Minutes of the Expert group meetings on Hepatitis B and Hib vaccines

Secretary (DHR) and DG (ICMR) had constituted an Expert Group on Hepatitis B and Hib vaccine. Three meetings of the Expert Group were held on 18th Jan, 16th Feb and 24th March 2010. The list of participants in each of the meetings is in Annexure 1.

The objectives of the meetings were to examine the following issues:

1. Hepatitis B spreads through both horizontal and vertical transmission. Whether there are other strategies available to identify key target groups to be given Hep.B vaccines rather than introducing for universal application even among low risk and no risk children
2. There is a proposal to introduce pentavalent vaccine that includes DPT, Hep.B and Hib. Is there adequate evidence about public health importance of Hib in the country? If so, is there a need for pentavalent vaccine?

Hepatitis B

There were two main view points:

View point I:

- Introduction of vaccines involves issues related to disease surveillance, pathogen variation in countries/populations; incidence levels of each disease that qualifies for mass vaccination; efficacy, safety and affordability of the vaccine in target population; rigorous cost-benefit analysis for each new vaccine, choice between indigenous development and/or procurement of vaccines; the role of public vs. private sector in vaccine R&D and production; choice of technologies, their access and affordability; individual vs. cocktail/multivalent combinations, choice

of selective vs. universal vaccination; national priorities vs. international obligations; personnel, logistics and resource mobilization

- There are very few studies and no conclusive evidence on actual prevalence of Hepatitis B. Meta-analysis of small studies in India estimates prevalence at 2.1% and carrier rate at 1.7%. According to ORGI (1991), jaundice was 1% of all cause death, deaths due to chronic liver cancer was 0.76% including both Hepatitis B&C. Therefore, Hepatitis B &C would be a relatively low priority disease for mass vaccination. US FDA licensed Hepatitis B vaccine while pending safety studies. Indian pilot studies did not generate data on the safety and efficacy of Hepatitis B in India.
- The carrier rate in a country is not important in itself, because with some strains, there is a higher chance of becoming an asymptomatic carrier and come to no harm.
- The vast majority of chronic carriers are completely asymptomatic all their lives. The analogy of H.pylori is striking. H. pylori can cause acid peptic disease and malignancy but for the vast majority, it is a commensal of little consequence. It is estimated that in some areas 90% of the population test positive for H.Pylori. Thus just because the organism is widely prevalent (90% in H. Pylori instead of 4% as in the case of Hepatitis B), and just because it can cause cancer in some - it does not mean that an effort to eradicate it from the population is imperative.
- Data is required on the numbers who develop cirrhosis and the numbers who develop Hepatocellular cancer. Data based on ICMR cancer registry shows that about 10000 persons die of HCC due to Hepatitis B every year. This figure is 25 fold less than the figure of 250000 deaths projected deaths in India by international organizations (Miller MA et al. Health Economics.2000;9:19-35). These projections used disease progression rates fro Hepatitis B for Taiwan where 1 in 4 male carriers die of the disease (Puliyel M Lancet.2004;363:659; Health Economics.2004; 13:1147; author reply 1147-8)
- A detailed review on the different strains in different countries was done by Norder et al ((Norder et al 2004. Intervirology 47; 289-309). Strains C and D have a greater chance than Strain A and B for vertical transmission, increased

duration of HBe positive status and increased progression to liver fibrosis and HCC. The modeling without reference to the local strain is an exercise in futility. The cost benefit assessment of Hepatitis B (Aggarwal R et al. J Hepatol.2003;38:215-22) too uses the Hep. B disease progression rates from Taiwan and comes up with predictions that are meaningless for India.

- Papers that justify the costs, like the consensus paper of the Indian Association for study of Liver (INASL) gives detailed costing using 250,000 as 'lives saved' (7) using 250,000 as 'lives saved'. In fact, after many errors in the calculations were pointed out (Sachdeva et al Ind J Gastroenterol 2001;20:205; Puliyel et al Ind J Gastroenterol 2002;20:251; Agarwal K. Ind J Gastroenterol 2002;21 87) the correspond Prof S K Sarin wrote that he could not defend the calculations any more and 'it would therefore be necessary for us to refer the concerns to the expert group again (Sarin SK Ind J Gastroenterol 2002;21:87). However a revised calculation has not yet to be published by the experts of INASL.
- In summary, 2-7% of the population are carriers, is by itself not sufficient reason to start universal immunization. Evidence of significant morbidity and mortality needs to be apparent. There is data on progression of Hep.B to cancer (HCC) but not that for cirrhosis. The numbers of deaths from HCC are so small that it is difficult to justify the expense of universal immunization.
- Universal immunization can be started at birth or delayed up to 6 weeks when the child comes for DPT immunization. The majority of births in India take place at home (not in health care facilities) and universal immunization for all starting within 24 hours after birth is impractical. Thus the pragmatic suggestion that universal vaccination be practiced starting from 6 weeks and a birth dose be given only to those babies born within health care facilities. It does not prevent vertical transmission from mother to child. This type of universal immunization starting at 6 weeks, after maternal to child transmission has already taken place, is akin to locking the stable after the horse has bolted. In fact an extensive search of world literature has not shown even one study where immunization starting at 6 weeks in the community has brought down carrier rate of HB (Puliyel JM, et al. Hepatitis B in India: Indian J Med Res. 2008;127:494-497).

- To support this schedule it is said that most of the transmission in India is horizontal rather than vertical. Most authors depend on reinterpretations of a study by Nayak done 25 years back. The original paper by Nayak says that 30% of their sample got infected at birth and other children are infected from this group who got the infection perinatally like in Africa and East Asian countries (Nayak et al. J Med Virology 1987 21 137-45). The question of selective immunization is not impractical (Sahni M et al. Hepatitis B immunization: Cost calculations in a community based study. Ind J Gastroenterol 2004.23 Pg.16-18). Universal testing of HBsAg status of pregnant primiparous mother any time during the 9 months of their pregnancy can be carried out and ensured that babies of the 2% HBsAg carrier mothers get vaccinated at birth. Subsequent pregnancy needs no testing.
- This argues for preventing vertical transmission as it would curtail horizontal transmission too
- Those who advocate immunization from 6 weeks say that Nayaks paper has shown that most of the transmission is horizontal rather than vertical and late vaccination will work to bring down the carrier rate. There is no study in world literature to support this. In the absence of any supporting literature that the 'pragmatic schedule' is effective in bringing down the carriage rate there is no justification to roll this out nationally in a country.
- Selective vaccination of high risk groups (medical, paramedical staff, blood donors, sex workers, soldiers) and selective vaccination of children born to Hep.B carrier mothers would be more cost effective. The first dose must be given at birth, as evidence shows that it is most effective and stops Hep.B transmission from mother to child.
- Only selective immunization of high risk groups rather than universal immunization should be recommended
- A small roll out of Hepatitis B and studies to see if the Hepatitis B carrier rate with different schedules and without vaccine and also simultaneously to collect deaths from Hepatitis B related cirrhosis are required. From this we can ascertain the need for the birth dose. If we find that the birth dose is needed, it will be

irresponsible to suggest a program where the majority gets the first dose only at six weeks.

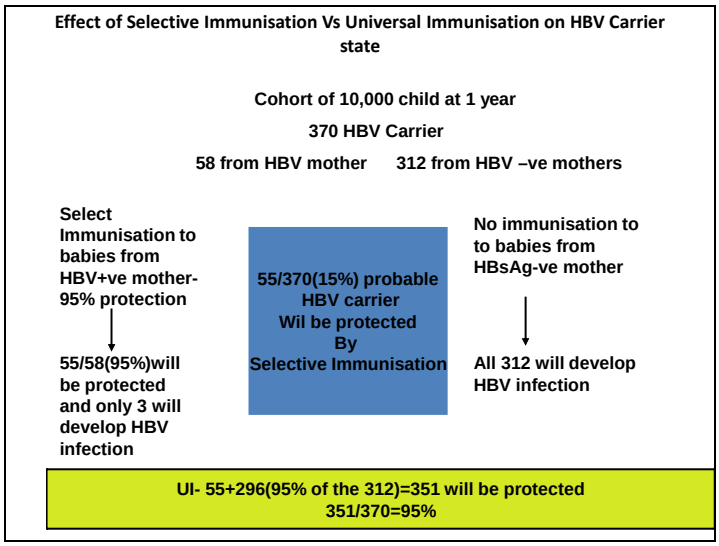
View Point II

- There is no registry for Hepatitis B in India till date. Information on incidence of hepatocellular carcinoma (HCC) is primarily derived from the ICMR Cancer Registry program. The projected cases of HCC from ICMR cancer registry in 2009 was 22238 cases. These are likely underestimates as the most common presentation of this cancer is with complications or sequelae of cirrhosis liver and thus may be missed from routine reporting of cancer from pathology, radiotherapy and radiology departments.
- A more appropriate method of assessing the disease burden of HBV related chronic liver disease and HCC should be assessed using modeling techniques based on HBV carrier frequency (reported in donor population, pregnant women, general population cohorts, high risk groups and disease burden among patients with liver disease) and by extrapolation of established natural course of the disease from HBV infected population
- Data from studies in pregnant women show that HBV carrier frequency among pregnant women is about 3%. Pregnant women are considered to be representative of the normal population, However, males often have a slightly higher frequency of HBsAg positivity than women; hence positivity rate in pregnant women is often an underestimate of HBV carrier rate in the population. In India, a study carried on HBV transmission by Nayak et al (1987) showed HBeAg positivity of 8% among pregnant women who were HBsAg positive and 92% were HBeAg negative. 87% of children born to HBeAg positive mothers and 10% of children born to HBeAg negative mothers were HBsAg positive. On the whole, 75% of HBV carrier acquires infection by horizontal spread before 5 yrs. of age and 25% presumably acquires it by vertical transmission. Thus vertical transmission in India is relatively low.

- In a meta-analysis of prevalence of Hep.B in India, the prevalence of HBV was 2.4% in non-tribal population and 15.9% in tribal population. From available published data in pregnant women and population based studies, the HBV carrier rate in India can be considered as at least 2 to 3 % indicating that about 20 to 30 million chronically infected HBV persons exist in India.
- There are 8 genotypes of HBV. The HBV genotypes prevalent in India are D in 60-70%, A -20-30% and C approximately 5% (mainly from East India).Studies have shown that D genotype is associated with a high viral load and increased perinatal transmission. However, there are some other studies which have not shown this association (Vivekanadan UG. 2008:27:142)
- There is rational evidence that the duration of the hepatitis B e-antigen (HBeAg) positive replicative phase varies for the different genotypes, being shorter for A&D which dominate in Africa, the Mediterranian region, the Middle East, and India, than for B and C which dominate in South East and East Asia. This is the reason for vertical transmission being common in the latter countries than in the former ((Norder et al 2004. Intervirology 47; 289-309). An ICMR study in tribal areas showed the prevalence of HBV to be between 1to 5% and genotype D was the predominant genotype associated with chronicity and morbidity (DHR Annual report 2009-2010 p.23-24).
- Untreated chronic HBV acquired early in life results in cirrhosis, liver failure or HCC in upto 40% of individuals**.**
- In patients with liver disease HBsAg positivity is seen in 12.5 – 21% of Acute viral hepatitis, 11-27% of acute liver failure, 40% of sub acute hepatic failure **,** 40-60% of chronic liver disease and 60-80% of hepatocellular carcinoma.
- Long term consequences of HBV infection depends on the chronicity of infection which in turn depends on the age at acquisition of infection – the younger the age at infection, the greater is the likelihood of development of chronicity.
- A study on HBV disease profile based on liver biopsy of consecutive patients who were HbsAg positive presenting to AIIMS from Jan. 2008 to June 2009,showed that 80% are silent infections. 44% of the patients were asymptomatic healthy carriers, 13% were immunotolerant, 28% were HBeAg positive chronic hepatitis

and 15% were HBeAg negative chronic hepatitis (Data from AIIMS:personal communication Dr.S.K.Acharya).

- Based on the natural course of the HBV infection and the disease profile at presentation (as given above for AIIMS) and considering an HBV carrier rate of 2% ,the annual frequency of cirrhosis will be 3 lakhs and HCC will be 21000.
- The cost of treating these patients is prohibitive. The estimated cost of treating these patients is Rs 12- 14 billion per year. At least one lakh deaths occur per year due to cirrhosis and HCC
- Besides the HBsAg positive state, a fair proportion of subjects in India have HBV DNA positive status in the absence of HBsAg positivity (occult HBV). This is truer of family contacts. In a recent study, nearly 18% of contacts were HBsAg positive and in addition about 15% were occult HBV positive
- A study on assessment of cost-effectiveness of Universal Hepatitis B immunization in India has shown universal immunization to be highly cost effective. Universal immunization reduced the HBV carrier rate by 71% and increased the number of years and QALY lived by a birth cohort by 0.173 years and 0.123 years respectively
- Rationale for Universal Immunization vs. selective immunization – Based on the evidence that HBV infection in childhood occurs by horizontal transmission in India (Nayak et al 1987), the effect of selective vs. Universal Immunization on HBV carrier state in a hypothetical cohort of 10,000 children at 1 year of age is given schematically below:



- Cost comparison of Universal Immunization vs. Selective Immunization in a cohort of 10,000 mothers and live births shows that that cost per carrier prevented is Rs. 4273 per carrier prevented and a total of 351 carriers/100,000 babies born prevented when all children all immunized vs. Rs. 4646 per carrier prevented for preventing 55 carriers/100,000 babies born when only children of pregnant women who are HBV positive are immunized.
- Selective vaccination will not prevent the disease transmission that is mostly occurring horizontally. The cost of screening followed by vaccination is greater than the cost of universal vaccination and impractical where antenatal care and hospital delivery are unassured. Thus the approach of screening followed by vaccination will not prevent a substantial part of even the vertical transmission
- The vaccine efficacy in preventing chronic carrier states for 6.10,14 weeks versus 0,1 month and 3 months was debated. There is limited data on efficacy of vaccine given in different schedules. One small study (Rashmi Ranjan Das et al, 2009.J Tropical Pediatrics 55(5): 328-331) showed that Hepatitis B vaccination by 0, 6 and 14 weeks and 6,10 and 14 weeks schedule are comparable in terms of sero-protection, sero-efficacy and geometric mean titre.

- Impact assessment studies should be part of ongoing programme. A framework for measuring impact should be made

Recommendation

- Given that available evidence suggests that the Hepatitis B prevalence in India is at least 2%, that horizontal transmission is more common and that Hep.B infection leads to serious consequences such as cirrhosis and Hepatocellular carcinoma which are extremely expensive to treat these patients, that not all deliveries take place in a hospital/health centre and so screening followed by vaccination will not prevent a substantial part of vertical transmission, and the fact that such selective screening will not prevent horizontal transmission, Universal immunization with Hepatitis B vaccine is recommended in some selected states depending on fund availability.
- This introduction in some states has to be linked with studies on impact of vaccination on carrier rate. Roll out to other states could be considered on the basis of the impact study
- A birth dose of the vaccine should given in all cases of institutional deliveries and in other areas where feasible.

Hib and pentavalent vaccine:

View Point I

- Invasive Hib disease is rare in India. In the Apache reservation USA invasive disease was 500 -1000 per 100,000 children-under-2, in Europe it was 12 to 54 cases per 100,000 children-under-5, in Ghana Africa Hib meningitis was 200 per 100,000 infants (Watt et al. J Pediatr 2003:143:S163-S187). In Dallas USA, 109 per 100,000 children-under-5 (Trudy et al.Pediatrics 1987;79:173-180). In the Apache reservation invasive disease of 500-1000 came down to 22 per 100,000

after Hib vaccination, in Gambia Hib meningitis 200 per 100,000 infants fell to 21 with immunization (Watt et al. J Pediatr 2003:143:S163-S187). In contrast invasive disease in Asia, without immunization was as low as 3 to 9 per 100,000 children-under-5 (Levine et al.Pediatr Infect Dis J. 1998;17:S95-S113; Lau et al.Pediatr Infect Dis J.1998; 17(9Suppl): S165-9.) An Editorial in the WHO Bulletin wonders if the vaccine is at all needed in Asia (Bulletin WHO 1999;77:867 -8).

- Invasive bacterial infections surveillance (IBIS. CID 2002; 34:949-57) which performed cultures for 4 years in 6 referral hospitals showed 125 positive cultures. Access to hospital was cited as the postulated reason for small number and suggested community based studies are needed. In 2002, Cherian et al (Indian Peditar 2002;39:1070-71) stated that based on available data, Hib vaccine cannot be recommended for routine use in India.
- Community based study looking for Hib meningitis (Minz et al. IJMR 2008; 128:57-64) using cultures and latex agglutination test showed Hib meningitis incidence of 0.007% in children followed up to 5 years. Most cases of Hib meningitis occurred in the first year. This will correspond to a life time risk of 0.0005% as nearly all cases prevented, occur only in the first year. The explanation given in that paper for the low rate observed are: (a) genetic factors causing low infection (b) early exposure to bacteria with cross-reacting antigens (c) low bacterial virulence locally. At the cost of Rs.300 per person (3 doses of Hib vaccine at Rs.100/dose), this cost works out to be Rs.10 lakhs per case of Hib meningitis prevented. This does not appear to be cost-beneficial as meningitis can usually be treated with antibiotics costing Rs.1000-5000 per case. We have to spend Rs.10 lakhs to save this expense of Rs.5000
- There is natural immunity to without vaccination well before 2 years of age (Puliyel et al. Vaccine 2001; 19:4592-4). Pre-vaccination antibody levels are seen well beyond the age of passive immunity. Without vaccination there is increasing antibody titres with increasing age. After vaccination, antibody levels increase ten times higher than normal values suggesting that child was immune before vaccination. The reason for low incidence in Asia is because infection with

organism like E coli with cross –reactive antigens may be responsible for natural immunity which protects against Hib. There are animal model studies for Hib cross-reactive antigen (Schneerson Inf and Immunol 1971;4:397-401;Bradshaw Lancet 1971;1095-98;Petrie Br J Exp Path 1971;13:380-94).

- Probe study is recommended for areas with low culture rate. Indonesia probe study (Gessner BD, Lancet. 2005;365:43-52) showed more cases of pneumonia among vaccinated and meningitis admissions are not reduced significantly.
- Bangladesh Case control study (Baqui Ped Infect Dis 2007;26:565-71) showed no significant vaccine effectiveness in radiological pneumonia or meningitis (matched community controls). Data dredging and post hoc analysis shows statistical significance against pneumonia after two doses.
- The data for Vellore shows deaths from all cause pneumonias as 0.24 and 0.08 deaths from all cause meningitis per 1000 child years of observation against WHO's projected pneumonia deaths of 14/1000. This undercuts the need for Hib and pneumococcal vaccine. Vaccination is not necessary especially since Hib is easily curable with antibiotics.
- A cluster randomized study is needed to see if there is fall in pneumonia and meningitis following Hib vaccine
- A Cochrane review on combined DTP-HV- Hib vaccine vs. separately administered DTP, HBV and Hib vaccine (Cochrane Data base of Sytematic Reviews 2009, Issue 3.Art No. :CD005530) shows combination is less effective than the vaccines given separately.
- There is evidence of relationship of Hib vaccination and diabetes (Classen et al Br.Med. J 1999; 319:1133, Classen et al Autoimmunity 2002; 35:247-53; Classen Medical Hypothesis 2001;57:532-38). A very large Finland study, where good follow up is available, Type I diabetes increased 58 cases per 100 000 (p=0.029).
- There are published studies on the fact that Hib vaccination causes replacement disease and by other invasive H.influenza (Tsang et al Clin Infect Dis. 2007;44:1611-4; Brown et al Clin Infect Dis 2009;49:1240–1243, Urwin G eta l .Clin Infect Dis. 1996 Jun; 22 (6):1069-76; Perdue DG et al. JAMA 2000 Jun 21;283 (23):3089 -94; McConnel A et al. Pediatr Infect Dis J. 2007; Nov

26(11):1025-31; Adderson EE et al Pediatrics 2001 Ju;108 (1):E 18; Can Comm Dis Rep.2006 Jun1;32(11): 125-30; Kalies H et al. BMC Infect dis. 2009 Apr 20; 9:45).

- Pentavalent vaccine cannot be seen in isolation. Vaccine efficacy, safety and affordability are relevant when need is proven. Many expensive and new combinations vaccines are flooding the markets. Introduction of the pentavalent vaccine will mean that DPT which now costs Rs.2.50 will no longer be used.). Combination vaccines are a backdoor entry of new and costly vaccines in the Universal Immunization Programme. (Y.Madhavi. Current Science 2006;90: 1465-69). The public sector units PSU manufacturing vaccines (that have been ordered to restart) will have no utilization of their vaccines and will be forced to be closed again. The cost of giving the DPT will escalate by the addition of Hep.B and Hib. Pentavalent vaccine will increase the price of DPT to over Rs.100 per dose. After closure of the PSUs, the country will be entirely at the mercy of private manufacturers for this important activity. If Hib is needed, it may be given as separate injections.
- Therefore until and unless the necessity, efficacy and safety of Hib vaccine in Indian population are scientifically established, Hib vaccination becomes highly contentious and unethical whether alone or in combination

View Point II:

- Pyogenic meningitis is a regular feature in all pediatric wards and constitute 2-4% of all pediatric admissions. Most of the children affected are less than one year to less than 2 years. Commonest cause of pyogenic meningitis is Hib and Strep. pneumoniae. Of the children with pyogenic meningitis, a third recover, a third die and a third survive with sequelae.
- Meningitis has a high cost in terms of diagnosis, treatment, brain damage and loss of life. Collecting and collating data are part of routine public health activity, but this is absent. Therefore evidence of Hib disease is from limited research

publications. Absence of evidence should not be confused with evidence of absence. Available data from research publications in India was reviewed.

- Data on disease surveillance in Kerala for 1999-2000 (John et al. IJMR 2004:120:86-93) showed 75 meningitis cases of which at least 27 were bacterial meningitis. Assuming that one third of this is due to Hib, for a 26 million birth cohort, the estimated Hib meningitis is 52000 per year.
- Hospital based studies (18 studies) on Hib meningitis report mortality due to H. influenzae ranging from 13 to 67% and about 20-30% of pyogenic meningitis is due to Hib and these indicate no major change over the years. Available data from hospital studies also show that Hib is a leading cause of pneumonia and the proportion ranged from 2 to 19%.
- Results of the ICMR study (Part A- site preparation for a vaccine probe study) showed an incidence of severe pneumonia ranging from 2717 to 7890 per 100,000 child years of observation and suspected meningitis ranged from 1971 to 2433 per 100,000 child years of observation. In the hospital based study arm, 7.9% 29.6% and 21.0% of csf samples with cell count more $\geq$ 100 WBCs/mm^3 were purulent and 16.7%, 22.7% and 29% had WBC $\geq$ 100 WBCs/mm^3 and Hib positive with culture or antigen at Chandigarh, Kolkatta and Vellore respectively. Nasopharyngeal carriage rate varied from 6 to 7.6% across the three sites.

  On the specific issue of data from Anaicut Block for the ICMR study, the study detected 67 cases of meningitis from children under 2 years of age. 14 of the 33 (42%) where etiological diagnosis was possible, were cases of Hib meningitis. Based on this, a conservative estimate of the Hib meningitis is 58/100,000 during the first two years of life (assuming that children with acute CNS infection could not have reached the hospital from distances greater than 50 kms and a catchment population of 1000000 and a birth rate of 16/1000 and 100% of children with meningitis coming to study hospitals). This is a gross underestimate as there are several other hospitals providing inpatient care even within the city and it was found that two children from the birth cohort died of acute CNS infection at home.

In the birth cohorts (1717 children) of the ICMR Hib study 8 cases of meningitis were identified. Assuming both deaths had purulent meningitis, four out of ten meningitis cases would be with csf cell count greater than 100 cells. These four cases would have 30% probability of Hib meningitis with cells between 10 and 100 would have a 6% probability of being meningitis (extrapolating rates from the hospital component of the study). This leads to a conservative estimate of 105/100000 children under two years of age. In the same period, the incidence of severe hospitalized pneumonia was 3.1 per 100 child years and the radiological pneumonia rate of 1.1 per 100 child years. That there was only one pneumonia death in hospital from the cohort was not surprising considering that these children were treated at with the best care medicine can offer and the cost for the same was underwritten by the study. Children were visited every 15 days at home and children who were ill were requested to go to the hospital. In such a situation the very fact that there were 47 deaths of which 11 were due to respiratory causes, 8 due to age and 3 due to meningitis was cause for concern. Most of these deaths happened either at home or on the way to a health facility indicating a delay in seeking health care. Unfortunately most of India is not privileged to be treated at such facilities and surely the case fatality rate in such studies should not be a metric for mortality due to these illnesses.

The argument that the cases of pneumonia included in the study were trivial is also unjustified since the proportion of cases with readable x-ray showing primary consolidation was 24/73 (33%).

The findings from Hib Probe study Part A from Vellore suggests that in each successive birth cohort in India, at least 40,000 cases of Hib meningitis occur in the first two years of life. Most these cases would occur between 6 to 15 months of age. Similarly, the cumulative risk of severe pneumonia in the first two years of life is 3.7% while that of radiological pneumonia is 2%. An estimated 15-30% of this radiological pneumonia is likely to be due to Hib and these contribute roughly 20% of pneumonia deaths.

- A population based study on incidence of Hib meningitis in India (Minz et al 2008) showed an incidence of Hib meningitis of 7.1 per 100,000 children under five years of age, 19 per 100,000 in children less than 2 years of age and 32 per 100,000 in infants. There was discussion whether the yardstick one should apply in measuring the incidence of Hib meningitis should be risk or rate. When the probability of disease is restricted to a narrow time interval, then the use of a rate can give an erroneous picture. In this context the relevant question is related to the probability of a child born in India developing Hib Meningitis by say, age two or five. This risk approach will give the same numerical value regardless of the duration one chooses because the probability of developing Hib meningitis is almost entirely restricted to the first two years. Similarly the risk of a child developing Hib meningitis would be 105/100,000 according to conservative estimates, based on the ICMR Part A study. It is suggested that the parameter to be used to measure burden of Hib meningitis be risk as opposed to rate as this would indicate the number of children who would develop hib meningitis in each successive birth cohort.
- Data from ongoing bacterial meningitis surveillance at CMC Vellore; Kalawati Saran Children's Hospital, Delhi; Institute of Child Health, Chennai and CSM (KG) Medical University, Lucknow showed that Hib was the dominant pathogen in confirmed meningitis cases. Age groups most affected children less than 2 years. Antibiotic was prior to LP was high in all the sites. High rate of antibiotic use prior to LP explains reasons for low sensitivity of culture and gram stain. In Kalawati Saran Children's hospital, of the confirmed cases 20% dies, 7% had sequelae; these estimates are low as 20% of children were lost to follow up. Hib vaccination in study population was highest in Vellore (44%).

  An earlier study from Kalawati Saran Hospital (Damodar et al .Indian Pediatrics 1996;33:763) in children aged 1 month to 12 years showed 34.1% of cases of confirmed bacterial meningitis was Hib; the case fatality was 16%.
- A study on the community effect of Hib vaccination carried out in Vellore (Verghese VP…John TJ et al. Ped Inf Dis J 2009; 28: 738-740), showed that for less than 4500 infants immunized, 7 cases of Hib meningitis was prevented which

work out to approximately 166 per 100000 infants and 33 per 100000 under five children immunized per year. When introducing change for development, ask how the poorest of poor will benefit from it (Adapted from Mahatma Gandhi). Hib vaccine is a popular private sector vaccine. There is large volume urban, peri-urban use. While the vaccine benefits the middle and upper class, the low income groups do not get the vaccine. It would be unscientific and unethical to withhold this completely safe and effective vaccine from the under-priviledged families that are increasingly adopting the small family norm.

- Pyogenic meningitis is a medical emergency to be diagnosed and treated within 8 hours. Health care system is unable to provide equitably health care and rehabilitation of assured quality to rural, peri-urban and urban poor. Hence prevention is ethical. Hib vaccine is effective even when immunization coverage is 50%.
- As available evidence confirms the wide prevalence of Hib meningitis in young under fives, as Hib vaccine coverage is increasing among the urban population who avail vaccines in private sector, the inclusion of Hib vaccine in UIP is recommended
- Hib disease occurs mostly in children less than 2 years and high antibody titres with increasing age could be the result of natural infection from Hib
- The findings of the Finnish studies on the association of Type 1 diabetes and Hib vaccination (Classen JB, Classen DC. Medical hypotheses 2001;57(5):532-538 ; and Autoimmunity,2002: 35(4): 247-253), has not been corroborated by other studies around the world (Karvonen M et al. British Medical Journal 1999; 318 (7192):1169-1172; Hummel M et al Diabetes care 2000; 23:969-974; EURODIAB Substudy 2 Study Group Diabetologia 2000; 43(1):47-53; Institute of Medicine StrattonK et al. 2000.http://www.nap.edu/books/0309083281/html/; Atkinson et al. Lancet 2001 July 21;358 (9277):221-9; Dahlquist G eta al Diabetologica 1995 Jul;38 (7):873-4; Destefano F et al. Pediatrics 2001 Dec ;108 (6) :E112 ; Wasfy JH.N Engl J Med.2004 Jul 15 ; 351(3) :298)

- Cochrane meta-analysis states that the authors could not conclude that the immune responses elicited by the combined vaccine were different from or equivalent to the separate vaccines
- Pentavalent vaccine is used by the West (but those who do not use Hep.B use IPV) or hexavalent vaccine. Pentavalent vaccine is also used by our neighbouring countries. Reports of serious adverse events from Sri Lanka with pentavalent vaccine have been investigated and there were not serious adverse events related to the vaccine. Pakistan has administered 16,473, 897 doses of pentavalent vaccine; the coverage was 88%. There have been no reports of adverse reactions. But at the beginning of introduction there was one death; investigation by EPI as well as WHO found it to be unrelated to the immunization.
- The pentavalent preparation of the vaccine is a programmatic decision that takes into consideration the cold chain, reduction of the number of injections to the child. Immunologically and epidemiologically the effectiveness of individual dose vs. combined doses is comparable.

Recommendations:

- In view of the fact that available information on Hib disease shows Hib to be a major cause of pyogenic meningitis and a cause of severe pneumonia in children; that the vaccine is not available to poor children who need it most, that the high herd immunity enables its use even in areas with low DPT coverage, Hib containing pentavalent is recommended to be introduced in selected states on pilot basis depending on fund availability. Simultaneously a study on impact of Hib vaccine on meningitis in these states should be carried out before it is considered for other states/ populations.

Annexure 1

List of Participants

1. Dr. V.M. Katoch, Secretary (DHR) Chairperson and DG, ICMR (18th Jan, 16th Feb. and 24th March)
2. Dr. Rajesh Kumar, PGIMER, Chandigarh (18th Jan, 16th Feb. and 24th March)
3. Dr. Jacob M. Puliyel, St.Stephens Hospital, Delhi. (18th Jan, 16th Feb. and 24th March)
4. Brig. (Dr.) A. Nagendra, Pune. (18th Jan, 16th Feb. and 24th March)
5. Dr. Renu Bhwardwaj, BJ Medical College, Pune (18th Jan, 16th Feb.)
6. Dr. Meera Sharma, PGIMER, Chandigarh (18th Jan, 16th Feb. and 24th March)
7. Dr. S.K. Acharya, AIIMS, Delhi (18th Jan, 16th Feb. and 24th March)
8. Dr. Y. Madhavi, NISTADS, Delhi(18th Jan, 16th Feb. and 24th March)
9. Dr. Yogesh Chawla, PGIMER (18th Jan, 16th Feb.)
10. Dr. T. Jacob John, Vellore (18th Jan, 16th Feb. and 24th March)
11. Dr. S.P.Shani, FDA Bhawan, Delhi (16th Feb.)
12. Dr. SD Khaparde, MOHFW (16th Feb)
13. Dr. Shashi Khare, NCDC, Delhi ((16th Feb.)
14. Dr.JP Muliyil,CMC, Vellore (16th Feb. and 24th March)
15. Dr. DA Gadkari, Pune (16th Feb. and 24th March)
16. Dr. V.Arankalle, NIV, Pune (16th Feb. and 24th March)
17. Dr. Aneja, Kalawati Saran Children's Hospital (16th Feb. and 24th March)
18. Dr. Vishwajeet Kumar, CSM, Lucknow (16th Feb.)
19. Dr. Saradha Suresh, ICH, Chennai (16th Feb. and 24th March)
20. Dr. P.Ramachandran (16th Feb. and 24th March)
21. Dr. Jacob John, CMC Vellore (16th Feb. and 24th March)
22. Dr. Rakesh Aggarwal, SGPGI, Lucknow (24th March)
23. Dr. SK Mittal, Delhi (24th March)
24. Dr. Lalit Kant, Head (ECD) ICMR (24th March 2010)

25. Dr.Ambujam Nair Kapoor (18th Jan, 16th Feb and 24th March)

Note: Inputs for the meeting was also provided by Dr.SK Sarin who could not attend the meetings.