

SAFETY AND REACTOGENICITY OF DTP_A-HBV-IPV/HIB AND DTP_A-IPV/HIB VACCINES IN A POST-MARKETING SURVEILLANCE SETTING

Fong Seng Lim¹, Kong Boo Phua², Bee Wah Lee³, Seng Hock Quak⁴, Yee Leong Teoh^{1,5}, Gunasekaran Ramakrishnan⁵, Htay-Htay Han⁵, Olivier Van Der Meeren⁵, Jeanne-Marie Jacquet⁵ and Hans L Bock⁵

¹National Healthcare Group Polyclinics, Singapore; ²Department of Pediatrics, KK Women's and Children's Hospital, Singapore; ³Mount Elizabeth Medical Centre, Singapore; ⁴Department of Pediatrics, National University of Singapore, Singapore; ⁵GlaxoSmithKline Biologicals, Wavre, Belgium

Abstract. Combination vaccines have been shown to improve the timeliness of vaccination and vaccine coverage. Safety and reactogenicity of combined diphtheria-tetanus-acellular pertussis-inactivated poliovirus and *Haemophilus influenzae* type b vaccine (DTP_A-IPV/Hib, *Infanrix*[™] IPV+Hib, GlaxoSmithKline Biologicals) was assessed in two clinical studies. In Study A, 2,590 subjects received DTP_A-IPV/Hib at 3, 4 and 5 months of age with a booster at 18 months. In Study B, 702 subjects received the same schedule but with DTP_A-hepatitis B-IPV/Hib (DTP_A-HBV-IPV/Hib, *Infanrix hexa*[™], GlaxoSmithKline Biologicals) vaccine administered at 5 months of age. Reactogenicity was assessed for four days after each dose using diary cards. Serious adverse events (SAEs) were assessed until 24 months of age. The vaccines were well tolerated. After primary vaccination, irritability was the most frequently reported grade 3 general symptom (0.8% of doses in both studies). Fever (axillary) >39°C was infrequent (0.3% of doses in Study A; 0.5% of doses in Study B). After the booster dose, the most frequently reported grade 3 symptom was redness (5%) in Study A and pain (0.5%) in Study B. An axillary temperature >39°C was reported in 1.1% of subjects. Throughout the study period, 646 SAEs were reported, of which 6 SAEs were considered to be vaccination-related. The reactogenicity and safety profile of the combined DTP_A-IPV/Hib vaccine was good when used for primary and booster vaccinations in over 3,000 Singaporean infants. Substitution of DTP_A-IPV/Hib with DTP_A-HBV-IPV/Hib at Month 5 reduced the number of injections required at this age by one.

Keywords: DTP_A-HBV-IPV/Hib vaccine, DTP_A-IPV/Hib vaccine, safety, reactogenicity

INTRODUCTION

Easy access to vaccines targeting diph-

Correspondence: Dr Fong Seng Lim, National Healthcare Group Polyclinics, 6 Commonwealth Lane, Level 7, GMTI Building, Singapore 149547.

Tel: +65 6496 6754; Fax: +65 6496 6753

E-mail: Fong_Seng_LIM@nhgp.com.sg

theria, tetanus, pertussis and poliomyelitis diseases, and their large-scale implementation as part of the Expanded Program on Immunization (EPI) in most countries, has led to a significant reduction in childhood morbidity and mortality due to these diseases worldwide. Nevertheless, the burden of disease remains substantial, particularly in developing countries where

vaccine coverage may be poor. According to World Health Organization (WHO) estimates, there were 4,000 deaths due to diphtheria and 198,000 deaths due to tetanus in 2002, among children <5 years old (WHO, 2007). There were 294,000 deaths across all age groups in 2002 due to pertussis (WHO, 2007). High global rates of vaccination against poliomyelitis have been achieved using inactivated poliovirus (IPV) and live attenuated oral poliovirus (OPV) vaccines. However, continued vaccination against poliomyelitis is needed in the years leading up to and following global eradication of polio disease (WHO, 2002a). In Singapore, the national immunization program for vaccines against diphtheria, pertussis, tetanus and polio has been in place for many years. As a result, the incidences of these diseases have reduced considerably since the late 1970's (Wong, 1982; Phua *et al*, 2008).

Hepatitis B is a viral disease of major global importance with an estimated two billion people affected worldwide. Perinatal infection results in chronic hepatitis B in up to 90% of cases (WHO, 2004). Thus, interruption of transmission to infants and young children by vaccination is critical to prevent chronic carriage and deaths from liver cancer and cirrhosis of the liver. Hepatitis B had been endemic in Singapore (Goh, 1997). Epidemiological surveys have demonstrated an overall infection rate of approximately 25% and a carrier rate of 5-6% for hepatitis B in the general population of the country (Goh, 1997). Routine immunization of all infants against hepatitis B was introduced in 1987 (Goh *et al*, 1989).

It is estimated that *Haemophilus influenzae* type b (Hib) causes three million cases of serious disease and 386,000 deaths world-wide annually, the majority of which occur in developing countries (Peltola, 2001; Aristegui *et al*, 2003; WHO,

2006). Prior to the introduction of Hib vaccines in Singapore, the annual incidence of invasive Hib disease was estimated at 5 per 100,000 in children aged less than 5 years (Tee and Lin, 1996; Phua *et al*, 2008). While Hib vaccination is not currently included in Singapore's routine vaccination schedule, it is widely administered in the private sector (Phua *et al*, 2008).

In accordance with the recommendation of the WHO to implement universal mass vaccination against hepatitis B and Hib (WHO, 2002b), GlaxoSmithKline (GSK) Biologicals, has developed a combined diphtheria-tetanus-acellular pertussis-IPV-Hib vaccine (DTPa-IPV/Hib, *Infanrix*TM IPV+Hib) and a combined hexavalent DTPa-hepatitis B-IPV-Hib vaccine (DTPa-HBV-IPV/Hib, *Infanrix hexa*TM). The immunogenicity and tolerability of these vaccines when used for primary and booster vaccination of infants has been established when administered in a range of schedules (Lim *et al*, 2007; Zepp *et al*, 2009). Use of combination vaccines, such as DTPa-HBV-IPV/Hib and DTPa-IPV/Hib, improves both vaccine coverage and timeliness (Meyerhoff and Jacobs, 2005; Kalies *et al*, 2006; Happe *et al*, 2009). Safety and reactogenicity of the DTPa-HBV-IPV/Hib and DTPa-IPV/Hib vaccines when used for the primary and booster vaccination of Singaporean infants were assessed in two clinical studies.

MATERIALS AND METHODS

Study design and subjects

Subjects were healthy infants enrolled in a randomized, placebo-controlled efficacy study of GSK's human rotavirus vaccine, *Rotarix*TM (ClinicalTrials.gov Identifier: NCT00197210). Parents/guardians of subjects were invited to participate voluntarily in either of two open, parallel

studies (A and B) designed to assess reactogenicity and safety of DTPa-IPV/Hib and DTPa-HBV-IPV/Hib given concurrently with *Rotarix*TM. In both studies, *Rotarix*TM or placebo was administered orally at 3 and 4 months of age. The safety and efficacy of the *Rotarix*TM vaccine are presented elsewhere (Phua *et al*, 2009).

In Study A (NCT00325156), subjects received a three-dose primary series of DTPa-IPV/Hib at 3, 4 and 5 months of age, and a booster dose at 18 months of age. In Study B (NCT00325143), subjects received DTPa-IPV/Hib at 3 and 4 months, one dose of DTPa-HBV-IPV/Hib at 5 months of age, and a booster dose of DTPa-IPV/Hib at 18 months of age.

In both studies, children were 11-17 weeks old at the time of first vaccination. In accordance with recommendations in Singapore, children in Study A received hepatitis B vaccine at 0 and 1 month of age, and were planned to receive a third dose of hepatitis B vaccine at 6 months of age after completion of the study. In Study B, children received hepatitis B vaccine at 0 and 1 month of age and the DTPa-HBV-IPV/Hib vaccine (representing the third dose of HBV vaccine) at 5 months of age.

Study A was conducted in eight centers in Singapore and Study B in three centers in Singapore, between December 2003 and August 2007. The studies were conducted according to the provisions of the Declaration of Helsinki, Good Clinical Practices. The study protocols and related documents were approved by the Ethics Committee of all the participating centers in Singapore. Written informed consent was obtained from the parent or guardian of each subject before enrollment.

Study vaccines

Each 0.5 ml dose of DTPa-HBV-IPV/Hib contained: 25 Lf diphtheria toxoid, 10

Lf tetanus toxoid, 25 µg pertussis toxoid (PT), 25 µg filamentous hemagglutinin (FHA), 8 µg pertactin (PRN), 10 µg recombinant hepatitis B surface antigen, 40 D antigen units poliovirus type 1 (Mahoney), 8 D antigen units poliovirus type 2 (MEF-1), 32 D antigen units poliovirus type 3 (Saukett) and 10 µg polyribosyl-ribitol-phosphate (PRP) conjugated to 20-40 µg tetanus toxoid. The antigen composition of DTPa-IPV/Hib was identical to DTPa-HBV-IPV/Hib but did not contain a hepatitis B component.

All vaccines were administered intramuscularly into the anterolateral part of the right thigh.

Assessment of safety

Parents/guardians used diary cards to record solicited local symptoms (pain, redness and swelling at injection site) and solicited general symptoms (drowsiness, fever, irritability/fussiness and loss of appetite) for four days (Days 0-3) after each vaccine dose. The intensity of adverse events was graded on a 3-point scale, where grade 3 was defined as pain that caused discomfort when the limb was moved, injection site redness or swelling >20 mm diameter or fever higher than 39°C (axillary temperature). Grade 3 irritability/fussiness was defined as "crying that could not be comforted/prevented normal activity". Grade 3 drowsiness was defined as "drowsiness that prevented normal activity". Grade 3 loss of appetite was defined as "did not eat at all".

A large swelling at the injection site, defined as swelling >50 mm, noticeable diffuse swelling or noticeable increase of limb circumference, were solicited and assessed by the investigator, after the booster dose.

All other (unsolicited) adverse events were recorded for at least 30 days after

DTPa-HBV-IPV/HIB AND DTPa-IPV/HIB VACCINE SAFETY IN INFANTS

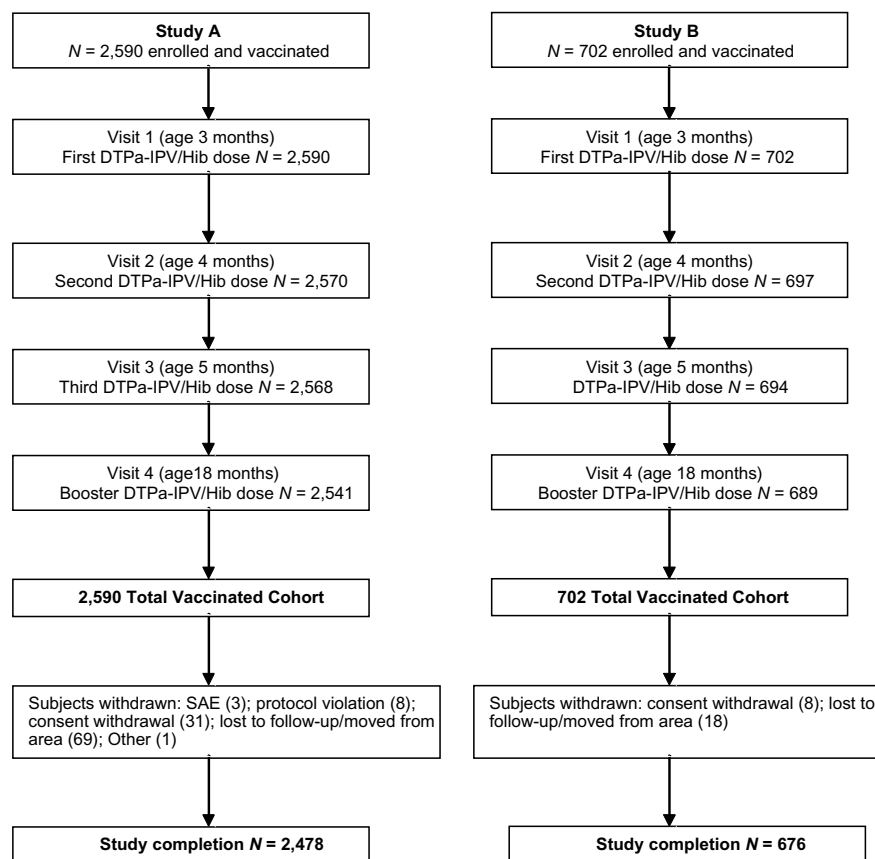


Fig 1—Subject disposition.

each vaccine dose. Serious adverse events (SAEs) were recorded throughout the study period. Six months after the last study vaccine dose, parents/guardians were contacted by telephone to report SAEs occurring until 24 months of age.

All local symptoms were considered to be related to vaccination. The investigator established whether a causal relationship was present between the occurrence of any other symptom and vaccination.

Statistical methods

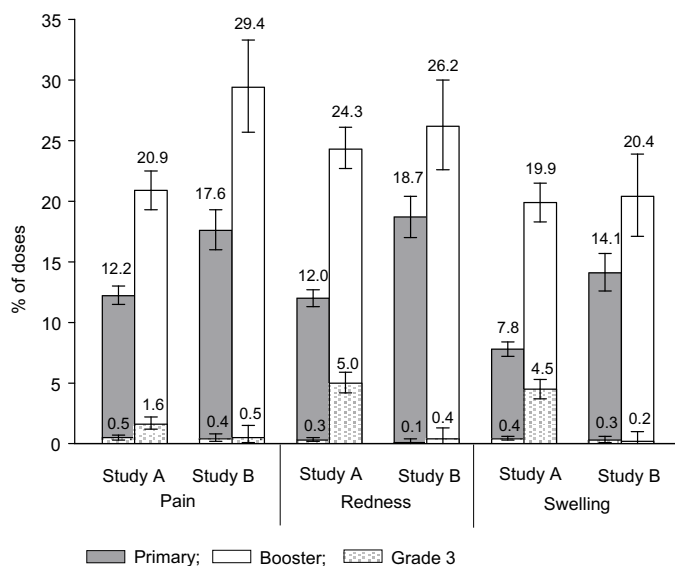
The analyses of safety and reactogenicity were performed on the total vaccinated cohort, comprising vaccinated infants for whom data concerning reactogenicity endpoint measures were available.

The studies were descriptive. The percentage of doses followed by at least one adverse event during the follow-up period for solicited symptoms, unsolicited symptoms and SAEs was tabulated with exact 95% confidence intervals (CI). All statistical analyses were performed using Statistical Analysis System (SAS) version 9.1 and StatXact-7.

RESULTS

Demography

The number of enrolled and vaccinated subjects were 2,590 in Study A, and 702 in Study B. Three subjects withdrew from Study A due to SAE. All withdrawals due to protocol violations were due to



The numbers above each bar represent the incidence (in %) of the corresponding solicited symptom. Error bars, 95% CI; Hatched regions, grade 3 symptoms.

Fig 2—Incidence of solicited local symptoms after primary vaccination (Study A, $N=7,694$ primary doses and $N=2,448$ booster doses; Study B, $N=2,053$ primary doses and $N=565$ booster doses).

deviations from protocol specified study intervals.

The mean age of subjects at the time of the first DTPa-IPV/Hib dose was 13.3 weeks [standard deviation (SD): 0.87 weeks] in Study A and 13.5 weeks (SD: 0.99 weeks) in Study B. The mean age of infants at the booster dose was 18.1 months (SD: 1.22 months) in Study A and 18 months (SD: 0.62 months) in Study B.

Primary vaccination

Solicited local and general symptoms. Pain and redness were the most frequently reported local symptoms after primary vaccination in Studies A and B (Fig 2). Pain was the most frequently reported grade 3 local symptom in both studies, reported in 0.5% of doses in Study A and 0.4% of doses in Study B.

Irritability was the most frequently recorded solicited general symptom in both studies, reported in 28.3% of doses (Fig 3). Irritability was the most frequently reported grade 3 general symptom in both studies, with an incidence of 0.8% in both studies. Axillary temperature $>39^{\circ}\text{C}$ was reported after 0.3% of primary doses in Study A and 0.5% of primary doses in Study B.

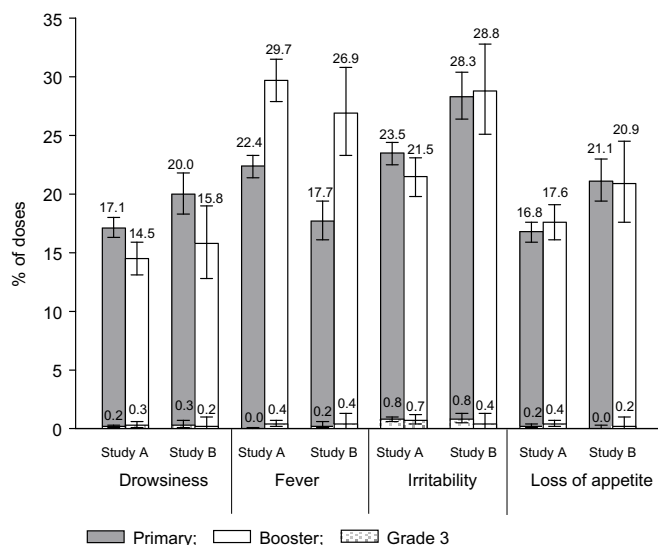
The incidences of solicited symptoms post-Dose 3 in both studies A and B are shown in Fig 4. With the exception of fever, the point estimate for the incidence of each local and general symptom tended to be higher in Study B. The incidences of grade 3 symptoms were low after both the DTPa-HBV-IPV/Hib and DTPa-IPV/Hib vaccinations: individual symptoms of grade 3 intensity were reported in no more than

0.4% of subjects receiving DTPa-IPV/Hib and in no more than 0.8% of subjects receiving DTPa-HBV-IPV/Hib.

Other symptoms. Unsolicited symptoms within one month of each dose were reported after 13.2% of doses in Study A and in 17.9% of doses in Study B. The percentages of primary doses followed by an unsolicited symptom considered by the investigator to be related to vaccination were 0.2% in Study A and 0.5% in Study B.

Booster vaccination

Solicited local and general symptoms. In both studies, the incidences of local solicited symptoms and fever tended to be higher after the booster dose than after primary vaccination (Figs 2 and 3). Fever ($\geq 37.5^{\circ}\text{C}$) and redness (of all grades) were the most frequently reported symptoms



The numbers above each bar represent the incidence (in %) of the corresponding solicited symptom. Error bars, 95% CI; Hatched regions, grade 3 symptoms.

Fig 3—Incidence of solicited general symptoms after primary vaccination (Study A, $N=7,694$ primary doses and $N=2,447$ booster doses; Study B, $N=2,053$ primary doses and $N=565$ booster doses).

after the booster dose in Study A, whereas pain and irritability (of all grades) were the most frequently reported symptoms after the booster dose in Study B. The most frequently reported grade 3 symptoms were redness (5%) in Study A and pain (0.5%) in Study B. Some variability in grade 3 symptoms between the studies occurred: redness and swelling >20 mm were reported in 5% and 4.5% of subjects, respectively, in Study A and in $\leq 0.4\%$ of subjects in Study B. Grade 3 pain was reported in 1.6% of subjects in Study A, and 0.5% of subjects in Study B. Axillary temperatures $>39^{\circ}\text{C}$ were reported in 1.0% and 1.1% of subjects in Studies A and B, respectively, after the booster dose. Other general symptoms (drowsiness, irritability and loss of appetite) of grade 3 intensity were reported in $<0.7\%$ of subjects in both studies.

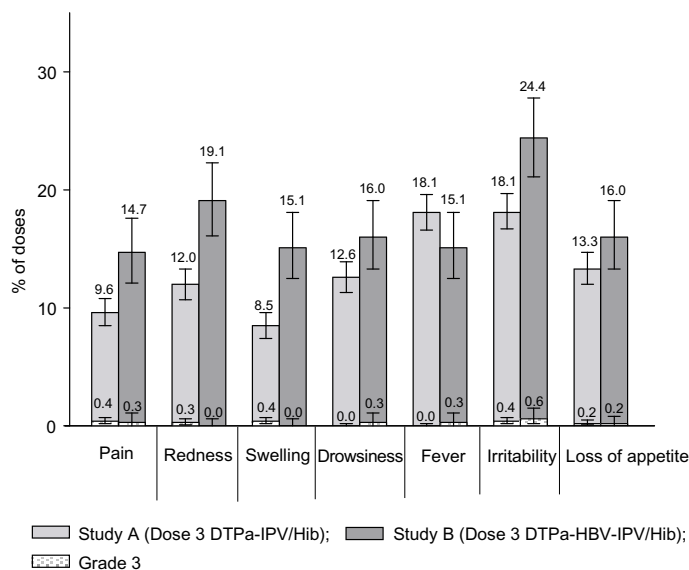
Large injection site reactions.

Large injection site reactions were reported in 11 subjects (0.4%, all in Study A) after the booster dose. All reactions began within two days of booster vaccination and the majority had resolved by the fourth day after vaccine administration. Ten out of 11 subjects had swelling limited to the injection site, with a maximum diameter of 100 mm. One subject developed a diffuse swelling reaction. None of the large swelling reactions involved an adjacent joint.

Other symptoms. Unsolicited symptoms within one month of the booster dose were reported in 6.5% of subjects in Study A and 10.8% of subjects in Study B. Six subjects in Study A (0.2%) and one subject in Study B (0.1%) had at least one unsolicited symptom that was considered by the investigator to be related to vaccination.

Serious adverse events. In Study A, a total of 538 SAEs were reported in 380 subjects. There was one death. The female subject aged 11 months died six months after the third dose of DTPa-IPV/Hib due to interstitial lung disease of viral etiology. The investigator considered the death unrelated to the study vaccines. Four SAEs [hematoma at the injection site; abscess at the injection site (two cases) and rash] were considered to be related to vaccination.

A total of 108 SAEs were reported in Study B. Of these, two SAEs reported in the same subject, were considered by the investigator to have a causal relationship with vaccination. The subject had a febrile convulsion two days after receiving a DTPa-IPV/Hib booster dose, followed three days later by exanthema subitum.



The numbers above each bar represent the incidence (in %) of the corresponding solicited symptom. Error bars, 95% CI; Hatched regions, grade 3 symptoms

Fig 4—Incidence of solicited local and general symptoms within the four day follow-up period after Dose 3.

DISCUSSION

The reactogenicity and safety profile of the combined DTPa-IPV/Hib vaccine was shown to be good when used for primary and booster vaccination of over 3,000 Singaporean infants enrolled in two clinical safety studies. The incidence of local reactions following primary vaccination with DTPa-IPV/Hib was lower than what was reported following primary vaccination (Cody *et al*, 1981; Dagan *et al*, 1997; Jefferson *et al*, 2003). The reactogenicity profiles of DTPa-IPV/Hib seen in Studies A and B were similar with previous published reports of DTPa-IPV/Hib when administered to infants in Europe (Dagan *et al*, 1997), Taiwan (Lin *et al*, 2003) and Singapore (Phua *et al*, 2008). In addition, it has been observed that the co-administration of the DTPa-IPV/Hib vaccine with other routine vaccines is safe and well tol-

erated by infants (Phua *et al*, 2008).

Incidences of local reactions at the injection site tended to increase after the DTPa-IPV/Hib booster dose at 18 months of age compared to post-primary incidence rates. This is a well recognized phenomenon observed with DTPa-based and DTPw-based combination vaccines (Deloria *et al*, 1995; Pichichero *et al*, 1997). Grade 3 local symptoms after a booster dose were reported by <5% of subjects in both studies, and grade 3 general symptoms by <1.1% of subjects, in both studies.

Large swelling reactions involving the entire vaccinated limb are a well-recognized phenomenon following booster vaccination with many vaccines, including DTPa, DT and DTPw vaccines, from all manufacturers (Woo *et al*, 2003). The cause of these large swelling reactions is not fully understood, however, they are generally not associated with significant impairment of function, and resolve without sequelae (Scheifele *et al*, 2006). Large swelling reactions after the DTPa-IPV/Hib booster dose were reported by 0.4% of subjects in Study A and by no subjects in Study B. Only one swelling reaction was reported as diffuse and none of the reported swellings involved an adjacent joint. This is well below the range of 2% to 6% following DTPa booster doses reported in the literature (Rennels, 2003).

In Study B, the hexavalent combination vaccine DTPa-HBV-IPV/Hib was substituted for the third primary vaccine dose at five months of age, coinciding with the third hepatitis B vaccine dose recommended at this age in Singapore. The im-

munogenicity and reactogenicity profile of DTPa-HBV-IPV/Hib has been established through clinical trials and eight years of post-marketing surveillance of vaccine effectiveness and safety (Zepp *et al*, 2009).

The incidence of grade 3 symptoms remained low with DTPa-HBV-IPV/Hib vaccination, and within the same range as that reported for the third DTPa-IPV/Hib dose. A study showed that when hepatitis B is co-administered with DTPa-IPV/Hib, the reactogenicity profile is comparable to that of DTPa-HBV-IPV/Hib (Zepp *et al*, 2004).

Combination vaccines targeting multiple diseases in a single injection have a growing role to play in meeting WHO objectives to achieve and maintaining high global vaccine coverage against diphtheria, tetanus, pertussis, hepatitis B, poliomyelitis and Hib (WHO, 2002a). Combination vaccines have the advantage of causing less discomfort to infants through fewer injections and visits to the doctor, increasing vaccine acceptance and compliance with vaccine recommendations, and easing the introduction of new pediatric vaccines into already crowded childhood vaccination schedules (CDC, 1999). In Singapore, infant vaccination against hepatitis B is well established. However, clinical safety data as well as published clinical immunogenicity data (Lim *et al*, 2007) indicate the combined hexavalent DTPa-HBV-IPV/Hib vaccine may be used at Month 5, removing the need for an additional injection of monovalent hepatitis B vaccine at this age. Although not currently included in the Singapore public immunization schedule, the Hib vaccine is commonly administered to children in the private sector in Singapore (Phua *et al*, 2008). Thus, use of the combined DTPa-IPV/Hib or DTPa-HBV-IPV/Hib vaccines allows administration of the Hib compo-

nent without the need for additional injections.

Combination vaccines have a growing role in maximizing vaccine acceptance, timeliness of administration and coverage. Primary and booster vaccination with DTPa-IPV/Hib resulted in an acceptable reactogenicity profile that was comparable to reports in the published literature. In addition, substitution of DTPa-IPV/Hib with DTPa-HBV-IPV/Hib at Month 5 reduced the number of injections required at this age by one.

ACKNOWLEDGEMENTS

The authors thank Joanne Wolter and Farah Mecci for medical writing; Ming Tung Lim and Roselynn Tien for manuscript coordination and editorial assistance. Joanne Wolter is a freelance writer, Farah Mecci, Ming Tung Lim and Roselynn Tien are employees of GSK Biologicals.

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