

# Typhoid Fever : Present and Future

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## Summary

Typhoid fever (TF), a systemic prolonged febrile illness, continues to be a worldwide health problem especially in developing countries where there is poor sanitation and poor standards of personal hygiene. The worldwide incidence of TF is estimated to be approximately 16 million cases annually with 7 million cases occurring annually in SE Asia alone. More than 600,000 people die of the disease annually. The pathogenesis of TF is beginning to be understood. The clinical features and diagnosis of TF are well known. New diagnostic methods have yet to gain universal acceptance. Traditional treatment with the first-line antibiotics (i.e. chloramphenicol, ampicillin and trimethoprim-sulphamethoxazole) though still being used in most developing countries are gradually being replaced with shorter courses of treatment with third generation cephalosporins or fluoroquinolones especially with the growing incidence of multi-drug resistant *S typhi* strains (MDR-ST). MDR-ST strains are particularly common in the Indian subcontinent, Pakistan and China. The presently available vaccines are far from satisfactory in terms of safety, efficacy and costs. Newer vaccines have been developed and are presently undergoing clinical trials in human volunteers.

**Key words:** Typhoid fever, Multi-drug resistant *Salmonella typhi*, Treatment, Vaccines

## Introduction

Typhoid Fever (TF) is a systemic prolonged febrile illness caused by *S typhi*. It continues to be a worldwide health problem, especially in developing countries where there is poor sanitation, poor standards of personal hygiene and contaminated food. Other contributing factors include delay in diagnosis, emergence of antibiotic-resistant strains, problems in the identification and management of carriers and the lack of availability of a safe, effective and cheap vaccine. Increase in regional movement of large numbers of migrants is another important factor in the Asia-Pacific region where there is rapid economic expansion. TF is also a problem in developed countries although the reason for this is different as most of the disease is acquired abroad or from chronic carriers who handle food.

## Epidemiology

Current estimates from the WHO suggest that the worldwide incidence of TF is approximately 16 million cases annually with >600,000 deaths<sup>1</sup>. More than 62% of TF occur in Asia and of these, 7 million cases occur annually in South East Asia. Other countries with a high incidence of TF include Central & South America, Africa and Papua New Guinea. The population-based annual incidence in endemic developing countries varies between 150 per 100,000 population in S. America to > 900 per 100,000 in Asia<sup>2</sup>.

In endemic countries, TF appears to be predominantly a disease of school children and young adults. In an outbreak of 649 cases in Penang in 1987, 52% of cases was between the ages of 1-24 years. In Indonesia, 3-19-year-olds accounted for 91% of typhoid cases<sup>3</sup>.

In developed countries, TF is acquired abroad or from chronic carriers who handle food. In a reported 16-year study of enteric fever in Scotland involving 267 cases, 81% of the patients gave a history of recent travel, 32 chronic carriers were also identified in that study. UK residents of Asian ethnicity returning from the Indian subcontinent accounted for 46% of the cases of typhoid fever<sup>4</sup>. Immunisation of travellers could therefore contribute significantly to reducing the incidence of TF.

The largest outbreak of TF in USA since 1981 occurred in 1989 among guests and staff of a New York Hotel. There were 43 culture-positive and 24 probable cases amongst the guests. 21 were hospitalized and 2 had bowel perforation. The cause of the outbreak was thought to be contaminated orange juice. *S typhi* was isolated from the stool of an asymptomatic food worker who handled orange juice but who was not known to be a typhoid carrier<sup>5</sup>.

### Pathogenesis

In contrast to other *Salmonella* species, human beings are the only reservoir for *S typhi*. The bacteria can survive several months in soil or water. TF is transmitted by faecally-contaminated water and food in endemic areas and especially by carriers handling food in developed countries.

The size of the inoculum and the type of vehicle in which the organisms are ingested will influence both the attack rate and the incubation period. A dose of  $10^9$  organisms will induce infection in most cases whereas a dose of  $10^3$  or less organisms will rarely produce symptoms in otherwise healthy individuals. *S typhi* is an invasive intracellular bacterial pathogen that possesses several virulence factors which allow it to enter and survive within its human host. Little is known about these factors principally because of the lack of a suitable animal model to test the hypothesis regarding specific *S typhi* virulence factors using genetically altered mutants. This is in contrast to virulence factors for *S typhimurium* which have been extensively studied. It appears that *S typhi* virulence is complex requiring several virulence factors for full pathogenicity. Some of the virulence factors that have been implicated include lipopolysaccharide (LPS) and

other toxins, motility, adhesins such as fimbriae, iron siderophores, Vi antigen and others<sup>6</sup>.

Host factors may also play a role. Gastric hypoacidity, for example, may increase the attack rate as gastric acid kills most of the bacilli that have been ingested. *S typhi* which escapes the gastric acid of the stomach will penetrate the small intestinal mucosa and reach the mesenteric lymph nodes via the lymphatics. The bacteria will then multiply and enter the blood via the thoracic duct (primary bacteremia). Most of them will be phagocytosed. Those remaining will proceed to the reticuloendothelial cells (RES) where they will multiply silently during the incubation period (usually 10-14 days but may vary between 3 days to 3 months depending on the infecting dose). At the end of this period, bacilli will be released again into the blood stream in large numbers, heralding the onset of the illness (secondary bacteremia).

The two most important sites normally affected are the Peyer's patches in the small intestine and the gall bladder. Patients with pre-existing gall bladder disease are prone to become carriers.

### Clinical features

While the incubation period of TF is 10-14 days, the duration of illness is approximately 4 weeks. The illness begins insidiously with mounting fever, headache, vague abdominal pain and constipation during the **first week**. Relative bradycardia and a palpable spleen may be present at the end of the 1st wk. During the **second week**, the patients will become dull and apathetic with a sustained fever. The abdomen will become distended and rashes (rose spots) may appear over the lower chest and upper abdomen between the 7-10th day of illness. During the **third week**, the patient will assume the "typhoid state" which is a state of prolonged apathy, toxæmia, delirium, disorientation and/or coma. Scanty bowel sounds will be heard over the distended abdomen. Diarrhoea will then become apparent. If left untreated by this time, there is a high risk of intestinal haemorrhage and perforation. Otherwise, the patient usually recovers by the **fourth week**.

Variations to the typical clinical picture described above

have been reported e.g. in patients with multiple drug resistance (MDR), in children where the onset may be more abrupt with diarrhoea occurring right from the onset, as well as in HIV-positive patients<sup>7</sup>. There are also patients who do not develop such high fever during the illness and may remain undiagnosed (*walking typhoid*).

Children with Multidrug Resistant Typhoid Fever (MDR-TF) are more toxic at admission and have a higher risk of life-threatening complications such as endotoxic shock, disseminated intravascular coagulation, encephalopathy, myocarditis and paralytic ileus<sup>8</sup>. This is thought to be due to the delay in initiating treatment rather than the virulence of the organism. The overall mortality reported during MDR-TF epidemics is between 7-16% which is higher than the 2% seen in drug-susceptible TF.

### Carrier state

Usually, only 4-5% of patients excrete organisms after 3 months. Of these 1-3% remain positive at the end of 1 year. This is due to persistent infection of the gall bladder resulting in *S typhi* being discharged into the gut and be excreted in the faeces. Carriage is often associated with cholecystitis and gallstones. The likelihood of becoming a chronic carrier increases with age, especially in women.

### Complications

Gastrointestinal complications are the commonest and manifest usually as haemorrhage and intestinal perforation (5-10%). One of the most lethal complications of TF is ileal perforation which especially affects young men. In a recent literature review which looked at 52 reports of TF all over the world since 1960, 1,990 cases of intestinal perforation were found. The overall frequency of intestinal perforation in TF was 3% with an overall mortality rate of 39.6%<sup>9</sup>. Other complications include cardiovascular insufficiency, myocarditis, meningitis, hepatic involvement (10%), cholecystitis, pleuropulmonary involvement, osteitis and thyroiditis.

### TF and cancer

A study of cancer risk in chronic T and PT carriers

showed a large excess of cancer of gall bladder, pancreas, colorectum, lung and all neoplasms. However only those with long-term typhoid carriage appear to be at risk. This has important implications for cancer prevention. Eradication for chronic carriage by use of antibiotics or elective cholecystectomy should be re-emphasised in the light of this finding<sup>10</sup>.

### Diagnosis

The diagnosis of TF has traditionally relied on the isolation of *S typhi* or *S paratyphi* from the blood, faeces, bone marrow or intestinal secretions.

The choice and time of collection of specimens are important. White blood cultures are positive in 90% of cases during the 1st week, stool cultures are usually positive (45-65%) during the 2nd - 3rd wk. Urine culture are only positive (30%) after the 3rd wk and they are less sensitive. Bone marrow aspirates cultures give the best confirmation with 85-95% recovery. Since it is often difficult to obtain bone marrow aspirates in many endemic areas, only blood specimens are cultured in most cases. Blood culture can detect only 45-70% of patients with TF depending on the amount of blood sampled, the bacteremic level of *S typhi*, the type of culture medium and the length of the incubation period.

The Widal test measures titres of serum agglutinins against somatic (O) and flagellar (H) Antigens and usually begin to appear during the 2nd wk. This test is however time-consuming and requires paired sera for interpretation. Accepted titres in endemic areas are not known and are difficult to interpret. The test is also only moderately positive (30% of positive blood culture specimens have negative results) and cross-reactions with other salmonella strains have been reported.

The limitations of the above traditional tests have prompted other novel tests to be developed.

Polymerase chain reaction (PCR) can be performed on peripheral mononuclear cells using primers that amplify a unique 343-base fragment of the *S typhi* flagellin gene<sup>11</sup>. The test is more sensitive than blood culture alone (92% compared with 50-70%) but requires significant technical

expertise. The practical value of PCR would be the detection of *S typhi* DNA in blood specimens from patients with suspected clinical findings but with negative cultures. The low level of bacteremia in typhoid patients can cause negative blood cultures especially those who have been previously treated with antibiotics.

Several new serologic tests have been developed to aid in the diagnosis of TF. However none of these is sufficiently sensitive, specific or rapid enough for clinical use.

## Treatment

### Traditional treatment

Traditional treatment of TF is with Chloramphenicol, Ampicillin and Trimethoprim-sulphamethoxazole (TMP-SMZ), the so-called first-line antibiotics for TF. Defervescence is usually achieved in 4-8 days and cure rates of 85-100% have been reported with these drugs. Several disadvantages of traditional treatment include low intracellular penetration of these drugs in macrophages and gall bladder wall, long duration of treatment and frequent relapses, (5-10%). An emerging problem of much concern is the emergence of resistant strains.

### Multi-Drug Resistant *S typhi* (MDR-ST)

The emergence of multiple drug resistance to *S typhi* (MDR ST) has been of major concern in recent years. MDRST is defined as strains of *S typhi* resistant to all three first line antibiotics for TF<sup>12</sup>. The number of reported Multi-Drug Resistant Typhoid Fever (MDR TF) increased rapidly throughout the world from 1989 onwards with most of the cases being from the Middle East and Asia especially in the Indian subcontinent, Pakistan and China. Since 1994, more countries have reported resistant strains and these include Philippines and Bangladesh<sup>13</sup>. Factors responsible for its emergence include indiscriminate antibiotic use and travel. The dramatic increase in volume and speed of world travel allows for the rapid spread of MDR-ST. A study in Singapore reported that 17.4% of patients with TF had imported MDR ST after recent travels to the Indian subcontinent<sup>14</sup>.

Presently, MDR ST is not a major problem in most SE Asian countries. In Singapore and Indonesia less

than 3% of *S typhi* isolates are resistant in the indigenous population<sup>15</sup>. Unpublished data from the Institute of Medical Research, Malaysia showed that the resistance of *S typhi* to Ampicillin increased from 0.5% in 1990 to 5.7% in 1995. Chloramphenicol resistance increased from 3.4% in 1991 to 5.7% in 1995. Resistance to all 3 first line antibiotics had also increased from 3.4% in 1991 to 5.7% in 1995.

Resistance to these agents is associated with a plasmid, the spread of which may be stimulated by selective pressure resulting from continual use of these drugs. Administration of antibiotics to patients with Salmonella gastroenteritis may be a factor. In one study, the majority of patients with MDR ST had received at least one antibiotic before presentation<sup>12</sup>.

With regards to MDR TF, the world can be categorised into 3 areas i.e. the *endemic* (Asia, Africa, Latin America and parts of China) the *pseudo-endemic* (Middle East countries) and the *non-endemic* (developed countries) zone depending on the observed percentage of resistant *S typhi* isolates in particular outbreaks<sup>12</sup>. In the endemic zones, 50-80% of *S typhi* isolates comprised MDR-ST strains. In the pseudoendemic and non-endemic regions the percentage of MDR-ST strains are 5-30% and <5% respectively.

Children with MDR TF have been found to be more ill at presentation, have a longer duration of illness and increase in mortality rate. In adults no special clinical features have been identified<sup>8</sup>.

### Short Course Treatment of Typhoid Fever

Studies evaluating the results of short course therapy for TF has attested to the efficacy of both fluoroquinolones and third-generation cephalosporins. Of the latter group, ceftriaxone has been shown to be the most effective compared to cefoperazone and cefotaxime. Tables I and II show the various regimens that have been used in the treatment of typhoid fever using cephalosporins (Table I) and fluoroquinolones (Table II). Table II also shows the percentage of MDR-TF in some of the studies.

From Table I it is obvious that a shorter course of

treatment with ceftriaxone is just as effective as the traditional 14-day course of treatment with chloramphenicol<sup>16,17</sup>. Most clinicians use a 3-day schedule when using ceftriaxone with good results. Table II shows the efficacy of fluoroquinolones in the treatment of TF. A 7-day regimen is often recommended. However, studies in Vietnam, using ofloxacin, especially on children with TF, used a 3-5 day regime with excellent results as well<sup>25,26</sup>.

Although cure rates for both third-generation cephalosporins and fluoroquinolones are similar (90-100%), the mean times to defervescence is longer with the former (5-8 days compared to 3-5 days). This prolonged period of fever is probably due to the relatively poor intracellular penetration of cephalosporins against *S typhi* compared to quinolones.

Most patients with MDR TF will respond to either fluoroquinolones or third generation cephalosporins. Treatment with either oral ciprofloxacin or IV ceftriaxone can both achieve a 95% cure rate with low

relapse and carriage rates following clinical cure of TF<sup>17,22,23</sup>. The advantages of a fluoroquinolone would be its favourable pharmacokinetic properties, its low toxicity profiles, its ability to penetrate into macrophages (site of *Salmonella* replication), the low risk of plasmid-mediated resistance and the fact that it can be given orally. They should however be used advisedly because indiscriminate use may result in early emergence of resistance. There are already reports of resistance to ciprofloxacin in children treated for TF<sup>29</sup>.

The shorter treatment regimen with and the shorter period of hospitalization with cephalosporins and quinolones will help improve compliance, limit toxicity and help reduce costs which may well make a difference in developing countries where TF is endemic.

#### Treatment of TF in children

Third generation cephalosporins have been found to be very safe in children but they are expensive and have to be given parenterally<sup>12</sup>. There are some

**Table I**  
**Treatment of typhoid fever using third-generation cephalosporins**

First author (year)	Drug	Dose	Duration (days)	No. of patients	Clinical cure (%)	FCT* (days)	Number of patients who relapsed n (%)
Acharya (1995) <sup>16</sup>	Chloramphenicol	40-60mg/kg/d	14	23	83		0
	Ceftriaxone	2gm/d or 50 mg/kg/d	3	23	87		0
Lasserre (1991) <sup>17</sup>	Ceftriaxone	3gm/d	3	19	95	4-13	22 (11)
	Ceftriaxone	4gm/d	3	20	100	5-11	0
	Chloramphenicol	2-3gm/d	14	20	100	3-9	3 (15)
Hien TT (1994) <sup>18</sup>	Ceftriaxone	3gm/d	3	25	72	8.2	1 (4)
Bhutta (1994) <sup>19</sup>	Cefixime	20mg/kg/d	12+	50	96	5.3	2 (4)
Girgis (1994) <sup>20</sup>	Cefixime	10mg/kg/d	14	25	88	8.3	1 (4)

\*FCT: Fever clearance time

**Table II**  
**Treatment of typhoid fever using fluoroquinolones**

First author (year)	Drug	Dose	Duration (days)	No. of patients	Efficacy rate (%)	FCT* (days) Mean (SD) or range	Number of patients who relapsed n (%)	MDR-ST
Uwaydah (1992) <sup>21</sup>	Ciprofloxacin	500mg bd	7-10	34	100	4.9	0	43.5%
	Ciprofloxacin	750mg bd	7-10	28	100	5.2	1 (4)	
Wallace (1993) <sup>22</sup>	Ciprofloxacin	500mg bd	7	20	100	4	0	50%
	Ceftriaxone	3gm/d	7	22	73	5.2	1 (5)	
Alam (1995) <sup>23</sup>	Ciprofloxacin	500mg bd	10	35	100	4.2	0	52%
	Ciprofloxacin	500mg bd	14	34	100	4.9	2 (6)	
Smith (1994) <sup>24</sup>	Ofloxacin	200mg bd	5	22	100	3.4	0	63%
	Ceftriaxone	3gm/d	3	25	72	8.2	1 (4)	
Hien TT (1995) <sup>25</sup>	Ofloxacin	15mg/kg/d	3	118	100	2.5	0	91%
	Ofloxacin	10mg/kg/d	5	110	100	3.0	1 (1)	
Vinh H (1996) <sup>26</sup>	Ofloxacin	15mg/kg/d	2	53	89	4.2	0	86%
	Ofloxacin	15mg/kg/d	3	47	96	4.4	1	
Ait-Khaled (1990) <sup>27</sup>	Perfloxacin	400mg bd	7	37	89.2 (94.6)	5.1	2 (5.4)	
Loza (1990) <sup>28</sup>	Perfloxacin	400mg bd	7-8	50	100	4	0	

concerns about using quinolones in children as they are potentially toxic to growing cartilage. Short courses of fluoroquinolones have however been shown to be safe<sup>25,26</sup>. A recent study showed no evidence of acute joint toxicity and height velocity in 326 children, aged 1-14 years, treated with single short courses of fluoroquinolones, compared to age-matched controls<sup>30</sup>.

Newer drugs that have been studied for the treatment of MDR-TF are Aztreonam, Azithromycin and Furazolidine. None of them has been well accepted as alternatives and further studies are awaited.

#### Empiric therapy for MDR-TF

Empiric therapy for MDR-TF should be considered for patients who are critically ill, develop complications during conventional therapy or has a history of travel to endemic areas. The current practice is to treat all

adults with suspected MDR-TF with either quinolones or ceftriaxone. Children under 10 years of age should be treated with ceftriaxone although recent data showing the safety and efficacy of short-courses of fluoroquinolones may well make this group of drugs a viable alternative as they can be given orally.

#### Prevention

##### Public Health Measures

Provision of safe water supply, improved sanitation and food handling practices will reduce the incidence of TF<sup>15</sup>. The annual incidence of TF in Singapore between 1980 and 1989 declined fivefold<sup>31</sup> and in Malaysia there was a similar decline from 17.37 per 100,000 population in the late 1970s to 4.46 per 100,000 population in 1995<sup>32</sup>.

**Table III**  
**Currently available vaccines for typhoid fever**

Type	Schedule	Efficacy (%)	Duration of protection	Side effects	Remarks
<b>Inactivated</b>					
• Parenteral whole cell vaccine (IM/deep SC)	Primary: 2 doses 0.5ml each 6 wks apart. Booster: every 3 yrs	60-67%	7 years	Frequent side effects Severe local reaction	Still used for immunocompromised patients in place of live vaccine
• Parenteral capsular polysaccharide vaccine Vi (ViCPS)	Single injection 25 mcg (0.5ml) No booster effect	64-72 95-100 (Tacket, 1986 & Arnold, 1992)	3 years	Well tolerated Local mild reactions	Can be used for children >2 years old Can be combined with other vaccines Not contraindicated in immunosuppressed patients
<b>Attenuated live vaccine</b>					
• Oral Ty21a mutant of <i>S typhi</i>	Primary: 3-4 capsules taken on alternate days Booster: every 5 years	60-96	5-7 years	Well tolerated	Not for children <6 years old* Not given together with antibiotics/Mefloquine Contraindicated in immunosuppressed patients

\* Ty21a vaccine found to be safe with 70% seroconversion in a Placebo-controlled trial of Thai children < 7 years old, probably because of liquid formulation used<sup>38</sup>

### Carriers

Carriers who are refractory to treatment should not be employed for food preparation. Those who have been successfully treated should be provided with proper instructions on personal hygiene.

### Vaccines

Despite effective treatment for TF, the increasing reports of MDR ST make it necessary for vaccines to be used as a public health tool in developing countries. Table III shows the various properties of currently available vaccines

### Adults

#### *Whole cell vaccine*

The heat-phenol inactivated whole-cell vaccine is the first parenteral vaccine which is available. Two doses (0.5 ml. each) administered 4-6 weeks apart are required. It confers some protection but at the expense of unpleasant systemic side effects and discomfort at the site of injection. It is becoming less popular.

#### *Vi polysaccharide vaccine*

The newer Vi polysaccharide vaccine (ViCPS) is composed of purified Vi virulence antigen which is the capsular polysaccharide elaborated by *S typhi* isolated from blood cultures. Antibodies to Vi are believed to be associated with TF protection. Compared with the older parental typhoid vaccines, ViCPS results in an equivalent immune response and protective efficacy with fewer side effects. A single 25 mcg injection of this vaccine, given IM or SC, produced seroconversion in over 90% of healthy adult volunteers in USA and Europe<sup>33</sup>. Studies carried out in endemic areas like Nepal and South Africa, provided 75-80% protection against blood-culture confirmed TF. Protection is obtained after the 10th day and lasts 3 yrs. It is well tolerated with only minor reactions in <10% of subject<sup>34,35</sup>. It appears to be a vaccine that is safe, immunogenic and efficacious and with good subject compliance. It is also safer than whole cell vaccine and may be used in children. Combination with all other vaccines is possible and there is no contraindication in immunocompromised patients.

The efficacy of this vaccine however has not been studied in travellers from non-endemic areas to endemic typhoid areas. There are also no controlled comparative efficacy studies of this vaccine with the previously available heat-phenol activated vaccine and the oral liver-attenuated Ty21a vaccine.

#### *The oral Ty21 a vaccine*

The oral vaccine is a live-attenuated Ty21a strain of *S typhi*. Three doses of this enteric-coated vaccine given within one week provided 67% efficacy during the first 3 years of follow-up<sup>36</sup> while four doses given within eight days were shown to be more effective than three doses<sup>37</sup>. It is cheaper than the parenteral vaccines and has few side effects. It is however contraindicated in patients with immunodeficiency. It also requires refrigeration for storage.

#### *Children*

The risk of infection in children under one year of age is low. Immunisation with whole cell vaccine is not recommended in this age group. The Vi polysaccharide vaccine has been shown to be useful in children as young as 2 years of age. A protective efficacy of 75% in children of >5 years of age has also been demonstrated<sup>38</sup>. Children under 18 months, however, may show suboptimal response to this vaccine. Its use therefore should be governed by the likely exposure to infection.

Oral vaccine is not suitable for children < 6 years of age. However, a placebo-controlled trial of Thai children aged 7 years or younger, showed that it was a safe vaccine with an overall seroconversion rate of 70% that increased with age 17<sup>38</sup>. This high seroconversion rate may have been due to an improved liquid vaccine formulation and to the high prevalence of previous *S typhi* infection in this population.

#### *HIV-positive individuals*

Only parenteral vaccines should be used. Oral vaccines which contain live organism are contraindicated.

All three vaccines have been reported to have an efficacy of approximately 70% with no protection for 14 days after completion of the primary vaccine series in all of them. The oral live-attenuated Ty21a vaccine is cheaper than the parenteral vaccines and is effective

for 5 years while the parenteral vaccines are only effective for 3 years. The choice of the vaccine will therefore depend on the cost and host factors (eg. age, compliance and immunocompetence status).

Vi polysaccharide vaccine is recommended for the following indications<sup>39</sup>,

- (i) for imminent prolonged travel to endemic countries when refrigeration requirements are not possible.
- (ii) for children age 2-6 years in whom the oral capsules are not recommended unless the liquid formulation of Ty21a is available.
- (iii) for travellers using mefloquine for malaria prophylaxis or who are taking an antimicrobial agents at the time the typhoid vaccine is required.
- (iv) in travellers who are immunocompromised or have antibodies to HIV
- (v) individual preference for a single injection rather than a four-capsule series taken over a 7-day period.

#### **New vaccines**

The newer vaccines presently being studied include new generations of attenuated *S typhi* as live oral vaccines and parenteral Vi polysaccharide-carrier protein conjugate vaccines.

#### **Attenuated *S typhi* strain CVD 908 and CVD 908-*htr A***

The attenuated *S typhi* strain CVD 908 is well tolerated and highly immunogenic following a single oral dose in clinical trials in humans. At  $5 \times 10^7$  cfu, 92% of the subjects studied manifest serum IgG O antibody seroconversion and evidence of priming of the intestinal immune system (gut-derived IgA O antibody-secreting cells or ASCs). A significant number of them manifested silent vaccinaemias which did not appear to have much clinical relevance, however<sup>40</sup>.

#### **CVD 908-*htr A***

The CVD 908-*htr a* strain is formed as a result of deletion mutation in gene *htr A* of CVD 908. In the mouse model, the inactivation of this gene was associated with attenuation of the wild type *S typhimurium*. It appeared to be as well tolerated as



CVD 908 with an excellent immune response (91% of subjects studied manifested significant increases in the serum IgG O antibody levels). Identical responses with comparable doses of CVD 908 were also demonstrated. No vaccinaemias however were observed with this vaccine. Both CVD 908 and CV 908-*htr* A are presently being studied in clinical trials to assess safety, efficacy and immunogenicity<sup>40</sup>.

### The parenteral Vi polysaccharide-carrier protein conjugate vaccines

The principal advantage of the Vi conjugate vaccine over the purified Vi polysaccharide is its behaviour as a T-lymphocyte-dependent antigen and animal studies have shown that the serum Vi antibody titres were boosted with subsequent doses of this vaccine<sup>40</sup>. The purified Vi polysaccharide (ViCPS) in contrast, behaves like T-lymphocyte-independent antigen with no booster effect observed in the serum antibody response with additional dose of the vaccine. Also, the immunogenicity of ViCPS in infants was somewhat less than that of older children. Further clinical studies in humans with Vi conjugate vaccines are ongoing.

The expected advantages of Vi conjugate vaccines compared to ViCPS would include the higher antibody titres following the initial vaccine dose, the induction of memory allowing a booster effect of Vi antibody titres following the 2nd immunisation and the higher lever of protection conferred.

### Conclusion

TF is a treatable disease today. Improvement in personal hygiene and sanitation, early diagnosis and better treatment options using more potent drugs have all improved the outcome of TF. However, the increasing reports of MDR ST is a cause for concern. Possible contributing factors, which include the misuse of antimicrobials and migration of human populations, need to be checked. Disease surveillance needs to be improved. Ongoing studies of salmonella pathogenesis will help us to understand better intracellular bacterial survival with the prospect of the development of new attenuated *S typhi* strains as oral vaccines and as multivalent vaccine vectors.

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## CONTINUING MEDICAL EDUCATION

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## MCQs for the Article on Typhoid Fever : Present and Future

1. The rose spot seen in typhoid fever:
  - a. is a poor prognostic sign
  - b. begins on the extremities
  - c. is presented by petechiae
  - d. does not occur in Paratyphoid Fever
  - e. usually lasts a week or more
  
2. The following statements about the diagnosis of typhoid fever are true:
  - a. Blood cultures may be positive in only 50-70% of patients
  - b. Stool cultures will yield organisms in only 50% of patients
  - c. Antibody titres against the O and H antigens are always positive when blood cultures are positive
  - d. Polymerase chain reaction will only be useful if the level of bacteraemia is high
  - e. Urine cultures are only positive in the first 3 weeks of the illness
  
3. The following are true of fluoroquinolones in the treatment of typhoid fever:
  - a. They are able to penetrate the macrophages which are the sites of *Salmonella* replication
  - b. The risk of plasmid-mediated resistance is high
  - c. Resistance to quinolones has not yet been reported
  - d. Using quinolones as treatment for typhoid fever can achieve a 95% cure rate
  - e. The mean time to defervescence is longer with quinolones compared to cephalosporins
  
4. The following are true of vaccines used against typhoid fever:
  - a. The heat-phenol inactivated vaccine confers 90% protection against typhoid fever
  - b. The parenteral capsular polysaccharide vaccine (ViCPS) requires 2 injections 4-6 weeks apart for optimal effect
  - c. The Oral Ty21 a mutant vaccine has a duration of protection of at least 10 years
  - d. The parenteral whole cell vaccine cannot be used for immunocompromised patients
  - e. The ViCPS cannot be combined with other vaccines as it will produce a nasty local reaction
  
5. The following about typhoid fever are true:
  - a. Human beings are the only reservoir for *S typhi*
  - b. The size of the inoculum does not influence the incubation period of typhoid fever
  - c. *S typhi* are resistant to gastric acid
  - d. Carriers of *Salmonella typhi* are at increased risk of developing carcinoma of the gall bladder
  - e. Perforation through the proximal ileum is the commonest complication of typhoid fever