Special Article

Typhoid Vaccines

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Abstract. Typhoid fever continues to be a major public health problem in developing countries with about 33 million cases per year. Protective efficacy of traditional acetone/phenol killed vaccines is similar to newer typhoid vaccines (Ty21A and Vi antigen vaccine) but side effects of these newer vaccines are considerably less. Though the mortality is low, typhoid fever causes considerable morbidity and loss of working days. Problems during treatment are increasing due to emergence and spread of multidrug resistant S. typhi. Hence to decrease the incidence of typhoid fever in addition to ensuring safe water supply and excreta disposal a typhoid vaccine needs to be introduced in the National Immunization Schedule. **[Indian J Pediatr 2001; 68 (8) : 733-736]**

Key words : *Typhoid vaccine; Typhoid fever.*

Typhoid fever is an acute generalized infection of the reticuloendothelial system, intestinal lymphoid tissue and gallbladder that is caused by Salmonella typhi. It is unique to man and there is no animal reservoir of S. typhi. It is transmitted by Feco oral route. Transmission of typhoid is more in areas of poor sanitation .Typhoid fever has virtually disappeared from developed countries but remains a major public health problem in developing countries and hence a threat to travellers visiting these countries . World wide upto 33 million cases occur in a year, though exact data from developing countries is not available due to lack of diagnostic facilities.[1,2]

Typhoid fever can occur at any age but it is considered a disease of mainly children and young adults between 5 - 15 years of age.[3] There is now increasing evidence of documented S. typhi bacteremia in infants but these cases tend to have atypical presentation and therefore may be clinically mislabeled.[4,5] Though the living conditions are improving in many parts of the country, slum population is increasing. It is estimated that 20% of population in major cities will be a slum population with extremely poor sanitary conditions.[6] Recently study from Delhi has shown that children below 5 years also have a high incidence of S. typhi infection.[7]

In the preantibiotic era mortality rate was 10 -20 % but it has come down to the level of 1.1 -2.5 % in the past few years.[8] However the incidence of multidrug resistant typhoid fever is increasing and becoming a problem to the treating physician. Plasmid encoded resistance to all oral antibiotics (ampicillin, chloramphenicol, trimethoprim-sulfamethoxazole) has been spreading since 1990.[9-12] Emergence of multidrug resistant typhoid fever during the last decade of the 20th century has led to an increase in the incidence of severe cases, hospitalization and complications as well as an increase in typhoid mortality. Multiple drug resistant S. typhi have been reported from various parts of India and Southeast Asia.[9-11]

NEED FOR VACCINATION

Eradication of typhoid fever depends primarily on the Universal availability of good water and sewage system, detection of typhoid carriers and the restriction of their occupations and surveillance of cases. It will take time for most developing countries to implement these measures of disease control to a magnitude to have an impact on decrease in incidence of typhoid fever. Incidence of typhoid fever has been estimated to be 227 to 810 per 100,000 population using data gathered during vaccine trial.[6,13] Although the mortality is low, typhoid fever causes considerable morbidity and loss of working days. The cost of treatment in terms of drugs, hospitalization, loss of wages and productivity is high. With changing times, increasing number of strains are becoming resistant to conventional antibiotics and now to quinolones and even to third generation cephalosporins.

In the current scenario of public health system prevailing in India, vaccination seems to be the only cost effective method of prevention of typhoid fever.

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All populations specially children and adolescent particularly belonging to lower socioeconomic strata and urban slum dwellers are at increased risk of developing the disease and therefore would benefit most from vaccination. Typhoid vaccine was essential component of National Immunization Schedule till 1987 when an apex committee of ministry of health recommended its discontinuation as routine vaccine because of low efficacy and high incidence of adverse reactions to phenol inactivated and acetone killed vaccines. The routine coverage of the typhoid vaccine was extremely poor and there was hardly any impact of vaccination on the overall disease burden.[16] A vaccine most appropriate for the endemic regions of developing countries would be one that :

1. Requires only a single administration to confer long term immunity.
2. Has minimal side effects.
3. Is cheap and has potential of being easily manufactured on a large scale within the country and
4. Can be introduced within the existing vaccination programme.[17]

There are different types of typhoid vaccines available for use in the world. The criteria for selection of individual vaccine depends on the cost effectiveness, ease of administration, availability and side effects. Various vaccines available and their characteristics are being presented.

PARENTERAL WHOLE CELL TYPHOID VACCINES

Immunization against typhoid has been practiced since the late 1890's. In 1950's and 1960's WHO sponsored a series of large scale field trials in several countries using phenol killed and acetone killed vaccines. The efficacy of phenolised vaccine varied from 51-66 % and that of acetone killed varied from 79 -88%.[18, 19, 20] It was also demonstrated that 2 doses 1 month apart are more effective in providing immunity for a longer time than a single dose of these vaccines.[20]

Improved protection with acetone inactivated vaccine was attributed to retention of Vi antigen which was lost in phenol killed vaccine. Although more efficacious, acetone killed vaccine is difficult to prepare and is largely unavailable. Phenolized vaccine is available in the liquid form whereas acetone killed is available in lyophilized form. Vaccine contains 1000 million heat killed phenolised or acetone inactivated bacteria per ml. Table 1. shows various typhoid vaccines and their schedule of administration.

Intradermal route is not recommended .Vaccines containing paratyphi A or B are not used because of increased side effects. Vaccine should be stored at 2-8°C and should not be frozen. Only contraindication to administration of one of the parenteral typhoid vaccines is a history of severe local or systemic reactions after a previous dose.

Adverse Effect

Common adverse effects are fever, severe headache, local pain, swelling or erythema. Incidence of side effects is high. About 7 -24 % individuals develop fever and 3 -35 % develop local pain to a dose of this vaccine.[22] More severe reactions as hypotension, chest pain and shock occur sporadically. Reactions are less common with the second dose of the vaccine and should not be a contraindication to finishing the schedule.

LIVE ORAL TYPHOID VACCINES

A mutant strain of S. Typhi was developed by Germanier and Furr in 1975 which has mutation in gal E gene and lacks enzyme UDP-Gal 4 (uridine diphosphate galactose-4). Absence of UDP-Gal 4 epimerase results in an incomplete lipopolysaccharide (LPS) formation making it highly immunogenic as well

TABLE 1. Immunization Schedule For Typhoid Vaccines

Vaccine	Formulation	Route	Age	No. of Doses	Interval between Doses	Booster
Ty21a live strain	Enteric coated capsule	Oral	>6 years	3	2 days	5 years
			> 2years	1		
Vi capsular polysaccharide	Liquid	IM 0.5 ml				3 years
Heat inactivated Phenol preserved	Liquid	S/C 0.25 ml 0.5 ml	6mo-10yrs 10 yrs	2	4 weeks	3 years*

*Only one dose required as a booster.

as avirulent.[23] This Ty21A strain is available as a live oral typhoid vaccine containing 2-6×10^9 CFu of Ty21a viable organisms. It is fully immunogenic and completely devoid of pathogenicity.

Large scale field trails have been carried out in Egypt, Chile, Indonesia and Santiago with Ty21A vaccine either as a liquid preparation or enteric coated capsule.[24,25,26] Protective efficacy in Egypt was 96 % compared to 60 -62 % in Chile. Efficacy in these trials varied from 13 -96% using various schedules and doses of vaccine. Lower efficacy in Chile is attributed to greater endemicity of typhoid fever in the region. Liquid vaccine is difficult to store and administer and hence enteric coated tablets are most commonly used now a days. In a trial in Indonesia efficacy of liquid preparation and enteric coated preparation was comparable. Duration of immunity varies from 30 -65% after 3-5 years in various trials.

Dosage, schedule of administration and age of vaccination are given in Table 1 . Capsule should be ingested on empty stomach with little water or milk. Potency decreases if stored in room temperature for more than 12 hours. Vaccine is contraindicated in congenital or acquired immunodeficiency, patients on chemotherapy for malignancy and acute febrile illness. Safety during pregnancy has not been established.[22]

Adverse Reactions

Diarrhea, vomiting, fever and rash may be seen in less than 1 % of cases. Rate of adverse reactions is markedly low compared to heat killed vaccine.

Disadvantages of Ty 21a

This vaccine cannot be given in children less than 5 years. Exact mechanism of attenuation is not known and multiple doses are required. It has not been adequately assessed in Indian population and the efficacy may turn out to be low in areas with high incidence of typhoid as in India.

Parenteral ViAntigen Polysaccharide Vaccine

Vi antigen is a capsular polysaccharide of S. typhi which is thought to inhibit both phagocytosis and serum bactericidal activity in man. Vi antigen thus has virulent properties. Purification technique of Vi antigen was mastered in 1970's. After initial volunteer studies in USA in 1980's two large randomized controlled trials were conducted in Nepal and South Africa.[13,16] A single 25ug IM dose of vaccine was well tolerated and provided 72 % protection at 17 months and 64 % protection at 21 months respectively. Recently in Kenya 435 primary school Children aged 5 -15 years were evaluated for safety, tolerance and immunigenicity of Vi polysaccharide vaccine. Protective immunity has been reported to be 76.2 % with mild local inflammatory reactions in 1.5 % children.[27]

Dosage and schedule is given in Table 1. Common adverse reactions are fever, headache and malaise in 0.5-3 % cases. Local pain is seen in 7 % cases. Vaccine is contraindicated in pregnancy and in cases with hypersensitivity to the vaccine.

Advantages of Vi CPS Vaccine

Vi CPS vaccine is relatively easy and inexpensive to produce. Only one injection is required. This vaccine is stable for a long time at ambient temperatures and stingent cold chain is not required. Cost per dose is less than oral typhoid vaccines .

Disadvantages

The presently available vaccine cannot be administered below the age of 2 years unless conjugation with some other protein is done since it contains polysaccharide component which cannot induce T-cell immunity before 2 years of age.

FUTURE VACCINES

Attempts are been made to develop a Vi conjugate vaccine with diphtheria and tetanus toxoid. This would increase the immunogenicity of the vaccine and confer it T-cell dependent properties.[28] Modern genetic techniques have been used to prepare mutant S. typhi strains, 541 Ty and 543 Ty. But these are less immunogenic than Ty 21a vaccine. Field trials are under way for a genetically engineered S. Typhi strain that produces abundant Vi antigen .These results are not presently available.[29,30]

CONCLUSION

A typhoid vaccine in the National Immunization Schedule is needed at present in view of increasing morbidity, loss of manpower and antimicrobial resistance. Incidence of typhoid is increasing in the younger age group. Protective efficacy of traditional acetone/phenol killed vaccines is similar to newer typhoid vaccines i.e Ty21a oral vaccine and Vi antigen parenteral vaccine. But side effects of these newer vaccines are considerably less. In addition to introducing a vaccine in the immunization schedule attempts should be made to ensure safe water supply and excreta disposal to decrease the incidence of typhoid fever.

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