World Health Organization
Global Vaccine Safety
Essential Medicines & Health Products
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INFORMATION SHEET
OBSERVED RATE OF VACCINE REACTIONS
TYPHOID VACCINE

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The Vaccines

Several typhoid vaccines are currently available and these can be administered orally or parenterally and are safe and efficacious for preventing typhoid fever (Fraser et al, 2007, see Table 1). Adverse events are mild in nature.

Oral vaccine

Live attenuated vaccine: (Ty21a) (Vivotif TM, Berna Biotech, Crucell; Zerotyph caps, Boryung). This vaccine was developed in the early 1970s, requires at least three doses for optimal protection, and is supplied as gelatin capsules coated with phthalate or sachets containing lyophilised Ty21a, a mutant strain of Salmonella enterica serovar Typhi (S. Typhi).

Parenteral vaccines

Monovalent typhoid vaccines: Vi polysaccharide is a well-standardized antigen that is effective in a single parenteral dose, is safer than whole-cell vaccine, and may be used in children 2 years of age or older (Plotkin and Bouveret-LeCam, 1995). The following vaccines contain the Vi antigen.

Capsular polysaccharide vaccines: (ViCPS) (TypherixTM, GSK; Typhim ViTM, Sanofi Pasteur; TypBar, Bharat Biotech; Shantyph, Shanta Biotech; Typho-Vi, BioMed; Zerotyph inj, Boryung, South Korea; Typhevac-inj, Shanghai Institute of Biological Products) is a one-dose injectable solution consisting 25 µg Vi antigen prepared from the surface polysaccharide of S. Typhi strain Ty2.

***Conjugate vaccine*:** (Vi-TT), where the Vi antigen is coupled to a carrier protein. At the time of review there is only one licensed conjugate vaccine (Peda-typhTM, BioMed). It consists of Vi coupled to tetanus toxoid (TT). This vaccine has been licensed only in India and only limited clinical data are available to document its safety and immunogenicity. Multiple other conjugates are in development consisting of Vi linked to tetanus toxoid or to other carrier proteins.

Multivalent combination vaccines: Combined ViCPS and hepatitis A vaccines (HepatyrixTM, GSK; ViatimTM, Aventis Pasteur) contain 25µg Vi polysaccharide antigen of S. Typhi combined with either 1440 EL.U. or 160 AU of inactivated hepatitis A virus grown in human diploid cells and adsorbed onto aluminium hydroxide.

Types of vaccines

Route	Vaccine antigens	Excipients
Oral	**Live attenuated vaccine (Ty21a) (Vivotif TM, Berna, Crucell; Zerotyph caps, Boryung). Each coated capsule contains 2 to 6 × 109 colony-forming units (CFU) of Ty21a, 5 to 50 × 109 nonviable Ty21a.** **Vaccine sachet contains 2 to 10 × 109 CFU of Ty21a, 5 to 60 × 109 nonviable Ty21a**	**Capsules:** **Sucrose: 26-130 mg, Ascorbic acid: 1–5 mg , Amino acid mixture: 1.4–7 mg , Lactose: 100–180 mg, Magnesium stearate: 3.6–4.4 mg.** **Sachets: 15 to 250 mg of sucrose, 0.6 to 10 mg of ascorbic acid, 0.8 to 15 mg of an amino acid mixture, 1.5 g of lactose, and 20 to 30 mg of aspartame.**
Parenteral	**Capsular polysaccharide vaccines (ViCPS) Each immunizing dose contains 25 µg of Vi polysaccharide, less than 1.25 mg of phenol in Typhim Vi and 1.1 mg in Typherix, and 0.5 mL (or as much as will suffice) of isotonic buffer (4.15 mg sodium chloride; 0.065 mg sodium dibasic phosphate, 2H2O; 0.023 mg sodium monobasic phosphate, 2H2O; and 0.5 mL [or as much as will suffice] of water for injection).** **Conjugate vaccine (Vi-TT),** **Vi antigen is coupled to tetanus toxoid. (Heretofore, there is only one licensed conjugate vaccine, Peda-typhTM, made by BioMed. One dose (0.5 ml) contains: Vi polysaccharide of Salmonella typhi 5 µg conjugated to 5 µg of Tetanus toxoid protein in isotonic saline.**	**0.25 - 0.5% phenol as a preservative**

Adverse events

Mild adverse events

Oral vaccine - Live attenuated vaccine (Ty21a)

Studies in volunteers and field trials have shown that adverse events are mild and consisted of diarrhea (1.2-3.9%), abdominal discomfort, nausea, vomiting (0.5-2.3%), fever (0.3-4.8%), headache and rash or urticaria (Gilman et al, 1977, Wahdan et al, 1980, Black et al, 1983, Levine et al, 1986, Cryz, 1993, Engels et al, 1998, Levine, 1999). Studies that have compared Ty21a vaccine to placebo show no significant increase in adverse events over placebo (Black et al, 1990, Simanjuntak et al, 1991). The liquid formulation was associated with more nausea and abdominal pain. Enteric capsules were associated with more mild adverse events (i.e. any adverse event) in one trial that reported this outcome (Fraser et al, 2007).
Review of the VAERS (Vaccine Adverse Event Reporting System) data from the United States between July 1990 and June 2002 identified 345 reports associated with Ty21a vaccine at a total frequency of 9.7 events / 100,000 doses distributed and a rate of 0.59 events / 100,000 doses distributed for serious events. In addition to previously recognized events such as gastroenteritis-like illness, the unexpected symptoms, fatigue and myalgia, were reported in association with Ty21a vaccination. The causal association between these events and typhoid vaccination cannot be established by passive reporting.

Parenteral vaccines

Monovalent vaccines:

ViCPS vaccines - In several trials, ViCPS produced the following adverse events; pain at the injection site (up to 80% of vaccinees), erythema or induration >1 cm (7%), fever (0–12%) and headache (1.5– 3%) (Tacket et al, 1986, Klugman et al, 1987, Cumberland et al, 1992, Keitel et al, 1994, Mirza et al,1995, Engels et al, 1998). In a phase 4 effectiveness study which enrolled >37,000 participants in India, common adverse events were erythema 4%, pain at injection site 18%, axillary temperature of >37.5C 1% and fatigue 4%. There were 10 deaths at 30 day follow up, none judged causally related with vaccination (Sur et al, 2009). When compared with other vaccines the ViCPS vaccine produced fewer local and systemic reactions than did a control 23-valent pneumococcal vaccine (Acharya et al, 1987) or a, control bivalent meningococcal vaccine (Klugman et al, 1987), or Hepatitis A vaccine (Sur et al, 2009). In one study, ViCPS produced less than half the frequency of local and systemic adverse events as the whole cell inactivated vaccine, probably because ViCPS contains negligible amounts of bacterial lipopolysaccharide (Cumberland et al, 1993).

Review of the VAERS data from the United States between July 1990 and June 2002 identified 321 reports associated with ViCPS. Reporting rates were 4.5 events per 100,000 Vi doses (for 1995–2002) and 9.7 events per 100,000 Ty21a doses (for 1991–2002). Serious event reporting rates were 0.34 events per 100,000 doses for Vi and 0.59 events per 100,000 doses for Ty21a. The most commonly reported symptoms included injection site reactions, fever, headache, rash, urticaria, abdominal pain, and nausea. Reported unexpected symptoms included dizziness and pruritus, and these were usually a transient component of the clinical picture accompanying other expected conditions. (Begier et al., 2004).

The vaccine is well tolerated, inducing only minor reactions in fewer than 10% of subjects. An antibody response occurred in about 90% of subjects and lasted about 3 years.

Vi-TT - There are no published large-scale prelicensure data or postlicensure data describing the safety of Peda TyphTM. The only safety data are from a small prelicensure clinical trial.

Combination vaccines:

Combined ViCPS and hepatitis A vaccines - Concurrent administration of a typhoid ViCPS with inactivated hepatitis A vaccine is considered safe (Dumas et al, 1997). Pain at the injection site was the most frequently reported local symptom and headache the most frequently reported systemic adverse event. All symptoms resolved without sequelae (Beran et al, 2000).

Serious adverse events

Oral vaccines

No serious adverse events have been reported for the Ty21a oral typhoid vaccine. Review of the VAERS data from the United States between July 1990 and June 2002 identified four serious adverse events that were reported when oral typhoid vaccine was solely administered: non-GBS demyelinating disease, symptoms of gastroenteritis, sepsis, and rheumatoid arthritis (Bergier, et al., 2004). The causal association between these events and Ty21a oral typhoid vaccine cannot be established on passive surveillance.

Parenteral vaccines

No serious adverse events have been reported following ViCPS, the combined ViCPS/hepatitis A or Vi-rEPA typhoid vaccines (Lin et al., 2001). Review of the VAERS data from the United States between July 1990 and June 2002 identified case reports of three serious adverse events when parenteral typhoid vaccine was solely administered: GBS, severe allergic reaction and acute abdomen (Bergier, et al., 2004) (see comment above).

Other safety issues

Immunodeficiency - Ty21a can be administered to HIV-positive, asymptomatic individuals as long as the T-cell count (CD4) is above 200/mm3 (WHO, 2000). ViCPS vaccine is also considered safe for HIV-infected individuals (WHO, 2000).

Summary of mild and severe adverse events

Nature of Adverse event	Description	Rate/doses
Mild		
Ty21a	**Fever** **Vomiting** **Diarrhoea**	**0.3-4.8 per 100** **0.5-2.3 per 100** **1.2-3.9 per 100**
ViCPS	**Low grade fever (<39C)** **Local erythema** **Soreness** **Swelling**	**0 – 2 per 100** **3-21 per 100** **8 – 33 per 100** **2 – 17 per 100**
Vi-TT	**Injection site pain** **Fever**	**Data not available** **Data not available**
Severe	**Case reports**	**Unconfirmed**

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