



KOMITE PENASIHAT AHLI IMUNISASI NASIONAL (Indonesian Technical Advisory Group on Immunization)

DECREE No. 904/MENKES/SK/VII/2010

SECRETARIAT : JL. PERCETAKAN NEGARA 29 JAKARTA PUSAT

TLP/FAX. 424-9024 – 425-7044

Evaluation of Hib (*Haemophilus influenzae type b*) vaccine into Pentavalent (DTP/HB/Hib) Vaccine for a national immunization program

Based upon Indonesian Technical Advisory Group on immunization (ITAGI) first meeting on the 7th of June 2007 in Jakarta, that was also attended by foreign experts, Philip Douclos (*WHO-HQ, Department of Immunization, Vaccine and Biologicals/IVB*); Dr. Kim Muholland (*Hib Adip/John Hopkin University of Public Health*); Dr. Brad Gessner (*AMP/Association pour l'Aide a la Medicine Preventive*), it was recommended to include Hib vaccine in Indonesian primary immunization program.

In the next meeting on the 10th of November 2008, it was recommended that the Hib vaccine that will be incorporated in national immunization program would be a nationally made. For the cost efficiency, time and storage it was also recommended to use a liquid form of Hib combined with DTP/HB.

In reference to letter from the Director of Immunization and Quarantine No T.U.04.02/II.5/382/2010 dated 23 February 2010, regarding Hib vaccine recommendation, ITAGI conducted an Hib vaccine evaluation during its meeting on the 4 March 2010. The meeting was also attended by Supporting Independent Immunization and Vaccine Advisory Committees (SIVAC) team, Representative of WHO-EPI Indonesia, ITAGI Team, Bio Farma, National Institute of Health Research and Development (Badan Lit Bang Kes), Sub Dir Immunization and Sub Dir URTI.

Regarding the dosage of dosis Hepatitis B antigen in the combination vaccine of DTP/HB/Hib it will be referred to Hepatitis Virus Working Group No. 04/H-V/III/2010 dated 24 March 2010. In that letter it was mentioned to use International standard, with Hepatitis B dosage of 10 µg /dose, since this will result in higher and longer lasting protective titer compared to dosage of 5 µg that is currently being utilized at present.

Results of scientific reference evaluation,

1. Epidemiology studies

- Indonesian mortality rate for below 5 years is 44/1000 live birth, highest among ASEAN countries. Major cause of deaths among children below 5 years of age: pneumonia is the leading cause for infants (22,3%) and also for children below 15 years of age (23,6%). From the World Health Organization's, Child Health Epidemiology, Reference Group - CHERG data, it is mentioned that approximately 60% of new cases of pneumonia are located in six countries that are India, China, Pakistan, Bangladesh, Nigeria, and Indonesia^{1,2}.
- National Basic Health Research data from 2007 showed that the incidence of pneumonia among infants age 29 days to 11 months is 24% and meningitis 9%, while incidence of pneumonia among children below 5 years of age is 15,5% and for meningitis/encephalitis it is 8,8%¹.
- Slightly less than 23% of serious pneumonia among children are caused by *Haemophilus influenzae type b*, and the rest are due to Pneumococcus, Staphylococcus, Streptococcus and Viruses.³
- *Haemophilus influenzae* can cause serious and fatal infection such as meningitis and pneumonia. CDC in 2000 reported Hib can cause meningitis (50%), epiglottitis (17%), pneumonia (15%), arthritis (8%), cellulitis (6%), osteomyelitis (2%) and bacteremia (2%)⁴.
- Prospective hospital-based studies among children (1 bulan – 5 tahun) found that *Streptococcus pneumoniae* (pneumococcus) is the etiologic agent for 30%-50% of all new pneumonia cases among children below 5 years of age, followed by *Haemophilus influenzae type b* with rate of 10%-30%⁵.



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2. Studies of Hib disease burden

2.a. Incidence

- Prior to Hib vaccination era, globally *Haemophilus influenzae* type b cause serious illness among 3 million children below age of 5, and cause $\geq 400,000$ deaths (WHO Estimation), thus it was the leading cause of mortality^{6,7}.
- Tri Ruspanji and his colleagues in 1981⁸ conducted a 2 years study at Dr Cipto Mangunkusumo Hospital (RSCM), Jakarta, managed to obtain 155 positive of cerebrospinal fluid cultures from 208 meningitis cases with age 2 days – 12 years, and the isolation rate was: *S. pneumoniae* 5,8 % and Hib 5,2 % with mortality of 44,4% and 25%, respectively.
- Hardiono D.Puspongoro and Hanifah Oswari in 1998⁹ reported 11 cases of meningitis at RSCM, Jakarta and Tangerang general Hospital, 6 cases showed positive cerebrospinal fluid cultures, 2 were Hib(33,3%), 1 Klebsiella, 1 Staphylococcus, 1 *Neisseria meningitides*, and 1 E. coli.
- Komang Kari and his colleagues at Sanglah Hospital in Denpasar, Bali in 2006¹⁰ reported that between 2000-2005 the highest incidence of Hib from 108 cases of meningitis was among children below two years of age. Post illness sequelae were hydrocephalus 28%, paresis 20%, deafness 20%, and epilepsy 20%.

2.b. Studies regarding Hib vaccination toward of Hib

- Mulholland, E.Kim, Adegbola, R A. in 1998¹¹ reported results clinical evaluation of Hib conjugated vaccine among infants in Gambia, and mentioned that Hib vaccination prevented severe pneumonia in 21%. This proved that *Haemophilus influenzae* type b bacteria is one of the etiologic agent of severe pneumonia.
- Indonesian NIHRD (*Badan Litbangkes*), PATH (Programme Appropriate Technology in Health) and AMP (*Association pour l'Aide a la Medicine Preventive*, a French NGO) in Lombok from 1998 through 2002 in their pilot project: The proportion of radiologically-confirmed and other pneumonias due to *Haemophilus influenzae* type B in Lombok Island, Indonesia, Using *Haemophilus influenzae* type b conjugate vaccine as probe, found that^{12,13}
 - A very high incidence of pneumonia and meningitis among children less than 2 years of age in Lombok. Incidence estimate of pneumonia among children <2 years was 30.430 per 100.000 children/year. Incidence estimate of clinical meningitis among children <2 years of age is 692 per 100.000 children/year.
 - Proportion of clinical meningitis due to Hib quite high, (22%).
 - Hib Vaccine was effective to provide protection against Hib meningitis, that was confirmed through laboratory examination with vaccine efficacy of 86%
 - The beneficial effect of Hib vaccine was reduction of absolute pneumonia incidence to 894 per 100.000 people/year
 - Data of serious VAERS (vaccine adverse event reporting system) among 50.000 infants that were immunized and audited by DSMB (Data Safety Monitoring Board) showed no causal correlation with the immunization.
- Suganda Tanuwidjaja and his co-workers, in 2004¹⁴ compared immunogenicity and safety of DPT/Hib vaccine (Tetract Hib[®] Sanofi Pasteur) with DTP vaccine (generic[®] Sanofi Pasteur)+Hib (ActHib) and DTP (generic Bio Farma) + Hib (ActHib) with immunization schedule of 2,3, and 4 months. The results showed that all study subjects had immunogenicity of anti-PRP $\geq 0.15\text{mcg/mL}$, and 99.2% study subjects had titer anti-PRP $\geq 1\text{mcg/mL}$. Response toward pertussis, diphtheri and tetanus was very good among all groups. Almost all vaccine reactions



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was observed in first three days post injection, there was only one serious case of VAERS but there no causal relation with the vaccination.

- Punjabi NH and his colleagues in 2006¹⁵ studied 1048 Indonesian infants regarding immunogenicity and safety of four different doses of *Haemophilus influenzae* type b-tetanus toxoid conjugated vaccine, combined with diphtheria-tetanus-pertussis vaccine (DTP-Hib), in Jakarta. There was no difference of antibody Hib-PRP titer between Hib dosages of 10 µg, 5 µg, 2.5 µg and 1.25 µg PRP-T. Most reported side effects were irritability and fever.
- Clinical evaluation of pentavalent DPwT/HepB/Hib produced by PT Bio Farma will be conducted after completion

3. Cost benefit analysis

- Health economic study showed that *Haemophilus influenzae* type b immunization inclusion in the national immunization program can significantly reduce morbidity and mortality in Indonesia, thus it is a cost-effective intervention¹⁶.
- A pentavalent (DPT/HB/Hib) is more cost-effective compared to a monovalent vaccine¹⁷.

4. Hib vaccine utilization is based upon

- 2006 WHO position paper on Hib conjugate vaccine recommendation mentioned that Hib conjugate vaccine is safe and has a good efficacy, thus it can be included in the national immunization program¹⁸.
- More than 108 countries already integrated Hib immunization in their national immunization program (EPI), including 75 countries that were eligible countries that receive GAVI (Global alliance vaccine and immunization)'s support in the their process of Hib vaccine introduction¹⁹
- SAGE (Strategic Advisory Group of Experts on Immunization) recommended that Hib vaccine to be combined with DPT/HB as a pentavalent vaccine (DPT/HB/Hib) to reduce number of injections given to the infants.

5. Preparation

a. Vaccine supply

- Bio Farma is able to produce a pentavalent DPT/HB/Hib liquid vaccine with hepatitis B antigen dosage of 10 µg as per International Standard
- The pentavalent DPT/HB/Hib vaccine registration and licensure to Indonesian FDA (BPOM) will be carried as soon as clinical evaluation completed.
- Bio Farma has agreed to produce sufficient amount of pentavalent DPT/HB/Hib vaccines necessary for the national immunization program.

b. Preparation vaccination implementation

- Advocating importance of Hib vaccine inclusion in national immunization program to decision makers.
- Step by step socialization in various sectors and programs all the way to the health care workers regarding utilization of pentavalent vaccine for national immunization program.

c. Program evaluation

- PMS (post marketing surveillance) must be carried out after utilization of the vaccine in the national immunization program.
- Hib infection surveillance (for pneumonia and meningitis cases) should be intensified to evaluate Hib vaccine effectivity in the pentavalent vaccine.
- To increase NIHRD (Litbangkes) as well other laboratorium capability to isolate Hib bacteria.



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5. Preparation

d. Vaccine supply

- Bio Farma has the capability to produce the liquid form of pentavalent DPT/HB/Hib vaccine with hepatitis B antigen dose of 10 µg as per international Standard
- The pentavalent DPT/HB/Hib vaccine registration to Indonesia FDA (BPOM) will be conducted right after completion of its clinical trial completed
- Bio Farma has agreed to produce sufficient amount of pentavalent DPT/HB/Hib vaccine as per national immunization program requirement.

e. Preparation for vaccination implementation

- Advocating importance of Hib vaccine inclusion in the national immunization program to the decision makers.
- Step wise familiarization and socialization of pentavalent vaccine to various sectors and programs all the way to health care workers in the national immunization.

f. Program evaluation

- PMS (*post marketing surveillance*) must be carried out after the pentavalent vaccine utilization in the national immunization program.
- Increase Hib infection surveillance (pneumonia and meningitis cases) to evaluate to evaluate affectivity of Hib vaccine in the pentavalent vaccine.
- Continue to improve NIHRD (Litbangkes) laboratorium, as well other laboratories capability in Hib bacteria isolation.

6. Recommendation regarding pentavalent DPT/HB/Hib vaccine schedule of administration:

AGE (months)	VACCINE
0	HB-0*, Polio-1, BCG
2	DPT/HB/Hib**-1, Polio-2
3	DPT/HB/Hib-2, Polio-3
4	DPT/HB/Hib-3, Polio-4
9	Measles

Keterangan: * HB-0: adminiminister as HB Uniject,

** DPT/HB/Hib: Vaksin Pentavalent combination of DPT, Hepatitis B and Hib

7. VAERS monitoring in the surveillance system

Active and passive monitoring and evaluation will be conducted in step wise fashion according to the integration schedule, by Dir Gen of PP& PI cq Sub Dir of Immunization, FDA (BPOM) and Bio Farma. If there is any serious VAERS (required hospitalization, death, disability, or cause rumors) an audit will be conducted, with VAERS National Committee or Local Committee.

8. Activities to be carried out during the period of Hib vaccine integration in the national immunization program:

- To improve surveillance for pneumonia and meningitis cases due to Hib (laboratory based surveillance).
- Improve case referral to hospital.
- Improve readiness and diagnostic capability of through laboratory, radiologic, and clinical examination.
- Improve case management.



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Conclusion

Hib vaccine Integration into the national immunization program will reduce morbidity, mortality and disability due to pneumonia and meningitis caused by Hib. Hib vaccine administration to the infants will fasten *Millennium Development Goal 4* achievement.

Jakarta, 04 June 2010

Chairman of Indonesian Technical Advisory Group on immunization

Signature

Prof. Dr. Sri Rezeki S Hadinegoro, dr., Sp.A(K)

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