IMMUNOGENICITY AND SAFETY OF QUINVAXEM® (DIPHTHERIA, TETANUS, WHOLE-CELL PERTUSSIS, HEPATITIS B AND HAEMOPHILUS INFLUENZAE TYPE B VACCINE) GIVEN TO VIETNAMESE INFANTS AT 2 TO 4 MONTHS OF AGE

Tran Ngoc Huu, Nguyen Thi Minh Phuong, Nguyen Trong Toan and Ho Vinh Thang

Ho Chi Minh City Pasteur Institute, Vietnam

Abstract. Vietnam plans to replace the routine childhood diphtheria, pertussis and tetanus combination (DPT) vaccine with a pentavalent vaccine. The present study was performed to assess the immunogenicity and safety of the combined diphtheria, tetanus, whole-cell pertussis, hepatitis B (HepB), and *Haemophilus influenzae* type b (Hib) (DTwP-HepB-Hib) Quinvaxem® vaccine in children. A total of 131 infants received the Quinvaxem® vaccine at 2,3 and 4 months. Antibody levels were measured at baseline, at one month after the third injection and one year after the first injection. Seroprotection rates were high for each vaccine antigen at one month after the third dose: 93.1% for diphtheria, 98.5% for tetanus, 99.2% for pertussis (seroconversion rate), 93.1% for HepB, and 100% for Hib (anti-PRP ≥0.15 μg/ml). The rate of children with protective antibodies persisting at one year after the first dose was 88.4% for diphtheria, 49.6% for pertussis, 82.2% for tetanus, 76.7% for HepB and 97.7% for Hib (anti-PRP ≥0.15 μg/ml). The Quinvaxem® vaccine was well tolerated and has a low rate of adverse events. Quinvaxem® given at 2, 3 and 4 months of age was immunogenic and safe for primary immunization among infants in Vietnam.

Keywords: diphtheria, tetanus, whole-cell pertussis, *Haemophilus influenzae* type b, hepatitis B, pentavalent combined vaccine, immunogenicity, safety, Vietnam

INTRODUCTION

The expanded program on immunization (EPI) was initiated by the World Health Organization (WHO) in 1974 and has since greatly reduced the burden of infectious diseases (Keja *et al*, 1988). EPI was first implemented in Vietnam in 1981 and initially targeted six vaccine-preventable diseases in children: diphtheria, tetanus, pertussis, measles, poliomyelitis and tuberculosis (Hoang *et al*, 2008). In 1990, the target of universal immunization of all Vietnamese children under 1 year old was achieved with 85%-95% of under 1 year old children immunized against the six targeted diseases and 75%-95% of childbearing women receiving tetanus toxoid immunization (NIHE, 2013). Since 1993, vaccination coverage has continuously been over 90%. As a result, Vietnam has eradicated endemic poliomyelitis,

Correspondence: Dr Ho Vinh Thang, Ho Chi Minh City Pasteur Institute, Vietnam.
Tel: +84 90 8007807; Fax: +84 8 38202814
E-mail: hovinhthang@gmail.com

eliminated neonatal tetanus (through immunization of pregnant women) and dramatically reduced the morbidity rates of measles, pertussis, and diphtheria. Since 1997, vaccines against hepatitis B (HepB), and, in high risk areas, Japanese encephalitis, cholera, and typhoid, have been added to the program. In 2010, vaccination against *Haemophilus influenzae* type b (Hib) was introduced into the routine immunization schedule (Nyambat *et al*, 2011). Children under 1 year of age throughout Vietnam are immunized free of charge with the combined vaccine against diphtheria, pertussis, tetanus, hepatitis B, and Hib (DTP-HepB-Hib). The DTP-HepB-Hib vaccine is administered to infants at 2, 3 and 4 months of age (NIHE, 2013). Although Vietnam is producing most of the vaccines used in the EPI (polio, DTP, HepB, Japanese encephalitis, cholera, typhoid, tuberculosis and measles) locally, it is currently unable to produce a Hib vaccine, and consequently unable to produce its own combined DTP-HepB-Hib vaccine.

Quinvaxem® is a fully liquid combined vaccine, containing the five components DTwP-HepB-Hib. The vaccine contains inactivated whole-cell pertussis (wP), which is considerably less expensive than acellular pertussis (aP), is effective in preventing pertussis and has an excellent safety record (WHO, 2010). Currently, wP-containing vaccines are used in the EPI in most developing countries. Quinvaxem® is free from preservatives and was the first five-component vaccine prepared in liquid form to make it ready for use without having to be reconstituted from lyophilized ingredients (Schmid *et al*, 2012). Thanks to these improvements, the vaccine is easy to use, avoids the risk of contamination during reconstitution, saves on health care costs, and reduces the number of injections while simultaneously preventing five different diseases in children. Quinvaxem® is indicated for the active immunization of young children who previously did or did not receive the hepatitis B vaccine shortly after birth (Gentile *et al*, 2011). Like other combination vaccines, Quinvaxem® is also used to boost the immune system in children with one additional dose injected when the children are 13 to 24 months old (Suarez *et al*, 2010; Aspinall *et al*, 2012).

Quinvaxem® was pre-qualified by the WHO in 2006 and is now widely used in the EPI of many countries worldwide (Schmid *et al*, 2012). As part of the licensing process stipulated by the Vietnamese Ministry of Health, vaccines must first be assessed for safety alone before assessing for immunogenicity and safety. Since Quinvaxem® was under consideration to be included in the Vietnamese EPI, a study assessing the safety of Quinvaxem® was conducted from November 2009 to February 2011 among 120 Vietnamese infants (Huu *et al*, 2011). The study showed that rates of post-injection adverse events were within the ranges of those reported in previous studies with the vaccine (Kanra *et al*, 2006; Gentile *et al*, 2011; Aspinall*et al*, 2012). Furthermore, a comparison with WHO statistics revealed that the rate of solicited local and systemic adverse events after the first injection of Quinvaxem® in the Vietnam study was lower than reported for DTwP, HepB, and Hib vaccines (WHO, 2001). The present study was conducted as part of the licensing procedure in Vietnam and assessed the immunogenicity and safety of Quinvaxem® when given as a three-dose primary vaccination course to Vietnamese infants at 2, 3 and 4 months.

MATERIALS AND METHODS

Study design

This open-label, non-controlled study (NCT01362517) was conducted from March 2010 to October 2010, with a follow-up to assess the immunogenicity and safety until September 2011. We enrolled infants from nine communities in the Ben Luc District, Long An Province, near Ho Chi Minh City, Vietnam.

The study protocol was approved by the Ethics Committee for Biomedical Research, Vietnamese Ministry of Health. The study was conducted in compliance with Good Practices Guidelines for Clinical Drug Trials issued by the Vietnamese Ministry of Health. Family Health International acted as an independent supervisor of Good Clinical Practice (GCP) compliance during the study.

Parents or legal guardians provided written informed consent before enrollment of subjects.

Subjects

Healthy, full-term (≥37 weeks) infants with a birth weight >2.5 kg, aged 2 to 4 months old, who had not previously received the DTP vaccine and who had no history of allergies were eligible for inclusion. Subjects were excluded if they were suffering from acute infections, had contraindications to any component of Quinvaxem®, were undergoing systemic corticosteroid treatment or were receiving immunoglobulin, were taking part in another clinical study, or if the family was planning to move from the study area.

Vaccine

The study vaccine Quinvaxem® (DT-wP-HepB-Hib combination vaccine, fully liquid) was produced by Berna Biotech Korea Corporation (Inchon, South Korea). Each 0.5 ml dose contained ≥30 IU purified diphtheria toxoid, ≥60 IU purified tetanus toxoid, ≥4 IU inactivated whole-cell *B. pertussis* suspension, 10 μg Hib oligosaccharide conjugated to approximately 25 μg CRM_{197}, and 10 μg hepatitis B surface antigen.

The vaccine was injected intramuscularly into the thigh or the deltoid area of the subject at approximately 2, 3, and 4 months of age.

Serology

Blood samples for antibody determination were obtained at baseline before the first dose, one month after the third dose, and one year after the first dose of the vaccine. Concentrations of anti-diphtheria and anti-tetanus antibodies were determined using a toxin binding inhibition (ToBI) assay (Hong *et al*, 1996) at the Nha Trang Vaccine Institute. A post-hoc analysis of the sera for diphtheria and anti-tetanus antibodies was performed at the University of Rochester, USA, using enzyme-linked immunosorbent assays (ELISA). The concentrations of antibodies to hepatitis B surface antigen was determined at the Ho Chi Minh City Pasteur Institute using a standard ELISA kit from Abbott (Chicaco, IL). Antibodies against Hib and pertussis were determined at the Turku University laboratory in Finland. For Hib, a commercial ELISA kit (VaccZyme™ Hib IgG, The Binding Site Group, Birmingham, UK) was used, while anti-pertussis antibodies were measured with an in-house ELISA. Seroprotective antibody concentrations were defined as: anti-diphtheria and anti-tetanus antibodies ≥0.1 IU/ml, anti-polyribosylribitol phosphate (for Hib) ≥0.15 μg/ml, and anti-HepB ≥10 mIU/ml. For pertussis, seroconversion was defined as an anti-pertussis antibody level ≥20 EU/ml or a 4-fold increase in antibody levels compared to baseline.

Safety assessment

Clinic staff monitored each subject for 30 minutes for immediate local or systemic post-injection reactions. After that, a network of healthcare workers monitored the subjects at home at time 6 hours, 24 hours, 48 hours, daily from days 3 to 7, and on day 28. They measured the subject's temperature, the diameter of redness and swelling at the injection site, and assessed solicited systemic symptoms such as rash, loss of appetite, vomiting, diarrhea, irritability, abnormal crying, persistent crying (>3 hours), and drowsiness/sleepiness. All expected and unexpected local and systemic adverse events were recorded in terms of times of onset and resolution, severity and treatment. Redness or swelling at the injection site with a diameter of ≥50 mm was graded as severe. Pain when the limb was moved indicated severe injection site pain. Fever was defined as an axillary temperature >38ºC (slight temperature; Michael Marcy *et al*, 2004), ≥39ºC (high temperature), or ≥40ºC (very high temperature). Vomiting and diarrhea leading to dehydration were considered severe. Abnormal crying, persistent crying (≥3 hours), and drowsiness/sleepiness were defined as severe when they interfered with breastfeeding. Other criteria for severe reactions were continuous irritability, a rash covering the whole body, and complete refusal to nurse. Serious adverse events were recorded and evaluated to determine their relationship with the vaccine throughout the study. Serious adverse events were defined as events resulting in death, any life-threatening event, any event causing disability or requiring hospitalization or prolonged hospitalization, any event that resulted in a congenital abnormality or birth defect, or any event that endangered a study subject or required intervention to protect the subject from one of the above.

Statistical analysis

The general objective of the study was to assess immunogenicity and safety of Quinvaxem® among healthy Vietnamese infants aged 2 to 4 months. More specifically, seroprotection/seroconversion rates for each component of the vaccine (D, T, wP, HepB and Hib) at one month after the three-dose primary vaccination and one year after the first injection, as well as the percentage of infants with adverse events and/or serious adverse events after each injection of Quinvaxem were evaluated.

Geometric mean titers (GMTs) were calculated by taking the anti-$\log_{10}$ of the mean of the $\log_{10}$ titer transformations. GMTs are presented with their 95% confidence intervals (CIs); they were calculated using the normal approximation method.

Safety data were analyzed descriptively by providing the numbers and percentage of subjects with a given adverse event after each dose of the vaccine.

RESULTS

Subjects

A total of 131 subjects (57 females, age range 60 to 127 days) were enrolled in the study. Out of these, 130 subjects received all three doses of the vaccine as scheduled. One subject was excluded because of a protocol violation due to inability to comply with the injection schedule stipulated in the protocol. A total of 129 subjects returned one year after the first injection and had blood samples taken. The subject dispositions are displayed in Fig 1.

Immunogenicity

The vaccine response rates and GMTs for each vaccine antigen are shown in Table 1. One month after the primary immunization, the seroprotection rates

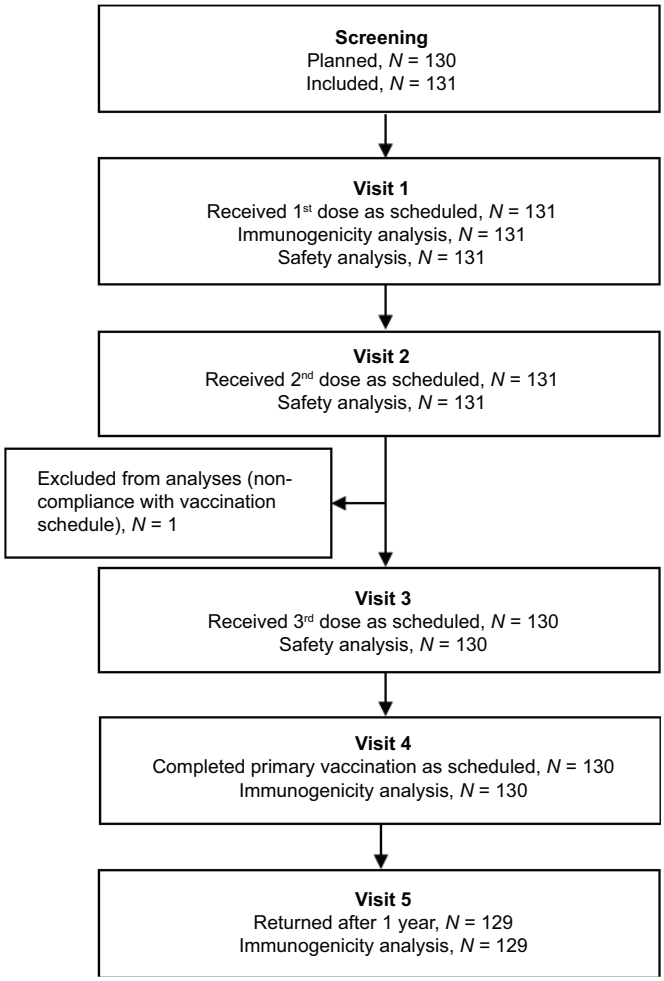

Fig 1–Subject disposition. *N*, number of subjects.

for hepatitis B and diphtheria were both 93.1%, the seroprotection rate for tetanus was 98.5% and the seroconversion rate for pertussis was 99.2%. All 130 evaluable subjects had a seroprotective anti-PRP (Hib) concentration of ≥0.15 μg/ml and 99.2% of subjects had a seroprotective anti-PRP concentration of ≥1.0 μg/ml.

One year after the first vaccination, the seroprotection rate for hepatitis B was 76.7%, for diphtheria 88.4%, and for tetanus 82.2%. The seroconversion rate for pertussis was 49.6%. The Hib seroprotection rates were 97.7% and 72.1% using anti-PRP cut-off values of 0.15 μg/ml and 1.0 μg/ml, respectively.

The GMTs observed one month after the third dose of the vaccine were all above the predefined levels of seroprotection (or seroconversion for pertussis): hepatitis B, 220.8 mIU/ml; diphtheria, 0.56 IU/ml; tetanus, 0.40 IU/ml; pertussis, 58.7 EU/ml; and Hib, 7.0 μg/ml. By one year post-first dose these values had fallen to 34.6 mIU/ml, 0.40 IU/ml, 0.24 IU/ml, 19.1 EU/ml and 1.8 μgl, respectively.

The seroprotection and GMT results from the ToBI assay for diphtheria and tetanus were lower than expected based on previous studies (Kanra *et al*, 2006; Gentile *et al*, 2011; Aspinall *et al*, 2012). Therefore, blood samples were reassessed post-hoc for these two antigens using an ELISA assay to allow a closer comparison with previous data. Table 2 shows the results of the post-hoc ELISA analyses. One month after the third vaccine dose, seroprotection rates were 100% for both diphtheria and tetanus. The seroprotection rates 1 year after the first vaccination were 91.3% and 97.6% for diphtheria and tetanus, respectively. The GMT for diphtheria was 2.00 IU/ml, and for tetanus was 3.14 IU/ml at 1 month after primary immunization. By 1 year after the first dose these values had fallen to 0.26 IU/ml and 0.50 IU/ml, respectively.

Safety and reactogenicity

Overall, 70.7% of subjects experienced at least one solicited adverse event, of which 33.0% experienced at least one solicited local adverse event and 37.7%

Table 1
Vaccine response rates and geometric mean titers at baseline, one month after the third dose and one year after the first dose.

	Baseline (*N*=131)	One month post-third dose (*N*=130)	One year post-first dose (*N*=129)
Diphtheria[a]			
Seroprotection rate, % (95% CI)	6.9 (3.2-12.6)	93.1 (87.3-96.8)	88.4 (81.5-93.3)
GMT, IU/ml (95% CI)	0.01 (0.008-0.012)	0.56 (0.46-0.69)	0.40 (0.33-0.49)
Pertussis			
Seroconversion rate, % (95% CI)	0.0 (0.0-4.2)	99.2 (95.8-100)	49.6 (40.7-58.5)
GMT, EU/ml (95% CI)	4.0 (3.6-4.4)	58.7 (55.5-62.1)	19.1 (17.0-21.3)
Tetanus[a]			
Seroprotection rate, % (95% CI)	88.6 (81.8-93.4)	98.5 (94.6-99.8)	82.2 (74.5-88.3)
GMT, IU/ml (95% CI)	0.58 (0.44-0.76)	0.40 (0.35-0.47)	0.24 (0.20-0.29)
Hepatitis B			
Seroprotection rate, % (95% CI)	38.2 (29.8-47.1)	93.1 (87.3-96.8)	76.7 (68.5-83.7)
GMT, mIU/ml (95% CI)	8.8 (6.4-11.9)	220.8 (168.1-289.9)	34.6 (25.6-46.8)
Haemophilus influenzae type b (anti-PRP ≥0.15 μg/ml)			
Seroprotection rate, % (95% CI) (anti-PRP ≥1.0 μg/ml)	57.3 (48.3-65.9)	100 (97.2-100)	97.7 (93.4-99.5)
Seroprotection rate, % (95% CI)	11.5 (6.6-18.2)	99.2 (95.8-100)	72.1 (63.5-79.6)
GMT, μg/ml (95% CI)	0.27 (0.23-0.32)	7.0 (5.8-9.0)	1.8 (1.5-2.2)

[a]Measured by ToBI assay; CI, confidence interval; GMT, geometric mean titers; *N*, number of subjects included in the analysis.

experienced at least one solicited systemic adverse event. Incidence rates of solicited adverse events gradually decreased over the immunization course with 57.0%, 25.9% and 19.2% of subjects reporting adverse events after the first, second, and third immunization, respectively. Swelling and pain at the infection site were the most frequent solicited local reactions, reported after 5.6% (range between the three doses 0 to 14.5%) and 4.1% (range 0 to 18.3%) of the combined vaccine doses, followed by redness, reported after 2.8% (range 1.5% to 5.3%) of doses (Table 3). Most local post-injection adverse events were of mild to medium severity. The exceptions were three severe cases of swelling, and one severe case each of redness and pain at the injection site. Fever (18.4%, range 13.8% to 26.0%) and irritability (7.9%, range 1.5% to 16.6%) were the most frequently reported solicited systemic adverse events, followed by diarrhea (3.0%, range 2.3% to 3.8%), loss of appetite (2.6%, range 0% to 7.6%), vomiting (1.0%, range 0% to 3%), and persistent crying and drowsiness/sleepiness (both 0.5%, range 0% to 1.5%). Most solicited systemic adverse events were of mild intensity. Very few severe events were reported and consisted of two cases each of vomiting and drowsiness/sleepiness, and three cases each of diarrhea and irritability.

Nine subjects experienced 11 serious

Table 2
Diphtheria and tetanus seroprotection rates and geometric mean titers (ELISA).

	Baseline (*N*=131)	One month post-third dose (*N*=130)	One year post-first dose (*N*=129)
Diphtheria			
Seroprotection rate, % (95% CI)	3.1 (0.8, 7.6)	100 (97.2-100)	91.3 (85.0-95.6)
GMT, IU/ml (95% CI)	<0.10 (<0.10)	2.00 (1.77-2.26)	0.26 (0.23-0.29)
Tetanus			
Seroprotection rate,% (95% CI)	98.5 (94.6-99.8)	100 (97.2-100)	97.6 (93.3-99.5)
GMT, IU/ml (95% CI)	1.36 (1.12-1.67)	3.14 (2.67-3.68)	0.50 (0.43-0.59)

CI, confidence interval; GMT, geometric mean titers; *N*, number of subjects included in analyses.

adverse events, all requiring hospitalization. One of the events led to exclusion of the subject from analysis sets (Fig 1). This subject was hospitalized due to a fever immediately prior to the third injection and received the third dose of Quinvaxem® outside the permitted time range. All of the 11 serious adverse events were commonly observed diseases during infancy: seven events concerned the respiratory tract (such as upper respiratory tract infection and pneumonia), three events were caused by viral infections, and one was a case of infectious diarrhea. Most of the serious adverse events were judged to be of mild to medium intensity and none of them was considered related to vaccination by the attending physician.

DISCUSSION

This study evaluated the immunogenicity and safety of a pentavalent DTwP-HepB-Hib vaccine (Quinvaxem®) given to Vietnamese infants at 2, 3 and 4 months. A total of 131 subjects in an age range of 60 to 127 days were included in the study; 130 received all three vaccine doses as scheduled.

The immunogenicity of the pertussis and Hib components observed in the present study at one month after the primary vaccination were above those seen in previous studies with Quinvaxem® among infants in South Africa, Argentina and Turkey (Kanra *et al*, 2006; Gentile *et al*, 2011; Aspinall *et al*, 2012). Seroconversion against pertussis, defined as anti-pertussis antibody levels ≥20 EU/ml or a 4-fold rise in antibody levels compared to baseline, was observed in 99.2% of subjects. The GMT of pertussis antibodies increased more than 14-fold between pre- and post-primary vaccination. All subjects (100%) had an anti-PRP (Hib) antibody concentration ≥0.15 μg/ml and 99.2% had an anti-PRP antibody concentration ≥1.0 μg/ml. The seroprotection rate for HepB was 93.1%, which is within the range of 91.4% to 98% observed in previous studies (Kanra *et al*, 2006; Gentile *et al*, 2011; Aspinall *et al*, 2012).

Elimination of neonatal tetanus is one of the goals of the Vietnamese national immunization program and has been achieved since 2005 through vaccination of women who are pregnant or of childbearing age (WHO, 2006; NIHE, 2013). Tetanus vaccination rates in this group of women currently reach 80% to

Table 3
Incidence of solicited local and systemic adverse events reported after each dose and overall.

	First dose (*N*=131) *n* (%)	Second dose (*N*=131) *n* (%)	Third dose (*N*=130) *n* (%)	Total (*N*=392) *n* (%)
Local adverse events				
Pain				
Any	24 (18.3)	0 (0.0)	0 (0.0)	24 (4.1)
Severe	1 (0.8)	0 (0.0)	0 (0.0)	1 (0.3)
Redness				
Any	7 (5.3)	2 (1.5)	2 (1.5)	11 (2.8)
Severe	1 (0.8)	0 (0.0)	0 (0.0)	1 (0.3)
Swelling				
Any	19 (14.5)	3 (2.3)	0 (0.0)	22 (5.6)
Severe	3 (2.3)	0 (0.0)	0 (0.0)	3 (0.8)
Systemic adverse events				
Appetite loss				
Any	10 (7.6)	0 (0.0)	0 (0.0)	10 (2.6)
Severe	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Abnormal crying				
Any	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Severe	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Persistent crying (≥3 hours)				
Any	2 (1.5)	0 (0.0)	0 (0.0)	2 (0.5)
Severe	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Diarrhea				
Any	4 (3.0)	3 (2.3)	5 (3.8)	12 (3.0)
Severe	1 (0.8)	0 (0.0)	2 (1.5)	3 (0.7)
Drowsiness/sleepiness				
Any	2 (1.5)	0 (0.0)	0 (0.0)	2 (0.5)
Severe	2 (1.5)	0 (0.0)	0 (0.0)	2 (0.5)
Fever				
Any	34 (26.0)	20 (15.3)	18 (13.8)	72 (18.4)
Severe	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Irritability				
Any	21 (16.0)	8 (6.1)	2 (1.5)	31 (7.9)
Severe	2 (1.5)	0 (0.0)	1 (0.8)	3 (0.8)
Rash				
Any	1 (0.8)	0 (0.0)	0 (0.0)	1 (0.3)
Severe	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Vomiting				
Any	4 (3.0)	0 (0.0)	0 (0.0)	4 (1.0)
Severe	2 (1.5)	0 (0.0)	0 (0.0)	2 (0.5)

Definitions: severe pain: pain when injected limb was moved; severe redness and swelling: diameter ≥50 mm; severe appetite loss: refusal to nurse; abnormal crying, persistent crying and drowsiness/sleepiness: interfering with breastfeeding; severe diarrhea and vomiting: leading to dehydration; severe fever: axillary temperature ≥40°C; severe irritability: continuous irritability; severe rash: covering the whole body; *N*, number of doses; *n*, number of subjects with an adverse event.

90% (NIHE, 2013). This is reflected in the present study by high levels of maternal antibodies rendering the vast majority of subjects (88.6%) protected against tetanus already at baseline. Although high seroprotection rates for the tetanus and diphtheria components one month after the third dose were achieved (93.1% for diphtheria and 98.5%for tetanus), these rates were slightly lower than those observed in studies conducted in South Africa, Argentina, and Turkey (Kanra *et al*, 2006; Gentile *et al*, 2011; Aspinall *et al*, 2012).The reason for this difference was that in previous studies tetanus and diphtheria antibodies were measured by the indirect ELISA method, which is more sensitive than the Tobi method used in the present study (Ebert *et al*, 1998). When samples were re-analyzed with the more sensitive ELISA method, seroprotection rates of 100% were found for both antigens and the corresponding GMTs were within previously observed ranges.

Although the seroprotection rates and GMTs for the D, T, HepB, and Hib components had decreased by one year after the first vaccine dose, the majority of subjects were still seroprotected by one year. Seroconversion against pertussis was still detectable in approximately half the subjects. The gradual decrease in seroprotection/seroconversion rates and GMTs over time has been observed with Quinvaxem® (Suarez *et al*, 2010; Aspinall *et al*, 2012) and for other DTwP-Hep-Hib vaccines (Faingezicht *et al*, 2002; Riedemann *et al*, 2002; Sharma *et al*, 2011). Despite the decrease in serum antibodies, it is assumed that children are protected for an extended period of time due to the presence of memory cells (Siegrist, n.d.; WHO, 1995). Nevertheless, the results highlight the need for a booster dose following the primary vaccination in order to stimulate a robust immunological memory (WHO, 1995, 2013). Following WHO recommendations the Vietnamese Ministry of Health added a booster dose with the DPT vaccine at 18 months of age to the national EPI in 2010 (NIHE, 2013). Abooster dose of Quinvaxem® helps reach two goals stipulated by the national EPI: Hib vaccination coverage >90% and a hepatitis B infection rate in <2% of children under 5 years of age (NIHE, 2013).

The tolerability of Quinvaxem® in the present study was good, as seen by the rate of solicited local and systemic events. Incidences of local post-injection adverse events included swelling in 5.6%, redness in 2.8%, and pain in 4.1% of subjects. These rates are within or below the ranges observed in previous studies of up to 41.1% for swelling, up to 27.6% for redness, and up to 77.3% for pain (Huu *et al*, 2011; Schmid *etal*, 2012). Thirty-seven point seven percent of subjects experienced at least one solicited systemic adverse event. Mild fever (axillary temperature ≥38.0ºC) was reported by15.8% and high fever (≥39ºC) by 2.6% of subjects. No incidence of very high fever (axillary temperature ≥40.0ºC) was reported. Irritability, diarrhea, and loss of appetite were observed in 7.9%, 3.0%, and 2.6% of subjects, respectively. Other solicited systemic adverse events (rash, vomiting, persistent crying, and drowsiness/sleepiness) were observed in ≤0.5% of all doses given. Most solicited adverse events were of mild to moderate severity. A total of 11 serious adverse events were reported in 9 subjects, all of them were assessed as unrelated to vaccination. No subject discontinued the vaccine regimen because of an adverse event. The safety results of this study are in line with previously published studies of Quinvaxem® (Kanra *et al*, 2006; Suarez *et al*, 2010; Gen-

tile *et al*, 2011; Huu *et al*, 2011; Aspinall *et al*, 2012; Schmid *et al*, 2012). Furthermore, a comparison with data published by the WHO revealed lower incidence rates of solicited adverse events for Quinvaxem® than other DTwP, HepB, and Hib vaccines (WHO, 2001).

In summary, the combined DTwP-HepB-Hib vaccine Quinvaxem® was found to be immunogenic for all antigens when administered to infants in Vietnam at 2, 3 and 4 months. The safety data confirm the favorable tolerability profile seen in earlier trials. Quinvaxem® met the criteria for inclusion in the Vietnamese national vaccination program.

ACKNOWLEDGEMENTS

The authors would like to thank the Ho Chi Minh City Pasteur Institute, the Long An Provincial Preventive Medicine Center, the Preventive Health Care Center of Ben Luc District, Long An Province, the Hospital of Ben Luc District, and the participating commune health stations of Ben Luc District. The authors also thank Dr Sonja Basta for writing the manuscript (funded by Crucell Switzerland AG). Funding for this study was provided by Berna Biotech Korea Corporation (South Korea; a Crucell company).

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