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REVIEW ARTICLE

Typhoid vaccines - Newer developments

Ajay Kalra¹, Premasish Mazumdar²**Abstract:**

Typhoid fever continues to be a major public health problem in the developing world. Antibiotic therapy has been the main stay of treating typhoid fever for decades. The emergence of multi drug resistant typhoid strains in the last 3 decades has been a major problem in tackling this scourge. Children constitute almost half of the total number of cases of multi drug resistant typhoid fever and are more vulnerable to its complications. In the absence of proper sanitation, vaccination is the only viable preventive option to control this disease. The first typhoid vaccine was introduced more than a century ago. It was a killed whole cell vaccine, found to be effective, but it fell into disrepute because of adverse effects and discarded. Developments in typhoid vaccine subsequently brought forth the Ty 21a oral typhoid vaccine and then the Vi capsular polysaccharide vaccine. These two vaccines showed limited efficacy with a better safety profile but were not effective in children less than 5 years of age. Development of conjugate polysaccharide typhoid vaccines has been the latest achievement. These and other oral typhoid vaccines under development are the typhoid vaccines of the future.

Keywords: Typhoid fever; conjugate polysaccharide vaccine

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Introduction

It is estimated that 33-60 million cases and 6 lakh deaths occur annually due to typhoid fever worldwide. As the disease is primarily associated with poor hygienic and sanitary conditions the major brunt of the disease occurs in developing countries (1). Around 5 million cases occur annually in India. Ten percent of cases occur in the infant age group when diagnosis may be difficult and mortality higher. A major problem in the last two decades of the 20th century has been the emergence of plasmid encoded multi drug resistance ranging from 17 – 90 as reported by various studies especially to the quinolones. Children constitute 40-50% cases of multi drug resistant typhoid fever with higher case fatality rates (2). The causative agents and mode of transmission of typhoid fever (feco-oral) is well known and principles of hygiene and public health should be the cornerstone of disease control as in the developed world. However with sanitary standards being a distant reality the only viable preventive option is that of effective vaccination.

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The history of typhoid vaccines dates back to more than a century. The first whole cell typhoid vaccine was invented in 1896 by Wright which was subsequently introduced in the British army (3). These vaccines were widely used in WHO sponsored large field trials in the 950s to 1960s. However because of the high incidence of severe side effects these vaccines fell in to disrepute inspite of their efficacy.

The need for a safe and effective vaccine was felt and a breakthrough occurred in 1975 when Germainer and Fuer invented the Ty21a mutant typhoid strain (4). This led to the availability of the first live oral typhoid vaccine. Another potential typhoid vaccine antigen the Vi capsular polysaccharide was identified way back in the 1930s; however the process of extraction denatured it rendering it ineffective for vaccine development. Dr Robbins group in the early 1980s isolated the un-denatured Vi antigen and elucidated its protective role (5), which was subsequently validated in field trials (6,7). The current stress in typhoid vaccines have been the development of conjugated polysaccharide vaccines and newer strains of oral typhoid vaccine.

Types of typhoid vaccines:

Parenteral whole cell typhoid vaccine

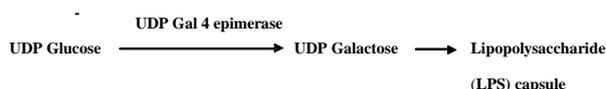
Various types were invented depending on the process of inactivation namely- heat inactivated phenol preserved, acetone inactivated, formal inactivated and alcohol inactivated vaccines. Among these the acetone inactivated and heat inactivated phenol preserved vaccines have been found to be the best in efficacy trials. Initially these were a combination of typhoid and paratyphoid A and paratyphoid B vaccines. However it was realized that paratyphoid is a less common cause of enteric fever and the vaccines have poor protection while at same time increasing the adverse effects. Hence from the TAB vaccine it became TA vaccine and later only T vaccine i.e S.typhi vaccine. The major antibodies that protect against disease are the serum anti flagellar - anti- H antibodies. The anti-H antibody response was better than anti-O antibody or anti Vi antibody response. There is hardly any secretory antibody response or cellular immune response following these vaccines. The efficacy of acetone inactivated preparation is better (79-88%) than the phenol killed (51-66%) vaccine (8,9).

A couple of decades ago only whole cell killed vaccines were available. The vaccine contains

10^9 organisms/ml. The primary dose schedule consisted of two doses given 4 weeks apart. The dose is dependent on the patients age. In children aged 6 months to 10 years, the dose is 0.25 ml while in older children it is 0.5 ml given subcutaneously preferably over the outer aspect of arm behind the posterior border of the distal part of deltoid muscle. The whole cell killed vaccines had the best efficacy when compared to the other types of typhoid vaccines and could be given to children as young as 6 months of age (10). This vaccine fell into disrepute because of its side effects ranging from local reactions like fever, swelling, pain redness, malaise to severe though rare reactions like shock and some reports of death. The adverse reactions were more with the acetone inactivated preparations and because of these problems the vaccines were withdrawn from the market.

Oral Ty21a live vaccine

Using mutagenic techniques, a mutant strain of S typhi was produced which has a mutation in the gal E gene and lacks enzyme Uridine diphosphate galactose-4 epimerase (4). This enzyme is necessary for capsular polysaccharide formation as shown.



This results in incomplete LPS which doesn't allow the bacteria to multiply beyond one or two generations making it immunogenic but not pathogenic (8).

This vaccine was available in 3 forms, gelatin sodium bicarbonate capsule, enteric coated capsule and liquid preparation. Though the liquid preparation had best efficacy in trials it was difficult to mass produce. Only the enteric coated preparation became commercially available containing $2-6 \times 10^9$ CFU of Ty 21a organisms per capsule. The oral Ty21a leads to good serum and secretory antibody response and even cellular immune response. Sero-conversion

occurs in 60-70% of the vaccines (8). Being a live vaccine this vaccine requires stringent temperature maintenance between 2-8°C. Dose consists of one capsule on alternate days for three doses. The vaccine has to be swallowed intact and should never be opened and taken which would render it ineffective by the gastric acid juices. This makes intake of the vaccine possible only in children above 6 years. Care has to be taken not to take too much of hot or cold food items half an hour before and after the dose. Antibiotics that act against typhoid fever should be avoided for a fortnight starting five days before the start of the first dose. Antimalarial drugs chloroquine and mefloquine should be avoided for a period of 24 hours following vaccination as they interfere with multiplication of vaccine strain. It can be simultaneously given with any injectable vaccine. However there should be an interval of 4 weeks between an oral polio vaccine dose and an oral typhoid vaccine dose. The protection begins a week after completion of the dose and lasts for 3-7 years. There are hardly any serious side effects. Nausea, rash, diarrhea, vomiting and fever have been reported in less than 1% of vaccinees(11).

Capsular Vi polysaccharide vaccine

This is a new generation subunit vaccine containing highly purified antigenic fraction of Vi antigen of salmonella typhi. Polysaccharide antigen stimulates B cells directly and T helper cells do not get stimulated. Being T cell independent it can induce only IgM antibody. IgM to IgG switch requires regulation by T helper cells. T independent antigens do not induce the production of memory T cells or memory B cells, so the serum antibody response is not boosted by administration of additional doses of Vi vaccine. As with other T cell independent purified polysaccharide vaccine it is not a good immunogen in children less than 2 years of age and most infants fail to respond to this antigen. Two randomized controlled trials suggest an efficacy of this vaccine in the range of 64%-72% mainly in children above 5 years of age(6,12). A recent study evaluated the

efficacy of this vaccine in the age group above 2 years (13). The level of protective effectiveness for the Vi vaccine was 61%. Children who were vaccinated between the ages of 2 and 5 years had a level of protection of 80% and among unvaccinated members of the Vi vaccine clusters, the level of protection was 44%. The overall level of protection among all residents of Vi vaccine clusters was 57%.

There have been concerns that as this vaccine does not protect against Vi negative salmonella wide spread use might make it the dominant strain causing typhoid fever, though these concerns have been largely unfounded scientifically.

The vaccine is available for use in children 2 years and above. Each dose contains 25µg of purified polysaccharide in 0.5 ml of phenolic isotonic buffer. The vaccine has to be stored between 2-8°C and can be given intramuscularly or subcutaneously. It protects against drug sensitive as well as multi-drug resistant strains of S. Typhi. The protection begins 2-4 weeks after the immunization and lasts for 3-5 years. It offers no protection against salmonella paratyphi A and B. It consists of a single dose which needs to be repeated every three years. The side effects are usually mild in nature ranging from local reactions to systemic in less than 5% of the vaccines. Compared to whole cell killed vaccine reactions are milder and uncommon (14).

Vi Conjugate vaccine:

A major breakthrough in the field of vaccinology has been the method to conjugate polysaccharide vaccines making them T cell dependent leading to immunogenic response even in infants and inducing long and lasting IgG response and T cell memory. After successful development of conjugate Hib, pneumococcal and meningococcal the latest to be developed is the conjugate polysaccharide typhoid vaccine.

The first typhoid conjugate polysaccharide vaccine Vi rEPA was developed by Szu et al in which the Vi

Table 1. Comparison of the various typhoid vaccines

Characteristics	Whole Cell Killed vaccines	Ty21a capsule vaccine	Vi polysaccharide vaccine	Vi polysaccharide conjugate vaccine
Type	Killed	Live	Subunit	subunit
Route	IM/SC	Oral	IM/SC	IM/SC
Doses	2	3	1	2
Revaccination	3-5 year	3-5 year	3 year	?
Immunogenicity	++	+	+	+++
Efficacy	51-79%	35-67%	55-72%	91%
Duration of efficacy	65% at 7 years	62% at 7 years	55% at 3 years	91% at 2.3 years
Herd immunity	?	Yes	?	?
Side effects	++++	+	++	++
Age	>6 months	>6 years	> 2 years	> 6 weeks
Boosting	-	-	-	++
Mass vaccination	Unsuitable	suitable	Suitable	suitable
Availability	No	No	Yes	Yes *

*Peda Typh in India

antigen of typhoid has been conjugated with the non toxic recombinant exotoxin A of the pseudomonas aeruginosa . Successful field trials in Vietnam in 13766 children aged 2-4 years have shown the vaccine to be highly immunogenic (100% showing at least 10 fold increase in Vi antibody levels) with efficacy as high as 93% at 27 months of age when two doses were given at 6 weeks interval and 89% at 46 months post vaccination.. Even with a single dose there was an efficacy of 91% and even the vaccines who developed typhoid had a milder disease (15). Further trials are going on to validate these results especially in the infant age group. The side effects of fever and local reactions were seen in less than 2% vaccines making it very safe.

In India Peda typhTM launched by Bio- Med, Vi capsular polysaccharide has been conjugated with tetanus toxoid toxin. A multi centric trial on 169 volunteers of which 50% were in the age group 3 months to 2 years, 25% in age group 2-5 years and 25 % more than 5 years evaluated its efficacy. The

vaccine (Peda TyphTM) under clinical trial has been claimed to be highly immunogenic in infants and children less than 2 years. However, the small sample size and incompatibility between sample and control groups is a cause for concern and further larger trials with this vaccine need to be conducted. Also, the study has not been published in a peer reviewed journal.

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