTRACT

Objective: To evaluate the effectiveness of seasonal influenza vaccine in preventing Emergency Department (ED) visits and hospitalisations for influenza like illness (ILI) in children.
Methods: We conducted a test negative case-control study during the 2011–2012 and 2012–2013 influenza seasons. Eleven paediatric hospital/wards in seven Italian regions participated in the study. Consecutive children visiting the ED with an ILI, as diagnosed by the doctor according to the European Centre for Disease Control case definition, were eligible for the study. Data were collected from trained pharmacists/physicians by interviewing parents during the ED visit (or hospital admission) of their children. An influenza microbiological test (RT-PCR) was carried out in all children.

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Case-control study
Laboratory-confirmed cases

Results: Seven-hundred and four children, from 6 months to 16 years of age, were enrolled: 262 children tested positive for one of the influenza viruses (cases) and 442 tested negative (controls). Cases were older than controls (median age 46 vs. 29 months), though with a similar prevalence of chronic conditions. Only 25 children (4%) were vaccinated in the study period. The overall age-adjusted vaccine effectiveness (VE) was 38% (95% confidence interval −52% to 75%). A higher VE was estimated for hospitalised children (53%; 95% confidence interval −45% to 85%).
Discussion: This study supports the effectiveness of the seasonal influenza vaccine in preventing visits to the EDs and hospitalisations for ILI in children, although the estimates were not statistically significant and with wide confidence intervals. Future systematic reviews of available data will provide more robust evidence for recommending influenza vaccination in children.

1. Introduction

Seasonal influenza represents an important cause of morbidity and mortality especially for the risk of secondary bacterial infections, which is higher in children and elderly than in the general population. The burden of influenza is highest in young children under 5 years of age likely due to immunological immaturity [1–3].

Increasing attack rates during epidemics lead to higher outpatient visit and hospitalisation rates [3–5]. Influenza-associated hospitalisation rates are well described in children with underlying chronic conditions; however accumulating evidence showed that the increased risk also affected otherwise healthy children [4]. Observational data indicated that although children with underlying conditions are at higher risk of death, the majority of paediatric deaths occur among healthy children [6].

The vaccination against influenza is recognised as an effective preventive intervention and each country is responsible for national programs and for defining targeted risk groups. In the majority of European countries, the influenza vaccine is recommended for children with underlying medical conditions. UK authorities announced plans to extend influenza vaccination to all children aged 2–16 years from 2014 [7]. At present, Finland is the only European country which has implemented the routine influenza vaccination of healthy children (6 months to <3 years) [8].

In Italy, the course of influenza epidemics generally extends between December and April, with a peak in February [9] and each year the Ministry of Health promotes a vaccination campaign between mid-October and December. The official recommendation identifies at risk children as a target group for influenza vaccination (provided free of charge); only sub-unit, split or virosomal seasonal vaccine formulations can be administered in children (6 months to 17 years of age) [10,11]. During the seasons 2011–2012 and 2012–2013, the composition of the vaccines varied only for the B virus strain (B/Wisconsin in 2011–2012, and B/Brisbane in 2012–2013), whereas the A(H1N1) and A(H3N2) antigens were present in both seasons. The two vaccine strains B/Wisconsin and B/Brisbane belong to two different lineages, i.e. B-Yamagata and B-Victoria respectively.

Most of the available evidence on the efficacy and effectiveness of seasonal influenza vaccine in a paediatric setting is derived from clinical trials and concerns almost entirely healthy children [12–15]. Although these studies adopted heterogeneous outcome definitions (e.g. from clinically defined influenza like-illness (ILI) in the outpatient setting to laboratory confirmed hospitalisations for influenza), they found efficacy estimates of around 70%, higher than those on effectiveness (around 40%). Despite the fact that influenza vaccination is primarily recommended in children with underlying conditions, insufficient evidence is available in this population. Moreover, the World Health Organization considers as a target group for influenza immunisation, children from 6 to 23 months, even though effectiveness data are scanty [16].

The objective of this national study was to determine the effectiveness of seasonal influenza vaccination against laboratory-confirmed influenza cases visiting the Emergency Department (hospitalised or not) in a large paediatric population over two consecutive seasons (2011–2012 and 2012–2013) and to provide evidence for vaccination recommendations in Italy.

2. Methods

In Italy, since 1999 an active surveillance on drug and vaccine safety in children has been conducted in various paediatric hospitals/wards located throughout the country [17]. Italian paediatric hospitals/wards can admit children from 0 to 17 years of age. Overall, the network includes 11 sites from seven regions representative of the whole Country, and around 400,000 children visited the EDs of the participating centres each year. The network organisation facilitated the prompt set up of the investigation on influenza vaccine effectiveness during the A/H1N1 pandemic (in 2009) and in two following influenza seasons (2011–2012 and 2012–2013). The results of the A/H1N1 pandemic vaccination campaign were reported elsewhere [18].

Consecutive children visiting the Emergency Departments (ED) with an ILI, as diagnosed by the doctor during the ED visit, were eligible for the study. The ILI case definition for children was adapted from the European Centre for Disease Control (ECDC) and used for influenza surveillance in Europe since the pandemic season [19,20]. In detail, the following definition of ILI was adopted, for children >5 years: sudden onset of fever $\geq$38 °C (for at least 24 h), in association with at least one respiratory symptom (cough, sore throat, coryza), and at least one general symptom (headache, asthenia, malaise). For children between 6 months and 5 years, in association with fever >38 °C, the following general signs and symptoms were considered: inadequate drinking or feeding, vomiting and/or diarrhoea, respiratory symptoms. All children hospitalised, or admitted to a Short Stay Unit (up to 24 h observation) were enrolled, and in some clinical centres also children visiting the ED but not admitted to hospital were included. Since influenza vaccine is indicated for children aged >6 months, younger children were not eligible.

Written informed consent was acquired from parents. Data were collected by trained pharmacists/physicians by interviewing parents during the ED visit (or hospital admission) of their children. Demographic data, medical history of chronic conditions, date of vaccination and type of vaccine were collected using a structured questionnaire. For the assessment of influenza vaccine effectiveness, children were defined as vaccinated if they had received at least one dose more than 14 days before symptom onset.

An influenza-confirmatory laboratory test was carried out in all children. The virus was detected through nasopharyngeal sample collection; stable viral transport medium was added to swabs. Specimens were collected and analysed by using a real-time reverse transcriptase-polymerase chain reaction (RT-PCR). In six centres

the tests were analysed in internal laboratories, whereas the others sent the specimens to certified external laboratories.

The first phase of the study was performed in the 2011–2012 influenza season and was used as a pilot study to refine the 2012–2013 investigation. In order to concentrate enrolment and laboratory tests in the epidemic period the coordinator centre gave the start-up on the basis of data on influenza epidemics in Italy provided from the National surveillance of ILI incidence [9]. The inclusion of children took place between 1 February and 31 March 2012 (for the 2011–2012 season), and between 14 January and 15 March 2013 (for the 2012–2013 season). The inclusion periods were the same for all centres.

Data were analysed according to a test-negative case-control study design: all children with a positive confirmatory laboratory test (to one of the viruses contained in the seasonal vaccine) were included as cases, whereas controls were children with a negative test. For effectiveness evaluation, odds of influenza vaccination were compared in cases and controls.

2.1. Study sites

The following paediatric hospitals and departments were participating: Giannina Gaslini Paediatric Hospital (Genova); Regina Margherita Paediatric Hospital (Torino); Department of Paediatrics, University of Padova; Paediatric Department, Treviso Hospital (Treviso); Anna Meyer Children's University Hospital (Firenze); Department of Paediatrics, University of Perugia; Pharmacology and Paediatrics and Developmental Neuroscience, Università Cattolica S. Cuore (Roma); Bambino Gesù Paediatric Hospital (Roma); Santobono-Pausilipon Paediatric Hospital-Virologic Unit Cotugno (Napoli); Giovanni Di Cristina Paediatric Hospital (Palermo); University Hospital of Messina. A common study protocol was approved by the Ethics Committee of each clinical centre. The study was coordinated by the National Centre of Epidemiology of the National Institute of Health in Rome.

2.2. Statistical analyses

Data were analysed with SPSS (v. 21.0). *T*-test was used to compare means, Wilcoxon–Mann–Whitney non-parametric test was used to compare medians and Chi-square test was used to compare percentages. Adjusted odds ratios (ORs) and 95% confidence intervals (CI) were estimated through a logistic regression model. ORs were adjusted for age, which was included in the logistic model as a continuous variable (in months). We estimated the seasonal influenza vaccine effectiveness (VE) as 1 minus the OR, expressed as a percentage.

3. Results

Among the 773 eligible children, 69 (9%) were excluded (Fig. 1). The main reason for exclusion was lack of informed consent either to collect the nasopharyngeal swab ($n = 25$) or to be included in the study ($n = 10$). The 704 remaining children were classified as cases (262 children tested positive for one of the influenza viruses) and controls (442 children who tested negative). The percentage of hospitalised children was 56% ($n = 148$) among cases and 75% ($n = 332$) among controls. Overall, the age of the enrolled children ranged from 6 months to 16 years.

The proportion of cases ranged from 12% to 56% in the 11 centres. In 69% of cases and 55% of controls the test was performed the same day of symptom onset. In 97% of cases and in 93% of controls the test was carried out within 2 days. Among cases, B virus was detected in 126 children (48%), A(H1N1) in 59 (23%), unspecified A virus in 33 (13%), A(H1N1)pdm09 in 22 (8%) and A(H3N2) in 22 (8%). In the 2012–2013 season the virology unit of one clinical centre was able to characterise 40 of the 126 cases positive for influenza B virus: they all resulted belonging to B/Yamagata/16/88 lineage.

Cases and controls were similar with regard to gender and prevalence of chronic diseases, whereas a statistically significant difference was observed for age (46 months in cases and 29 months in controls) (Table 1).

The median duration of symptoms before the visit to the ED was similar in the two groups (3 days vs. 2), as it was the level of fever (median of 39 °C in both groups). According to the ILI definition all children presented fever ≥38 °C. Cough was the most frequently associated symptom in both cases and controls (85% vs. 83%), followed by rhinorrhea, malaise, sore throat and asthenia. Vomiting or diarrhoea were more frequently reported in younger children (40% in patients up to 5 years and 21% in older ones). Sixty-eight percent of children were hospitalised through the EDs and the mean duration of hospitalisation was not statistically different in cases and controls (3.6 and 4.3 days respectively).

Only 25 children (4%) were vaccinated against influenza: seven of the 262 cases and 18 of the 442 controls (they had been vaccinated between October and mid-January). The date of vaccination was not available for six children (one case and five controls). However, it is likely that these children were vaccinated at least

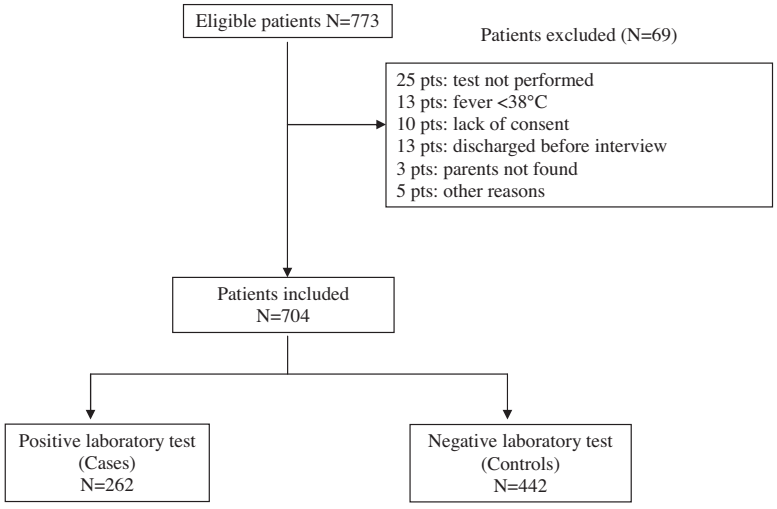

Fig. 1. Flow chart concerning the study population included in the study.

Table 1
Main characteristics of cases and controls.

	Cases	Controls	*p*
Number	262	442	
Median age, months (IR)	46 (26–71)	29 (15–54)	**<0.001**
% females	45	47	0.78
Chronic diseases: *N.* (%)	47(18)	67(15)	0.34
Duration of symptoms before admission to ED, median days	3	2	**0.01**
Symptoms of ILI at admission to ED			
Fever, median °C	39	39	0.13
Cough, *N* (%)	224(85)	365(83)	0.31
Rhinorrhea, *N* (%)	122(47)	217(49)	0.52
Malaise, *N* (%)	111(42)	166(38)	0.21
Sore throat, *N* (%)	85(32)	135(31)	0.60
Asthenia, *N* (%)	62 (24)	88 (20)	0.24
Vomiting, *N* (%)	58(22)	130(29)	**0.04**
Diarrhoea, *N* (%)	27 (10)	76(17)	**0.01**
Bronchitis, *N* (%)	22 (8)	73 (17)	**0.002**
Hospitalisation, *N.* (%)	148 (56)	332 (75)	**<0.001**
Length of stay[a] (mean, days)	3.6	4.3	0.20
Type of virus, *N* (%)			
B	126 (48)	–	
A (H1N1)	58(23)	–	
A (unspecified)	33(13)	–	
A (H1N1) pdm09	22 (8)	–	
A (H3N2)	22 (8)	–	

IR: interquartile range, ED: Emergency Department.
[a] Among hospitalised children.

14 days before hospital admission, since they were hospitalised between the end of January and February. Twelve out of the 25 vaccinated children (46%) reported a chronic disease (asthma, allergy, cardiomyopathy, spinal muscular atrophy [SMA 1 or 2], immunodeficiency, aplastic anaemia, coeliac disease, West syndrome).

The overall age-adjusted VE was 38% (95% CI: −52% to 75%) (Table 2). A slightly lower VE was estimated in the 2012–2013 season (VE 26%; 95% CI: −153% to 78%). Three out of seven vaccinated children were positive to unspecified A virus (one child) or A/H3N2 virus (two children) in the 2011–2012 season, whereas the remaining four vaccinated cases in the 2012–2013 season were positive to B virus. Nine children (one case and eight controls) received two doses of the vaccine in the same season (VE 79%; 95% CI: −57% to 100%).

When the analysis was restricted to hospitalised children a higher estimate of VE, with respect to the overall, was obtained (53%; 95% CI −45% to 85%).

4. Discussion

Our study estimated around 40% reduction in visits to EDs and hospitalisations for ILI in children, although not statistically significant and with wide confidence intervals.

Even though the confidence intervals of the estimates were largely overlapping, a slightly lower effectiveness was estimated in the second year. The four vaccinated cases in the 2012–2013 season were positive to the B virus. Data from our study and virological surveys performed in Italy [21] showed that the B/Yamagata lineage was circulating in the latter season (whereas B/Brisbane strain, belonging to a different lineage, was included in the seasonal vaccine), which may explain the lower VE of the 2012–2013 vaccine with respect to the 2011–2012, when the A(H3N2) and A(H1N1) were mostly present. The matching between the vaccine and circulating strains of influenza season is a recognised factor influencing the VE [22].

The main limitation of the study derives from the low vaccination coverage observed in the Italian paediatric population (4% in the control group). This proportion was similar to that observed in Italy during the 2009 pandemic [23]. Due to the few vaccinated children it was not possible to perform stratified analyses by variables of interest, such as type of virus/vaccine, age groups, presence of chronic conditions and prior vaccination status. Assuming as true the estimate of efficacy in our study, to reach statistical significance we should have had (with alpha error of 5% and power 80%), either a 25% proportion of vaccinated children or a study population of ILI larger than 4000. However, the number of children enrolled in our study is large in comparison with other recently published articles. In the I-MOVE study, the paediatric population (1–14 years) amounted to 512 children who were included in five European countries [24].

The adopted study design allows to control for the confounding effect of baseline clinical status. The reason relies on the definition of the control group, consisting of children who tested negative for the influenza virus vaccine [25]. It is well documented that several conditions increase the likelihood of developing an ILI and represent, at the same time, an indication for vaccination. In our study, case and control subjects were similar with reference to the prevalence of chronic conditions, but not for symptoms at onset. For

Table 2
Vaccine effectiveness in the two influenza seasons.

Influenza vaccine	Cases *N* (%)	Controls *N* (%)	Total	Crude OR (95% CI)	Adj VE[a] (95% CI)
Yes	7 (3)	18 (4)	25	35% (−65% to 77%)	38% (−52% to 75%)
No	255 (97)	424 (96)	679		
Total	262 (100)	442 (100)	704		
Season 2011–2012					
Influenza vaccine	**Cases *N* (%)**	**Controls *N* (%)**	**Total**	**Crude OR (95% CI)**	**Adj VE[a] (95% CI)**
Yes	3 (5)	10 (8)	13	38% (−152% to 89%)	41% (−126% to 84%)
No	58 (95)	119 (92)	177		
Total	61 (100)	129 (100)	190		
Season 2012–2013					
Influenza vaccine	**Cases *N* (%)**	**Controls *N* (%)**	**Total**	**Crude OR (95% CI)**	**Adj VE[a] (95% CI)**
Yes	4 (2)	8 (3)	12	23% (−194% to 83%)	26% (−153 to 78%)
No	197 (98)	305 (97)	502		
Total	201 (100)	313 (100)	514		

[a] Vaccine effectiveness adjusted by age.

instance, vomiting and diarrhoea were more frequent in controls. These symptoms are more often associated with ILI presentation in younger children. The age difference is in line with that observed in other European countries. In the I-MOVE study, the difference in the mean age between cases and controls in the paediatric population (1–14 years) was 1.5 years, similar to the difference observed in our study [24].

Almost all nasopharyngeal swabs were carried out within 2 days from symptoms onset to the ED, which is associated with a greater specificity. The fact that results were obtained several days after having conducted the test, excludes the possibility that the exposure information may have been biased by the knowledge of case/control status (and consequently no recall or ascertainment bias may have played a role).

In Italy, influenza vaccination remains an unmet priority, as only 4% of children were vaccinated in the recent seasons [23]. Efforts should focus on paediatricians to discuss the importance of influenza vaccination for preventing major complications in both at-risk and healthy children. Systematic reviews and meta-analysis of existing studies may provide the basis for a new awareness on the positive benefit-risk profile of the influenza vaccination even among healthy children.

Our study provides additional data on the effectiveness of the seasonal influenza vaccination in preventing visits to the Emergency Departments and hospitalisations for ILI, and adds further evidence for vaccination recommendations especially in children.

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