Exhibit K3(a)

Report of the Pentavalent Vaccine Committee

as per

G.O.(Rt) No.3678/2011/H&FWD dated 20/10/2011

The Govt. of India has decided to implement the use of Pentavalent vaccine (DTwP-HepB-Hib) instead of the present DPT vaccine in the Universal Immunisation Programme in India. In view of the better coverage of immunization programmes, the States of Kerala and Tamil Nadu are chosen for the initial phase of the pilot project. However, there have been reports in the media about apprehension of a group of civil society and medical fraternity regarding the utility and safety of the vaccine. Hence a committee was appointed by the Govt. of Kerala to examine the controversies arisen relating to the utility and safety of Pentavalent vaccine, as per G.O (Rt) No: 3678 / 2011 / H & FWD dated 20/10/2011.

The Committee Members are:

1. Dr. Noel Narayanan, Former Head of Dept, Paediatrics, Thiruvananthapuram Medical College, (Chairman)

2. Dr. Lalitha Kailas, Head of Department, Paediatrics, Thiruvananthapuram Medical College (Member)

3. Dr. K. Leelamoni, Head of Department of Community Medicine, Amrita Institute of Medical Sciences, Kochi (Member)

4. Dr. P.K. Jameela, Director of Health Services, Thiruvananthapuram, (Convenor)

The committee met 3 times on 31/10/2011, 4/11/2011 and 11/11/2011 at the Chamber of Director of Health Services, Thiruvananthapuram and discussed in detail the issues related to the introduction of the Pentavalent Vaccine, taking into consideration,

the disease magnitude with special reference to Kerala and the controversies related to the utility and safety of the vaccine. After going through the available data, both published and unpublished, the committee has given their specific recommendations regarding the use of Pentavalent Vaccine in Kerala.

Introduction:

Pentavalent vaccine is a combination of five vaccines indicated for active immunization of infants against 5 lethal diseases namely Diphtheria, Tetanus, Pertussis (Whooping cough), Hepatitis B and invasive Haemophilus influenzae group b disease. Vaccine is supplied as a homogeneous liquid formulation and composed of toxoids of Diphtheria &Tetanus, inactivated whole cell pertussis organism, non infectious particles of Hepatitis B surface antigen and H. influenzae type b capsular polysaccharide conjugated to a protein. Vaccine is adsorbed on to Aluminium phosphate and thiomersal in permissible concentration is used as a preservative.

DTP is a major component of Universal Immunization Programme (UIP) and has been in regular use in India for many years. Recently Hepatitis B vaccine was added to the UIP. The current recommendation is to include Haemophilus Influnenzae type b (Hib) Vaccine also in the UIP and to administer all vaccines together as a Pentavalent Vaccine at 6, 10, and 14 weeks to all infants. The vaccine is administered as intramuscular injection on the anterolateral aspect of the thigh. All precautions like maintenance of proper cold chain, asepsis and monitoring for any adverse reactions are taken.

Utility and Efficacy of the vaccine

DTP and Hepatitis B vaccine are already in use under UIP. Hib vaccine component of the Pentavalent vaccine, has nearly eliminated Hib disease in many

developed and developing countries where it was introduced more than a decade ago. The efficacy of Hib vaccine, was demonstrated in numerous clinical trials in Europe, the US and developing countries.

A gambian study comparing Hib vaccine plus DTP to DTP alone, showed a protective efficacy of 95% against all invasive Hib disease after 3 doses.(15). In a case control study in Banglasesh, it was reported that three doses of Hib conjugate vaccine reduced rates of laboratory confirmed meningitis by 90% and radiologically confirmed pneumonia by 16-32%. Several studies in India have shown that the combination vaccine is highly immunogenic. Both DTwP/HB/ Hib combination vaccination and Hib vaccine combined with locally produced DTwP proved as immunogenic as single antigen Hib vaccine (16,17,18,19). As per meta analysis in Cochrane Review 2009, no conclusion could be made on the immune response elicited by combined vaccine and separate vaccines, though some studies showed the combination vaccine to be less immunogenic. But the level of evidence provided by the studies was low.

Herd immunity

Nasopharyngeal carriage of H influenzae among infants is found to be common in India with an estimated prevelance of 6.8 – 16.3 % as per ICMR data. In a multicenter study(ISCAP Trial 2000 to 2002) in 7 major hospitals in India, 2065 children aged 2 to 59 months with non severe pneumonia were studied. 32.5% of these children showed positive culture for H. Influenzae on throat swab. As part of this study, SAT hospital, Thiruvananthapuram recruited 321 children with pneumonia, out of whom 115 (35.8%) were positive for H. influenzae from throat swab. These data show a high carrier rate of H. Influenzae in children throughout India including Thiruvananthapuram.

The Hib vaccination reduces nasopharyngeal colonisation of the organism, leading to a substantial reduction in disease transmission and incidence of disease. Immunization of a proportion of children, reduces carrier state and helps to prevent

spread of disease to unimmunized children living in the same community. Therefore a population need not be fully immunized for a substantial benefit to be seen.

Burden of Disease: Haemophilus influenzae type b (Hib) is a major cause of acute pyogenic meningitis and pneumonia in children less than five years old, although other bacteria and virus can also produce the same illness. Bacterial meningitis is fatal, unless treated immediately and even with proper treatment 3-25% of affected children may die (1). The mortality of Hib meningitis is 15-25%, especially in young infants and those who present with fulminant disease. Approximately 45% of children are left with sequlae which may vary from mild neurological impairment in 15-25%, significant impairment in 20-40% and severe handicapping neurological sequlae in 10%. Other long term problems include epilepsy, hearing loss, moderate to severe developmental delay and mental retardation. (2)

A review of available data show that upto 20% of severe bacterial pneumonia is due to Hib. Approximately 410,000 (19%) underfive deaths are caused by pneumonia out of which an estimated 70,000 are caused by Hib. Hib can also rarely cause other serious diseases like epiglottitis and septic arthritis.

H. influenzae type b (Hib) was recognized as a common cause of childhood meningitis before use of Hib Vaccine in routine infant immunization in many parts of the world (3). In pre- Hib vaccine era in developed countries, the reported incidence of Hib meningitis was 11-50 per 100,000 in the 0-4 years age group (4,5). In developing countries like the Gambia, Chili and The Philipines also, a comparable incidence has been reported (6,7). In Sri Lanka the incidence of Hib meningitis is reported as 20.1 per 100,000 among underfives.

In India even though there is paucity of data on prevalence of Hib disease, the report that Hib disease is rare in India may not be absolutely true. In the absence of good community based data on Hib burden in India, the only source of information is hospital based studies. Isolation of the organism is also difficult as proper collection, storage and

transport are essential and the fastidious organism require sheep blood enriched media for culture. Hence the overall burden of Hib is several fold greater than the burden of laboratory proven Hib meningitis and pneumonia in children in India (8,10).

The available hospital based studies conducted in different parts of the country show that Hib is a common cause of meningitis (during the years 1950-2000) with a prevalence rate ranging from 10-45 %. This wide variation again shows the difficulty with which the organism can be isolated. The incidence of Hib meningitis in children is reported as 32 per 100,000 in 0-11 months of age and 19 per 100,000 in 0-23 months (8). The estimated incidence of the Hib Pneumonia will be about 44 per 1000 children in less than 5 years old in India. (9). Data observed from Madras Medical College, Chennai in a study during 2006 – 2008 showed confirmed Hib meningitis in 12 cases (out of 21 cases) with 30% mortality. Another study in Chennai in 2011 showed 54 confirmed meningitis cases out of which 30 were Hib positive.

The emergence of resistant strains of H influenzae to commonly used antibiotics is also a grave concern (11,12,13,14). The IBIS study (Invasive Bacterial Infection Surveillance) conducted in 6 centres in India from 93-97, also reported that 60% of all isolates were resistant to antibiotics. In developing countries like ours, the emergence of resistant organisms can escalate the cost of treatment and lead to increase in mortality and morbidity.

Kerala picture

According to hospital data from SAT Hospital, Govt. Medical College, Thiruvananthapuram which is one of the major referral hospital of the state, in the year 2006 alone there were 447 cases of meningitis out of which 10 children died and 30% were left with sequlae. In the same hospital 1760 cases of pneumonia were admitted in 2006, out of which 77 died. Annual admissions due to pneumonia in SAT Hospital varies from 1430-1760 causing 34-40% of total deaths in children. 70-74% of these deaths occurred in children younger than 2 years. Invasive procedures are required to obtain

bacterial culture in case of pneumonia, which are seldom performed, and growth of H. influenzae from secretions is often unreliable. However from the above data, H. inluenzae can be considered as the leading pathogen for pneumonia in children below 2 years of age.

Analysis of a study conducted in SAT Hospital (1997 – 1998) , of the 60 cases of pyogenic meningitis 10 were culture positive with 3 due to H. influenzae. Various complications were observed in more than 50% of cases. These limited data indicate that H. influenzae infections do occur in the state, though the exact magnitude cannot be ascertained in view of the small number of children studied.

Cost effectiveness

According to a cost effective study conducted in low and middle income countries, Hib was found to be cost effective. (20) In an Indonesian study in 2008, it was found that a large burden of Paediatric illness and death due to Hib can be prevented by routine Hib vaccination (21). Another Indonesian study published in Oxford Journal of Public Health in 2007 shows that implementation of Hib vaccination would avert more than 76,700 cases of invasive infections and more than 7150 deaths indicating significant cost effectiveness on implementation of a Hib vaccine programme for Indonesian Society. A US study showed that the Universal Vaccination Programme using the Hib conjugate vaccines in US in 2000 was cost saving. Without a Hib Vaccination Programme, the direct cost of Hib invasive disease would be $ 1.35 billion while the cost of the vaccination programme was estimated as $ 0.39 billion, showing a substantial cost savings (22).

Though the vaccine at present is expensive, the cost is likely to come down, based on the trends of other vaccines in National programme. The cost of treatment estimated for meningitis in Kerala varies from Rs. 5000 to 10000 per case. With emerging resistance of organism to commonly used antibiotics, the cost is likely to go up further. In a case control study in SAT Hospital during the year 2001 to 2003 to find out the prevalence of meningitis and pneumonia in Hib vaccinated and unvaccinated children, it

was found that both diseases showed a marked reduction in vaccinated children, compared to children who did not receive Hib vaccine.

In any case, it is unethical and unscientific to equate vaccine cost against the life of young children and deny them a safe and effective vaccine when it is available to protect them against two lethal diseases, which can cause brain damage or loss of life. Current evidence indicates that the benefit from vaccine greatly outweigh the risk associated with vaccination.

Safety issues

No vaccine is one hundred percent safe or effective. Many studies have shown Pentavalent vaccine to be generally safe and effective. Globally millions of doses of Hib vaccine administered in the last two decades have been found to be extremely safe. The reported general symptoms following immunization was 0.8%. The Cochrane meta analysis indicates that there was no significant difference in the incidence of serious adverse events, though minor reactions were more in the combined vaccine. Deaths reported following vaccinations in neighboring countries have been subjected to scrutiny and found to be not directly related to the vaccine. Pentavalent vaccine had been used in Europe and United States for more than a decade and no death has been reported. A study in Finland has shown slightly increased incidence of type I Diabetus Mellitus in children given Hib vaccination. This has not been corroborated by other studies. There is a postulation that Hib vaccination can lead to replacement disease by various other groups of Haemophalus Influenzae other than type b. At present there is no evidence that this is happening. However, continued surveillance for such an occurrence is justified . Causal relation between SIDS (sudden infant death syndrome) and DTP has not been proved.

However, following adverse reactions can be expected.

1. Fever up to 48 hours and anorexia and fretfulness
2. Local reaction in the form of tenderness, warmth, swelling, and redness may be seen at the site of injection in upto 25%.
3. Occasionally a palpable nodule and very rarely a sterile absess may develop.
4. High fever and inconsolable crying lasting 3 hours or more can occur. This however

is of no consequence. Studies have shown that frequency of local and systemic reactions were not higher in Pentavalent vaccine as compared to DTP given alone.

5. Rarely severe reactions like convulsions, loss of consciousness, breathing difficulties, cyanosis and anaphylactic (allergic) shock can occur.

Pentavalent vaccine has been in use in many private hospitals in the country and in Kerala for the last several years. No serious adverse reaction has been reported from any of these hospitals in this state. In the case of one death in Malappuram District which occured one day after vaccination, it was considered to be due to vomiting and milk aspiration and not due to the vaccine.

Combined vaccines – Advantages,

Combined vaccines are widely used against many diseases. The advantages of combined vaccines are many :

1. Decreased number of injections. Instead of giving DTP, Hep B, and Hib separately to an infant three times resulting in a total of 9 injections, use of combined Pentavalent vaccine needs only three injections.
2. Compliance of parents to bring the children for immunization will be better.
3. Immunization coverage and completion of immunization schedule will be more.
4. Avoidance of multiple injections on the same day will save time and cost.
5. No special system or strategy is needed when DTP is replaced by Pentavalent Vaccine.

Though it is reported by some that antigenicity of combined vaccine is less compared to separate vaccines, our aim is to ensure adequate protection and it has been conclusively proved that adequate immunogenicity is produced by combined pentavalent vaccine.

In view of the above facts, the committee strongly feels that there is need for Hib vaccination in Kerala and recommends that Pentavalent vaccine should be included in the infant immunization schedule in Kerala under UIP.

The committee has also given the following specific recommendations regarding strengthening of the existing monitoring and surveillance measures in immunization programme, which will help to alleviate the anxiety and apprehension among the society and public at large.

Specific recommendations:

1. A doctor should be present when immunization is given.
2. Vaccine should not be administered if there is history of any serious reaction during previous vaccination or if any contraindication is present.
3. Treatment of anaphylaxis should be available at the site of vaccination.
4. Parent should be given a contact phone number in case of any serious adverse reaction and services of 108 ambulance given, where available.
5. All vaccinated children are to be monitored for any adverse events atleast 48 hours following vaccination.
6. ASHA workers , ANMs and Anganwadi workers should be responsible for such follow-up and they should record and notify any reaction observed.
7. A post introduction evaluation should be done for atleast 2 years to observe the status of vaccination and its impact on the incidence of meningitis or pneumonia in children.
8. Steps to be initiated for local production of vaccine at Government level to bring down the cost of vaccine in future.
9. Creation of awareness among health workers about the Pentavalent vaccine
10. Proper orientation of media is also essential before starting the Pentavalent vaccination through UIP in the state.
11. Continuation of Hepatitis B vaccine as a birth dose (within 24 hours) to prevent vertical transmission and booster doses of DTP vaccine at 16-24 months and 5-6 years should be continued as before.

Conclusion:

Invasive Haemophilus Influenzae infection is a common cause for two serious diseases in young children namely pyogenic meningitis and pneumonia. Both are medical emergencies and unless detected and treated early, death or disability is certain to occur. Treatment of these conditions are difficult and expensive and bacterial resistance to commonly used antibiotics is another emerging problem. Since a safe and effective vaccine is now available, prevention of invasive Hib disease with vaccine is certainly the correct choice. Current evidence indicates that the benefit from vaccine is far greater than the risk associated with the vaccination. At present the benefit is enjoyed only by the rich and affluent who can afford this expensive vaccine and poor children who are in need of it most, are denied of this vaccine. Inclusion of Hib vaccine in UIP will benefit millions of children in India.

Dr. Noel Narayanan, MD,DCH,FRCP.

(Chairman)

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