Report of the Ad-hoc consultation on typhoid vaccine introduction and typhoid surveillance

18-20 April 2011
Plaza Athenee Hotel, Bangkok
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1. Introduction

An ad-hoc consultation on typhoid vaccine introduction and typhoid surveillance was held in Bangkok from 18-20 April 2011. The objectives of the consultation were to:

- Update the participants on the current knowledge on typhoid and, in particular, on typhoid vaccines and vaccination,
- Share country experiences on the use of typhoid vaccines,
- Discuss strategies for introducing typhoid vaccines, and
- Discuss surveillance issues for typhoid.

The meeting was opened by Dr Maureen Birmingham, WHO Representative, Thailand. A total of 32 participants attended this meeting (see Annex 2), representing 10 countries from four WHO Regions.

The meeting was organized so that the first day was devoted primarily to update on the current status of knowledge of typhoid and the current policy on typhoid vaccination, and sharing experiences from countries where vaccine is used. Mr. Leon Ochiai from the International Vaccine Institute (IVI), Seoul, Korea, first provided a detailed update on the current state of the knowledge on typhoid epidemiology and the challenges in diagnosing typhoid fever. He also gave a talk on the experiences of the use of Vi-polysaccharide (ViPS) typhoid vaccine in Asia from the Bill & Melinda Gates Foundation (BGMF) funded IVI Diseases of Most Impoverished (DOMI) Programme. Dr. Pem Namgyal from WHO/HQ gave an update of the most recent WHO Position Paper on Typhoid Vaccines, and summarized the information on the experiences on the use of typhoid vaccines from different countries. Dr. Nguyen Van Cuong, Deputy National EPI Manager, Viet Nam, summarized the impact of ViPS in Viet Nam, including the challenges the programme faces in trying to scale up typhoid immunization activities. Dr. Yang Jin, Guangxi CDC, China, outlined the experiences from China on the use of ViPS vaccine to control and prevent typhoid and the impact it has had on the epidemiology of the disease. Dr. Weili Liang, Department of Diarrheal Diseases, National Institute of Communicable Disease Control and Prevention, Chinese Center for Disease Control and Prevention, gave a talk on the prevalence and spatial temporal cluster analysis of typhoid and paratyphoid fever in China. Dr. Jacob Kool, WHO Fiji Country Office, gave a brief overview of the Fijian experience of mass vaccination with ViPS to control a large outbreak of typhoid following a devastating cyclone in Fiji in 2010. Although no participant could attend, the experience of Delhi State in India was also presented; it is an example where typhoid vaccination with ViPS vaccine can very well be integrated into existing EPI programme. Similarly although the invitee from Nepal could not attend the meeting, his presentation was sent and Mr. Ochiai gave a talk on the burden of typhoid disease in Nepal and the
role of laboratory-based data collection for typhoid surveillance. Finally, Dr. M. Imran Khan, IVI, gave an update on Vi-based Vaccine’s for Asia (VIVA) Initiative’s innovative project of using school-based vaccination including cost recovery from higher economic tiers of the society to subsidize vaccination in poorer schools in Pakistan.

The next two days were devoted mainly to group work. Three groups were formed and, following very brief introduction to the work of the day, all the groups were provided the same issues/questions for discussion. Further, for the purpose of discussion at this meeting, two background papers were prepared. One dealt with options on the strategies for the adoption of typhoid vaccines and, the other on the strengthening of typhoid surveillance in countries to generate quality data to enable evidence-based policy decision at the country level.
2. Typhoid vaccines and vaccine introduction strategies

1. Typhoid vaccines

There are currently two vaccines against typhoid. The Vi-polysaccharide which is a single-dose injectable vaccine and the oral Ty21a, which is available in strips of either four or three capsules per strip. For more details on the vaccines, please refer to Annex 3.

2. Typhoid vaccine introduction strategies

The WHO Position Paper on Typhoid Vaccines (WER No. 6, 2008, 83, 49-60) stated that “In view of the continued high burden of typhoid fever and increasing antibiotic resistance, and given the safety, efficacy, feasibility and affordability of 2 licensed vaccines (Vi and Ty21a), countries should consider the programmatic use of typhoid vaccines for controlling endemic disease. In most countries, the control of the disease will require vaccination only of high-risk groups and populations.” The WHO PP further defines the scope of vaccination by clearly stating that it should be focused on risk groups or populations at risk. “Decisions on whether or not to initiate programmatic use of typhoid vaccines should be based on knowledge of the local epidemiological situation. Important information includes data on subpopulations at particular risk and age-specific incidence rates, as well as on the sensitivity of the prevailing S. Typhi strains to relevant antimicrobial drugs. Ideally, cost effectiveness analyses should be part of the planning process. Immunization of school-age and/or preschool-age children is recommended in areas where typhoid fever in these age groups is shown to be a significant public health problem, particularly where antibiotic-resistant S. Typhi is prevalent. The selection of delivery strategy (school or community-based vaccination) depends on factors such as the age-specific incidence of disease, subgroups at particular risk and school enrolment rates, and should be decided by the concerned countries.”

In order to determine whether a country needs a typhoid immunization programme, and if it does, in order to define target area or populations based on typhoid endemicity, good epidemiological data is vital to define appropriate immunization strategies suitable to the local situation. Based on the incidence of typhoid, endemicity is categorized as follows (Crump, JA, Luby SP, & Mintz ED. The global burden of typhoid fever. Bull of WHO, May 2004; 82(5): 346-35):

- **High** when typhoid fever incidence is >100/100,000 cases/year,
- **Medium** when typhoid fever incidence is 10-100/100,000 cases/year, and
- **Low** when typhoid fever incidence is <10/100,000 cases/ year
The first task, therefore, for any country considering the use of typhoid vaccine is to examine carefully the available data on typhoid with particular attention to the local epidemiology so that sub populations or groups at most risk can be defined. Even within typhoid endemic areas, typhoid epidemiology can vary significantly from location to location. Due to this fact, typhoid vaccination is recommended as a risk-based strategy, targeting only “at risk” groups or defined population catchment; typhoid immunization needs rarely be considered for universal immunization across the entire country.

If a country has no data on the occurrence of typhoid, then it may be more appropriate to consider setting up surveillance to gather such data prior to any decision on the introduction of typhoid vaccines.

The broad strategies recommended for typhoid immunization are as follows:

- **Routine vaccination with or without an initial catch-up campaign**
- **Vaccination to curtail an outbreak,** and
- **Vaccination of special groups such as food-handlers**

### 2.1. Routine typhoid vaccination

1) In countries where typhoid endemicity is high, a catch-up campaign would be necessary. It is generally recommended to include children aged 2-15 years in the catch-up campaign. However, the age groups to be included in such a campaign should be decided based on local disease epidemiology, health systems capability, available resources and the logistics capacity of the country. Following the catch-up campaign, the vaccine may be introduced on a routine basis, either through schools or through existing EPI vaccines delivery infrastructure.

2) In countries where typhoid endemicity is medium to low, introducing the vaccine into routine programme, either as a school based programme or into the routine immunization programme, is recommended. Where school enrolment is high and where already strong school health programmes exist, school-based strategy is probably the best strategy. A catch-up campaign may not be necessary. Even in areas or countries where typhoid endemicity is low, demonstration of significant antibiotic resistance should be a strong motivation for the use of vaccine against typhoid.

In high endemic areas (typhoid incidence rates >100/100,000 cases/year), it would be ideal to mount a catch up vaccination campaign, targeting children 2 to 15 years of age. However, depending on availability of resources and programme capacity, the cohorts included for the catch-up campaign may vary from country to country. Following the catch up campaign, the vaccine should be introduced as a routine programme.

The age to start will depend on the epidemiology of the disease. In South Asia (e.g. Kolkata and Karachi) typhoid rates as high as 413 cases/100,000/year are seen in school age children. In some Asian sites such as Karachi, the incidence was higher in pre-school than in school age children. In sites that demonstrate a high incidence of severe typhoid disease in pre-school children, starting vaccination at ≥2 years of age may be considered an appropriate strategy.
Following the initial catch-up campaign, a country may start routine typhoid vaccination starting at ≥2 years of age if ViPS vaccine is used. If the oral Ty21 vaccine is used for the routine programme, then the vaccination starting age would be 5 years or older.

Following the 1st dose, a repeat dose is recommended (after 3 years if ViPS; after 5 to 7 years if Ty21a).

In large population settings, it would be logistically challenging to mount a campaign that may include all children aged 2 to 15 years, even with a single dose vaccine such as the ViPS vaccine. Therefore, if necessary, a staggered approach may be adopted as follows:

- In the first year, conduct the campaign for all children aged 2 to 5 years
- In the second year, conduct a campaign for all children aged 7 to 10 years, and
- In the third year, conduct a campaign for all children aged 12 to 15 years
- At the same time, ensure that all children aged 2 years are routinely immunized from the second year onwards of the start of typhoid immunization programme.

For large urban slums in Asia, particularly in South-East Asia, periodic campaigns may be an appropriate strategy, particularly given that in many such places, health delivery infrastructure and system to reach such population are either weak or non-existent.

For such a strategy, depending on the resources available and the ability of the health system to deliver the vaccine, a country may decide to target children 2 - 5 years old, or may even reach higher age groups, say up to 10 years in the first year of the start of vaccination. In subsequent years, campaigns can be repeated every three or four years, targeting only children aged 2 - 5 years.

2.2. **Typhoid vaccination to curtail a typhoid outbreak**

1) When a typhoid fever outbreak is confirmed, the rapid deployment of typhoid vaccines can effectively curtail such an outbreak. The WHO PP clearly states that “*Given the epidemic potential of typhoid fever, and observations on the effectiveness of vaccination in interrupting outbreaks, typhoid fever vaccination is recommended also for outbreak control.*”

2.3. **Typhoid vaccination to prevent potential spread through food handlers**

1) Where typhoid is endemic, countries are encouraged to put in place policies to ensure that groups such as food-handlers are regularly vaccinated. A food handler is any person who handles and prepares food and beverages for public consumption like in a restaurant, or for groups of individuals in an institution such as boarding schools or hospital kitchen. Health workers are usually considered at “risk” group due to their vocation and, therefore, should be considered for regular vaccination.
Most, if not all, countries have a reporting system for health events such as Morbidity and Mortality reports, or Annual Health Bulletin etc. Such reports are generated annually, at least at the national level, and more frequently (monthly or quarterly) at provincial and district levels. Some of the countries have such a system oriented towards supporting (programme) management, calling such a system as Health Information Management System (HMIS). For a sustainable system for reporting morbidity and mortality from typhoid, it is best to have it integrated into existing health events reporting systems such as HMIS. If information on typhoid is not included in the national HMIS, efforts should be made to do so. However, reports of events in such a system may be largely from clinical impression or based on established algorithmic diagnosis; laboratory diagnosis, if included, usually is based on serological and not blood culture confirmation.

Only if there is no existing system to report morbidity and mortality from diseases, then one may contemplate setting up a surveillance system only for typhoid. But this should be a rare necessity.

The initial presentations of typhoid fever are similar to any other febrile illnesses, thus making the diagnosis of typhoid fever a challenge. There are serology based rapid diagnostic tests, but none of them were found to be specific enough to be outstanding. These tests are Widal, Tubex, and Typhidot. There is certainly some applicability as rapid testing, but in terms of accurate diagnosis and to report the true burden of typhoid fever, it is essential to use blood culture and to take isolation of the organism as the gold standard for diagnosis.

Blood culture requires not only the time, but also the proper facility and logistics. It is also not sensitive. Based on previous studies to compare the organism isolation with different body fluid has shown bone marrow culture to be the most sensitive, but this is unpractical. More common approach to tackle this problem is to multiply the incidence of blood culture positive typhoid cases by two considering the approximate blood culture sensitivity being 50%.

It is also important to note that very similar illness, paratyphoid fever, is caused by different organism – *Salmonella* paratyphi A, B, or C. Especially at the early stage of the illness, typhoid and paratyphoid fevers cannot be clinically differentiated. Therefore, it is also important that blood culture confirmation to be done in order to assess the proportion of enteric fever caused by these different organisms.

### 3. Typhoid Surveillance
1. Rationale for surveillance

The primary goal of disease surveillance is to identify high risk and high burden populations in order to target programmatic interventions, including vaccination.

Where typhoid vaccination is already ongoing, the purpose of surveillance is to monitor the impact of vaccination on disease burden and identify high-risk/high burden populations in need of improved vaccination activities.

2. Case definition

**Confirmed case of typhoid fever**

A patient with fever (38°C and above) that has lasted for at least three days, with a laboratory-confirmed positive culture (blood, bone marrow, bowel fluid) of *S. typhi*.

**Probable case of typhoid fever**

A patient with fever (38°C and above) that has lasted for at least three days, with a positive serodiagnosis or antigen detection test but without *S. typhi* isolation.

**Suspected case**

A patient that meets the criteria for Acute Febrile Illness (AFI): current fever (38°C and above) that has lasted for at least three days.

**Chronic carrier**

Excretion of *S. typhi* in stools or urine (or repeated positive bile or duodenal string cultures) for longer than one year after the onset of acute typhoid fever. Short-term carriers also exist but their epidemiological role is not as important as that of chronic carriers. Some patients excreting *S. typhi* have no history of typhoid fever.

3. Types of surveillance

3.1 Active typhoid fever surveillance

Active surveillance is an intense activity that requires well defined protocols for implementation with the aim to generate data that will allow generation of reliable and representative incidence data for the disease under surveillance. Such a surveillance system is mostly set up for short periods of observation, more often in a research setting.

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1. Background Document: The diagnosis, treatment and prevention of typhoid. WHO/V&B/03.07 (case definitions taken directly from this document without alterations)
Active surveillance can be set up reaching the whole population under consideration or by focusing on a selected number of sentinel sites (laboratories).

- For the **population based active surveillance**, regular house visits are necessary. House visits may be made either weekly (Pakistan) or monthly (India) by a trained surveillance worker who inquires for any cases of fever lasting 3 days or more in the period since the worker’s last visit.

- **Facility-based active surveillance** can also cover whole population if all such facilities are included in the surveillance system and these facilities cater to a relatively stable catchment population. Hospital-based surveillance data, therefore, has limitation, as there is limited information on healthcare utilization by the population, as well as the ambiguity of the hospital's catchment population.

- Otherwise, choosing carefully the best located facility for **sentinel sites-based active surveillance** is the most suitable option. There can be more than one site participating in such a surveillance system. In such a system, the participating health facility (or facilities) ensure that any person presenting to the facility with history of fever for more than three days are screened and a blood sample collected for culture. However, the caveat to note is that all such patients may not appear at facility where the surveillance is being carried out.

It will be ideal if the point of blood collection has blood culture facility, but in most cases, that is not feasible due to cost and management. In such cases, transport of blood-inoculated culture bottles must be arranged to the central facilities. Blood culture bottles, after inoculation of blood, may be left in ambient temperature until it reaches the central facility.

### 3.2 Advantages and disadvantages of active surveillance

The advantages of active surveillance, particularly those that include entire population of interest, is its ability to generate high quality data that will enable the generation of representative incidence data.

Facility-based active surveillance, if carried out in all such facilities that cater to a defined catchment population, can also generate data that can be representative, but not as robust as those data generated through active surveillance of defined population carried out through systematic house-visits based on enumerated population data.

Facility-based sentinel site surveillance, even if actively implemented, cannot provide representative data nor incidence data. However, it can provide better temporal trend data than that generated through passive surveillance.

The disadvantages of active surveillance are that they are expensive, human-resource intensive, and difficult to maintain for long periods of time.
3.3 Passive typhoid fever surveillance

Passive surveillance is where no special efforts are made to screen potential “cases” but rely only on testing those that an examining physician decides to refer for a test. This is generally the kind of system that most countries have where they rely on the data generated from health facilities, either from laboratory, or only of clinical diagnosis of typhoid from outpatient registers, or a combination of both. Given the non-specific presentation of typhoid, especially in the early phase of illness, a clinical impression is often likely to be wrong. Unfortunately, in most developing country situation, the physician would, to err on the right side, put such a patient on antibiotics and treat it as such even if there is no possibility of confirming the diagnosis through blood culture or other tests.

Focusing on a few well performing laboratories can supplement the clinical reports of typhoid, and consistent work in such facilities over a period of time can provide information on the temporal trend of the disease.

3.4 Surveillance for antimicrobial resistance

Antimicrobial resistance by Salmonella is well established in many parts of the world where the usual antibiotics are no more effective and that clinicians must now resort to third generation cephalosporin or other more expensive antibiotics for treatment, thus raising the cost of treatment by several fold. Therefore, in countries where antimicrobial resistance level is high, even if the endemicity of the disease is low, it may well justify the introduction of vaccines against typhoid. Even if it is not possible by all laboratories to do this, it is necessary to have at least one reference laboratory in the country that can carry out regular antimicrobial sensitivity studies to track any changes that may occur over time.
4. Discussions

Extensive discussions took place on what would be the best strategy for typhoid vaccination. There was general consensus that in high endemic areas, a catch-up campaign was necessary, but opinion was divided for catch-up campaign for medium endemicity. There is consensus that no catch-up campaign is needed in low endemic countries. Further, for the catch-up campaign there was general consensus to include 2-15 years of age where feasible. Including age groups higher than 15 years was debatable.

An idea, less favoured by the majority, was to recommend only periodic campaigns as a strategy to deliver typhoid vaccine, and repeat the campaign every four years in the same areas (i.e. if ViPS vaccine is used).

All agreed that school-based strategy was probably the best but concerns were raised that out-of-school children will be missed where school enrolment may not be high. In addition, while it may not be suitable for a mass campaign, the oral Ty21a vaccine has potential for use for school-based programmes if the vaccine is affordable.

There was a lot of discussion on the need for repeat doses. WHO position paper suggests at least one repeat dose, at least for the ViPS vaccine, and subsequent need for repeat doses was uncertain. However, experience from both China and Viet Nam shows that even one dose of ViPS given to children in high risk areas had significant impact on reducing the incidence of typhoid in those communities thereby demonstrating that, on a population level, even a single dose vaccination can significantly reduce the prevalence of the disease. The Delhi typhoid vaccination programme also provides only one dose of ViPS to children aged 2-5 years and, available data seems to suggest significant reduction in the prevalence of typhoid fever.

Discussion on surveillance issues revolved around the question of what type of surveillance is necessary for typhoid vaccination purpose. It was agreed that where communicable diseases surveillance exist, attempt should be to strengthen such surveillance to obtain better data on typhoid, and not start a separate parallel surveillance for typhoid fever alone. However, at least a few sentinel hospitals with high quality laboratory capacity should be included in the surveillance system to carry out blood culture and antimicrobial sensitivity studies.
The case definition for “suspect” case using only fever needs to be reviewed for its suitability in a routine surveillance. It was felt that the current definition with fever only is more suitable for active surveillance primarily for research settings; the use of the definition as it exist now for a routine surveillance would simply overwhelm the laboratory capacity to test if only fever is used as the sole criterion to screen “suspect” typhoid fever. It was felt that additional criterion or criteria are needed, e.g. a clinicians impression, or an abdominal sign etc.. It was agreed that this need to be referred to an expert group to improve the case definition for “suspect” cases of typhoid.

Finally there was discussion on the population to be included in a mass campaign as a response to an outbreak. In China outbreak response targets primarily school-children and does not extend to whole communities. In Fiji, all people were targeted in the affected areas. It was felt that the final decision on the age cohorts to be included in a mass campaign should be decided at the local level, based on disease epidemiology and local capacity to carry out large-scale mass campaigns.
5. Other measures to prevent and control typhoid

The meeting felt that the ultimate aim for countries should be to invest in improving water, sanitation and living conditions of the people to ultimately control typhoid. Vaccination is only a stop-gap measure and, by itself, may control the disease but as long as the conditions for it prevail, the potential for the disease to again become a public health concern if vaccination ceases is real.

Typhoid fever is a disease perpetuated through the faeco-oral transmission resulting from polluted water and poor sanitation and hygiene practices. In most developed countries, improved sanitation and hygiene practices, safe sewage disposal systems and clean water supplies have eliminated typhoid as a public health problem. However, investment in such capital infrastructure development is beyond the available resources of most developing countries and, in the immediate period, unlikely to be available to much of the people who live in typhoid endemic areas. While governments and donor communities are encouraged to invest in the improvement of sanitation and living conditions of the people as well as improve access to safe water supplies, there are also steps that can be taken at the household and individual levels. Some of these are summarized below.

1. Enhance access to safe drinking water and improve sanitation condition

1.1 Water systems

- Encourage government and development partners to invest in increasing access to piped water and improvement of other infrastructure for safe water supplies,
- Water treatment (Chlorination), both at the supply level as well as at the user-level (e.g. packaged chlorine solutions)
- Other point-of-use household interventions (filtration, improved water storage practices, etc.)

1.2 Sanitation

- Improve sewerage systems
- Encourage the construction and use of latrines at household level

1.3 Educate and Communicate on good hygiene practices

- The importance of hand washing using soap
- Discourage open de-faecation by children, and open latrines for adults
- Teach people on the proper disposal of faeces and garbage
Annex 1: Agenda

Ad-hoc Consultation on Typhoid Vaccine Introduction and Typhoid Surveillance
18-20 April 2011, Bangkok, Thailand
Provisional Agenda

Day 1 — Monday, 18 April 2011

08:30 – 08:45  Registration
08:45 – 09:00  Welcome and introductions  WR Thailand (?)
09:00 – 09:15  Objectives of the workshop and expected outcome  P. Namgyal
09:15 - 09:45  Global typhoid disease burden and challenges of typhoid surveillance  L. Ochiai
09:45 - 10:15  Typhoid vaccines and WHO recommendations on their use  P. Namgyal
10:15 - 10:45  Tea/coffee/photo opportunity
10:45 - 11:15  Discussion
11:15 - 11:45  Typhoid vaccine use -experience from domi project and the feasibility of typhoid vaccine use in public health programmes  L. Ochiai
11:45 - 11:15  The viva project  I. Khan
12:15 – 12:30  Discussion
12:30 – 13:00  Experiences from countries on the use of typhoid vaccines
   • Typhoid vaccine use in China and its impact  Y. Jin
13:00 – 14:00  Lunch

Annex 1: Agenda
14:00 – 15:30 Experiences from countries on the use of typhoid vaccines (contd/...)
- Typhoid vaccination to control and outbreak in Fiji J. Kool
- Typhoid vaccination of high risk groups in Sri Lanka S. Peiris
- Typhoid vaccination integrated into routine immunization in Delhi state TBD
- Typhoid vaccine use in Vietnam and its impact N.V. Coung

15:30 – 16:00 Discussion
16:00 - 16:30 Tea/coffee
16:30 – 17:15 Introduction to the draft tool to aid decision analysis for typhoid vaccine introduction P. Namgyal

Day 2 — Tuesday, 19 April 2011
08:30 – 09:00 Briefing on group work P. Namgyal
09:00 – 10:30 Group work
10:30 – 11:00 Tea/coffee
11:00 – 13:00 Group work continued
13:00 – 14:00 Lunch
14:00 - 15:30 Report of group work & Discussion Group rapporteur
15:30 – 16:00 Tea/coffee
16:00 – 16:30 Laboratory based surveillance for typhoid, experience of Nepal B. Basynet

16:30 – 16:45 Discussion
16:45 – 17:30 Introduction to typhoid surveillance P. Namgyal
17:30 – 17:45 Briefing on group work P. Namgyal
18:00 End of day

Day 3 — Wednesday, 20 April 2011
08:30 – 10:30 Group work
10:30 – 11:00 Tea/coffee
11:00 - 13:00 Group work continued
13:00 – 14:00 Lunch
14:00 – 15:30 Report of group work & Discussion Group rapporteur
15:30 – 16:00 Tea/coffee
16:00 – 16:15 The coalition against typhoid C. Nelson
16:15 - 17:00 The next steps
17:00 Close
Annex 2:
List of Participants

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<td>21</td>
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<td>22</td>
<td>EURO</td>
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<td>23</td>
<td>WPRO</td>
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<td>24</td>
<td>HQ</td>
</tr>
</tbody>
</table>

Annex 2: List of Participants
<table>
<thead>
<tr>
<th>MoH Participant</th>
<th>Name</th>
<th>Region</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Other participants</td>
<td></td>
<td></td>
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<tr>
<td>25 CDC</td>
<td>Kashmir DATE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>26 IVI</td>
<td>R. Leon OCHIAI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>27 IVI</td>
<td>M. Imran KHAN</td>
<td></td>
<td></td>
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<tr>
<td>28 CaT Secretariat</td>
<td>Dr Chris NELSON</td>
<td></td>
<td></td>
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<tr>
<td>29 Government of Sindh Pakistan</td>
<td>Mazhar Ali KHAMISANI</td>
<td></td>
<td></td>
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<tr>
<td>30 Government of Sindh Pakistan</td>
<td>Syed Hashim Raza ZAIDI</td>
<td></td>
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<tr>
<td>31 Independent consultant, Pakistan</td>
<td>Dr. Durenaz Jamal</td>
<td></td>
<td></td>
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<tr>
<td>32 Independent consultant, Pakistan</td>
<td>Dr. Saira</td>
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</table>
There are two internationally licensed vaccines against typhoid, a Vi capsular polysaccharide and a live attenuated Ty21a.

1. Types of vaccines - Vi capsular polysaccharide, or ViPS

A Vi capsular polysaccharide vaccine which contains extracted cell surface Vi polysaccharide of Salmonella enterica serovar Typhi, S typhi Ty2 strain in a sterile solution. It is an injectable vaccine, recommended for intramuscular use. It is produced by several internationally recognized vaccine manufacturers and easily available globally.

The Vi polysaccharide is a T-cell independent antigen and, therefore, is poorly immunogenic in children aged <2 years and, more importantly, does not confer immunologic memory. Thus, the protection conferred is of limited duration (2-3 years). Although there is not much experience with ViPS typhoid vaccine per se, there is some experience from the use of 23-valent pneumococcal polysaccharide vaccine and meningococcal C polysaccharide with regards to the safety and efficacy of administering repeated doses of polysaccharide vaccine.

There is evidence that those who were revaccinated were more likely than those who were receiving the vaccine for the first time to experience local adverse reactions, albeit mild and rapidly self-limiting ones. Adverse events considerations would be even more important in populations with high rates of HIV infection or other immunocompromised individuals.

Another phenomenon with polysaccharide vaccine is the lower antibody response to revaccination where repeated doses of the vaccine seem to induce a state of immune hyporesponsiveness. These are important considerations when developing an immunization strategy to use Vi polysaccharide vaccine.

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2 Torling J, Hedlund J, Konradsen HB et al. Revaccination with 23-valent pneumococcal polysaccharide in middle-aged and elderly persons previously treated for pneumonia. Vaccine 22 (2003); 96-103
The single dose ViPS injectable vaccine provides about 65% protection against blood-culture confirmed typhoid fever for up to three years.

More recently a cluster randomised effectiveness trial of Vi Typhoid vaccine in India showed a 80% protection in children who were vaccinated between ages 2 and 5 years over two years of follow-up. More importantly even among the unvaccinated the protection was 44%, thus demonstrating significant herd effect with the use of ViPS vaccine.4

The ViPS is an injectable vaccine (liquid) that is available as single dose pre-filled syringe, and 5 and 20-dose vials. ViPS is to be administered intramuscularly, 0.5 ml preferably using an auto-disable syringe. The injection is given either in the deltoid region of the arm and, in the case of younger children, in the upper outer quadrant of the thigh.

2. Live attenuated oral Ty21a typhoid vaccine

The Ty21a is a live attenuated vaccine, formulated as a enteric coated capsule for oral administration. Protection from Ty21a vaccine is based on different surface antigens, including O- and H-antigens; it lacks Vi-antigen and protection is therefore independent of Vi-expression by the bacteria. In the past a liquid formulation of the same was also available, but not available now although production can be re-started if there is sufficient demand.

A “liquid” formulation that consists of the vaccine in a sachet and buffer in another, which are combined with water before administration, is licensed but is not currently being manufactured5. The capsules are recommended for individuals aged ≥ 5 years; (the liquid suspension when available was indicated for children aged ≥ 2 years). Both formulations are recommended as a three dose regimen with doses given at an every other day schedule; in the USA and Canada, non-endemic countries, a 4-dose regimen is recommended for travelers visiting endemic countries. For both the vaccines, a re-immunization is recommended 5-7 years after the initial immunization. Ty21a stimulates long-lived cell-mediated immune responses and immunologic memory that account for the long-lived protection. Thus, there is no recognized evidence of hyporesponsiveness to subsequent immunization with Ty21a.

In studies in Chile on the use of Ty21a typhoid vaccine, three doses (given every alternate day) of enteric coated capsule of Ty21a conferred 67% protection over three years and 62% protection over seven years of follow up.6 The Ty21a vaccine is a blister of 3 capsule for each course.

The advantages and disadvantages of the current vaccines are presented in Table 1.

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5 Personal Communications seems to indicate that the liquid Ty21a is not produced anymore, although production can be re-started if there is sufficient demand.

6 Levine, MM, Ferreccio C, Abrego P et al. Duration of efficacy of Ty21a, attenuated Salmonella typhi live oral vaccine. Vaccine 17(1999); S22-S27
Table 1: Advantages and Disadvantages of the Vi PS and Ty21a typhoid vaccines

<table>
<thead>
<tr>
<th>Type of Vaccine</th>
<th>Advantages</th>
<th>Disadvantages</th>
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<tbody>
<tr>
<td>Vi PS</td>
<td>• Single dose</td>
<td>• Injectable, requires trained personnel to administer</td>
</tr>
<tr>
<td></td>
<td>• Suitable for mass campaigns</td>
<td>• Injection waste management needed</td>
</tr>
<tr>
<td></td>
<td>• Monitoring coverage is easier</td>
<td>• Injection safety issues</td>
</tr>
<tr>
<td></td>
<td>• Cheaper (approx $ 0.5 only)</td>
<td>• Cannot be given to children ≤ 2 years</td>
</tr>
<tr>
<td></td>
<td>• Multiple manufacturers</td>
<td>• Protection is short-lived (&lt; 3 years)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Does not elicit immunologic memory</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Hyporesponsiveness may occur in some subjects re-immunized after 3 years</td>
</tr>
<tr>
<td>Ty21a</td>
<td>• Oral administration; needs no special training to administer</td>
<td>• Campaigns are challenging as 3 doses must be given on alternate days</td>
</tr>
<tr>
<td></td>
<td>• Capsule, easy to handle</td>
<td>• Monitoring coverage can be complicated</td>
</tr>
<tr>
<td></td>
<td>• No injection equipment required</td>
<td>• Can be more expensive (projected price $ 1.25 per capsule)</td>
</tr>
<tr>
<td></td>
<td>• No injection waste and no injection safety issues</td>
<td>• Fewer producers at present</td>
</tr>
<tr>
<td></td>
<td>• Can easily be administered in a settings such as schools, military bases, refugee camps etc.</td>
<td>• Cannot be given to children ≤ 5 years (capsule), and children ≤ 2 years (liquid formulation)</td>
</tr>
<tr>
<td></td>
<td>• No problem with hyporesponsiveness upon re-vaccination</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Partial cross protection against Salmonella Paratyphi B (but not against S. Paratyphi A)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Longer duration of protection and less frequent reimmunization</td>
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3. Interchangeability

The ViPS and the Ty21 vaccines work through different immune mechanism. The ViPS does not stimulate immunologic memory and response is typically antibody-mediated. Oral Ty21a elicits strong immunologic memory and long-lived evidence of cell mediated immunity. There is no harm in completing a Ty21a series with ViPS except that the protection provided by the two vaccines work through independent mechanisms.

For repeat doses, using the two vaccines interchangeably is acceptable; that is to say that if a child had received ViPS as the first vaccination, subsequent repeat dose can be with Ty21a oral vaccine.
4. **Storage temperature and shelf life**

Both the vaccine are recommended to be stored at +2°C to +8°C, and freezing should be avoided, particularly for the ViPS vaccine.

ViPS has a minimum shelf life of two years, while the Ty21a vaccine has a minimum shelf life of 1.5 years.

5. **Contraindications**

There are no specific contraindications to the use of this vaccine other than established previous hypersensitivity reaction to vaccine components. HIV positivity is not a contraindication for the ViPS, but induction of protective antibodies is directly correlated to the levels of CD4 positive T-cells. Similarly the Ty21a vaccine can also be given to HIV-positive asymptomatic individuals.

6. **Safety and adverse events following immunization (AEFI)**

Both the vaccines have no more adverse events than what is usually seen with other EPI vaccines currently in use. For the injectable ViPS the adverse reactions were predominately minor and transient local reactions, such as injection site pain, erythema and induration; these local reactions almost always resolved within 48 hours of vaccination. Further, the ViPS can be coadministered with other routine childhood vaccines.

Drugs such as proguanil and antibiotics should be stopped from 3 days before and until 3 days after giving Ty21a, as such drugs may harm live bacterial vaccines. Ty21a can be administered together with the antimalarials chloroquine, mefloquine, or the combinations pyrimethamine/sulfadoxin or atovaquone/proguanil. There is no contraindication to the concomitant use of Ty21a with parenteral and other live vaccines.

7. **Future typhoid vaccines**

One of the key challenges to integrate typhoid vaccines into national immunization programmes is the lack of a vaccine with profiles that fit with the current immunization schedule for infants. Fortunately, there are several promising candidate typhoid conjugate vaccines in development. The advantages of the conjugate vaccine are, (i) that it can be administered to infants and, (ii) that it stimulates immune memory which provides long lasting immunity for the individual vaccinated.
Table 2: Future typhoid vaccines in development

<table>
<thead>
<tr>
<th>Types of Vaccines</th>
<th>Candidates/Developers</th>
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<tbody>
<tr>
<td>Parenteral</td>
<td>• Vi polysaccharide conjugated to protein carriers</td>
</tr>
<tr>
<td></td>
<td>– Vi-EPA (NIH, USA): Vi polysaccharide conjugated with the protein of Pseudomonas aeruginosa as carrier protein</td>
</tr>
<tr>
<td></td>
<td>– Vi-DT (IVI, Korea; China): Vi polysaccharide conjugated with the Diphtheria toxoid as carrier protein</td>
</tr>
<tr>
<td></td>
<td>– Novartis Vaccines Institute of Global Health: Vi polysaccharide conjugated to CRM197</td>
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<tr>
<td>Oral</td>
<td>• Live attenuated vaccines through genetic manipulation</td>
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<td></td>
<td>– CVD 909 (CVD, USA): live attenuated</td>
</tr>
<tr>
<td></td>
<td>– ZH09 (Emergent Biosolutions, UK): live attenuated</td>
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<tr>
<td></td>
<td>– Ty800 (Avant, USA): live attenuated</td>
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</table>

Although some of these candidate vaccines are well advanced in their clinical development, it is not expected that any of the new vaccines would be available for several years. In the meantime, it would be most beneficial for typhoid endemic countries to take advantage of the available ViPS and the Ty21a vaccines to address typhoid issues in their countries.
The World Health Organization has provided technical support to its Member States in the field of vaccine-preventable diseases since 1975. The office carrying out this function at WHO headquarters is the Department of Immunization, Vaccines and Biologicals (IVB).

IVB’s mission is the achievement of a world in which all people at risk are protected against vaccine-preventable diseases. The Department covers a range of activities including research and development, standard-setting, vaccine regulation and quality, vaccine supply and immunization financing, and immunization system strengthening.

These activities are carried out by three technical units: the Initiative for Vaccine Research; the Quality, Safety and Standards team; and the Expanded Programme on Immunization.

The Initiative for Vaccine Research guides, facilitates and provides a vision for worldwide vaccine and immunization technology research and development efforts. It focuses on current and emerging diseases of global public health importance, including pandemic influenza. Its main activities cover: i) research and development of key candidate vaccines; ii) implementation research to promote evidence-based decision-making on the early introduction of new vaccines; and iii) promotion of the development, evaluation and future availability of HIV, tuberculosis and malaria vaccines.

The Quality, Safety and Standards team focuses on supporting the use of vaccines, other biological products and immunization-related equipment that meet current international norms and standards of quality and safety. Activities cover: i) setting norms and standards and establishing reference preparation materials; ii) ensuring the use of quality vaccines and immunization equipment through prequalification activities and strengthening national regulatory authorities; and iii) monitoring, assessing and responding to immunization safety issues of global concern.

The Expanded Programme on Immunization focuses on maximizing access to high quality immunization services, accelerating disease control and linking to other health interventions that can be delivered during immunization contacts. Activities cover: i) immunization systems strengthening, including expansion of immunization services beyond the infant age group; ii) accelerated control of measles and maternal and neonatal tetanus; iii) introduction of new and underutilized vaccines; iv) vaccine supply and immunization financing; and v) disease surveillance and immunization coverage monitoring for tracking global progress.

The Director’s Office directs the work of these units through oversight of immunization programme policy, planning, coordination and management. It also mobilizes resources and carries out communication, advocacy and media-related work.