Immunization Dialogue

Typhoid Vaccine

Dr. T. Jacob John, Professor and Head, Department of Microbiology and Virology, Christian Medical College Hospital, Vellore, Tamil Nadu 632 004 answers important questions in relation to Typhoid Vaccine. Professor Jacob John, a leading international Vaccinologist, is an Adviser on Immunization to the World Health Organization and other International Agencies. He is the current Chairman of the IAP Committee on Immunization.

Q.1. Is pediatric immunization against typhoid fever desirable in India considering the low sanitation profile and the poor socio-economic status in general ?

A.1. A categorical answer (such as yes or no) is not easy for the following reasons. Measles, poliomyelitis, pertussis and diphtheria are due to infections that were universal, are transmitted essentially person to person and preventable only by immunization. *Salmonella typhi* is transmitted through contaminated food or water; hence, environmental sanitation, safe drinking water and hygienic food habits are the ideal methods of primary prevention. These steps are not only for preventing typhoid fever, but a number of other food/water borne infections as well. Immunization may, therefore, be described as the 'second line' for primary prevention of typhoid fever.

In geographic areas where childhood typhoid fever is prevalent, particularly in situations in which the pediatrician perceives any risk of typhoid fever, immunization is highly desirable.

Whenever possible, the pros and cons of typhoid fever immunization as well as the need for good food and water sanitation and hygiene must be discussed with the parents in order to make them also participate in the decision making process. For under-privileged families with risk of disease, immunization should be positively recommended and offered.

Q.2. What are the various vaccines against typhoid fever currently available in India ?

A.2. Three types of typhoid fever vaccines are available in India. They are: *(a)* Whole cell inactivated vaccine; *(b)* Live oral vaccine (strain Ty 21a); and *(c)* Vi capsular polysaccharide vaccine.

The whole cell inactivated vaccine has been in use for several decades in India. The vaccine is prepared by growing a standard strain of *S. typhi* and killing with heat and phenol. Although acetone-killed vaccine has better efficacy than heat-killed vaccine, the former is not available in India. In a way this is good, since acetone killed vaccine should not be given intradermally, whereas heat killed vaccine may be so given, with certain advantages. In India, heat killed *S. paratyphi* A may also be included in the typhoid fever vaccine when it is known as TA vaccine. Previously *S. paratyphi* B also used to be included (TAB vaccine) but since this

organism is not widely prevalent in India, this vaccine has been discontinued.

The live oral and Vi vaccines are relatively newer products which are not manufactured in India but are imported and marketed in India with approval from the Drug Controller of India.

Q.3. What are the mechanism(s) of action of these three vaccines?

A.3. The exact mechanism of protection by the TA and oral vaccines are not clearly understood; the Vi vaccine protects exclusively through the induction of antibodies to the Vi capsular polysaccharide.

The whole cell vaccine induces both humoral and some cell mediated immunity against several cell wall proteins and lipoproteins of the organism. Fairly high levels of antibodies against the O and H antigens are detectable after TA immunization. The TA vaccine strain of *S. typhi* is poorly capsulated; hence it does not induce Vi antibodies.

The oral Ty 21a vaccine does not infect the gastrointestinal tract in the strict sense of the term infection. The organisms are genetically defective and cannot multiply more than one or two generations and they do not invade the tissue. Thus the vaccine induces very little systemic antibody production. However, there is induction of local immunity in the gastrointestinal tract which results in protection. The mechanism of protection may be through inhibition of attachment of virulent *S. typhi* to intestinal mucosa, or through cytotoxic immune mechanisms or other cell mediated local immunity.

The most interesting lesson is that the three vaccines act through totally independent mechanisms. In the absence of a clear understanding of the pathogenetic mechanisms of typhoid fever nor of the real virulence factors of *S. typhi,* the vaccine induced immunities offer some important clues. Firstly, local immunity without significant systemic immunity can protect. Second, antibodies against Vi polysaccharide alone can protect. Third, antibodies and perhaps CMI against somatic proteins and lipoproteins, but without Vi antibodies also can protect. Thus, virulence and pathogenicity must include ability to infect and invade; the presence of Vi capsule; and factors other than Vi, such as somatic cell wall components.

Q.4. It is postulated that the vaccine efficacy will be drastically reduced in a developing country (for example, India) with a low sanitation profile and high endemicity of the disease. How true are these fears ? Is there any available data on the efficacy of these vaccines in such areas ?

A.4. Several studies for the efficacy of the newer typhoid vaccines have been conducted in locations with poor sanitation and relatively high endemicity of typhoid fever such as Egypt, Chile and Indonesia (oral vaccine) and Nepal and South Africa (Vi vaccine). The efficacy of oral vaccine has shown a wider range than the Vi vaccine. Apart from reports in the 1950's and 1960's, there have been no recent studies of the TA vaccine. Moreover, none of these vaccines have been properly evaluated for efficacy in the pediatric age group, especially in preschool children. However, many studies have included adults

and school age children; therefore, it is safe to assume that all vaccines have reasonably acceptable efficacy in school age children. Based on immunogenic effects, TA vaccine may be effective in preschool children including older infants and Vi vaccine may be effective from 2 years of age.

There have been anecdotal experiences in India wherein the introduction of TA vaccine has resulted in marked decline in the incidence of pediatric typhoid fever cases.

Q.5. What are the relative advantages and disadvantages of one type vis-a-vis the other available forms ?

A.5. Definitive data on the efficacy and duration of protection of the three vaccines are not available in India in general and in pre-school age group anywhere else either. Therefore, comparisons will be made on available information plus some assumptions which are reasonable and rational.

Regarding cost, TA vaccine is extremely cheap and even poor families, indeed especially poor families who need the vaccine most, can easily afford it. Primary immunization requires two clinic visits one month (or 4 weeks) apart.

Oral vaccine is given in 3 doses on alternate days, requiring 3 visits, or a refrigerator at home to keep the second and third doses at home in order to avoid the repeated visits. The current price is between Rs. 100-200 for the primary immunization.

The Vi vaccine is a single dose injection; but this is the most expensive one at the present time, costing about Rs. 350.

Regarding side effects, the oral vaccine causes virtually none; the Vi vaccine causes very few (< 5%) instances of local pain or systemic malaise and fever; the TA vaccine causes local pain often with some swelling and some fever and malaise in a large (25-40%) proportion of children. The reactions are short lived, with no sequelae; parents accept these without complaint if they are briefed about the same. Moreover, paracetamol gives considerable relief to these symptoms.

Extrapolating from available data, we assume that the three vaccines have approximately equal efficacy in India. We also assume that the protective efficacy of about 70-80% will last for about 3 years, after which one booster dose of TA vaccine, or repeat immunizations with oral or Vi vaccines will be necessary. The TA booster can be given intradermally, when side effects will be minimal.

There is one other technical point of some academic interest. The immune response to TA (O and H antibodies) and to Vi (Vi antibodies) vaccines can be measured, but not to oral vaccine.

Q.6. Which vaccine should be preferred if cost is a deciding factor and if cost is not a deciding factor ?

A.6. When cost is a deciding factor, TA vaccine should be preferred to the others. If cost is not a deciding factor, and if immunization is desired below 5 years, Vi vaccine should be chosen. The Vi vaccine seems to be effective from 2 years of age, but it should not be given below 2 years. If immunization is to be given at or after 6 years, oral or Vi vaccine may be chosen; if parents are edu-

cated, they could participate in the choice. Since data are available from a study in Nepal, the Vi vaccine may have more predictable efficacy in India than the oral vaccine for which data are currently not available in the Indian subcontinent.

Q.7. Does vaccination against typhoid fever confer some protection against paratyphoid fever?

A.7. The Vi vaccine will not protect against paratyphoid fever since S. *paratyphi* does not have Vi capsule. The TA vaccine contains killed S. *paratyphi* A intended to protect against paratyphoid A fever; whether it actually does or not has not been evaluated. There is no data if oral vaccine affords any protection against S. *paratyphi* A or B.

Q.8. What is the recommended age for immunization and how often are boosters needed ?

A.8. The oral vaccine is recommended at 6 years of age and above. It may be repeated after 3 to 5 years of interval. The Vi vaccine is recommended at 2 years of age and above. It may be repeated after 3-5 years interval. In the above statements, the word booster is avoided since there is insufficient data to show if subsequent doses act as boosters for oral and Vi vaccines. The repeat dose for oral vaccine consists of 3 doses on alternate days just as the primary immunization. Most probably there is no booster effect.

The TA vaccine may be given at 6-9 months of age and above. Booster doses may be given at 3-5 years interval. Here, there is a good booster effect.

In all cases, the first booster or repeated dose is recommended 3 years after the primary dose. Thereafter the interval may be increased to 5 years.

Q.9. Currently, multi drug resistant typhoid fever is being increasingly reported in children below two years of age ? Should immunization against typhoid fever, if given, be routinely started below two years of age ? What form of oral vaccine can be used below two years of age since younger children may not swallow capsules ?

A.9. The protective efficacy of these three vaccines has not been evaluated in preschool children and assumptions in relation to this age group are based on immunogenic studies. Where typhoid fever is prevalent below two years of age, only TA vaccine can be given to infants (6-9 months and above). The Vi vaccine being a polysaccharide vaccine, is unlikely to be immunogenic below 18-24 months of age. The oral vaccine in enteric coated capsule form is unsuited to be given to children below 5 or 6 years of age.

A protein conjugated Vi vaccine is undergoing experimental evaluation. If successful, such a vaccine may become useful even in infancy. The oral vaccine, in it's liquid form may be given to children younger than 6 years, provided certain additional precautions #re taken, including oral antacids given before the vaccine intake. However, the liquid form is not available in the market, nor has it been evaluated in children below 5-6 years of age.

We believe that these 3 vaccines will be effective against both the chloramphenicol sensitive as well as multi-drug resistant strains of *S. typhi.* Where *S. typhi* infection is common before 2

years, the whole cell vaccine should be started between 6 and 12 months of age.

Q.10. Can typhoid vaccine be administered with other available vaccines ?

A.10. The two injectable typhoid vaccines can be safely administered simultaneously with other vaccines, either injected or oral. While the oral Ty 21a vaccine may be given concurrently with any injectable vaccine, it is not advisable to give oral poliovirus vaccine simultaneously, since no data exist regarding their compatibility. We recommend an interval of 4 weeks or more.

Q.U. What are the contraindications and precautions for administering typhoid vaccine ?

A.11. There are no major contraindications for giving any of the typhoid fever vaccines. However, the live organisms in the oral vaccine are susceptible to antibiotics. Antibiotics to which S. *typhi* are usually sensitive should therefore, not be given for a short period of time immediately before or for a few days after intake of oral vaccine. The vaccine manufacturers recommend that such antibiotics should be avoided for upto 3 weeks after vaccine intake. Chloroquin and mefloquin have an inhibitory effect on the oral vaccine; hence these drugs should be avoided for about 24 hours when the oral vaccine is given.

The oral vaccine is supplied in enteric coated capsule since the live organisms are sensitive to the acidity in the stomach. If the contents are extracted from the capsule, the utility of the enteric coating is lost. Strict cold chain conditions (2-8°C) must be maintained for oral vaccine at all times; however, TA and Vi vaccines are more tolerant to temperature fluctuations.

Q.12. How much time after vaccination does an individual become "protected" from typhoid fever ?

A.12. In general, protection begins after the immune response is established as a result of immunization. For TA vaccine, while protection may exist by about 2 weeks after the last dose, it is safer to consider that protection occurs after about 4 weeks. For Vi vaccine also, protection begins 2-4 weeks after immunization. In the case of oral vaccine, protection may indeed begin about one week after the third oral dose.

Q.13. After immunization, is "protection" absolute or can it be overcome with a high infection load ?

A.13. The protective efficacy of the vaccines was stated to be about 70%. However, even in these 70% persons, the protection is not absolute, but may be overcome when the inoculum dose of infection is very high. This phenomenon is generally true for most bacterial vaccines except toxoids.

Indeed the variations in the efficacy results of a given typhoid vaccine in different geographic locations are partly due to the deviations in the inoculum sizes of the infections. For example, when infection is food borne, organisms may multiply several generations making the inoculum dose quite heavy. On the other hand, when infection is water borne, the inoculum size is usually much smaller.