

Adverse reactions to simultaneous influenza and pneumococcal conjugate vaccinations in children: randomized double-blind controlled trial

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In a randomized double-blind controlled trial, the safety was assessed of simultaneous administration of influenza and pneumococcal conjugate vaccines in children with previous physician-diagnosed respiratory tract infections. In total, 579 children aged 18–72 months were assigned to receive simultaneous intramuscular influenza and pneumococcal heptavalent conjugate vaccinations (IV + PV), influenza and placebo vaccinations (IV + plac) or control hepatitis B and placebo vaccinations (HepB + plac) in separate extremities. Local and systemic adverse events were recorded in parental diaries for 7 days after vaccination. No immediate adverse reactions were recorded. In most children local adverse reactions disappeared 2 days after vaccination. Local and systemic reactions were more prevalent (30% and 10% more) in the IV + PV group compared with the IV + plac and HepB + plac group. These results are important for designing future vaccination schedules.

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Respiratory tract infections continue to be the leading cause of acute illnesses worldwide. Especially children are prone to respiratory tract infections. Often these children are treated with courses of antibiotics and ear-nose-throat surgery despite only marginal effects of both treatments (1–3). Moreover, bacterial resistance to antibiotics is a growing problem (4). Therefore, preventive strategies like vaccination should be explored.

Influenza virus and *Streptococcus pneumoniae* are frequent pathogens of respiratory infections and together they account for considerable morbidity and mortality (5). The incidence of confirmed influenza has been estimated around 20% during influenza seasons (6). A recent study demonstrated that in 33% of the nasopharyngeal aspirates taken from children presenting to primary care with cough and fever during winter

season, for which the antibiotics were considered, influenza viruses were detected (7). *Streptococcus pneumoniae* is the most common bacterial pathogen of pneumonia in pre-school children and is known to be the leading cause of acute otitis media, accounting for 28–55% of all episodes (8–12). Moreover, influenza virus infections appear to predispose to bacterial superinfection like acute otitis media, in particular with *S. pneumoniae* (13). Evidence suggests that influenza virus and *S. pneumoniae* interact synergistically in causing complicated infections (5). Given that vaccines for both pathogens are available, combined immunization against the influenza virus and *S. pneumoniae* may be particularly effective. The potential beneficial effect of these immunizations should however be weighed against possible side-effects. As the infant's immunization schedule is becoming crowded with an

increasing number of pathogens against which children are being immunized, it is important to know whether it is safe to give multiple vaccinations simultaneously. In the Netherlands, only recently (April 2006) pneumococcal conjugate vaccination has been added to the national infant vaccination programme without a catch-up programme for children less than 5 yr of age. Influenza vaccination is only advised for children with high-risk medical conditions. The current study aimed to assess the safety of simultaneous administration of influenza and heptavalent pneumococcal conjugate vaccines (IV + PV) in pre-school children by means of a randomized controlled double-blind trial.

Methods

Participants and recruitment

The current study was part of the Prevention of Respiratory Infections and Management (PRIMAKid) study, a randomized double-blind controlled trial that aims to establish the effects of influenza and pneumococcal vaccinations on the occurrence rates of febrile respiratory tract infections among children with previous physician-diagnosed respiratory tract infections (14). Parents were informed about the study by general practitioners. Parents willing to participate signed a consent form to enrol their child in the study. The study was undertaken in accordance with the European statements for good clinical practice which includes the provisions of the Declaration of Helsinki of 1989. The medical ethical review board of the University Medical Center Utrecht, The Netherlands approved the study protocol.

Children aged 18–72 months with previous respiratory tract infections were selected by general practitioners in the Netherlands within the province Utrecht and its surroundings. The characteristics of the population covered by these general practices are similar to the Dutch population as a whole (15). Inclusion criterion for the study was a history of two or more episodes of general practitioner-diagnosed respiratory tract infections prior to the study entry. Respiratory tract infections were defined according to the International Classification of Primary Care (16, 17): acute otitis media (H71), cough (with fever) (R05), acute upper respiratory infection (R74) including common cold and pharyngitis, sinusitis (R75), acute tonsillitis (R76), acute laryngitis/tracheitis (R77), acute bronchitis/bronchiolitis (R78), influenza (R80), pneumonia (R81), pleurisy/pleural effusion (R82) and other respiratory

infections (R83). Exclusion criteria were asthma or recurrent wheezing chronically treated with corticosteroids and other disorders pre-disposing for recurrent respiratory tract infections. Children with clinically significant hypersensitivity to eggs or previous serious adverse reactions to vaccines were also excluded. Furthermore, children who previously had influenza, pneumococcal or hepatitis B vaccinations were excluded as well as children with conditions for which these vaccinations are recommended.

Procedure and vaccines

The children were randomly assigned in blocks of three to combined influenza and pneumococcal vaccinations (IV + PV), influenza and placebo vaccinations (IV + plac) or control hepatitis B and placebo vaccinations (HepB + plac) in a 1:1:1 ratio. Three cohorts of children were enrolled during the periods October to November of 2003, 2004 and 2005. Inactivated trivalent sub-unit influenza vaccine (Influvac[®]) was supplied by Solvay, Weesp, The Netherlands. Strains in the 2003–2004 formulation were A/New Caledonia/20/99 (H1N1), A/Moscow/10/99 (H3N2) and B/HongKong/330/01; in the 2004–2005 formulation A/New Caledonia/20/99 (H1N1), A/Fujian/411/2002 (H3N2) and B/Shanghai/361/2002; and in the 2005–2006 formulation A/New Caledonia/20/99 (H1N1), A/California/7/2004 (H3N2) and B/Shanghai/361/2002. The heptavalent pneumococcal conjugate vaccine (Prevnar[®]; Wyeth, Berkshire, UK) consisted of 2 µg each of capsular polysaccharides of pneumococcal serotypes 4, 9V, 14, 19F and 23 F, 4 µg of serotype 6B polysaccharide and 2 µg of serotype 18C oligosaccharide, each conjugated individually to the CRM₁₉₇ protein. The placebo consisted of a standard diluent (0.9% NaCl phosphate-buffered; Solvay). Control vaccine was the recombinant hepatitis B vaccine (Engerix-B Junior[®]; Glaxo-SmithKline, Rixenart, Belgium).

Assignments to treatment groups were not revealed to parents, investigators, research personnel involved in follow-up or non-study health care providers, all of whom remained blinded throughout the study. Administration of the injections was performed by non-blinded research nurses who were not involved in subsequent follow-up of the children. To evaluate blinding, parents of the last two cohorts of included children were asked what vaccinations they thought their child had received just after the vaccinations were set and at the end of the study. Just after the vaccinations, 87% of the parents did not know or mentioned the wrong

set of vaccinations, and at the end of the study this was 80% indicating that blinding was successful. All children had a similar vaccination schedule. Children received two sets of vaccinations, administered intramuscularly in deltoid or gluteal muscles (in separate extremities) 4–8 wk apart in the year of inclusion. Pneumococcal and placebo vaccines were administered in the right extremity, and influenza and hepatitis B vaccines were administered in the left extremity.

Safety evaluation

Following vaccinations, children were observed for 15 min for immediate hypersensitivity reactions and parents completed diaries for the day of immunization and the six following days recording local and systemic adverse events after the first set of vaccinations. Local reactions solicited included erythema, tenderness, swelling and interference with limb movement. Systemic events solicited included malaise, headache and myalgia. Besides these solicited questions, parents were able to write down other complaints in the diary. In addition, parents measured their child's temperature by a tympanic membrane thermometer provided by the trial centre (Braun Thermoscan pro 3000® and Braun Thermoscan pro 4000®) on the evening after vaccination and the subsequent six evenings (18). Parents were asked to contact the researchers directly in case of severe adverse events.

Analysis

The occurrence of adverse events was evaluated after the first set of vaccinations. With an available-case analysis, i.e. study subjects were included that provided valid information, and an intention-to-treat analysis, frequencies of adverse reactions were determined for the three different groups. Risk differences were calculated with Episheet (Rothman K. Episheet: spreadsheets for the analysis of epidemiologic data, 2002). Furthermore, the course of adverse reactions during the observation period was determined.

Results

Five hundred and seventy-nine children were randomized, and 567 parents (97.9%) completed the diary (Fig. 1). The 12 subjects without follow-up information were equally divided between the study groups. The study groups were similar with regard to age, sex and medical history (Table 1).

No immediate adverse events were recorded. During follow-up, local reactions for at least 1 day were mostly reported in the IV + PV group; 66.8% [95% confidence interval (CI): 59.9–73.1] in the IV + PV group vs. 37.8% (95% CI: 31.0–45.0) in the IV + plac group and 36.0% (95% CI: 29.5–43.1) in the HepB + plac group (Table 2). Tenderness was the most prevalent local adverse reaction in all groups, with the highest risk difference between the IV + PV

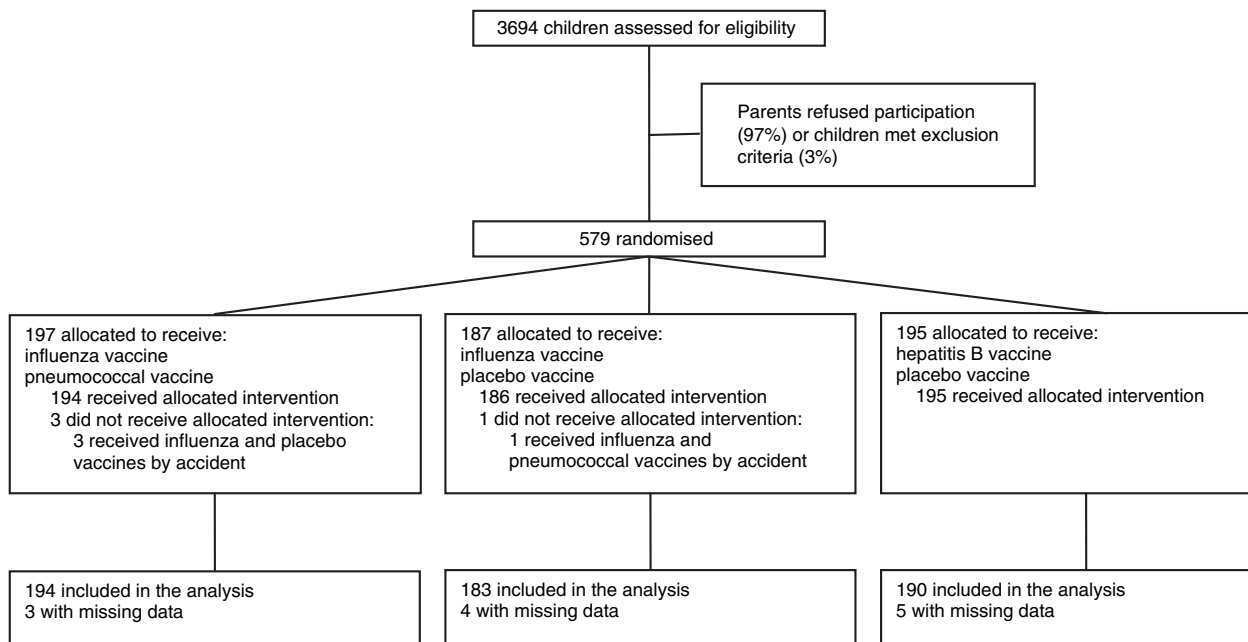


Fig. 1. Flow diagram of study groups.

Table 1. Patient characteristics by study group

	IV + PV (n = 197)	IV + plac (n = 187)	HepB + plac (n = 195)
Sex (% male)	116 (59)	104 (56)	98 (50)
Age (mean)	3.0	3.1	3.1
(History of) Atopy (%)	82 (42.5)	73 (39.9)	81 (43.1)
More than three general practice-attended respiratory tract infections in the year prior to study entry (%)	62 (34.1)	58 (33.5)	62 (30.9)
History of ear-nose-throat surgery* (%)	56 (28.6)	51 (27.6)	56 (29.5)

*That is (adeno-)tonsillectomy and/or tympanostomy tubes.

IV + PV, influenza and pneumococcal vaccines; IV + plac, influenza and placebo vaccines; HepB + plac, hepatitis B and placebo vaccines.

group and the two reference groups. The prevalence of local reactions in the IV + PV group was highest during the first two days after immunization (46.3–50.0%) after which it decreased to 23.6% at day three and 7.4% at day five (Fig. 2a). For the IV + plac and HepB + plac groups the course of local reactions was similar, with the highest prevalence at day one (28.7–30.2%) thereafter decreasing to 7.1–7.4% at day three, and 3.9–4.3% at day five after vaccination.

Within the IV + PV group most local reactions were localized in the right extremity where the pneumococcal vaccine was administered. When comparing the local reactions in the left extremity between the IV + PV and IV + plac groups, i.e. the extremity in which the influenza vaccine was administered, influenza vaccine in the IV + PV group was associated significantly more often with interference of limb movement,

namely 13.2% (95% CI: 9.1–18.7) in the IV + PV group vs. 3.4% (95% CI: 1.5–7.1) in the IV + plac group.

During follow-up, any systemic reaction was reported in 63.9% (95% CI: 56.8–70.5) of the children in the IV + PV group, 52.3% (95% CI: 44.9–59.7) in the IV + plac group and 50.9% (95% CI: 43.5–58.2) in the HepB + plac group (Table 2). Fever, i.e. temperature of 38.0°C or higher for at least one day, was significantly more reported in the IV + PV group (26.4%, 95% CI: 20.4–33.4) compared with the HepB + plac group (15.1%, 95% CI: 10.5–21.2), but not compared with the IV + plac group (21.0%, 95% CI: 15.5–27.7). Systemic reactions were more prevalent in the first two days after immunization in the PV + IV group (30.1–30.3%) compared with the other study groups (12.6–21.9%), but after day two the course of systemic reactions was more or less similar in all the three groups (Fig. 2b).

In 44 children (3.6%), parents reported gastrointestinal complaints (respectively 10, 19 and 15 in the IV + PV, IV + plac and HepB + plac groups). In total, 14 children (2.4%) reported a visit to their primary care physician during follow-up (three in the PV + IV group, eight in the IV + plac group and three in the HepB + plac group). Of these visits 10 were (follow-up) visits because of ear complaints, impetigo, an infected finger, throat infection or common cold and cough. The other four visits were because of a rash starting on day four after vaccination (HepB + plac group), excessive crying and vomiting starting on day four after vaccination (IV + plac group) and two with coughing and

Table 2. Local and systemic adverse reactions by study group during a follow-up of 7 days

	IV + PV (%)	IV + plac (%)	Risk difference* (95% confidence interval)	HepB + plac (%)	Risk difference† (95% confidence interval)
Local adverse reactions					
Erythema	49/189 (25.9)	17/179 (9.5)	16.4% (8.9–24.0)	21/185 (11.4)	14.6% (6.8–22.3)
Swelling	62/187 (33.2)	32/179 (17.9)	15.3% (6.5–24.1)	17/185 (9.2)	24.0% (16.0–31.9)
Tenderness	103/191 (53.9)	54/181 (29.8)	24.1% (14.4–33.8)	47/186 (25.3)	28.7% (19.2–38.1)
Interference with limb movement	42/188 (22.3)	8/171 (4.5)	17.9% (11.2–24.6)	10/176 (5.4)	17.0% (10.2–23.7)
Any local reaction	127/190 (66.8)	68/180 (37.8)	29.1% (19.3–38.8)	67/186 (36.0)	30.8% (21.2–40.4)
Systemic reactions					
Fever					
Temperature ≥38°C	46/174 (26.4)	35/167 (21.0)	5.5% (–3.5–14.5)	26/172 (15.1)	11.3% (2.9–19.8)
Temperature ≥39°C	9/170 (5.3)	6/162 (3.7)	1.6% (–2.9–6.0)	10/169 (5.9)	–0.6% (–5.5–4.3)
Malaise	100/189 (52.9)	79/181 (43.6)	9.3% (–0.9–19.4)	83/187 (44.4)	8.5% (–1.54–18.6)
Headache	15/186 (8.1)	8/179 (4.5)	3.6% (–1.4–8.5)	14/184 (7.6)	0.5% (–5.0–5.9)
Myalgia	18/191 (9.4)	4/181 (2.2)	7.2% (2.6–11.9)	9/185 (4.9)	4.6% (–0.6–9.7)
Any systemic reaction	117/183 (63.9)	90/172 (52.3)	11.6% (1.4–21.8)	88/173 (50.9)	13.1% (2.9–23.3)

*IV + PV index, IV + plac reference.

†IV + PV index, HepB + plac reference.

IV + PV, influenza and pneumococcal vaccines; IV + plac, influenza and placebo vaccines; HepB + plac, hepatitis B and placebo vaccines.

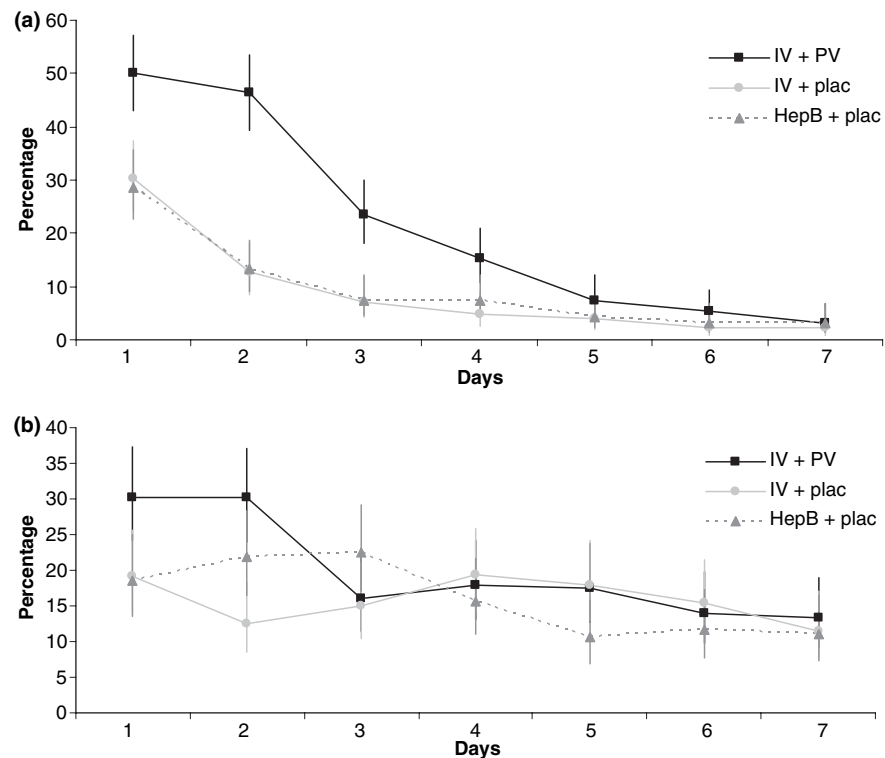


Fig. 2. (a) Proportion of all subjects experiencing local adverse reactions during the first 7 days after vaccination. (b) Proportion of all subjects experiencing systemic adverse reactions during the first 7 days after vaccination. IV + PV, influenza and pneumococcal vaccines; IV + plac, influenza and placebo vaccines; HepB + plac, hepatitis B and placebo vaccines.

shortness of breath (IV + plac group). In total, 21 children (3.6%) withdrew from further immunization following the first vaccination (four in the IV + PV group, nine in the IV + plac group and eight in the HepB + plac group). Of these children, 16 (76.2%) withdrew because of fear for further injections and/or family circumstances. The remaining five children withdrew (partly) because of medical reasons, i.e. two in the IV + PV group with rash (one child with local rash and one with generalized rash), one in the IV + plac group with generalized rash and two in the HepB + plac group because of malaise lasting up to 3 wk post-vaccination.

Discussion

No immediate anaphylactic or severe adverse reactions were recorded after simultaneous administration of influenza and pneumococcal conjugate vaccines. Most local and systemic reactions were mild and transient. About 30% more often local adverse reactions and 10% more often systemic adverse reactions were reported in the IV + PV group compared with the IV + plac and HepB + plac groups during a follow-up of 7 days.

Major advantages of the current study are its design (randomized double-blind controlled trial) and the fact that it is, to our knowledge, the first trial presenting the safety of simultaneous influ-

enza and heptavalent pneumococcal conjugate vaccination in pre-school children. The study population appeared representative for all pre-school children with frequent respiratory tract infections. Age and gender of the included children were similar to corresponding figures for all eligible children, and the mean number of general practice-attended consultations was only slightly higher in the study population (0.2 consultations more) (14). Additionally, adverse reactions were recorded with standardized diaries provided on the day of immunization which limited recall bias. Finally, adverse reactions were documented during a follow-up of 7 days.

However, some possible limitations should be discussed. First, for the parents of the youngest children in our study it may have been hard to assess some of the adverse reactions (particularly headache and myalgia). However, most of the solicited adverse reactions were easy to assess even in small children. Second, we did not include a control group with placebo vaccines only. The medical ethical review board of the University Medical Center Utrecht did not allow including a study arm with placebo injections only. We therefore used the hepatitis B vaccine as control, which is not included in the Dutch standard national infant immunization schedule. We did also not include a study group with pneumococcal vaccine only. Consequently, we were not able to assess whether the higher

frequency of adverse reactions in the PV + IV group compared with the IV + plac group was solely due to the pneumococcal vaccine or also to the combination of influenza and pneumococcal vaccines. Additionally, it may be claimed that administering the vaccines in the right, mostly dominant, arm may have led to more side effects, and therefore this may have affected blinding. However, we verified that blinding was maintained. Finally, we did not impute missing data. This is unlikely to have affected the results, as the number of children with missing data was small.

Studies on the safety of the inactivated influenza vaccine among young children demonstrate fairly variable designs and presentation of data (19). Consequently, the results of those studies are difficult to compare with ours. Moreover, the small number of children studied warrants cautious interpretation of the findings (20). However, generally influenza vaccines appeared well tolerated and safe in children (20), which compares favourably with the safety profile of influenza vaccine in this study. A previous study assessing the safety of the heptavalent pneumococcal conjugate vaccine in children aged 24–36 months, reported local reactions (erythema, induration or tenderness) in 32–40% within 72 h and fever ($\geq 38^{\circ}\text{C}$) in about 9% within 7 days post-immunization (21). In our study, erythema was reported with similar frequency, but tenderness and fever was reported more often in the IV + PV group of our study. We do not know whether the combination of the influenza and pneumococcal had a synergistic effect on causing adverse reactions. However, the fact that the prevalence of interference of limb movement was higher in the extremity where influenza vaccine was injected in children of the IV + PV group compared with that extremity in children of the IV + plac group supports a synergistic effect.

In adults several studies assessing the safety of simultaneous administration of influenza and pneumococcal vaccines were reported (22–32). Most of these studies were not randomized or blinded, and in all studies pneumococcal polysaccharide vaccines were used which are not immunogenic in young children. However, simultaneous influenza and pneumococcal vaccination in adults seemed well tolerated and safe (22–32) although in some studies it was associated with a higher rate of adverse reactions compared with the administration of either of the vaccines alone (22, 23, 27, 31, 32).

In conclusion, the current study among pre-school children demonstrated that adverse reactions were more prevalent in the IV + PV group compared with the IV + plac and HepB + plac

groups, although the adverse reactions were non-severe and mostly short-term.

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