



## Conference report

**Working Group on quality, safety and efficacy of typhoid Vi capsular polysaccharide conjugate, vaccines, Jeju, Republic of Korea, 5–7 September 2012**

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## ABSTRACT

Typhoid fever is a gastrointestinal disease transmitted through the ingestion of contaminated water or food. The bacterium, *Salmonella enterica* subspecies *enterica* serovar Typhi is an important cause of illness and death in many poor countries where access to safe water and basic sanitation is limited. Humans are the only natural host and reservoir of *S. Typhi*. Typhoid fever causes around 21 million cases and at least 200,000 deaths per year. Currently, several groups are developing typhoid conjugate vaccines that are expected to be safe and effective in infancy or early childhood. The World Health Organization convened a meeting, in collaboration with the Korea Food and Drug Administration, with experts group in September 2012 to develop guidelines for regulatory evaluation of the quality, safety and efficacy of typhoid conjugate vaccines. This report summarizes collective views on scientific and technical issues that need to be considered in the guidelines.

## 1. Introduction

Typhoid fever is a gastrointestinal disease transmitted through the ingestion of contaminated water or food. The bacterium, *Salmonella enterica* subspecies *enterica* serovar Typhi is an important cause of illness and death in many poor countries where access to safe water and basic sanitation is limited. Humans are the only natural host and reservoir of *S. Typhi*. It is estimated that typhoid fever causes around 21 million cases and at least 200,000 deaths per year [1]. Children are most at risk in typhoid endemic countries such as, India, Pakistan, Nepal and Bangladesh and children aged two to nine years are the most vulnerable.

Typhoid fever is clinically indistinguishable with paratyphoid fever caused by *S. enterica* subspecies *enterica* serovar Paratyphi A or B (rarely C), or other *S. enterica* strains. They are collectively termed as enteric fever. Enteric fever is difficult to distinguish by clinical symptoms from other endemic diseases including dengue and malaria.

Vaccination is an effective preventive intervention, especially when coupled with hand washing, access to safe water, and other preventive measures. Two safe and effective typhoid vaccines are available: the oral *S. Typhi* Ty21a vaccine and the injectable Vi polysaccharide (PS) vaccine. However, the live attenuated Ty21a strain vaccine requires multiple oral immunizations, is effective only in adults, and has a limited duration of protection. The attenuated Ty21a vaccine confers up to seven years of protection following immunization of school age children, but requires three oral doses to achieve this [2]. The purified Vi PS parenteral vaccine is effective in a single dose but protection is of limited duration (not more than three years), so that regular revaccination is required, and it is poorly immunogenic in children under 2-years of age. The level of clinical efficacy of each of these

vaccines is approximately 65–70%. When used extensively they have a significant impact on public health. The older generation of inactivated whole cell typhoid vaccines are no longer used since high adverse effects occurred. In recent years, the development of effective, affordable vaccines against typhoid that provide high levels of durable protection starting in infancy has become a priority. Conjugate technology, which has proven so effective in developing vaccines against other invasive bacterial infections, provides one means to achieve this goal.

The late stage of clinical development of some of Vi conjugate vaccines calls for broader agreement on harmonised regulatory expectations on the evaluation of clinical data and on technical specifications for the manufacture and quality control of a vaccine product to guide their possible use either in routine vaccination programs or in mass vaccination campaigns.

The objectives of the meeting were to review scientific basis for regulatory evaluation of typhoid Vi PS conjugate vaccines under clinical development and to initiate developing new WHO guidelines on the quality, safety and efficacy of typhoid conjugate vaccines that will be submitted to the WHO's Expert Committee on Biological Standardization (ECBS). In the following text, key points are highlighted on the following subjects: (i) general considerations, (ii) manufacturing and quality control, (iii) nonclinical evaluation, and (iv) clinical evaluation.

## 2. General considerations

**2.1. A better understanding of the burden of disease to support decisions on vaccine introduction**

The most recent estimate is that there are at least 21.6 million cases of typhoid per annum causing 216,000 deaths [3].

Due to the difficulties in rapid, reliable, sensitive and specific diagnosis of typhoid and paratyphoid fever versus other febrile illnesses with similar symptoms, clinicians commonly treat patients with antibiotics based on clinical suspicion of disease. *S. Typhi* carrying R factors encoding resistance to multiple clinically relevant antibiotics have been circulating in South and Southeast Asia since the late 1980s. Many strains also encode chromosomal resistance to fluoroquinolone antibiotics. This complicates accurate assessment of the profile of disease in the community, which is compounded by the fact that typhoid is predominantly a disease of poverty. Reported mortality rates are also highly variable.

Based on passive surveillance through hospital episodes, the peak age incidence of typhoid has historically been in school age children, with a peak incidence usually in subjects 5–9 years of age, with lower incidence rates in children between 2 and 4 years. Passive surveillance of children visiting health centres showed that some mild febrile illnesses in children under two years of age were due to *S. Typhi* and *S. Paratyphi A* and *B*; many of these illnesses were mild and resolved spontaneously [4]. Active household surveillance in communities in Delhi (India) and Dhaka (Bangladesh), to detect fever, followed by collection of blood culture from febrile subjects also showed a high incidence of *S. Typhi* infection in children 1–4 years of age [5,6]. Notably, in those studies *S. Typhi* disease was uncommon in infants under 12 months [5,6]. Children 12–48 months of age would probably benefit from the use of a conjugate vaccine, as the existing purified unconjugated typhoid Vi PS vaccines are not immunogenic in this age group.

Blood culture-based surveillance to detect invasive bacterial infections including *Salmonella* infections in children less than two years of age as well as in older children has been ongoing for at least a decade in a handful of centres in sub-Saharan Africa [7–12], and additional sites have also enjoined in such surveillance activities [13]. WHO has helped to set up sentinel blood culture surveillance in additional sites in order to obtain better data upon which programme decisions can be made. In parallel, the International Vaccine Institute (IVI) has set up a sentinel network in sub-Saharan Africa to obtain incidence data, and the Coalition against Typhoid (CaT), funded by the Bill and Melinda Gates Foundation, is a global forum of health and immunization experts working to expedite and sustain evidence-informed decisions regarding the use of typhoid vaccination to prevent childhood enteric fever as part of a comprehensive strategy that includes immediate measures such as timely access to appropriate antibiotic treatment, with sustainable long-term solutions like access to safe water, basic sanitation and promotion of good hygiene practices such as hand washing [14].

## 2.2. Development of a consensus on the programmatic use of a typhoid Vi conjugate vaccine

Optimal vaccine use within a given population depends, but not limited to, on the profile of disease incidence rates in different age groups, patterns of transmission, and the importance of herd effects. This is likely to differ from country to country, and within countries. It has been generally accepted that in countries with incidence rates above 100 cases per 100,000 population per year, vaccination is regarded as important, but in the range between approximately 10–100 cases per 100,000, it is less clear that population-wide vaccination is the best option. This will influence the vaccines given, the number of doses and the ages at which they are given, and the desired immunological outcome. This background enables national purchasers to argue for suitable products. On the other hand, external funding of vaccination programmes, a necessity for many of the countries in

greatest need of the Vi conjugate vaccine, will be facilitated by use of these vaccines in mass paediatric vaccination programmes compliant with the expanded programme of immunization (EPI) schedule. Various models were proposed to enable this to be achieved, but no clear consensus emerged on this issue. Vi conjugate vaccines that provide long-lasting protection starting in infancy are under development. The anticipated development of bivalent enteric fever vaccines containing components protecting against paratyphoid disease will further complicate this decision.

## 3. Nonclinical evaluation

Guidance for the nonclinical evaluation of vaccines is covered in existing WHO documents, and guidelines for individual vaccines highlight only product-specific issues. In addition, the successful use of a range of conjugate vaccines provides a template for the requirements for nonclinical evaluation of Vi conjugates. The major factors to be considered are vaccine characterization, immunogenicity and toxicity. Stability assessments should be made over both the preclinical and clinical development phases, and preclinical assessments should be repeated if the manufacturing process is changed significantly during vaccine development. Reference to good laboratory practice (GLP) and good manufacturing practice (GMP) requirements will be made, and the availability of reference materials. In the absence of animal models in which to test Vi conjugate vaccines, it is likely that a broader range of immunological responses in humans will need to be considered.

## 4. Clinical evaluation

### 4.1. Support to clinical trials for Vi conjugate vaccine registration

The lack of a rapid and reliable diagnostic test for typhoid complicates clinical trials of Vi conjugate vaccine efficacy. These will be based on culture-confirmed cases, which may compromise sensitivity, although retaining high specificity. Therefore there is a strong desire, in order to avoid having to conduct efficacy trials for Vi conjugate vaccine registration, to create correlations with validated measurements of vaccine immunogenicity, either total anti-Vi antibody, anti-Vi IgG antibody levels determined by ELISA, or functional antibodies assessed through bactericidal assays, opsonophagocytic assays, or opsonophagocytic killing assays. Some of these correlates are being developed as a result of work carried out by the US National Institutes of Health (NIH) group which has sera from children who participated in a field trial and were immunized with a highly protective conjugate vaccine. Wider application will require the availability of suitable reference serum for inter-laboratory comparison of antibody assay data.

Choice of an appropriate comparator vaccine, for noninferiority immunogenicity assessment, is another issue. Trials in children and adults can use a licensed (ideally WHO-prequalified) Vi polysaccharide vaccine, but these products are neither effective nor licensed for use in infants under 2 years, and bridging studies may be required. To date there is no consensus on the appropriate clinical dose of Vi conjugates for infants, and individual conjugates may differ one from another in this age group.

Clinical trials are carried out in areas of high endemicity, and it will be important to understand how this relates to efficacy in regions of lower endemicity, as these data underpin decisions on widespread use in mass immunization campaigns and in routine EPI programs.

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