Vaccine 32 (2014) 4466–4470

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

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

Francesca Menniti-Ippolito[a,*], Roberto Da Cas[a], Giuseppe Traversa[a], Carmela Santuccio[b], Patrizia Felicetti[b], Loriana Tartaglia[b], Francesco Trotta[b], Pasquale Di Pietro[c], Paola Barabino[c], Salvatore Renna[c], Laura Riceputi[c], Pier-Angelo Tovo[d], Clara Gabiano[d], Antonio Urbino[d], Luca Baroero[d], Daniele Le Serre[d], Silvia Virano[d], Giorgio Perilongo[e], Marco Daverio[e], Elisa Gnoato[e], Michela Maretti[e], Beatrice Galeazzo[e], Giulia Rubin[e], Stefania Scanferla[e], Liviana Da Dalt[f], Chiara Stefani[f], Claudia Zerbinati[f], Elena Chiappini[g], Sara Sollai[g], Maurizio De Martino[g], Francesco Mannelli[g], Sabrina Becciani[g], Martina Giacalone[g], Simona Montano[g], Giulia Remaschi[g], Alessia Stival[g], Mario Furbetta[h], Piera Abate[h], Ilaria Leonardi[h], Nicola Pirozzi[i], Umberto Raucci[i], Antonino Reale[i], Rossella Rossi[i], Cristina Russo[i], Livia Mancinelli[i], Onori Manuela[i], Concato Carlo[i], Nadia Mores[j], Costantino Romagnoli[j], Antonio Chiaretti[j], Adele Compagnone[j], Riccardo Riccardi[j], Giovanni Delogu[j], Michela Sali[j], Valentina Prete[j], Vincenzo Tipo[k], Michele Dinardo[k], Fabiana Auricchio[k], Teodoro Polimeno[k], Giuseppe Sodano[k], Alessandra Maccariello[l], Concita Rafaniello[l], Fortunata Fucà[m], Eleonora Di Rosa[m], Domenica Altavilla[n], Anna Mecchio[n], Teresa Arrigo[n], Italian Multicentre Study Group for Drug and Vaccine Safety in Children

[a] *National Centre of Epidemiology, National Institute of Health, Roma, Italy*
[b] *Italian Medicines Agency, Roma, Italy*
[c] *Giannina Gaslini Paediatric Hospital, Genova, Italy*
[d] *Regina Margherita Paediatric Hospital, Torino, Italy*
[e] *Department of Paediatrics, University of Padova, Italy*
[f] *Department of Paediatrics, Treviso Hospital, Treviso, Italy*
[g] *Anna Meyer Children's University Hospital, Firenze, Italy*
[h] *Department of Paediatrics, University Hospital, Perugia, Italy*
[i] *Emergency Department and Virology Unit, Bambino Gesù Children Hospital, Roma, Italy*
[j] *Pharmacology, Microbiology and Virology, Università Cattolica S. Cuore, Roma, Italy*
[k] *Santobono Paediatric Hospital and Virology Unit-Cotugno, Napoli, Italy*
[l] *Department of Experimental Medicine, Second University, Napoli, Italy*
[m] *Giovanni Di Cristina Paediatric Hospital, Palermo, Italy*
[n] *Department of Paediatric, Gynecologic, Microbiologic and Biomedical Sciences, University Hospital, Messina, Italy*

ARTICLE INFO

Article history:
Received 4 December 2013
Received in revised form 20 March 2014
Accepted 11 June 2014
Available online 21 June 2014

Keywords:
Influenza vaccine effectiveness
Children

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.

* Corresponding author. National Centre of Epidemiology, Surveillance and Health Promotion, Italian National Institute of Health, Viale Regina Elena, 299 00161 Rome, Italy. Tel.: +39 0649904252.
E-mail address: francesca.menniti@iss.it (F. Menniti-Ippolito).

http://dx.doi.org/10.1016/j.vaccine.2014.06.048

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