# COMPARATIVE STUDY OF THE REACTOGENICITY OF A THREE-COMPONENT ACELLULAR PERTUSSIS VACCINE AND WHOLE-CELL PERTUSSIS VACCINE ADMINISTERED TO HEALTHY SINGAPOREAN INFANTS

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**Abstract.** The objective of this study was to assess and compare the reactogenicity of GlaxoSmithKline (GSK) Biologicals' diphtheria-tetanus-tricomponent acellular pertussis vaccine (DTPa) and the locally used combined diphtheria-tetanus-whole-cell pertussis vaccine (DTPw) as a primary vaccination course in healthy infants at the age of 3, 4 and 5 months. A phase IV, single-blinded, randomized comparative clinical study involved one hundred and eighty healthy infants with two study groups in a 2:1 ratio to receive either DTPa or DTPw vaccine which were administered intramuscularly at the right anterior-lateral aspect of the thigh. The incidence and intensity of local solicited symptoms such as pain, redness and swelling at injection site and general solicited symptoms such as fever and fussiness were evaluated. Serious adverse events were followed for one month after each vaccination. The overall incidence of local and general symptoms was significantly higher in the group receiving locally used DTPw vaccine as compared to the group receiving GSK DTPa vaccine. Solicited local symptoms, pain (47.4% *vs* 15.1%), redness (95.9% *vs* 84.9%) and swelling (46.2% *vs* 18.5%), were reported more frequently in the group receiving DTPw vaccine than in the group receiving DTPa vaccine. Fever (≥37.5°C) (52% *vs* 14.6%) and fussiness (60.8% *vs* 33.6%) were also more commonly reported in the DTPw group. There were six serious adverse events reported (4 with DTPw and 2 with DTPa). None of them related to the study vaccines, as considered by the investigators. Thus it was found that GSK Biologicals' DTPa vaccine was significantly less reactogenic as compared to the locally used DTPw vaccine manufactured by Commonwealth Serum Laboratories when administered as a 3-dose primary vaccination course to healthy infants at the age of 3, 4 and 5 months in Singapore.

## INTRODUCTION

Pertussis was once a major cause of mortality and morbidity among infants and young children worldwide. Since the introduction of a combined diphtheria, tetanus and whole-cell pertussis vaccine in the 1940s, the incidence of pertussis has markedly declined. Although the whole-cell pertussis vaccine has substantially reduced the mortality and morbidity of pertussis, in the 1970s, concerns about the reactogenicity and potential neurological damage induced by whole-cell pertussis vaccines produced a decreased vaccine intake and in some countries an increase in morbidity and the return to pertussis epidemics (Muller *et al,* 1986; Romanus *et al,* 1987).

The declined acceptance of whole-cell pertussis vaccines and improved knowledge of the components of organism have led to the development of acellular pertussis vaccines in the 1980s. Acellular pertussis vaccines contain only well-defined and highly purified bacterial antigen components and they have been proven efficacious and less reactogenic. DTPw vaccines are progressively being replaced by DTPa vaccines in many countries worldwide.

In Singapore, the acceptance level of vaccination with DTPw in infant immunization programs was still high (>90%) in 1990s (Anony-

mous, 1997). With the availability of new acellular pertussis vaccines, we wanted to investigate the reactogenicity of DTPa vaccine in such a population. Thus a comparative study between an acellular and whole cell pertussis vaccine was conducted in Singapore, in order to compare the reactogenicity of these two vaccines.

## MATERIALS AND METHODS

### Subjects

A total of 180 healthy male and female infants (60 in group 1 and 120 in group 2), between 12 and 16 weeks of age at the time of the first vaccination were enrolled from Children's Medical Centre, National University Hospital in Singapore. The study was conducted according to Good Clinical Practice and in accordance with the Declaration of Helsinki. The protocol and written informed consent forms were approved by the Institutional Ethical Committee and the Ministry of Health, Republic of Singapore prior to study initiation. Written informed consent was obtained from the parents/guardians of the subjects prior to entry into the study.

### Vaccines

Each 0.5 ml dose of Commonwealth Serum Laboratories' (CSL) DTPw vaccine contained $\geq$ 30 IU of diphtheria toxoid, $\geq$ 60 IU of tetanus toxoid, $\geq$ 4 IU of *Bordetella pertussis*, 50 $\mu$g of thiomersal as preservative and 1 mg aluminium phosphate.

Each 0.5 ml dose of GSK Biologicals' DTPa vaccine contained 25 $\mu$g pertussis toxoid, 25 $\mu$g filamentous hemagglutinin, 8 $\mu$g pertactin, $\geq$ 30 IU diphtheria toxoid, $\geq$ 40 IU tetanus toxoid, 0.5 mg aluminium salts and 2.5 mg phenoxyethanol as preservative. One commercial lot of each vaccine was used.

### Study design

This randomized, single-blind comparative study involved one hundred and eighty healthy infants who were randomly assigned, in a 2:1 ratio, to receive either DTPa or DTPw vaccine intramuscularly into the right anterolateral aspect of the thigh. The vaccine was administered according to a 3, 4, 5 months schedule. Each subject received the same vaccine lot for all three doses. Since the physical appearance of the vaccines was different, the study was a single-blind. The parents or guardians of the subject, who had to record the solicited symptoms, were unaware of the identity of the vaccine administered.

An 8-day follow-up of adverse events after each vaccination was performed by the parents/guardians of the vaccinees. Solicited local symptoms (pain, redness and swelling) and general symptoms (fever, irritability/fussiness, vomiting, diarrhea, loss of appetite, restlessness or sleeping less than usual and sleepiness or sleeping more than usual) were recorded by the parents using individual diary cards. The intensity of these signs and symptoms was graded as described in Table 1. The relation of these adverse events to the vaccine given was assessed by the investigator and reported as being "related", "possibly related", or "not related". Any adverse event that occurred within a time frame starting 30 days before and ending 30 days after the last dose of study vaccine was recorded by the investigator in the subject case sheet.

### Statistics

For each group, the incidence over the 8-day follow-up period (day 0 and the 7 subsequent days) was calculated for each solicited symptom, in addition to the relationship, intensity and onset during the first 48 hours of vaccination. The incidence was calculated after each vaccination and overall. Incidences of any fever, pain, redness, swelling and incidences of fever (all subjects), pain, redness and swelling 'graded 3' were compared between both groups, using Fisher's exact test.

## RESULTS

A total of 180 subjects were enrolled in the study and 177 subjects completed the study. The mean age in the group receiving the locally used DTPw vaccine was 13.2 weeks and 13.5 weeks in the group receiving the DTPa vaccine. The three dropouts belonged to the DTPw vaccine group. Of these three, two dropouts were due to high fever after the 1st dose and the other was due to consent withdrawal. Therefore, a total of 534 doses were administered to the 180 subjects enrolled in the study. Of these 534 doses, data from 528 local and 530 general symptom sheets were included for the reactogenicity analysis.

The incidence of local (p = 0. 0002) and general (p<0.0001) symptoms were significantly higher in the group receiving local DTPw vaccine as compared to the group receiving GSK Biologicals' DTPa vaccine. Both groups reported more local than general symptoms. Pain, redness, and swelling were reported after 47.4%, 95.9% and 46.2% of the 534 doses, respectively among the vaccinees who received DTPw vaccine. However, among the vaccinees who received DTPa vaccines, these events were reported after 15.1%, 84.9% and 18.5% of the total documented doses. There were 86 reports (33.3% in group 1 and 8.1% in group 2) of areas of redness larger than 20 mm and 16 reports (8.2% in group 1 and 0.6% in group 2) of areas of swelling larger than 20 mm. The incidence of so-

licited local symptoms after vaccination is presented in Table 2. Among the solicited general symptoms, fussiness was the most prevalent symptom in both groups, reported 60.8% in group 1 (DTPw) and 33.6% in group 2 (DTPa). Fever (≥37.5°C ) was the second most prevalent solicited general symptom, reported 52.6% in group 1 and 14.6% in group 2. Five cases of high fever (>39.5°C) were reported, of which 3 cases (59.1% in group 1 and 10.6% in group 2) were determined by the investigator to have a 'probable' or 'suspected' relationship to the study vaccine. The overall incidence of general solicited symptoms after vaccination is presented in Table 3.

Four subjects in group 1 (DTPw) reported serious adverse events within 30 days post- vac-

Table 1
Assessment of intensity.

| Adverse event | Intensity grade | Intensity |
|---|---|---|
| **Local symptoms at injection site** | | |
| Pain | 0 | Absent |
| | 1 | Minor light reaction to touch |
| | 2 | Cried or protested to touch |
| | 3 | Cried or protested when the leg was moved |
| Redness (largest surface diameter in mm) | 0 | 0 |
| | 1 | 0.1-5 |
| | 2 | 5.1-20 |
| | 3 | >20 |
| Swelling (largest surface diameter in mm) | 0 | 0 |
| | 1 | 0.1-5 |
| | 2 | 5.1-20 |
| | 3 | >20 |
| **General symptoms** | | |
| Fever (axillary temperature in °C) | 0 | <37.5 |
| | 1 | 37.5-38.0 |
| | 2 | 38.1-39.0 |
| | 3 | >39.0 |
| Irritability/fussiness | 0 | Behavior as usual |
| | 1 | Crying more than usual with no effect on normal activity |
| | 2 | Crying with effect on normal activity |
| | 3 | Crying that could not be comforted |
| Other adverse events | 0 | No adverse event |
| | 1 | Adverse event which was easily tolerated. |
| | 2 | Adverse event sufficiently discomforting to interfere with daily activities. |
| | 3 | Adverse event which prevented normal every-day activities and needed medical advice. |

Table 2

The overall incidence of solicited local symptoms after vaccination with DTPw and DTPa vaccines.

| Symptoms | Intensity | DTPw N = 171 | | DTPa N = 357 | | p-value |
|---|---|---|---|---|---|---|
| | | n | % | n | % | |
| Pain | Total | 81 | 47.4 | 54 | 15.1 | <0.0001 |
| | Grade 3 | 9 | 5.3 | 2 | 0.6 | 0.001 |
| Redness | Total | 164 | 95.9 | 303 | 84.9 | 0.0001 |
| | Grade 3 | 57 | 33.3 | 29 | 8.1 | <0.0001 |
| Swelling | Total | 79 | 46.2 | 66 | 18.5 | <0.0001 |
| | Grade 3 | 14 | 8.2 | 2 | 0.6 | <0.0001 |

Group 1 received CSL's DTPw vaccine lot no. 00507.
Group 2 received GSK Biologicals' DTPa vaccine lot no. 85842A.
Grade '3': adverse event which prevented normal everyday activities or largest diameter of redness/swelling > 20 mm.
N: total number of symptom sheets returned overall; n: number of sheets with symptoms reported.

Table 3

The overall incidence of solicited general symptoms after vaccination with DTPw and DTPa vaccines.

| Symptoms | DTPw N = 171 | | DTPa N = 357 | | p-value |
|---|---|---|---|---|---|
| | n | % | n | % | |
| Fever | 91 | 52.6 | 52 | 14.6 | <0.0001 |
| Diarrhea | 12 | 6.9 | 21 | 5.9 | 0.7 |
| Fussiness | 104 | 60.8 | 120 | 33.6 | <0.0001 |
| Loss of appetite | 59 | 34.1 | 75 | 21.0 | 0.0014 |
| Restlessness | 44 | 25.4 | 78 | 21.8 | 0.38 |
| Sleeping more than usual | 39 | 22.5 | 45 | 12.6 | 0.005 |
| Vomiting | 10 | 5.8 | 25 | 7.0 | 0.71 |

Group 1 received CSL's DTPw vaccine lot no. 00507.
Group 2 received SB Biologicals' DTPa vaccine lot no. 85842A.
N: total number of symptom sheets returned overall; n: number of sheets with symptoms reported; Fever: Temperature =37.5°C (axillary).

cination and two subjects in group 2 (DTPa) reported serious adverse events after 30 days post-vaccination. All serious adverse events reported were determined by the investigator to be 'not related' or 'unlikely' related to the study vaccine, and all events resolved within a maximum of 14 days from their date of onset.

## DISCUSSION

Several comparative studies conducted with DTPa and DTPw vaccines have invariably found the acellular pertussis vaccines to have a superior reactogenicity profile than the whole-cell vaccine (Picichero *et al,* 1994; Wiersbitzky *et al,* 1996). In this study, the three component acellular DTPa vaccine has also significantly fewer local and general symptoms than the locally used DTPw vaccine.

These results are in line with other studies conducted in Europe and the United States (Bernstein *et al,* 1995; Bogaerts *et al,* 1996;

Schmitt *et al,* 1996) The incidences of grade '3' redness, swelling (≥20mm) and fever (≥39.5°C) in this study are also in line with the data reported in other studies (Bernstein *et al,* 1995; Bogaerts *et al,* 1996; Schmitt *et al,* 1996). However, the overall incidence of pain, redness and swelling following vaccination with both DTPw and DTPa vaccines in this study was higher than previously reported results (Picichero *et al,* 1994; Wiersbitzky *et al,* 1996). This might be due to the low limit of redness and swelling defined as anything less than 5 mm and a higher degree of observation and attention. An acellular pertussis vaccine containing separately purified antigens of *Bordetella pertussis*: pertactin (PRN), pertussis toxin (PT) and filamentous hemagglutinin (FHA) was developed by GlaxoSmithKline Biologicals. Each component of the pertussis vaccine was selected on the basis of its importance in pertussis pathogenesis and its role in inducing protection against pertussis (Oda *et al,* 1984; Thomas *et al,* 1989; Capiau *et al,* 1990; Bernnan *et al,* 1998; Edwards *et al,* 1999). These antigens are combined with diphtheria and tetanus toxoids in order to produce a multicomponent DTPa vaccine. Previous clinical studies have shown that the GSK Biologicals' DTPa vaccine is safe and immunogenic (Bernstein *et al,* 1995; Decker *et al,* 1995; Bogaerts *et al,* 1996; Patel and Wagstaff, 1996; Schmitt *et al,* 1996), with a protective efficacy of 84-89% (Greco *et al,* 1996; Schmitt *et al,* 1996; Giuliano *et al,* 1998; Salmaso *et al,* 1998) and has been licensed for primary and booster vaccinations in several countries. The tricomponent DTPa vaccine was licensed in Singapore in 1996 for use in primary and booster vaccination in infants and it is now the cornerstone of combined DTPa-based pediatric combinations, including vaccines against *Hemophilus influenzae* (Hib) and poliomyelitis (IPV), which have recently become available in Singapore.

The whole-cell pertussis vaccine remains an appropriate choice for public health immunization programs in some countries, especially in terms of cost and tighter budget commitments. However, due to the reactogenicity of the whole-cell vaccine, WHO has endorsed the use of acellular pertussis vaccines in countries where pertussis vaccination is not widely accepted (Anony-mous, 1999). ACIP/CDC (USA) has recommended the use of acellular pertussis vaccines for all doses of the pertussis vaccination since January 2000 (Anonymous, 2000). Furthermore, large studies comparing DTPa and DTPw have shown a reduction of rare, severe systemic reactions, such as hypotonic, hyporesponsive episodes, generalized cyanosis and seizures, in addition to the benefit in reduction of frequently reported local and general reactions (Greco *et al,* 1996; Rosenthal *et al,* 1996).

In conclusion, GSK Biologicals' DTPa vaccine was significantly less reactogenic as compared to Commonwealth Serum Laboratories' DTPw vaccine when administered as a 3-dose primary vaccination course to healthy infants at the age of 3, 4 and 5 months in Singapore, and it can be considered a good alternative for primary immunization of children.

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