SAFETY OF A CRM_{197}-CONJUGATED HAEMOPHILUS INFLUENZAE TYPE B VACCINE IN KOREAN CHILDREN

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Abstract. *Haemophilus influenzae* type b (Hib) is a major cause of meningitis and pneumonia with high morbidity and mortality rates in young children. The introduction of effective and well-tolerated conjugate Hib vaccines, has nearly eradicated this disease in many countries. We investigated the safety of the Hib PRP-CRM_{197} vaccine in a multi-center post-marketing surveillance (PMS) study. Korean children (*N*=764) aged 1–33 months were enrolled when receiving a routine primary immunization or a booster vaccine with Hib PRP-CRM_{197} and solicited and unsolicited adverse events (AEs) were recorded using a diary card for 7 and 28 days after each vaccination, respectively. In this study, AEs were reported by 66% of subjects but were generally mild, with 42% of subjects reporting solicited AEs and 46% reporting unsolicited AEs. Among the unsolicited AEs, 98% were determined to be unrelated to the study vaccine. The studied Hib PRP-CRM_{197} vaccine was well tolerated by the study group and found to have a similar safety profile to that reported in other clinical studies. This vaccine is suitable for routine immunization against Hib disease among Korean children. AEs due to this vaccine will continue to be monitored.

Keywords: post-marketing surveillance, Haemophilus influenzae type b, vaccine, PRP-CRM_{197}, Korea

INTRODUCTION

Haemophilus influenzae type b (Hib) is an encapsulated, gram-negative coccobacillus and a leading cause of serious invasive disease in children under age five years (WHO, 2006). Bacterial meningitis and pneumonia are its most frequent manifestations, but it can also cause infections in other parts of the body (Watt *et al*, 2009). Annually, Hib infections cause an estimated three million cases of meningitis and severe pneumonia worldwide, along with approximately 386,000 deaths (WHO, 2006), primarily in resource-poor countries. The only option for preventing disease is through vaccination (WHO, 2006). With the advent of highly effective

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and well-tolerated conjugate Hib vaccines more than 20 years ago, invasive Hib diseases have been virtually eliminated in both developed and developing countries where they are routinely used (Murphy *et al*, 1993; Wenger, 1998; Peltola, 2000; Cowgill *et al*, 2006; Watt *et al*, 2009).

In Korea, there is no nationwide surveillance of Hib meningitis. One retrospective epidemiology study found Hib meningitis cases during 2001-2005 decreased by one third from1996 and 2000 (Cho *et al*, 2010). This decrease in Hib-related bacterial meningitis is thought to be due to the introduction of Hib vaccines in Korea during the 1990s, leading to to wide-scale anti-Hib immunization.

The World Health Organization (WHO) recommended the inclusion of a conjugate Hib vaccine in the routine immunization program for infants in 2006 (WHO, 2006). Hib vaccines were added to the National Immunization Program (NIP) in Korea in 2013. Prior to this, Korea already had a Hib vaccine coverage rate of 85.4% for the primary series and 61.6% for the booster series (Choe *et al*, 2013). It is expected the vaccine coverage for Hib is even higher since being added to the Korean NIP.

The Hib PRP-CRM_{197} vaccine (Vaxem®Hib; Novartis Vaccines) is a monovalent vaccine that contains the Hib oligosaccharide, conjugated with the mutant diphtheria toxoid CRM_{197} protein. It was first licensed for pediatric use in Italy in 1995 and has since been repeatedly shown to be highly immunogenic and well-tolerated in Phase II, III and IV clinical trials (Kanra *et al*, 1999, 2003; Matjila *et al*, 2004; Pancharoen *et al*, 2004; Jun *et al*, 2013; Zhao *et al*, 2013). The Hib PRP-CRM_{197} is one of several Hib vaccines licensed in Korea since 2009.

The current Hib immunization schedule recommended for Korea is a primary series given at 2, 4, and 6 months, and a booster given at 16-20 months of age (Lee *et al*, 2010). Studies from many countries have shown Hib vaccines to be immunogenic and well-tolerated (Matjila *et al*, 2004; Kim *et al*, 2012; Chen *et al*, 2013; Jun *et al*, 2013; Zhao *et al*, 2013). Since similar methods were used for safety data collection among these reports, data can be compared across these studies. The methods used in Korean PMS studies differ by manufacturer; therefore, it is not possible to make similar comparisons. The aim of this PMS study among Korean children was thus to obtain safety data about the Hib PRP-CRM_{197} vaccine using a comparable method (diary cards) to that used in the above-mentioned Phase II-IV studies. These findings should help provide a better understanding of Hib vaccine safety in clinical practice. This will lead to accurate product-related information, which can guide appropriate vaccination strategy decisions by health care providers and policy makers in Korea.

MATERIALS AND METHODS

Study design

This multi-center, post-marketing surveillance (PMS) study (NCT01404962) was conducted at 23 clinical sites in Korea between March 2009 and October 2012. The study was conducted according to the Declaration of Helsinki and principles of Good Clinical Practice, with applicable local regulatory requirements. Written informed consent was obtained by parents/legal guardians of the children prior to enrollment in the study. The primary objective was to assess the safety and reactogenicity of the Hib PRP-CRM_{197} vaccine in Korean children, by evalua-

tion of solicited, unsolicited and serious adverse events (AEs). Ethical approval was obtained at each clinical site.

Subjects

A total of 764 male and female children aged two months to five years who were to receive one, two or three vaccinations (primary series), or one booster of the studied vaccine were included in this study. Children were enrolled at any point during the vaccination series, including those who had already started the primary series or who were due to receive the booster vaccine. Each subject was enrolled in the study and followed for at least one vaccination without any obligation to receive other vaccinations during the study. Subjects were followed for 28 days after each vaccination for a maximum of 5 months.

Hib PRP-CRM_{197} vaccine

Hib vaccination was administered according to the manufacturer's recommendations at the time periods specified for Korea (age 2, 4 and 6 months). The booster vaccine was given to children aged 16-20 months.

Each 0.5 ml dose of Hib PRP-CRM_{197} vaccine (Vaxem®Hib, Novartis Vaccines) contained 10 μg of Hib capsular oligosaccharide conjugated to approximately 25 μg of the non-toxic mutant diphtheria toxoid (CRM_{197}) and 1.36 mg of aluminum phosphate adjuvant. The vaccine was supplied in a pre-filled single dose and administered intramuscularly (IM) to subjects following routine standards of care.

Safety assessment

After obtaining informed consent, the child was given the vaccine and observed for 30 minutes post-injection for AEs.

The parents/guardians were asked to record any reactions and body temperature daily on a diary card for seven days following vaccination. They were also asked to record any other symptoms, and any medication use for 28 days post-vaccination. The diary cards were collected at a subsequent follow-up visit or by mail. Solicited local reactions included tenderness, erythema, and induration. Solicited systemic reactions included irritability, persistent crying, changes in eating habits, vomiting and diarrhea. Serious adverse events (SAEs) were collected throughout the entire study period. All AEs and SAEs were classed by the investigator as mild (no limitation of normal activity), moderate (some limitation of normal activity) or severe (unable to perform normal activity), and as unrelated, possibly related or probably related to the study vaccine. Solicited AEs and all AEs in which a causal relationship with the study vaccine could not be ruled out were considered adverse drug reactions (ADRs). No clinical laboratory or serology testing was performed in this study. The AEs were recorded per study subject rather than per time of vaccination to prevent over reporting of an AE in the same individual for two different vaccinations.

RESULTS

Subjects

Of the 764 enrolled subjects, 368 (48%) were male. The mean age of the subjects was 5.3 ± 4.6 months (range 1-33 months). Seventy two percent of subjects (n=547) were aged less than six months, 16% (n=121) were aged 6-12 months, and 13% (n=96) were aged ≥13 months. The mean body weight of subjects was 7.4 ± 1.8 kg (range 4.2-16.0 kg) and the mean height was 65.2 ± 7.5 cm (range 50-97.5 cm). Seven hundred sixty-two subjects (99.7%) were Korean and the remaining 0.3% (n=2)

Table 1
Subject demographics.

	Total *N*=764
Gender	
Male	368
Female	396
Ethnic origin	
Korean	762
Other	2
Age (months)	
Mean ± SD	5.3 ± 4.6
Median	3.5
< 6 Months	547 (71.6%)
6 Months-12 Months	121 (15.8%)
≥ 13 Months	96 (12.6%)
Weight	
Mean ± SD	7.4 ± 1.8
Min-Max	4.2 - 16
Height	
Mean ± SD	65.2 ± 7.5
Min-Max	50 - 97.5
Number of Hib vaccinations received during the study	
One	472 (61.8%)
Two	183 (24.0%)
Three	109 (14.2%)

N, number; SD, standard deviation; Min, minimum; Max, maximum.

had one Korean parent (Table 1).

Hib PRP-CRM$_{197}$ administration

Among the enrolled subjects, 62% (*n*=472) were vaccinated once, 24% (*n*=183) were vaccinated twice, and 14% (*n*=109) were vaccinated three times during the study period, following standard clinical practice. Analysis of vaccination sites (for up to three vaccinations per subject) revealed that 62% of subjects (*n*=721) received vaccination in the left thigh, 31% of subjects (*n*=364) received vaccination in the right thigh, and 7% of subjects (*n*=80) received vaccination in the left or right deltoid.

Safety cohort analysis

Only subjects who completed the protocol were assessed for safety. Ninety-seven percent of 764 participating subjects (*N*=743) completed the study protocol; 3% (*n*=21) were lost to follow-up. Of the 743 subjects who completed the protocol, three were excluded due to violation of inclusion/exclusion criteria. The remaining 740 subjects were included in the safety analyses.

Adverse events

During the course of this PMS study, 1,457 solicited and unsolicited AEs were reported in 491 subjects (66%). Of these, 720 were solicited AEs in 309 subjects (41.8%). Local solicited AEs were reported in 152 subjects (20.5%), and systemic solicited AEs were reported in 248 subjects (33.5%; Table 2). Tenderness was the most commonly reported local AE (14.5%), and irritability the most commonly reported systemic reaction (29%). All solicited AEs were considered to be ADRs.

A total of 737 unsolicited AEs were reported in 340 subjects (46%). Among these, seven cases of pyrexia (1%), three cases of injection site induration (0.4%), two cases of erythema (0.3%) and one case of rhinorrhea were considered to be possibly or probably related to the study vaccine. Table 3 summarizes the unsolicited AEs and ADRs (reported by >1% of subjects). The majority of unsolicited AEs were mild (91%; *n*=647), 8% (*n*=61) were moderate, and less than 1% (*n*=3) were severe. Complete recovery occurred in nearly all AEs (99%; *n*=727); 1% of unsolicited AEs (*n*=10) persisted until the end of the study period. Unsolicited AEs were determined to be unrelated to the study vaccine in 98% of cases (*n*=724). Two cases of erythema, five cases of pyrexia, and one case of injection site induration (*n*=8,

Table 2
Number of subjects experiencing ADRs and number of ADRs.

	Adverse drug reactions	
	No. of subjects experiencing ADRs (%)	No. of ADRs
Solicited adverse events[a]		
Local reactions	152 (20.5)	202
Tenderness	107 (14.5)	107
Erythema	55 (7.4)	55
Induration	40 (5.4)	40
Systemic reactions	248 (33.5)	518
Irritability	215 (29.0)	215
Persistent Crying	125 (16.9)	125
Change in Eating	86 (11.6)	86
Vomiting	49 (6.6)	49
Diarrhea	43 (5.8)	43
Total	309 (41.8)	720

[a]All solicited adverse events were considered ADRs (in accordance with Korean regulations).

1%) were considered possibly related to the studied vaccine. Five AEs (<1%) were considered probably related to the studied vaccine: one case of rhinorrhea, two cases of pyrexia, and two cases of injection site induration. There were no changes to the vaccination schedule in any subject due to AEs.

Seven SAEs occurred in six subjects (<1%): one case each of upper respiratory tract infection, bronchiolitis, tonsillitis, urinary tract infection, pneumonia, asthma, and pyrexia (Table 4). In all cases, subjects recovered without sequelae and none of the SAEs were considered related to the studied vaccine.

DISCUSSION

Out of 740 subjects analyzed in this PMS study, two-thirds reported solicited and/or unsolicited AEs following the administration of Hib PRP-CRM_{197} vaccine. A total of 720 solicited AEs (in 309 subjects; 41.8%) were considered ADRs, with tenderness, irritability and persistent crying the most commonly reported ADRs. Nearly all of the unsolicited AEs were mild and considered unrelated to the study vaccine. The findings from this study have now been updated in the Vaxem-Hib prescribing information for Korea, as required by Korean regulations (Pharmaceutical Affairs Act, 2011).

In the present investigation, a detailed diary card was implemented to collect solicited and unsolicited local and systemic AEs. While it is not possible to directly compare the present results to those of previous Hib PRP-CRM_{197} vaccine clinical studies due to differences in study populations, vaccination schedules/numbers, and different concomitant vaccines, the high rate of solicited AEs reported in this study (41.8%) is consistent with rates reported in other studies using diary cards for AE collection (Kanra *et al*, 2003; Jun *et al*, 2013; Zhao *et al,* 2013). Since the solicited

Table 3
Number of unsolicited adverse events (AEs) and adverse drug reaction (ARDs) reported by subjects (≥1%).

	Adverse events		Adverse drug reactions	
	No. of subjects experiencing unsolicited AEs (%)	No. of AEs	No. of subjects experiencing unsolicited ADRs (%)	No. of ADRs
Unsolicited adverse events				
Rhinorrhea	117 (15.8)	142	1 (0.14)	1
Cough	112 (15.1)	127	0 (0.0)	0
Pyrexia	61 (8.2)	67	7 (1.0)	7
Bronchitis	40 (5.4)	45	0 (0.0)	0
Nasopharyngitis	36 (4.9)	40	0 (0.0)	0
Upper respiratory tract infection	24 (3.2)	26	0 (0.0)	0
Diarrhea	22 (2.0)	23	0 (0.0)	0
Gastroenteritis	18 (2.4)	21	0 (0.0)	0
Otitis media	18 (2.4)	18	0 (0.0)	0
Rash	17 (2.3)	17	0 (0.0)	0
Bronchiolitis	13 (1.8)	14	0 (0.0)	0
Pharyngitis	13 (1.8)	13	0 (0.0)	0
Rhinitis	13 (1.8)	13	0 (0.0)	0
Productive cough	13 (1.8)	13	0 (0.0)	0
Dermatitis	12 (1.6)	12	0 (0.0)	0
Vomiting	10 (1.3)	11	0 (0.0)	0
Conjunctivitis	10 (1.3)	10	0 (0.0)	0
Urticaria	10 (1.3)	10	0 (0.0)	0
Nasal obstruction	9 (1.2)	9	0 (0.0)	0
Dermatitis diaper	8 (1.1)	8	0 (0.0)	0
Eczema	8 (1.1)	8	0 (0.0)	0
Total	340 (46.0)	647	8 (0.01)	8

AEs recorded in these studies are similar, broad comparisons can be made in regard to specific AEs. For example, in contrast to the current study, erythema was the most commonly reported solicited local AE in previous studies (Kanra *et al*, 2003; Jun *et al*, 2013). While irritability was the most frequent systemic solicited AE in both this and a previous study employing a similar vaccination schedule (2, 4 and 6 months; Kanra *et al*, 2003), fever was the most common systemic AE reported from other studies (Jun *et al*, 2013; Zhao *et al*, 2013).

The overall rate of AEs reported in both this and previously mentioned studies was higher than that reported for Korea's domestic Hib vaccine (MFDS, 2013). The different methods used for data collection may be the reason for this discrepancy. Support for this explanation comes from a study by Hatz *et al* (2011), who found the rate of AEs reported by subjects using an unsolicited self-reporting approach was lower than that using a solicited self-reporting approach (Hatz *et al*, 2011). Safety results could differ

Table 4
Serious adverse events (SAEs).

Serious adverse event	No. of subjects experiencing SAEs (%)	Severity	Schedule change	Outcome	Relationship to study vaccine
Upper respiratory tract infection	1 (0.1)	Severe	None	Full recovery	Not related
Bronchiolitis	1 (0.1)	Moderate	None	Full recovery	Not related
Tonsillitis	1 (0.1)	Moderate	None	Full recovery	Not related
Urinary tract infection	1 (0.1)	Severe	None	Full recovery	Not related
Pneumonia	1 (0.1)	Moderate	None	Full recovery	Not related
Asthma	1 (0.1)	Moderate	None	Full recovery	Not related
Pyrexia	1 (0.1)	Severe	None	Full recovery	Not related

significantly, even for the same vaccine, depending on the AE collection method used (*eg*, solicited *vs* unsolicited/open questioning; Hatz *et al*, 2011). In a Korean PMS study of a hepatitis A vaccine, subjects who did not return their diary card but were interviewed retrospectively by telephone reported fewer solicited and unsolicited symptoms than those who returned their diary cards (Choi *et al*, 2008). Unsolicited questioning and/or retrospective collection of AEs without using a diary card may risk under-reporting AEs. This could explain the large differences in AE rates reported from Korea. There are large differences in AE rates between companies and within the same vaccine category (*eg*, 1.4% to 39.4% for hepatitis A vaccines, 1.2% to 42.2% for inactivated influenza vaccines; Crucell, 2013a,b; GlaxoSmithKline, 2013; Sanofi Pasteur, 2013a,b; SK Life Sciences, 2014). Although further research is needed to confirm this theory, these findings suggest the rates of AEs reported for vaccines may be less dependent on a vaccine's intrinsic characteristics and more dependent on the study safety collection method.

PMS are a main component of the re-examination system for new drugs in Korea, and is required for a new drug or vaccine to retain its license in Korea (Choi and Park, 2007). Results from PMS are then included in the prescribing information for the drug/vaccine. Considering the influence that such safety information has on the public and on decision makers, a more transparent, standardized and valid strategy needs to be used for PMS for Korea. Because vaccines are typically administered to healthy individuals and because national immunization programs are conducted on a large scale, proper safety monitoring of vaccines is essential not only for public health, but also for development of optimal vaccination strategies (Tozzi, 2004). Given the perception of AEs is important for implementing a vaccination program (Lopalco *et al*, 2010), having a valid, consistent method of AE collection is important for monitoring vaccine safety.

Some regulations for PMS in Korea are in place (*ie*, number of subjects required for re-examination reports and the minimum study period), but there are no guidelines for comprehensive, reproducible data collection (MFDS, 2009).

The PMS for Korea has historically been considered as merely a requirement for maintaining a license or for commercial use rather than for genuine safety surveillance of new drugs and vaccines (Choi and Park, 2007). Diary cards are not routinely used, which can lead to under-estimation of AEs, as mentioned previously. In the USA and European Union, vaccine safety monitoring and research is considered a key component to the success of any public health program (Bonhoeffer *et al*, 2012). As a result, these countries provide scientific advice about the methodology and development of a scientific framework for vaccine safety monitoring at the national level. Korean regulatory agencies should place a similar emphasis on enforcing comprehensive vaccine safety monitoring and on encouraging sponsors to apply more scientific and meticulous methods for PMS of vaccine safety.

In summary, the present PMS study found the Hib PRP-CRM_{197} vaccine has a good safety profile and is well tolerated by Korean infants and children. It is also the first study to examine the safety of the Hib PRP-CRM_{197} vaccine in a large Korean pediatric population. Since the study was conducted under routine conditions, there were limitations. The subjects did not necessarily visit the same site for successive vaccinations, so the reactivity following sequential doses could not be compared, nor could the number of vaccinations be correlated with the severity of AEs. Likewise, the time period between vaccinations varied among subjects depending on when an infant entered the trial. For example, the interval for infants receiving a first and second dose might be different from infants receiving a third and booster dose. Therefore, it is inappropriate to correlate reactions to the number of doses received. Finally, we could not obtain information about the subjects' reactions to previous vaccinations; therefore, we are unable to determine whether infants with a disproportionately high or low number of AEs were included in the study. Since the method of safety data collection was similar to other clinical studies, which found similar safety results, our findings suggest that the Hib PRP-CRM_{197} vaccine has a good safety profile. The use of a valid standardized method for conducting Korean regulatory PMS studies is important for interpreting results and for meaningful safety evaluation. The method used in the present study is comprehensive, reproducible and is a useful tool for evaluating PMS safety data for vaccines in Korea.

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Conflicts of interest

HYS, HB, AG, MC, and FB were all full time employees of Novartis group companies at the time of the study. HB, AG and MC are currently employees of GlaxoSmithKline group companies. HYS is currently a researcher at Seoul St Mary's Hospital, The Catholic University of Korea. FB is currently an employee of Takeda Pharmaceuticals International GmbH. YHK, SIA, KHS, DSY have no conflicts of interest to disclose.

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