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Impact of a quadrivalent inactivated influenza vaccine on influenza-associated complications and health care use in children aged 6 to 35 months: Analysis of data from a phase III trial in the Northern and Southern Hemispheres

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ABSTRACT

Background: A multi-season phase III trial conducted in the Northern and Southern Hemispheres demonstrated the efficacy of a quadrivalent split-virion inactivated influenza vaccine (IIV4) in children 6–35 months of age.

Methods: Data collected during the phase III trial were analysed to examine the vaccine efficacy (VE) of IIV4 in preventing laboratory-confirmed influenza in age subgroups and to determine the relative risk for IIV4 vs. placebo for severe outcomes, healthcare use, and parental absenteeism from work associated with laboratory-confirmed influenza.

Results: VE (95% confidence interval [CI]) to prevent laboratory-confirmed influenza due to any A or B strain was 54.76% (40.24–66.03%) for participants aged 6–23 months and 46.91% (23.57–63.53%) for participants aged 24–35 months. VE (95% CI) to prevent laboratory-confirmed influenza due to vaccine-similar strains was 74.51% (53.55–86.91%) for participants aged 6–23 months and 59.78% (19.11–81.25%) for participants aged 24–35 months. Compared to placebo, IIV4 reduced the risk (95% CI) by 31.28% (8.96–89.34%) for acute otitis media, 21.76% (6.46–58.51%) for acute lower respiratory infection, 40.80% (29.62–55.59%) for healthcare medical visits, 29.71% (11.66–67.23%) for parent absenteeism from work, and 39.20% (26.89–56.24%) for antibiotic use.

Conclusion: In children aged 6–35 months, vaccination with IIV4 reduces severe outcomes of influenza as well as the associated burden for their parents and the healthcare system. In addition, vaccination with IIV4 is effective at preventing against influenza in children aged 6–23 and 24–35 months.

Trial registration: EudraCT no. 2013-001231-51.

1. Introduction

Children, especially those aged <5 years, are at the highest risk of suffering from serious complications from influenza infection, including acute otitis media (AOM),[1] bacterial co-infections, acute respiratory infection, hospitalisation, and death [1–5]. Severe outcomes of influenza are frequently associated with underlying conditions [1,2] but occur even in children without risk factors [5].

Influenza illness is caused by A and B virus subtypes, both of which can cause epidemics and lead to hospitalisation and death in all age groups [6,7]. Efforts to reduce influenza B illness have been complicated since the 1980s, when two immunologically distinct lineages of B virus, Victoria and Yamagata, began co-circulating worldwide [8–10]. The distribution of these two lineages varies greatly between and even within seasons and regions, resulting in frequent mismatches between the B strain in trivalent influenza vaccines and the circulating B strains [9,10]. Due to uncertainty about cross-lineage protection [11–13] and the potential for decreased vaccine efficacy (VE) [14], quadrivalent influenza

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[1] ALRI, acute lower respiratory infection; AOM, acute otitis media; CI, confidence interval; IIV4, quadrivalent split-virion inactivated influenza vaccine; ILI, influenza-like illness; RR, relative risk; VE, vaccine efficacy.

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vaccines containing both B lineages have been developed [15] and, since the 2013–2014 influenza season, have been included in World Health Organization recommendations.

A quadrivalent split-virion inactivated influenza vaccine (IIV4; VaxigripTetra™, Sanofi Pasteur) is licensed for individuals aged ≥6 months. A recently completed multi-season placebo-controlled phase III trial conducted in the Northern and Southern Hemispheres demonstrated the efficacy of IIV4 in children 6–35 months of age [16]. Overall VE to prevent laboratory-confirmed influenza was 50.98% (97% confidence interval [CI], 37.36–61.86%) against any A- or B-type influenza and 68.40% (97% CI, 47.07–81.92%) against influenza caused by vaccine-similar strains. The trial also showed that safety profiles were similar for IIV4, the placebo, and comparator trivalent split-virion inactivated influenza vaccines.

As part of the phase III trial, data were collected on healthcare use, antibiotic use, parental absenteeism from work, and the occurrence of severe outcomes of influenza, including AOM, acute lower respiratory infection (ALRI), and inpatient hospitalisation. Here, we describe the efficacy of IIV4 based on these additional endpoints. Furthermore, to add to the evidence for efficacy of IIV4 in the youngest children, we determined VE for different age subgroups.

2. Material and methods

2.1. Study design

This was an analysis of data from the phase III, randomised, multi-centre, placebo-controlled trial of IIV4 in healthy children aged 6–35 months (EudraCT no. 2013-001231-51).[2] The participants were randomised to receive two full doses (15 μg hemagglutinin per strain) 28 days apart of (i) IIV4; (ii) the licensed trivalent split-virion inactivated influenza vaccine (Vaxigrip®, Sanofi Pasteur), (iii) an investigational trivalent split-virion inactivated influenza vaccine containing the World Health Organization-recommended A strains and a strain from the alternate B lineage (Victoria); or (iv) a placebo (saline). Further details of the study design and the primary efficacy, immunogenicity, and safety results are described elsewhere [16].

The objective of the current analysis was (a) to examine the VE of IIV4 in preventing laboratory-confirmed influenza in age subgroups; and (b) to determine the relative risk for IIV4 vs. placebo for severe outcomes (AOM, ALRI, and inpatient hospitalisation), healthcare medical visits (outpatient visits, outpatient hospitalization, and inpatient hospitalization), and parental absenteeism from work associated with laboratory-confirmed influenza within 15 days after the onset of the influenza-like illness (ILI).

VE was calculated for the co-primary endpoints of the trial, i.e. the occurrence of influenza-like illness starting ≥14 days after last vaccination and laboratory-confirmed as positive for (a) any circulating influenza A or B types or (b) vaccine-similar strains [16]. Briefly, influenza was confirmed by reverse transcription-polymerase chain reaction or viral culture of nasal swabs, and subtypes and strains were identified by Sanger sequencing, ferret antigenicity testing, or both. Genetic sequences identified by Sanger sequencing were compared with a database of known sequences corresponding to the vaccine and major circulating strains from 2005 up to the time of testing.

AOM, ALRI, and healthcare utilization were recorded during ILI-associated visits occurring within 10 days of the onset of ILI and during follow-up phone calls 15 days after the onset of ILI. AOM was defined as a visually abnormal tympanic membrane suggesting an effusion in the middle ear cavity, concomitant with at least one of the following symptoms: fever (≥38 °C), earache, irritability, diarrhoea, vomiting, acute otorrhea not caused by external otitis, or other symptoms of respiratory infection. ALRI was defined as a chest X-ray confirmed pneumonia, bronchiolitis, bronchitis, or croup (laryngotracheobronchitis). Inpatient hospitalisation was defined as a hospital admission resulting in an overnight stay. Outpatient hospitalisation was defined as hospitalization without an overnight stay (i.e., emergency room). An outpatient visit was defined as an unscheduled ambulatory visit with a physician or other health professional.

2.2. Ethics

The phase III trial was approved by the independent ethics committee or institutional review board for each study site and was conducted in accordance with Good Clinical Practice and the Declaration of Helsinki. Written informed consent was provided by the parents or legal representatives of all participating children.

2.3. Statistical analysis

VE in preventing laboratory-confirmed influenza caused by any A or B strain or by vaccine-similar strains was examined by age subgroup (6–23, 24–35, 6–11, and 12–23 months). The analysis was performed according to randomisation in the full analysis set for efficacy, defined as all randomised participants who received two doses of study vaccine and had at least one successful surveillance contact at least 14 days after the last dose.

Relative risk (RR) in preventing laboratory-confirmed influenza associated with AOM and ALRI were performed in the per-protocol analysis set for efficacy, defined as all randomised participants without significant protocol deviations. RR in preventing laboratory-confirmed influenza associated with healthcare medical visits, inpatient hospitalisation, parent absenteeism, and antibiotic use were calculated in the full analysis set for efficacy. RR was calculated as 100% × [number of confirmed influenza cases in the IIV4 group/total number of participants in the IIV4 group]/[number of influenza cases in the placebo group/total number of participants in the placebo group].

The 95% CIs for VE and RR were calculated by an exact method conditional on the total number of cases in both groups. The study protocol did not include statistical tests for these endpoints, so no assessment of statistical significance was made. Missing data were not replaced. Statistical analysis was performed using SAS® version 9.4 (SAS Institute, Cary, NC, USA).

3. Results

3.1. Participants

This analysis included the 5436 participants in the phase III trial who were randomised to receive IIV4 or placebo, as described previously [16]. The IIV4 and placebo groups were balanced for sex, age, and prevalence of at-risk conditions, regions, and ethnicities.

3.2. Laboratory-confirmed influenza associated with AOM and ALRI

Five participants in the IIV4 group (0.2%) and 16 in the placebo group (0.6%) had AOM associated with laboratory-confirmed influenza, and five participants in the IIV4 group (0.2%) and 23 in the placebo group (0.9%) had ALRI associated with laboratory-confirmed influenza (Table 1). The RR (95% CI) of IIV4 vs. placebo was 31.28% (8.96–89.34%) for AOM and 21.76% (6.46–58.51%) for ALRI.

[2] The protocol for this clinical trial is available at https://www.clinicaltrialsregister.eu/.

3.3. Laboratory-confirmed influenza associated with healthcare medical visits, inpatient hospitalisation, parental absenteeism, and antibiotic use

Compared to placebo, IIV4 reduced the risk of healthcare medical visits (RR = 40.80 [95% CI, 29.62–55.59%]), parent absenteeism from work (RR = 29.71% [95% CI, 11.66–67.23%]), and antibiotic use (RR = 39.20% [95% CI, 26.89–56.24%]) associated with laboratory-confirmed influenza (Table 2). Inpatient hospitalisation associated with laboratory-confirmed influenza occurred for three participants (0.12%) in each group, resulting in no difference in risk between IIV4 and placebo.

3.4. VE vs. laboratory-confirmed influenza by age subgroups

VE (95% CI) against any A or B strain was 54.76% (40.24–66.03%) for participants aged 6–23 months and 46.91% (23.57–63.53%) for participants aged 24–35 months (Table 3). For vaccine-similar strains, VE was 74.51% (53.55–86.91%) for participants aged 6–23 months and 59.78% (19.11–81.25%) for participants aged 24–35 months. Further exploration of the 6–23 month age group showed a VE against any A or B strain of 35.06% (−3.23–59.68%) for participants aged 6–11 months and 63.13% (47.26–76.64%) for participants aged 12–23 months and a VE against vaccine-similar strains of 43.63% (−87.30–85.16%) for participants aged 6–11 months and 80.54% (59.76–91.63%) for participants aged 12–23 months.

Table 1
Relative risk vs. laboratory-confirmed influenza associated with acute otitis media or acute lower respiratory infection.

Occurrence of	IIV4 N = 2489 n (%)	Placebo N = 2491 n (%)	Relative risk, % (95% CI)
Acute otitis media	5 (0.20)	16 (0.64)	31.28 (8.96, 89.34)
Acute lower respiratory infection	5 (0.20)	23 (0.92)	21.76 (6.46, 58.51)

Abbreviations: CI, confidence interval; IIV4, quadrivalent split-virion inactivated influenza vaccine.

Table 2
Relative risk vs. laboratory-confirmed influenza associated with healthcare and antibiotic use.

Occurrence of	IIV4 N = 2584 n (%)	Placebo N = 2591 n (%)	Relative risk, % (95% CI)
Healthcare medical visit[a]	59 (2.3)	145 (5.6)	40.80 (29.62, 55.59)
Inpatient hospitalisation	3 (0.12)	3 (0.12)	Not calculated
Parent absenteeism	8 (0.3)	27 (1.0)	29.71 (11.66, 67.23)
Antibiotic use	43 (1.7)	110 (4.2)	39.20 (26.89, 56.24)

Abbreviations: CI, confidence interval; IIV4, quadrivalent split-virion inactivated influenza vaccine.
[a] Includes outpatient visits, outpatient hospitalization, and inpatient hospitalization.

4. Discussion

A recent phase III trial conducted over four influenza seasons in the Northern and Southern Hemispheres demonstrated the efficacy and safety of two full doses of IIV4 in children 6–35 months of age in preventing laboratory-confirmed influenza [16]. The current analysis, based on exploratory endpoints in the phase III trial, demonstrated similar efficacy of IIV4 in reducing the risk of severe outcomes of influenza (AOM and ALRI) in these children as well as on the burden of influenza for their parents and the healthcare system.

The World Health Organization stated in 2012 that they had only moderate confidence in the efficacy of inactivated influenza vaccines in children aged 6 months to <2 years due to limited evidence [17]. In the current study, we confirmed that IIV4 can protect children aged 6–23 months against laboratory-confirmed influenza. Efficacy was also confirmed in the subgroup of children aged 12–23 months but not in children aged 6–11 months, most likely because of insufficient numbers.

Efficacy of another full-dose split-virion quadrivalent influenza vaccine in children aged 6–35 months was also demonstrated in a multinational randomised placebo-controlled trial across five influenza seasons [18]. The VE (97.5% CI) was reported to be 50% (42–57%) against RT-PCR-confirmed influenza, which is similar to the overall VE in the current trial. Although age subgroups were different, they also demonstrated efficacy in children aged <2 years (43% [95% CI, 28–56%] in children aged 6–17 months).

Our analysis also demonstrated that IIV4 reduced antibiotic use associated with influenza. Despite current guidelines, unnecessary antibiotic use in influenza remains common and is an important cause of antibiotic drug resistance [19]. A retrospective analysis of the US Impact National Benchmark Database from 2005–2009 found that antibiotics were prescribed for about 22% of patients with influenza, 79% of which was judged to be inappropriate because the patient had neither a secondary infection nor evidence of comorbidity [19]. Another study in Europe showed that influenza results in antibiotic prescriptions in 7–55% of cases [20]. This may be because both influenza and bacterial infections can cause high fever, AOM, and ALRI in young children [21,22]. Thus, although influenza accounts for a relatively small proportion of antibiotic use, IIV4 can help reduce their inappropriate use in young children.

The findings of this analysis should be widely applicable because they are based on a large study conducted over a wide geographical area in both hemispheres and over several influenza seasons. However, there are some limitations. Most importantly,

Table 3
Vaccine efficacy vs. laboratory-confirmed influenza by age group and subgroup.

Strains	Age group/subgroup	IIV4 N	IIV4 n (%)	Placebo N	Placebo n (%)	Vaccine efficacy % (95% CI)
Any A or B	6–11 months	545	32 (5.87)	553	50 (9.04)	35.06 (−3.23, 59.68)
	12–23 months	1111	43 (3.87)	1105	116 (10.50)	63.13 (47.26, 76.64)
	6–23 months	1656	75 (4.53)	1658	166 (10.01)	54.76 (40.24, 66.03)
	24–35 months	928	47 (5.06)	933	89 (9.54)	46.91 (23.57, 63.53)
Vaccine-similar	6–11 months	545	5 (0.92)	553	9 (1.63)	43.63 (−87.30, 85.16)
	12–23 months	1111	9 (0.81)	1105	46 (4.16)	80.54 (59.76, 91.63)
	6–23 months	1656	14 (0.85)	1658	55 (3.32)	74.51 (53.55, 86.91)
	24–35 months	928	12 (1.29)	933	30 (3.22)	59.78 (19.11, 81.25)

Abbreviations: CI, confidence interval; IIV4, quadrivalent split-virion inactivated influenza vaccine.

the trial was not powered for the calculations included in this analysis. Indeed, insufficient numbers likely precluded efficacy from being confirmed in children aged 6–11 months. This also can explain the failure to confirm an effect on influenza-associated inpatient hospitalisation. Another limitation, shared by all influenza vaccines, is that efficacy depends on the specific strains circulating, so care should be taken when applying results to a specific region or season.

5. Conclusions

The analysis showed that in children aged 6–35 months, vaccination with two full doses of IIV4 can protect against influenza and reduces the frequency of severe outcomes of influenza. IIV4 thereby helps reduce the burden of influenza in young children, their parents, and the healthcare system. These findings reinforce evidence that influenza vaccination can protect and can be used for infants and young children aged 6–35 months.

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S.P. helped draft the article, and S.P., M.D. and I.D.B conceived and designed the study. In addition, all authors helped analyse or interpret the data, provided critical revision, approved the final version of the manuscript, and agreed to be accountable for the accuracy and integrity of its contents.

Conflict of interest

All authors are employees of the study sponsor, Sanofi Pasteur.

Author contributions

All authors attest they meet the ICMJE criteria for authorship.

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