Vaccine xxx (2018) xxx–xxx

Contents lists available at ScienceDirect

Vaccine

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

Brief report

Safety and efficacy of DTaP-IPV vaccine use in healthcare workers for prevention of pertussis

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ARTICLE INFO

Article history:
Received 23 November 2017
Received in revised form 21 May 2018
Accepted 21 August 2018
Available online xxxx

Keywords:
Bordetella pertussis
Diphtheria-tetanus-acellular pertussis and polio (DTaP-IPV)
Pertussis toxin (PT)
Filamentous hemagglutinin (FHA)
Fimbriae 2 (Fim2)
Fimbriae 3 (Fim3)

ABSTRACT

Pertussis can be fatal for infants. The best way to prevent infant pertussis is to promote adult immunization. However, Tdap has not been licensed in Japan, so we investigated the effect and safety of the DTaP-IPV vaccine instead. The study examined 154 pediatric healthcare workers. Participants without effective levels of antibodies against pertussis toxin were given DTaP-IPV, reduced to 0.2 mL. In total, 48 of the 154 participants (31.2%) were seronegative for pertussis toxin. After vaccination of the seronegative participants, 40 of the 41 measured (97.5%) had acquired an effective response, and all 35 of those tested maintained a protective antibody level ten months after vaccination. Redness was observed in 14 of the 41 (34.1%) and soreness in 19 (46.3%). This study demonstrated that vaccination with reduced 0.2 mL DTaP-IPV successfully provided effective immunity. At least ten months after vaccination, all subjects maintained an adequate level of antibodies.

1. Introduction

Pertussis, or whooping cough, is an acute respiratory tract infection caused by *Bordetella pertussis*, the sole causative organism of epidemic pertussis. Whooping cough remains a serious infectious disease, especially for newborns and infants. Infected infants may develop apnea and cyanosis, and this is sometimes fatal [1,2]. Pertussis is also highly contagious and siblings or adults with pertussis cause a transmission of pathogen to infants [3].

Pertussis has also been linked to sudden infant death syndrome (SIDS). A prospective study of SIDS cases in Germany showed that 5.1% of the 254 infants tested positive for *B. pertussis* [4]. During the pertussis outbreak in the United Kingdom in the 1970s and 1980s, postperinatal mortality increased [5]. About 90% of deaths from pertussis are in infants under 6 months old [6], suggesting that newborns and infants are very vulnerable to this disease. Even previously healthy infants may die, and infants hospitalized for other conditions are at extremely high risk of developing severe symptoms. Several outbreaks have been described in a variety of healthcare settings [7].

Despite decades of high immunization coverage rates in Japan and other developed countries, pertussis has remained endemic and has re-emerged as a public health concern [8]. The reason for this concerning trend is likely to be natural attenuation over time after routine vaccination [9]. As a result, many countries carry out booster vaccination with tetanus-diphtheria-acellular pertussis (Tdap) for preteens, teens, and adults. However, Tdap has not been licensed for use in Japan, where the only pertussis vaccine available is diphtheria-tetanus-acellular pertussis-polio (DTaP-IPV). There have been no studies in Japan about the effect and safety of reduced-dose DTaP-IPV vaccine, or the duration of the immunity it provides.

2. Materials and methods

2.1. Ethics statement

The study design and protocol were approved by the ethics committee at the Yokohama City University Medical Center Review Board (D1508030). We explained the purpose of the study and obtained informed consent from all participants.

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https://doi.org/10.1016/j.vaccine.2018.08.047
0264-410X/

Table 1
Comparison of composition per dose of selected vaccines containing pertussis components.

Vaccine	Trade name	Manufacturer	Dose (mL)	Amt (μg) of indicated pertussis antigen				Lf value for	
				PT	FHA	PRN	FIM 2 + 3	Diphtheria toxoid	Tetanus toxoid
Tdap	Adacel	Sanofi pasteur	0.5	2.5	5	3	5	2	5
Tdap	Boostrix	GSK	0.5	8	8	2.5	–	2.5	5
DT	–	Kitasato	0.1	–	–	–	–	3.2	0.7
DTaP/IPV	Quattrovac	Kaketsuken	0.5	8	32	–	–	16.7	2.5
DTaP/IPV	Quattrovac	Kaketsuken	0.2	3.2	12.8	–	–	6.7	1

GSK, GlaxoSmithKline Biologicals.
PT, pertussis toxin.
FHA, filamentous hemagglutinin.
PRN, pertactin.
FIM 2 + 3, fimbriae 2 and 3.
Lf, limit of flocculation unit.

2.2. Subjects

Subjects were 154 pediatric healthcare workers at Yokohama City University Medical Center. They included general pediatricians, neonatologists, obstetricians, clinical nurses, midwives, assistant nurses, and pharmacists.

2.3. Vaccines

In Japan, three DTaP-IPV products are commercially available. This study used Quattrovac (Kaketsuken, adsorbed diphtheria-purified pertussis-tetanus-inactivated polio combined vaccine). The vaccine was reduced in amount to 0.2 mL from 0.5 mL (Table 1), and administered to any participants without effective levels of antibodies.

2.4. Serology

We measured four types of serum antibodies: pertussis toxin (PT), filamentous hemagglutinin (FHA), fimbriae 2 (Fim2) and fimbriae 3 (Fim3) in each subject. Antibodies against PT and FHA were examined using enzyme immunoassay kits (Denka Seiken, Tokyo, Japan). Antibodies against Fim2 and Fim3 were examined using the modified fluorescent immunosorbent assay [10]. We defined PT titers of over 10 EU/mL as protective against pertussis [11]. Antibody titers were measured immediately before, one month and ten months after vaccination.

2.5. Adverse events

Adverse events during the 7 days after vaccination were surveyed using an individual questionnaire sheet by self evaluation. We asked about the presence or absence of redness, soreness, swelling of the injection site as a local reaction and any fever (at axillary temperature 37.0 degrees C or more) or headaches as a systemic reaction.

2.6. Statistical analysis

Statistical analysis used JMP Pro version 12.2.0 for Windows.

3. Results

This study was conducted in March 2015. No pertussis epidemic was confirmed in the areas surrounding the hospital during the study period. In total, 48 of the 154 participants (31.2%) were seronegative for PT (<10 EU/mL) (Fig. 1). The age-specific distribution of PT titers before vaccination is shown in Fig. 2. The mean PT titer was lowest in subjects aged 25–29 years old (16.7 EU/mL), and increased slowly with age to a maximum of 40.8 EU/mL among the 50–54 year olds. PT titers by occupation are shown in Fig. 3. Data for the single pharmacist are not shown. There were no significant differences among occupations (p = 0.187).

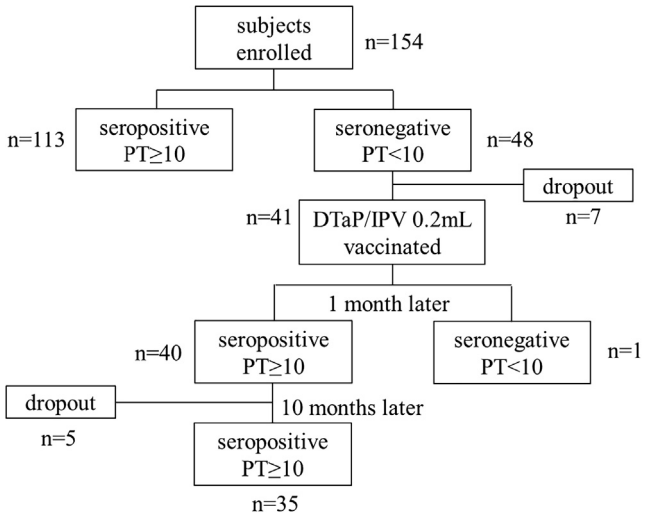

Fig. 1. A total of 154 healthcare workers were enrolled. 48 of the 154 subjects were seronegative for PT (<10 EU/mL). Among the 48, 41 subjects were vaccinated with 0.2 mL DTaP-IPV subcutaneously. 40 subjects had acquired an effective immune response one month after vaccination, and 35 of the 35 tested after 10 months maintained a protective antibody level.

In total, 40 out of 41 (97.5%) of the seronegative subjects had acquired an effective immune response one month after vaccination, and 35 of the 35 tested after 10 months (100.0%) maintained a protective antibody level at that point (Fig. 4a). Anti-FHA antibodies were also significantly elevated one month after vaccination (Fig. 4b). Anti-Fim2 and Fim3 antibodies changed very little over time (Fig. 4c and d).

Redness was observed in 14 of the 41 (34.1%), soreness in 19 (46.3%) and swelling of the injection site in eight (19.5%). Febrile reaction and headaches were observed in just one of the 41 participants (2.4%). There were no other significant adverse events related to vaccination.

4. Discussion

This study demonstrated that vaccination with 0.2 mL DTaP-IPV successfully provided effective immunity to 97.5% of healthcare workers. At least ten months after vaccination, all subjects maintained an adequate level of antibodies against pertussis.

Pertussis remains a major public health concern worldwide despite high vaccine coverage among various age groups. The US

Please cite this article in press as: Shimizu H et al. Safety and efficacy of DTaP-IPV vaccine use in healthcare workers for prevention of pertussis. Vaccine (2018), https://doi.org/10.1016/j.vaccine.2018.08.047