FEEDBACK FROM THE REGIONS AND COUNTRIES ON THE IMPLEMENTATION OF SAGE RECOMMENDATIONS ON TYPHOID VACCINES

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WHO/IVR
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1.0.0 INTRODUCTION

In the November 2007 meeting of the WHO's Strategic Advisory Group of Experts (SAGE) on Immunization reviewed the available global evidence on global typhoid disease burden, assessed the experiences and the usefulness of typhoid vaccines as complementary tools in the control and prevention of typhoid, and made several recommendations [WER No. 1, 4 January 2008, 83; 1-6]. The WHO was requested to report back to SAGE with the feedback from the WHO regional offices and countries on the implementation of these recommendations [see Annex I]. WHO is pleased to report, in the following sections, the progress in the introduction of typhoid vaccines in countries, and some of the challenges countries face in the implementation of SAGE recommendations on typhoid vaccine use.

As the first and most critical step in the implementation of SAGE recommendations, based on the SAGE recommendations, the WHO revised its Position Paper on Typhoid vaccines and published it in the Weekly Epidemiological Record in February 2008 [WER No.6, 8 Feb 2008, 83, 49-60].

2.0.0 ENGAGEMENT WITH WHO REGIONAL OFFICES

Although typhoid is seen globally, the highest incidence is in South-Central Asia and South-East Asia. Studies in selected sites in five Asian countries showed that the annual typhoid incidence varied from 24.2 and 29.0 per 100,000 person years in Viet Nam and China, to 180.3 per 100,000 person years in Indonesia, and 412.9 to 493.5 per 100,000 person years in Pakistan and India, respectively [Ochiai et al, A study of typhoid fever in five Asian countries: disease burden and implications for controls. Bull of WHO, April 2008, 86 (4)]. Though the incidence rates may be an underestimate of the true burden, as blood culture method is only about 50% sensitive, this study was the first to be conducted in the region in standardized comparable manner. Therefore, the South-East Asia (SEA) Region was the priority focus, followed by the Western Pacific Regions, and then the Eastern Mediterranean and the European Regions of WHO. Only limited efforts were made to engage the Regions of the Americas and the Africa were made.

Engagement with the Regional Offices included regular email and telephone contacts with the Regional Advisers and New Vaccines Medical Officer (where available) with the aim to put typhoid discussions on the agenda of important regional meetings. Wherever possible, participation in close collaboration with partners was sought to bring focus on typhoid issues in Regional activities. In 2008 at the SEA Region Technical Advisory Group on Immunization Meeting in July, typhoid was discussed. It was recommended that countries review their surveillance for typhoid to get better data on the epidemiology of typhoid in the countries. Further, at the SEA EPI Programme Managers meeting in August 2009, the topic was revisited.
Two visits were made to the South-East Asia Regional Office. At the regional meeting of the focal points for pandemic preparedness in September 2009, typhoid was discussed individually with country representatives where Nepal, Sri Lanka and Bhutan expressed interest to look at typhoid issues in their countries. This was followed by participation at the SEA GAVI Regional Working Group (RWG) Meeting in Katmandu in February 2010. Following the RWG meeting, another visit was made to the SEA Regional Office and India, Delhi in particular.

3.0.0 ENGAGEMENT WITH COUNTRIES

Based on the currently available information (see section 2.0.0) priority regions are the South-East Region followed by the Western Pacific and the Eastern Mediterranean Regions and, on a limited scale, the European Region of WHO. In addition, based on the initial interest in typhoid issues expressed by some countries, discussions and solicitation for information were initiated with key technical personnel and policy makers in these countries. Colleagues in the WHO regional and country offices played crucial role in facilitating the follow up with countries on their status, vis-à-vis, typhoid control and use or intention to use typhoid vaccines.

In close collaboration with WHO Country offices direct contacts were made with key policy makers and EPI programme managers in typhoid endemic countries. The countries were provided brief summaries of what information/data exist for their respective countries, and the information on typhoid vaccines, global policies on the use of vaccine. Information was also solicited from countries with regards to plans or intentions to use typhoid vaccine, typhoid surveillance and reporting in countries, etc.

In addition to the above, Bhutan, Fiji and Nepal, Sri Lanka were visited once; India was visited twice.

Attempts were also made to encourage countries to include discussion on typhoid in their National Immunization Technical Advisory Meetings; it is known that the India NTA GI did discuss it in at least in one session; Nepal NITAG discussed it once, and Pakistan NITAG planned to do so but got postponed.

And finally at key global meetings such as the GAVI Partners Forum in Hanoi in November 2009, the Global Vaccine Research Forum in Mali in December 2010, the GIM in February 2009 in Geneva, and the SEARO EPI Programme Managers and Partners Meetings in July 2010, typhoid was put on the agenda either as satellite sessions or as one of the main agenda items. Such fora also provided the opportunity for engagement with individual country officials on the sidelines of the meetings to discuss country specific issues and plans. [for country-by-country details, see Annex II]

4.0.0 ENGAGEMENT WITH PARTNERS AND THE GLOBAL COMMUNITY

Even at the global level typhoid has been featured regularly at important meeting. Such events include the meeting of the Diarrheal and Enteric Vaccines Advisory Committee (DEVAC), in Malaga in September 2009, the GAVI Partners’ Forum, Hanoi, in November 2009, the Global Vaccine Research Forum, in Mali in December 2009, the Global Immunization Meeting (GIM) in Geneva in February 2010. Apart from these formal meeting, informal contacts through
teleconferences and email changes were maintained on a regular basis with the International Vaccine Institute (IVI), the Coalition against Typhoid (CaT), and Delivery Team focal point at the Bill & Melinda Gates Foundation.

5.0.0 FEEDBACK FROM THE REGIONS AND COUNTRIES ON THE IMPLEMENTATION OF SAGE RECOMMENDATIONS ON TYPHOID VACCINES

5.1.0 GLOBAL USE OF TYPHOID VACCINE AND EFFORTS TO ACCELERATE UPDATE

- In the WHO/UNICEF Joint Reporting Form (JRF), several countries indicate use of typhoid vaccine, mostly targeting specific risk groups, e.g. food handlers, or high risk areas. Details about high risk areas are not available.

Table 1. Countries reporting typhoid vaccine use in the WHO/UNICEF Joint Reporting Form (JRF), excluding vaccination of travelers

<table>
<thead>
<tr>
<th>WHO Region</th>
<th>Country</th>
<th>Target vaccine recipient</th>
</tr>
</thead>
<tbody>
<tr>
<td>Africa Region</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Region of the Americas</td>
<td>Argentina, Brazil, Cuba</td>
<td>Army, Special groups, 10, 13, 16 years</td>
</tr>
<tr>
<td>Eastern Mediterranean Region</td>
<td>Iraq, Kuwait, Oman, Qatar, Saudi Arabia, United Arab Emirate</td>
<td>High risk groups, Food handlers, Food handlers, Groups not specified, Food handlers</td>
</tr>
<tr>
<td>European Region</td>
<td>Cyprus, Kazakhstan, Slovenia, Uzbekistan</td>
<td>Only if specific indications, High risk groups</td>
</tr>
<tr>
<td>Western Pacific Region</td>
<td>Brunei Darussalam, Malaysia, Republic of Korea, Viet Nam</td>
<td>Not specified, Food handlers, High risk groups, Part of the country</td>
</tr>
</tbody>
</table>


- Countries who use typhoid vaccine, in at least in parts of the country, but do not report this in the JRF are China, India and Pakistan.
- It is known that most developed countries offer the vaccines for travelers to typhoid endemic countries. It is also known that many armies around the world use the vaccine although only Argentina reports it in the JRF.
- Most recently Sri Lanka started typhoid vaccination, targeting high risk groups (e.g. health workers, food handlers, etc.) and populations residing in high risk areas. In 2009,
Sri Lanka procured 20,000 doses of ViPS and used to control and outbreak that occurred in the camps of the people displaced by war. Early this year they procured 200,000 doses and distributed the vaccine to 20 districts with guidelines on the risk groups to be targeted. Although they are currently using the ViPS, Sri Lanka expressed some interest in the oral vaccine but the current price is clearly beyond their reach.

- Similarly Fiji started a campaign with ViPS to immunize 70,000 people (above 2 years of age) residing in high endemic areas. They plan to introduce the vaccine as a school-based routine programme as well as those considered 'high risk' groups such as food handlers.
- Nepal is keen to introduce typhoid vaccine in the Katmandu Valley to start with, but due to lack of resources, the planning has been kept on hold at present.
- Similarly Bhutan wants to strengthen surveillance in the capital city, Thimphu, but also wants to introduce typhoid vaccine in one of the districts where outbreak of typhoid occurs regularly. And preferably they would like to use the Ty21a oral vaccine.
- The Kyrgyzstan Republic has interest to carry out a pilot project but before resources could be found for this activity, the country was engulfed in political violence. Plans to follow up are on hold right now. Kyrgyzstan, too, would prefer the oral Ty21a vaccine.
- The VIVA Initiative, funded by the Bill and Melinda Gates Foundation and administered by the IVI, is working with both governmental and non-governmental sectors in Karachi, Pakistan, and Lalitpur, Nepal to pilot introduce the ViPS vaccine for school children. The program targets 240,000 and 120,000 students, respectively.

5.2.0 FEEDBACK ON SPECIFIC ASPECTS OF THE TYPHOID VACCINATION RECOMMENDATION AND THE CHALLENGES TO THEIR SUCCESSFUL IMPLEMENTATION BY COUNTRIES

5.2.1 Financing

- The SAGE recommendations did stimulate interest in countries to look at their typhoid disease burden and to explore the possibility of using vaccines as an adjunct to improved water and sanitation to control and prevent typhoid. However, countries have competing priorities with multiple public health initiatives vying for funding, often from the same source. Further, even within the current vaccines portfolios, e.g. Hib, rotavirus and pneumococcal vaccines, countries struggle to balance their priorities, despite committed GAVI Alliance support for all of these vaccines. Typhoid, at this time, has no donor commitment and, despite being included in GAVI’s Vaccine Investment Strategy Portfolio, is not currently supported by GAVI.

- Financing is a constraint, not only for roll out of vaccines, but even to establish credible surveillance for typhoid. And in most countries the disease burden data is not well established and, where in existence, certainly not good enough to provide the basis for identifying "risk areas" to implement the "risk-based approach" recommendation.

- As a potential alternative financing approach, the above-mentioned VIVA Initiative is experimenting cross-subsidization scheme to support the cost of the program. The scheme charges one sector (private schools in Karachi and tourism industry in Kathmandu) to subsidize the program cost of the main target population. The cost recovery rate will be available after the conduct of the program in one year time.
5.2.2 Program strategy
- Typhoid vaccines are one of the few new vaccines that do not fit the routine EPI schedules, but may well provide the opportunity to realise the GIVS goal of vaccination beyond the infant age group. Despite the challenges the typhoid vaccines pose as they would require strategies outside the routine EPI, some of the countries (I talked to) are keen to pilot vaccine introduction programme (Fiji, Sri Lanka, Viet Nam, Delhi etc.).
- Countries see school-based vaccination as a viable option and the majority of those countries considering adoption of typhoid vaccine would like to deliver through a time-bound, short campaign at some period of the school year, preferably at the start of scholastic year. However, the Delhi experience [see Annex II] has demonstrated the feasibility of delivering a vaccine outside the EPI Schedule by using the same infrastructure and delivery system of the existing routine immunization programme.
- Implementing a risk-based vaccination strategy is a challenge for most countries due to the difficulty of defining high-risk groups and populations. All countries emphasize the need to strengthen surveillance to generate better epidemiological information on typhoid, but they all need support at least in the initial few years to kick-start such activities.
- With two vaccines that differ vastly in characteristics and with a recommendation of risk-based introduction as compared to universal, decision on the introduction of a typhoid vaccine is a complex process. In order to aid decision makers, a draft decision making tool for the introduction of typhoid vaccines, is in the process of being finalized.

5.2.3 Vaccines options-injectable vs. oral
- Although ViPS, as a single dose vaccine, has its advantages particularly in a campaign setting, some countries I visited are also interested to explore possibilities of the use of oral vaccine to reduce the number of injections, if oral vaccine is affordable.
- Right now the widespread use of the oral typhoid vaccine is limited by its relative high cost compared to the ViPS vaccine and, also, because of the need to provide at least three doses given on alternate days. There is no experience in the use of the oral vaccine in a real programme setting.
- Given the limited duration of protection by the currently available vaccines, countries may need to consider the need for revaccination depending on the local epidemiology. And this has logistic and cost implications for an immunization programme.

5.2.4 Surveillance
- All countries have a morbidity/mortality reporting system and most of them include typhoid. However, the terms typhoid and enteric fevers are not well defined in such reports.
- Further, the diagnosis of typhoid is often only based on clinical observation and not backed by laboratory confirmation. Blood culture facilities are not available in most health facilities, particularly in the periphery of the health infrastructure networks, and simple diagnostic kits are not widely available.
- There is no example of sentinel surveillance targeting pre-school and school-aged children.
5.2.5 Diagnostics

- Typhoid diagnosis is a real challenge for countries. In most hospitals blood culture is not widely available. And where available, quality is uncertain. Even in the best of circumstances blood culture can pick up barely 50% of the true cases of typhoid.
- Most hospitals use serological test, Widal being the most common. However, Widal takes up to 18 hours to process and it is relatively expensive (at $5-20 per test). The result is often based on a single test, which may not have any significance.
- Several other serological tests to detect acute S. Typhi infection have been developed with sensitivity around 70% and specificity around 80%. But none of the tests exceed 60% of diagnostic accuracy and can’t be considered as a “point of care” (POC) test.
- POC testing, defined as diagnostic testing at or near the site of patient care, can increase the likelihood of disease confirmation, and improve disease-specific treatment and public health surveillance.
- All countries express the desire to have an affordable and an accurate diagnostic test for typhoid.

5.2.6 Outbreak control

- One of the important parts of the SAGE recommendations refers to the use of typhoid vaccine to interrupt outbreaks. Experience from China on the use of ViPS vaccine to control typhoid outbreak is document. In recent times, there are a few other experiences from countries.
- Pondicherry, India, following the 2004 Tsunami, 17,000 doses of ViPS was used as a preventive vaccination campaign targeting primarily children below 5 years of age. No typhoid cases were reported in Tsunami affected areas.
- Following the Pakistan earthquake in 2005, a pediatric Vi vaccination campaign was undertaken in affected camps with over 50,000 doses administered. No cases were recorded in the camps in question over the following 4-6 months in routine surveillance.
- Cyclone Tomas struck North and North-Eastern part of Fiji in March 2010. By June a mass campaign to reach 70,000 people in typhoid endemic areas with the ViPS vaccine was initiated and by end of August, more 60,000 were immunized. Although no epidemiological evaluation to assess the impact has been done to date, it is reported that the number of cases of typhoid reported have declined.

5.2.7 The challenge of S. Paratyphi

- S typhi is, according to the available epidemiological information, still the major cause of typhoid fever. However, experience from Thailand as well as China show that as S. Typhi incidence declines, there is a concomitant rise in the incidence of S. Paratyphi. In some cases it may an un-masking effect; in some cases, possibly replacement phenomenon.
- Guilin, China, has discontinued active promotion of ViPS vaccine due to the rise of paratyphoid cases which resulted in people questioning the efficacy and utility of ViPS against S. Typhoid.
- In Nepal, the Public Health Laboratory in Kathmandu found that the proportion of S. Paratyphi was 32.9% and 62.5% in 2007 and 2008, respectively.
- In the absence of a vaccine against S. Paratyphi, many countries are uncertain whether introduction of a vaccine against S. Typhi would have any impact at all on enteric fevers.
5.3.0 FEEDBACK ON WHO PREQUALIFICATION OF TYPHOID VACCINES

- WHO prequalification of a vaccine is an important step to assure countries of the quality of the product, particularly in those countries where national regulatory authorities do not have the capacity to assess vaccine quality. SAGE recognized that and urged the prequalification of the currently licensed improved typhoid vaccines. WHO prequalification is also a requirement for UNICEF procurement and GAVI Financing.
- The system in place to assess the acceptability, in principle, of vaccines has been effective in promoting confidence in the quality of the vaccines shipped to countries through UN purchasing agencies.
- Prequalification process for three typhoid vaccines produced by different manufacturers have been initiated. Two out of three are purified Vi capsular polysaccharide of Salmonella typhi (Ty2 strain) based vaccines. The third one is the live oral attenuated Ty21a vaccine.
- Currently the prequalification of one of the polysaccharide based vaccines is expected by October-November 2010. The live oral attenuated vaccine is advanced in the process and prequalification may be expected early 2011. The third vaccine is still on the initial stages of the process but prequalification may be expected by 3Q 2011

5.4.0 UPDATE ON NEW INITIATIVES

5.4.1 Sub-Saharan Typhoid Surveillance Project

- The International Vaccine Institute (IVI) is conducting the Multi-Country Typhoid Fever Surveillance Program (TSAP) in sub-Saharan Africa with support from the Bill & Melinda Gates Foundation. The program’s aim to generate standardized data on enteric fever-related illness and death in countries of sub-Saharan Africa in order to drive evidence-based decision-making on enteric fever control and prevention interventions, including vaccination. The program requires the achievement of several objectives: 1) to develop a network of sentinel enteric fever surveillance sites in sub-Saharan Africa; 2) to estimate the burden of typhoid and paratyphoid through standard surveillance methods; 3) to identify additional endemic areas through multi-site disease burden studies; and 4) to advocate for the establishment of evidence-based enteric fever control and prevention policy that includes vaccination.
- A consortium of scientific and public health institutions working in the region was created and comprises of TF experts in the fields of epidemiology, laboratory testing, and public health (PH). Based on an evaluation of epidemiological setting and laboratory infrastructure, sites were either considered Group 1 Sites (G1S) or Group 2 Sites (G2S). G1S have an existing surveillance infrastructure for typhoid fever while G2S are lacking adequate surveillance infrastructure at the moment. G1S include Ghana, Kenya, South Africa, Tanzania, Nigeria, and Uganda. G2S include Burkina Faso, Ethiopia, Guinea Bissau, Madagascar, Senegal, and Sudan. A general protocol has been completed along with a standardized study design, which includes assessment of catchment population, inclusion and exclusion criteria, Case Report Form, data management, and laboratory requirements for the culturing of Salmonella Typhi, as well as automated blood culturing systems, and the development of QC/QA and proficiency testing approaches.
For the majority of the sites, surveillance activities will be hospital-based. Subjects are those who present at the hospital’s in- and out-patient wards, reside in the catchment area with scientifically define population, and fulfill the inclusion criteria. Population-based surveillance will be conducted in the Kibera slums of Nairobi, Kenya, in collaboration with the U.S. CDC and Kenya Medical Research Institute (KEMRI). Laboratory-based surveillance will be conducted with the South African National Institute of Communicable Diseases where subjects will be identified by specimens testing positive for TF in the laboratory. Thus, TSAP will provide a unique opportunity to compare three types of PH surveillance in the African setting.

5.4.2 Coalition against typhoid (CaT)

The Coalition against Typhoid, CaT, is an initiative lead by the Sabin Vaccine Institute with support from the Bill & Melinda Gates Foundation. The main objective of the initiative is to coordinate typhoid stakeholders towards common objectives for typhoid control and prevention, and act as the catalyst to develop comprehensive and concrete work plans and facilitate implementation of such plans in countries.

The purpose of this group is to serve as a well-respected, independent voice that is comprised of typhoid experts and global health immunization stakeholders who can directly address the issues facing the vaccine community and develop a global work plan for use of vaccines to control typhoid.

To lead this coalition and provide specific oversight to various activities, the Sabin Vaccine Institute has begun to chair the sessions of the coalition, which includes members from: the Agha Kahn University, Bharat Biotec, the Bill and Melinda Gates Foundation, the Centers for Disease Control and Prevention, Crucell, the GAVI Alliance, the International Vaccine Institute, Novartis Vaccines Institute of Global Health, PATH, Sanofi-Pasteur, the United Nations Children’s Fund, University of Maryland Center for Vaccine Development, and the WHO

6.0.0 NEXT STEPS AND THE FUTURE

Typhoid is a disease that affects the weakest sections of society who often do not have the opportunity to voice their needs. Therefore, a concerted global effort to support countries through the initial steps are needed, even if not on the same scale of investment for preparatory processes prior to introduction of other new vaccines in recent past, a modest investment to support countries is essential and a necessary pre-requisite. The international donor community, including alliances committed to the achievement of the Millennium Development Goals through reduction of mortality and morbidity from common diseases, need to come together to create funding mechanisms to help countries understand their disease burden better, help them prepare for possible use of vaccines and provide financial assistance to the countries most in need but unable to help themselves to have access to typhoid vaccines.

The commitment of several countries to address typhoid issue is evident in that they are already moving ahead with plans to introduce typhoid vaccines despite the absence of significant support from anywhere. We need to continue to build the momentum.

While the coming of conjugate vaccine against typhoid is much anticipated, there is room to explore the option for an oral vaccine that is available and affordable. As the
infant immunization schedule gets more crowded with injectable vaccines, an oral vaccine is seen as something less complicated to handle. The global community needs to rise to this challenge by offering options to expand the range of immunization schedules

- The scientific and the global communities need to rise to the challenge to develop an easy to use, accurate and affordable diagnostic tool for typhoid
- In the coming years, more focus will be placed on Africa, and resources to support work in Africa is critical if we are to make any progress in the continent with typhoid control and prevention
- The recent announcement of the support from the Bill & Melinda Gates Foundation for the Coalition against Typhoid (CaT) is indeed welcomed, and this consortium will certainly go a long way in bringing more focus on the neglected issue of typhoid.
- As a continuation of the feedback to SAGE, WHO IVR is committed to facilitate endemic countries to seek for a sustainable public health response to control and prevent typhoid in their countries.
1. 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 polysaccharide and Ty21a), countries should consider the programmatic use of typhoid vaccines for controlling endemic disease.

2. In most countries, control of the disease will require vaccination targeted only at high-risk groups and populations.

3. Countries should decide on the selection of populations and age groups to target, and on the delivery strategy (e.g. school-based or community based vaccination), which will depend on the local context (age pattern of the disease, school enrolment rates, etc.).

4. Countries should select typhoid vaccines depending on the capacity of the local Expanded Programme on Immunization and other logistic and cultural factors, and should utilize opportunities coupled with other public health interventions in the age groups referred to in paragraph 3.

5. The availability of the above-mentioned licensed typhoid vaccines will be enhanced by pre-qualification by WHO of these products and by enhanced global awareness and commitment to reduce the burden of typhoid disease.

6. Due to the epidemic potential of typhoid, and observations on the effectiveness of vaccination in interrupting outbreaks, typhoid vaccination is recommended for outbreak control.

7. Typhoid vaccination programmes should be implemented in the context of other efforts to control the disease, including health education programmes, improvements in water quality and sanitation, and programmes to train health professionals in diagnosis and treatment.

8. Given the importance of information on disease incidence for targeting vaccination and assessing its impact, priority should be given to strengthening surveillance systems for typhoid fever, including sentinel site surveillance in pre-school (2–4 years old) children and school-aged children (5–15 years old). The development of reliable and appropriate diagnostics assays for use in developing countries is required.

9. Development and research on new typhoid vaccines (such as the Vi conjugate vaccine) are encouraged, particularly for use in infants and young children, but this should not limit the use of currently available vaccines for control of endemic disease.

# Annex I

**Salient features of the SAGE recommendations on typhoid vaccines, Nov. 2007**
DETAILED UPDATE OF THE FOLLOW UP ACTIVITIES WITH REGIONS AND COUNTRIES AND THEIR CURRENT STATUS OR FUTURE PLANS.

1.0 SOUTH-EAST ASIA REGION

At the South-East Asia Regional Immunization Technical Advisory Group meeting in July 2008 that the topic of typhoid control and prevention was first discussed. The SEA-ITAG recognized that typhoid was a major public health concern in many Member States. However, the ITAG highlighted the need to first focus on strengthening surveillance for typhoid so that better data would be available to aid future decisions. The recommendation from the ITAG meeting was then fed to the Immunization Programme Managers meeting the same year (August 2008) where countries were encouraged to review their surveillance system and to see how they can be strengthened to include typhoid. However, most countries did not take any specific actions on the matter.

In early 2009, the South-East Regional Office assisted the International Vaccine Institute, Seoul, to conduct a meeting on typhoid in Bangkok in March 2009, which brought together experts, programme managers and government officials from some of the typhoid endemic countries to discuss how best to take forward the typhoid agenda in the Region.

Subsequent to these, after July 2009, IVR actively engaged with the Regional Office as well as with countries using both formal and informal channels. In August 2009, taking advantage of the SEA Regional Pandemic Influenza Vaccine Deployment workshop being held in Delhi, discussion on typhoid vaccine was also included, in addition to discussion with individual country delegates on the side lines of the meeting. Subsequent to that individual country high level delegates were met at the GAVI Partners Forum in Hanoi in November 2009. In February 2010, typhoid was also included on the agenda for the meeting of the South-East Asia Regional Working Group (SEA RWG) in Katmandu and, at the Immunization and Partners Meeting in Delhi in July 2010.

Apart from these regional focused activities, individual country discussions were held and given below are information specific to each country on typhoid related issues.

Bangladesh

- Discussions with high level delegates from Bangladesh at the GAVI Forum, Hanoi, in November 2009
- Several rounds of discussions, email exchanges with the EPI Programme Manager as well as WHO medical officer in Dhaka too place
- Also, commissioned a brief review of available information on typhoid in the country. Data on typhoid is included for routine collection only from 2008. Typhoid is ranked as the 8th most important cause of hospital admission with over 400,000 cases admitted in hospitals with typhoid in 2008. Other prospective studies [Brooks et al. Bacteremic typhoid fever in children in urban slum, Bangladesh. Emerging Infect Dis, Vol. 11, No. 2, Feb 2005] puts the incidence of typhoid fever as high as 390 per 100,000 person-years, clearly highlighting the major public health burden due to typhoid.
With GAVI Alliance’s support, in recent years, Bangladesh has introduced hepatitis B and *Haemophilus influenzae* type b (as the pentavalent). And currently they are actively planning for possible introduction of rotavirus and pneumococcal vaccines and, even cholera vaccine. Therefore, Bangladesh feels that they do not have the capacity or the resources to take up typhoid in any significant way at present. Nevertheless they are interested to seek for support to strengthen typhoid surveillance in the country.

**Bhutan**

- Despite its small population (around 750,000) more than 2000 cases of typhoid are reported annually with occasional outbreaks, even forcing schools to close. Following the discussions with the high delegation at the GAVI Partners Forum in Hanoi in November, a country visit was made in June 2010.
- Bhutan is keen to explore the possibility of using typhoid vaccines to control/prevent typhoid. They have specifically asked for assistance to strengthen surveillance in the capital city, and to explore the feasibility or the appropriateness of introducing a typhoid vaccine (Ty21a preferred) in one small district where typhoid outbreaks occur annually. Further discussions is on going

**Myanmar**

- Like other countries, the Myanmar high level delegation at the GAVI Partners Forum in Hanoi were briefed about the possibilities of typhoid vaccination. It is known (although getting data is challenging) that typhoid is endemic in most parts of the country.
- This was followed up with several informal contacts with the EPI PM Manager, but nothing concrete has happened and there is no clear signal from the country on how we move forward.
- Like other health interventions for Myanmar, donor assistance will be needed on a long term if we are to start any programme.

**Nepal**

- Following the discussions with the high level delegation at the GAVI Partners Forum, a country visit was made in Feb 2010 preceded by discussions with both the WHO country office and the EPI Programme in the Ministry of Health, Nepal.
- Typhoid and cholera are major issues in Nepal, particularly so in the Katmandu valley. In the Annual Report published by the Department of Health shows 203,172, 271,437 and 463,104 cases of typhoid reported for the years 2005/06, 2006/07 & 2007/08, respectively.
- A network of 11 laboratories across the country participates in a bacterial diseases surveillance, primarily to track multidrug resistance. The Public Health Laboratory in Katmandu serves as the reference laboratory for this surveillance. Salmonella was included on the list of pathogens since 2004. For the years 2006, 2007, 2008 & 2009, they identified 1611, 1512, 1697 and 1307 salmonella isolates at the National Reference Laboratory, with an increasing trend in the proportion of *S. Paratyphi* identified.
- Drug resistance is present but at very low level, and also seems to indicate a slight rise in trend
Nepal has had experience with the use of ViPS vaccine as one of the important trials with ViPS was carried out in Nepal [Acharya et al. Prevention of typhoid fever in Nepal with the Vi capsular polysaccharide of Salmonella Typhi. The New England Journal of Medicine, Vol. 317, No. 18, October 1987.]

IVI is initiating a pilot study to assess acceptability and usefulness of charging for the vaccines to groups that can pay to subsidize groups that cannot pay for the vaccine but need it.

Nepal is very keen to start typhoid vaccination, initially targeting Katmandu Valley, although typhoid is reported from almost all parts of the country. However, they will need assistance (technical & financial) to initiate the programme.

The VIVA Initiative is pilot introducing Vi polysaccharide vaccine utilizing a cross-subsidization scheme. The program targets 120,000 students in Lalitpur District (one of the three districts of Kathmandu Valley) using public health infrastructure. The program will also examine the viability and sustainability of cross-subsidization scheme where adults in the tourism sector will be vaccinated for a minimal user fee, which is to be deposited in the vaccine revolving fund to support financing the public health school-based typhoid vaccination program.

Indonesia


Further, with Bio Farma in Indonesia, prospect for sustainability is high if vaccines were to be used.

IVI is currently in discussion with Bio Farma for technology transfer for production of Vi polysaccharide and conjugate vaccine development through VIVA Initiative.

India

Typhoid is undoubtedly a major public health issue in India. In their routine reporting for morbidity and mortality, typhoid is included. It is reported from the Central Bureau of Health Intelligence, Government of India, that in 2007 and 2008, at least 820,360 and 934,469 cases of typhoid were reported nationwide, and typhoid is listed among diseases that cause significant death. [http://www.cbhidghs.nic.in/writereaddata/linkimages/8%20Health%20Status%20Indicators4950277739.pdf, accessed 7 September 2010]

However, other than Delhi State, no other places use typhoid vaccine on a regular basis.

The National Technical Advisory Group on Immunization (NTAGI) did have a brief discussion on typhoid in their meeting in 2009. The group recognized that typhoid is important and recommended the strengthening of surveillance for typhoid, particularly to look at differentials between urban rural settings.

In February 2010, during a visit to Delhi, detailed discussions were held with key persons in the immunization unit of the Ministry of Health as well the Indian Council
for Medical Research (ICMR). The immunization unit recognized the value of vaccination but indicated that there are other priorities that the central government is engaged in right now and that there are no immediate plans to include typhoid vaccines within their national immunization programme. On the issue of surveillance, the ministry was looking to other agencies or partners to initiate surveillance.

- When the issue was broached to ICMR to initiate a few select centers around India as study sites to look at typhoid burden, ICMR did not think it was its core responsibility and felt that surveillance is a central government activity.
- Delhi state introduced ViPS since 2004 as part of its routine immunization programme but targeting children aged 2 to 4 year olds. The vaccine is delivered through the same service infrastructure as routine immunization and by now they are reaching about 300,000 children annually. Delhi State has a population in excess of 20 million people.
- Delhi was encouraged to conduct a review of the impact of the programme, but the would need assistance. We explored possibilities with National Institute of Cholera and Enteric Diseases (NICED), Kolkata, who were partners with IVI in conducting the ViPS effectiveness trial in Kolkata [Sur et al. A Cluster-Randomized Effectiveness Trial of Vi Typhoid Vaccine in India. N Engl J Med, 361;4: July 23, 2009]. Although they showed some interest, no specific steps have been taken to carry out the evaluation.
- Following the 2004 Tsunami, the Union Territory of Pondicherry carried out a mass campaign with ViPS vaccine targeting about 17,000 under five children as a preventive campaign against potential typhoid outbreak. There were no cases of typhoid reported in the wake of Tsunami.

**Sri Lanka**

- Sri Lanka has a long history of using the whole cell typhoid vaccine, targeted mainly at health workers and known high risk areas. However the use of this vaccine was discontinued in the early 1990's due to its severe adverse events following immunization. In recent years Sri Lanka has restarted the programme with ViPS vaccine in high endemic areas
- The incidence rate of typhoid fever in Sri Lanka is 11.48 per 100,000 populations in 2009. But this distribution is uneven throughout the country. The highest incidence rate 90.56/100,000 population has been reported from Vavuniya District, then from Mannar District (140.76/100,000). The medium level incidence reported from Jaffna (98.27/100,000), Nuwara Eliya (27.21/100,000) and Puttlam Districts (10.32/100,000).
- The vaccination with ViPS is recommended by the Sri Lankan MOH to those deemed at high risk in areas known for typhoid outbreaks. High risk groups include health workers, food handlers, people living in typhoid endemic areas where water and sanitation facilities are considered poor or inadequate, etc. For 2010 they have procured 200,000 doses of ViPS and distributed to 20 districts with general guidelines on the risk groups to be vaccinated.
2.0 **Western Pacific Region**

**China**

- Typhoid is endemic to many Chinese Provinces, particularly in the south, south-east, and south-western part of the country. Typhoid vaccine, mainly Vi polysaccharide had been used in China for many years.
- In June 2010, in collaboration with IVI and the Guangxi Centers for Disease Control and Prevention (GXCDC), organized a workshop in Guilin where representatives from four provinces and one autonomous region of China, two vaccine Chinese vaccine manufacturers, National CDC, and National Institute for the Control of Pharmaceutical and Biological Products (NICPBP) were represented, in addition to participants from IVI, WHO and Bill & Melinda Gates Foundation. The main objective of the workshop was to learn about typhoid vaccination and the impact it has had, and the most recent available data and the trend in the disease epidemiology following the use of ViPS vaccine in these provinces.
- Typhoid vaccination is not part of the national immunization programme and, therefore, the vaccine is not available free as the ones on the national EPI Programme list. The vaccine is sold by the local CDC and the average cost is about US $ 1 per dose of ViPS.
- Common strategies employed are school-age vaccination in high risk areas, vaccination of food handlers, outbreak response, and high risk focused regular immunization campaigns.
- Although coverage varied across and within provinces, the vaccine has proven to be effective in reducing typhoid incidence to very low level and, also, seems to be effective in curtailing transmission during outbreaks.
- However, in recent years the rise in the incidence of paratyphoid has complicated both the epidemiology of the disease and the measurement of the impact of ViPS vaccination against S. Typhi.
- Where vaccines are not available free, price is an important determinant of uptake as the ones in most need of the vaccines are often the ones who can afford it least.

**Fiji**

- Fiji, a South Pacific island nation, consists of over 350 islands and islets, of which approximately 100 are inhabited, but the majority of the population (about 87%) resides on the two main islands- Vanua Levu and Viti Levu. In 2007 Fiji had a population of 837,271 [http://www.statsfiji.gov.fj/Census2007/census07_index2.htm] with an approximate birth cohort of 20,000. Of the total population about 25% reside on the island of Vanua Levu and the remaining mainly on Viti Levu; the capital, Suva, in also on this island.
- Typhoid is known to be endemic in many parts of the country. In a 2006 study, WHO estimated that Fiji has an incidence of typhoid of between 136 and 1000 cases per 100,000 population per year, which is one of the highest rates reported in the World. In recent years the geographical area where typhoid is reported is expanding from the historical 'hotspot' in the North and cases are now routinely reported in parts of Western and Central/Eastern Division. Following cyclone Tomas in March 2010, an increase in notifications of typhoid was reported and, by end of July 2010, there
were 110 cases reported for 2010 compared with 58 for the same time period last year.

- Discussions were initiated with WHO country office towards the latter half of 2009 about instituting a regular typhoid control programme. Even a draft vaccine introduction plan was developed and circulated for discussions. Then early 2010, cyclone Tomas, a Category IV Storm, brought destruction and disease in its wake. Suddenly typhoid control became an urgent matter.

- With support from AusAID the Government of Fiji decided to vaccinate approximately 70,000 people aged above two years with the ViPS vaccine. The outbreak response was targeted mainly for those populations residing in the known high endemic spots as well as high risk areas from where cases were being reported regularly. By the end of July 2010, more than 40,000 people were already vaccinated.

- In August, a meeting was convened by the Government of Fiji in collaboration with the WHO Country Office. Experts were invited from WHO HQ, WPRO, CDC (US) and the International Vaccine Institute (IVI). After a two-and-half days of meeting, the following recommendations were made for typhoid vaccination in Fiji:
  - to complete the present 70,000 targeted immunization with ViPS vaccine [the MoH is keen to expand the mass campaign to reach more people if additional resources can be found],
  - introduce a single dose ViPS at school entry, and possibly a repeat dose after three years or at primary level exit as options.
  - Immunize all health care workers and hospital laboratory workers,
  - Regular Immunization for food handlers
  - Maintain a small stockpile of ViPS vaccine to respond to outbreaks,
  - to continue the surveillance activity in the three laboratories that are already involved in doing blood and stool culture from suspect cases of typhoid. It was emphasized that keeping up the surveillance at the same level and quality is important so that after a few years, a proper impact assessment of the vaccine is possible.

- The proposal will be vetted by the government and donor agents. Fiji, therefore, can most likely be one of the countries to have a regular typhoid vaccination programme as part or EPI work.

### 3.0 Eastern Mediterranean Region

**Pakistan**

- A long and extensive discussion was held with the WHO Pakistan Country Office on typhoid and typhoid vaccination. Brief meeting was also held with a few senior government figures at the GAVI Forum in Hanoi.

- Although typhoid is considered a public issue, there isn't the kind of urgency or pressure to do anything immediately. This is partly because there is no donor funding to support it. And further, the national 5-year development plans for the cycle 2012-2017 is already finalized and budget envelopes for various sectors decided; typhoid control programme cost is not included and, by the time discussions were initiated towards end of 2009, it was too late (I was told).
Following the DOMI typhoid project in Karachi, Pakistan, there was a concerted effort towards a school based vaccination strategy in Sindh and Punjab. Several meetings were held in Islamabad, Lahore and Karachi and expressions of interest obtained from the Ministries of Health in Punjab and Sindh for pilot projects in the cities of Faisalabad and Karachi. However, lack of donor funding was a problem and interest waned with the change in governments.

As a starting point, it was planned to include discussions on typhoid at the National Immunization Technical Advisory meeting in December 2009. That got postponed to early 2010, and then it never happened. Then the floods came.

Further, it was clear that without donor support, it is unlikely that Pakistan Government will make any specific moves towards a typhoid control programme that includes vaccines as part of the package.

Similar to the program in Nepal, VIVA Initiative has commenced a pilot introduction of Vi polysaccharide vaccine utilizing a cross-subsidization scheme. The program targets 240,000 students in two townships of Karachi using public health infrastructure. The program will also examine the viability and sustainability of cross-subsidization scheme where students in high-fee private schools will be vaccinated for a minimal user fee, which is to be deposited in the vaccine revolving fund to support financing the typhoid vaccination program for public schools and madrassahs.

4.0 European Region

The Kyrgyz Republic

The former Soviet states in Central Asia, namely Uzbekistan, Tajikistan and the Kyrgyz Republic, are known to have periodic large outbreaks of typhoid. Amongst them the Kyrgyz Republic have long expressed an interest to explore the feasibility of vaccination (with Ty21a as the preferred choice) to control and prevent typhoid. The International Vaccine Institute had provided technical assistance to initiate a pilot project and a proposal was developed. However, no funding support could be mobilized and the plan did not proceed any further.

A discussion was held with the WHO Regional Office in Copenhagen and the WHO Country Office to develop a plan of action to push this forward, and it was agreed that a visit from WHO HQ would be a useful first step. Unfortunately before that could take place, political turmoil rocked the country into uncertainty.

It would be only reasonable that no further actions can be taken till normalcy returns to the country.

Other countries in the same region have not expressed any interest, but that also maybe because no efforts were made to reach out to them.

5.0 The African Region

Enquiring through the Regional Adviser for Immunization in the Africa Region, it appears that no country in Africa has expressed interest in typhoid vaccination on any significant scale except Kenya who has initiated a programme of vaccinating food handlers in schools. Although many countries have reported confirmed
outbreaks of typhoid there has never been any serious attempt to define better the disease burden of typhoid in Africa, at least till now.

- No serious efforts were made to follow up with countries on their interest in typhoid as it was known that a multi-country surveillance system was being put in place by the International Vaccine Institute which, in the near future, will generate better data on typhoid for Africa.

- The Division of Vaccines & Immunization, Ministry of Public Health & Sanitation, Kenya, has begun a typhoid vaccination program targeting food handlers in boarding schools nationwide. There are 2,422 boarding schools in Kenya for primary-age children and in each institution, there are estimated 20 staff handling food for them. In the initial year, they planned to cover 967 of these schools in 61 districts within 7 provinces. They have procured approximately 20,000 doses of Vi polysaccharide vaccine for this program and planning to complete the vaccination within 2010.
**UPDATE ON THE DEVELOPMENT OF NEW TYPHOID AND PARATYPHOID VACCINES**

This Appendix was prepared by Professor Myron M. Levine of the Center for Vaccine Development of the University of Maryland School of Medicine, Baltimore, Maryland, with input from Dr. Linda Martin and Dr. Allan Saul of the Novartis Vaccines Institute of Global Health, Siena, Italy and Dr. John D. Clemens of the International vaccine Institute, Seoul, Korea.

1. **Impetus to develop new typhoid and paratyphoid vaccines.**

Whereas parenteral Vi and oral Ty21a, the second generation typhoid vaccines, are very well tolerated and confer upon vaccinated subjects a moderate level of protection against typhoid fever, each nevertheless suffers from some drawbacks. For example, although Vi is able to provide moderate protection after administration of just a single dose, giving additional doses does not further boost the titers of serum IgG Vi antibody; rather Vi behaves like a T-independent antigen that does not elicit immunologic memory. Consequently, protection conferred by Vi does not extend beyond three years.[1] With some other purified unconjugated polysaccharide vaccines, such as meningococcal C and A and polyvalent pneumococcal polysaccharide vaccines, repetitive administration to subjects leads to B cell depletion and attainment of lower antibody levels than are seen following the initial administration of the polysaccharide.[2-4] Heretofore, there are insufficient data available to conclude whether or not this happens with Vi.

The main drawback of Ty21a is the need to administer three spaced doses to achieve the moderate level of long-lived protection that this vaccine can elicit. In many situations in developing countries, this requirement to administer three doses constitutes an impediment that makes mass vaccinations, as in community or school-based campaigns, logistically more complex than mass vaccination with a single-dose vaccine.

Fortunately, immunologic knowledge and advances in biotechnology have allowed a third generation of new typhoid vaccines to be prepared that overcome the drawbacks of Vi and Ty21a. These new vaccines are described briefly below. The new vaccines include much more immunogenic attenuated strains that serve as single-dose live oral vaccines. The new vaccines also include parenteral conjugate vaccines consisting of Vi polysaccharide covalently linked to different carrier proteins. The new Vi-based parenteral conjugate vaccines aim to stimulate immunologic memory and to elicit longer-lived antibody levels of higher affinity and avidity and thereby to achieve a higher level of protection and sustain it longer than with unconjugated Vi. Since Ty21a does not express Vi, it confers long-term protection by immunologic responses other than serum Vi antibody.

There are no licensed vaccines to prevent enteric fever caused by S. Paratyphi A or S. Paratyphi B. This is a notable gap in the public health armamentarium, since S. Paratyphi A carrying a stable R factor plasmid encoding resistance to multiple antibiotics is rapidly emerging in Asia.

---

1 Contributed by Professor M. Levine
Thus, *S. Paratyphi A* is a problem in endemic areas [5,6] like South and Southeast Asia and also among travellers [7] from industrialized countries who visit endemic countries.

2. New generation typhoid and paratyphoid vaccines under development

2.1. Typhoid vaccines

2.1.1. Attenuated strains as single-dose oral vaccines. Several new strains of *Salmonella Typhi* have been genetically-engineered to contain precise attenuating mutations. As summarized in Table 1, four of these engineered strains have been successfully tested in Phase I and II clinical trials and have been shown to be well tolerated and immunogenic after ingestion of just a single oral dose. These strains were all derived from virulent wild type parent strain Ty2, which is also the parent of Ty21a. These live strains remain oral vaccine candidates that could eventually be brought to licensure if industrial partners chose to make the necessary investments.

The live oral vaccine candidates include:
- strain M01ZH09, with deletion mutations in *aroC* and *ssαV* (a component of the type III secretion system encoded by *Salmonella* pathogenicity island-2)[8-10];
- strain Ty800, deleted in *phoP/phoQ* [11];
- strain CVD 908-htrA, with deletion mutations in *aroC, aroD* and *htrA* [12,13];
- strain CVD 909, a further derivative of CVD 908-htrA that constitutively expresses Vi capsular polysaccharide.[14,15]

2.1.2. Parenteral Vi conjugate. Booster doses of purified Vi do not raise antibody titers over those elicited by a single dose of vaccine; i.e., immunologic memory does not occur. To remedy this, Vi polysaccharide has been conjugated to various carrier proteins. The first conjugate vaccine to undergo extensive clinical testing was a product in which Vi was linked to recombinant exotoxin A of *Pseudomonas aeruginosa* in an attempt to confer T-cell-dependent properties upon the Vi antigen, including the induction of immunologic memory. In children and adults in endemic areas booster doses of Vi conjugate vaccine clearly increase the titers of antibody over those elicited by a priming dose.[16-18] A randomized, controlled field trial of Vi conjugate in children immunized at ages 2-4 years in the Mekong Delta of Vietnam demonstrated 91.5% (CI, 77-97%) vaccine efficacy over 27 months of active surveillance[17] and 82% efficacy (CI, 22-99%) during an additional 19 months of follow-up that utilized a passive surveillance system.[18]

Despite the highly impressive field results cited above, the Vi conjugate based on use of recombinant exotoxin A as a carrier did not progress in development and was not adopted by any vaccine manufacturer. Accordingly, several groups have developed alternative conjugates that utilize other carrier proteins to link to Vi. One such conjugate (PedaTyph® manufactured by Bio-Med P) that utilizes Vi linked to tetanus toxoid is already licensed in India on the basis of a limited amount of safety and immunogenicity data.[19,20] Another tetanus toxoid-based conjugate is being developed by Bharat Biotech. Shanta Biotech and the International Vaccine Institute are developing a conjugate that utilizes diphtheria toxoid as the carrier protein,[21] while the Novartis Institute of Global Health has initiated clinical trials with a conjugate consisting of Vi linked to CRM197.[22]
2.1.3. Immune response to the new generation typhoid vaccines

2.1.3.1. Single-dose live oral typhoid vaccine candidates. As discussed above, several live attenuated S. Typhi strains have been developed using recombinant DNA technology. Among the candidates that have been evaluated in Phase I and II clinical trials are M01ZH09,[9,10,23,24] Ty800,[11] CVD 908-htrA,[12,13] and CVD 909.[15] Oral immunization of adult volunteers with these vaccine strains elicited gut-derived IgA ASC and serum IgG and IgA antibodies to S. Typhi lipopolysaccharide O antigen. In the clinical trials with CVD 908-htrA, CMI responses were also intensively studied. CVD 908-htrA elicited robust CMI responses including S. Typhi-specific CD4+ T cells with the capacity to produce Th1-type cytokines (i.e., IFN-γ and TNF-α in the absence of interleukin 4 [IL-4] and [IL-5]), as well as CD8+ cytotoxic T cells that kill S. Typhi-infected target cells.[25] Immunization with CVD 909 also elicited a wide array of CMI responses similar to those induced by CVD 908-htrA.[26] Further studies of these responses revealed that oral immunization with attenuated S. Typhi strains elicits diverse S. Typhi-specific IFN-γ-secreting CD4+ and CD8+ T central memory (T_{CM}) and T_{EM} subsets that express, or not, integrin α4/β7. Thus, these cells are able to migrate to the gut (if they express α4/β7) or secondary lymphoid tissues (if they express integrin).[27] Taken together, these results provide strong evidence for the contention that memory/effector B and T cells recirculate in humans. However, the studies to characterize these cells are only just beginning. Lymphoproliferative responses and IFN-γ production were also observed in subjects immunized with M01HZ09.[10]

In clinical studies conducted in the US and Vietnam, M01Z09 was well tolerated and immunogenic in children 5-14 years of age, as well as in adults.[9, 10, 23, 28] Collectively, these results illustrate the wide range of effector responses that can be elicited by a single immunization with the new generation of attenuated S. Typhi vaccine strains in different age groups, all of which are believed to play important roles in protection.

2.1.3.2. Vi conjugate. Most of the serologic data that demonstrates the enhanced immunogenicity of Vi conjugates over purified unconjugated Vi polysaccharide vaccine come from publications of clinical trials with the Vi-rEPA conjugate in a series of clinical studies that included adults and living in the US and in endemic areas and children living in endemic areas. Children of school age and pre-school age from endemic areas who received the Vi-rEPA conjugate vaccine had increased levels of Vi IgG antibodies compared with those who received the unconjugated Vi polysaccharide vaccine.[16,17] The immunogenicity of the Vi conjugate was shown to be dosage-dependent, with higher doses of Vi-rEPA inducing higher levels of Vi IgG antibodies.[29] A dose of 25 µg of Vi as Vi-rEPA was recommended for immunization of 2-5 year old children. This dose induced the strongest serum IgG responses from the three doses tested (5, 12.5 and 25 µg) and conferred protection for at least 4-years.[18] The Vi antibodies elicited by the conjugate vaccine are long-lasting, reflecting the long-lived protection. At a point 42 months after children 2-5 years of age had been vaccinated, the geometric mean antibody level was 3.66 EU (interquartile range, 2.2 – 5.8 EU) compared to a geometric mean of 0.80 EU in children of the same age who had received placebo 42 months earlier (interquartile range, 0.30 – 2.26 EU).[18] Preliminary data from ongoing long-term follow up studies in adults suggest Vi IgG antibody levels may remain elevated (> 7-fold over baseline) for as long as 10 years after vaccination.

It is expected that serological response data will be available soon from clinical trials with other Vi conjugate vaccines that utilize carrier proteins other than rEPA.
2.1.3.3. **Vi polysaccharide entrapped in a cross linked protein matrix.** One biotechnology company is preparing for Phase I clinical trials a parenteral typhoid vaccine that consists of large aggregates of a matrix of CRM$_{197}$ mutant diphtheria toxin protein chemically cross linked by glutaraldehyde with Vi polysaccharide embedded within the matrix. Although there is no evidence that the Vi is covalently linked to the protein (but is rather simply physically entrapped), in pre-clinical studies the resultant Vi-protein matrix appears to elicit immunologic memory like a Vi conjugate vaccine. These polysaccharide/protein matrix aggregates are selectively sized to include larger moieties that exceed in size the diameter of virus-like particles.

2.2.0 **Paratyphoid A vaccines**

2.2.1 **Live oral vaccine candidates**

Heretofore, only one live oral S. Paratyphi A vaccine candidate, CVD 1902, is known to be in clinical trials (Table 3). CVD 1902, which harbors independently attenuating deletion mutations in *guaBA* and *clpX* is currently completing a dose-escalating Phase I clinical trial in which groups of subjects ingest $10^6$, $10^7$, $10^8$ or $10^9$ colony forming units, or placebo to assess the safety, preliminary immunogenicity, excretion pattern and transmissibility of the live vaccine. Other S. Paratyphi A live vaccine strains have been evaluated in pre-clinical studies in animals but have not entered clinical trials in humans.[30]

2.2.2. **Paratyphi A conjugate vaccine candidates**

Several public sector research groups and companies that are working on Vi conjugate vaccines against typhoid fever have announced their intention to develop companion conjugate vaccines to prevent disease caused by S. Paratyphi A. The goal will be a bivalent vaccine to prevent the two main causes of enteric fever. In each instance the same carrier protein as is used in the Vi conjugate will be used to link the O polysaccharide of S. Paratyphi A (Table 4). Heretofore, results of only one set of clinical trials with two prototype S. Paratyphi A conjugates utilizing tetanus toxoid as the carrier protein have been reported.[31]
Reference List


typhoid vaccine M01ZH09 is well tolerated and highly immunogenic in 2 vaccine presentations. *J Infect Dis* 2005, 192:360-366.


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<table>
<thead>
<tr>
<th>Vaccine strain</th>
<th>Mutated genes</th>
<th>Phase of development</th>
<th>Developers</th>
</tr>
</thead>
<tbody>
<tr>
<td>M01HZ09</td>
<td>aroC,ssaV</td>
<td>Phase II</td>
<td>Emergent</td>
</tr>
<tr>
<td>Ty800</td>
<td>phoP/phoQ</td>
<td>Phase II</td>
<td>Celldex</td>
</tr>
<tr>
<td>CVD 908-htrA</td>
<td>aroC,aroD,htrA</td>
<td>Phase II</td>
<td>Center for Vaccine Development, University of Maryland (previously in conjunction with Medeva)</td>
</tr>
<tr>
<td>CVD 909</td>
<td>aroC,aroD,htrA, P.tac-tviA</td>
<td>Phase II</td>
<td>Center for Vaccine Development, University of Maryland</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Carrier protein to which Vi is linked (or cross-linked)</th>
<th>Developers</th>
<th>Phase of development</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tetanus toxoid (Peda Typh®)</td>
<td>BioMed (P)</td>
<td>Licensed in India</td>
</tr>
<tr>
<td>CRM197</td>
<td>Novartis Vaccines Institute of Global Health</td>
<td>Phase I</td>
</tr>
<tr>
<td>Tetanus toxoid</td>
<td>Bharat Biotech</td>
<td>?</td>
</tr>
<tr>
<td>Diphtheria toxoid</td>
<td>Shanta Biotech and the International Vaccine Institute</td>
<td>Pre-clinical (Phase I planned, Q2 2011)</td>
</tr>
<tr>
<td><em>Pseudomonas aeruginosa</em> recombinant exotoxin A</td>
<td>U.S. NIH</td>
<td>Phase III</td>
</tr>
<tr>
<td>CRM197 matrix in which Vi is entrapped rather than covalently linked</td>
<td>Matrivax</td>
<td>Phase I planned for Q4 2011</td>
</tr>
</tbody>
</table>
### Table 3. Live oral paratyphoid A vaccines in clinical trials

<table>
<thead>
<tr>
<th>Vaccine strain</th>
<th>Mutated genes</th>
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<tbody>
<tr>
<td>CVD 1902</td>
<td>guaBA,clpX</td>
<td>Phase I</td>
</tr>
</tbody>
</table>

### Table 4. Paratyphoid A conjugate vaccines that are in clinical trials or are being prepared for clinical trials

<table>
<thead>
<tr>
<th>Carrier protein linked to S. Paratyphi A O polysaccharide</th>
<th>Developer</th>
<th>Phase of development</th>
</tr>
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<td>Tetanus toxoid</td>
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<td>Phase I</td>
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<tr>
<td>CRM&lt;sub&gt;197&lt;/sub&gt;</td>
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<td>Pre-clinical</td>
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<tr>
<td>Tetanus toxoid</td>
<td>Bharat Biotech</td>
<td>?</td>
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<tr>
<td>Diphtheria toxoid</td>
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