



**FONDATION MERIEUX**

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**Report of the Meeting on  
Typhoid Fever, a Neglected Disease:  
Towards a Vaccine Introduction Policy**

*Annecy, France, Les Pensières, April 2-4, 2007*

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## Contents

Executive Summary .....	<u>2-3</u>
I. Background .....	<u>4</u>
II. Meeting Objectives .....	<u>4</u>
III. Summary of Presentations and Discussions .....	<u>5</u>
Welcome Addresses and Keynote Lecture	
Session 1: Update on typhoid fever in Asia and the status of production of new-generation typhoid vaccines	6-10
Session 2: Recent experiences with typhoid vaccination using different delivery strategies	10-15
Session 3: Typhoid vaccine financing issues	15-20
Session 4: Programmatic and introduction issues regarding typhoid vaccination	20-22
Session 5: Recommendations from Working Groups	22-25
Meeting summary and wrap-up	25-27
ANNEX I – Meeting Agenda .....	<u>27</u>
ANNEX II – List of Participants .....	<u>30</u>

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## Executive Summary

Typhoid fever continues to be a serious public health program in many countries, especially in children. Two new-generation vaccines have replaced the old, reactogenic inactivated whole-cell vaccines: the oral live-attenuated Ty21a vaccine, which requires a three-dose regimen, and the parenterally-administered, single-dose Vi polysaccharide vaccine. Immunization using these vaccines was recommended since 1998 by WHO in areas where typhoid remains a significant public health problem and where antibiotic resistance is prevalent. However, typhoid vaccines have been used in the public sector in very few countries to date and only in a limited fashion. Considerable new data on typhoid and typhoid vaccination have been generated in recent years by the Gates-funded Diseases of the Most Impoverished (DOMI) Program, which had typhoid research programs in five Asian countries. *The purpose of this two-day meeting, attended by more than 60 participants, was to bring together typhoid experts, donors, and international and country-level policymakers to present and discuss these new data, to reach a consensus on the need for typhoid vaccination in endemic countries and on preferred vaccination strategies, and to agree on an action plan to move the agenda forward for the expanded introduction of typhoid vaccines.*

Key messages and conclusions of the meeting include:

- Global mortality estimates for typhoid fever (216,000 – 600,000 or more) place typhoid in the range of several priority infectious diseases, including HPV, rotavirus and Hib;
- Very high rates of typhoid incidence were found in several DOMI sites, providing further evidence that typhoid continues to be a serious problem. High risk groups include not only school-aged children (traditionally considered to be the highest at risk), but also pre-schoolers in some Asian countries;
- A case of typhoid averaged \$100 in the five DOMI sites, with most costs borne by families;
- Antibiotic resistant strains of *S. typhi* are increasing rapidly, including multi-drug resistant strains and those less sensitive to quinolones, such as ciprofloxacin. We are running out of treatment options, making vaccination against typhoid even more imperative;
- The potential is high for a sufficient supply of low-cost Vi vaccine to meet an increased demand, if the vaccine is introduced into public health programs in endemic countries, since there are a growing number of Vi suppliers, including several emerging suppliers. The supply of Ty21a could also be greatly increased;
- Experience with Vi and Ty21a vaccination through demonstration projects and real-life introduction have demonstrated the feasibility and popularity of both school- and community-based vaccination in several countries. School-based Vi vaccination in Guilin, China over the past 10 years has virtually wiped out typhoid in the area;

- Typhoid vaccination using Vi could be cost-effective, according to analyses using epidemiological and economic data from the DOMI field sites. Programs involving user fees for those less at risk or more able to pay to subsidize free vaccination of public school children could be a workable and financially-sustainable means of introducing typhoid vaccines in some countries;
- There is now a broad range of financing options – both external and internal – available for immunization (e.g., GAVI, IFFIm, AMCs, debt relief initiatives) that can be considered for the introduction of typhoid vaccines;

***Key recommendations to move typhoid vaccines to broader use in endemic countries included the following:***

- Present the case for typhoid vaccination at the next meeting of the WHO Scientific Advisory Group of Experts (SAGE), in the aim of an updated SAGE recommendation for typhoid vaccination in endemic countries;
- Do not wait until Vi conjugate vaccines become available (7-10 years at the earliest) before introducing typhoid vaccination, since there are two safe, effective vaccines already available;
- Make the pre-qualification of typhoid vaccines by WHO an immediate priority, since the lack of WHO pre-qualified typhoid vaccines is a critical barrier to expanded introduction;
- Conduct additional vaccine demonstration and pilot projects and evaluate existing typhoid vaccination programs to demonstrate their feasibility and impact in specific countries;
- Collect additional data on disease burden in endemic countries to determine need, identify high-risk areas and create a market for better point-of-use typhoid diagnostics;
- Conduct studies to define and measure the potential market for new-generation typhoid vaccines, in order to encourage producers to scale up production and promote the vaccines;
- The single-dose Vi vaccine should be used for outbreak control;
- All typhoid vaccine introduction programs should be implemented in the context of efforts to improve sanitation and hygiene;
- The selection of school- or community-based vaccination against typhoid should depend on the local context (e.g., age pattern of the disease, school enrollment rates, etc.), since both have been demonstrated to be feasible in developing country settings.

## I. Background

Typhoid fever continues to be a serious public health problem in many developing countries. The disease, which disproportionately strikes children, leads to serious complications, including hypotensive shock, perforation of the gut and gastrointestinal hemorrhage, in 10-15% of cases. Global estimates range from 17 to 22 million cases per year and 216,000 to 600,000 deaths. Even using the lower estimate, which is based on a conservative case fatality rate of 1%, (CFR reported from 1% to 4%), the number of typhoid-related deaths each year is comparable to that of cervical cancer caused by HPV and is greater than that of Japanese encephalitis and meningococcal meningitis – all diseases that are top priorities for disease control in the global health community. Rapidly rising rates of antibiotic resistance documented in Asia have increased the difficulty and cost of treatment and threatens to increase the case fatality of the disease.

Two new-generation vaccines are currently available – the oral live-attenuated *S. typhi* Ty21a vaccine, which requires a three-dose regimen, and the parenterally-administered, single-dose Vi polysaccharide vaccine. In a 2000 position paper, WHO recommended their use among school-aged children “*in areas where typhoid fever is a significant public health problem, and particularly where antibiotic resistant S. typhi strains are prevalent*”. Nonetheless, new-generation typhoid vaccines have only been introduced by the public sector in certain areas of three countries (Vietnam, China and Delhi State, India) and are still not among the priority new and under-utilized vaccines being considered for introduction by WHO, the GAVI Alliance and the overall global health community.

A substantial amount of new evidence on the disease and economic burden of typhoid fever in Asia, and on the feasibility, costs and effectiveness of typhoid vaccination (through Vi demonstration projects) has been generated by the Diseases of the Most Impoverished (DOMI) Program, funded by the Bill & Melinda Gates Foundation and implemented by the International Vaccine Institute (IVI). Moving from data and demonstration project experience to actual vaccine introduction in typhoid-endemic countries, however, will require further advocacy and action by country policymakers, WHO, donors and the broader global health community. This meeting was organized to bring together typhoid experts, donor and international agencies, and country-level policymakers to reach a consensus on the need for typhoid vaccination in endemic countries and to agree on an action plan to increase the priority of typhoid vaccination among donors, technical agencies and national policymakers, in order to make typhoid control through immunization a reality in the near future.

## II. Meeting Objectives

The goal of the meeting was to develop a strategy for typhoid fever control through immunization, beginning with Asia. The specific objectives were to:

- Raise the visibility of typhoid fever and typhoid vaccination in the Asian region;
- Make the case for the need for typhoid vaccination in endemic areas;
- Develop a consensus on preferred vaccination strategies; and
- Develop an action plan to push the agenda forward.

### **III. Summary of Presentations and Discussions**

#### ***Welcome Addresses and Keynote Lecture***

Benoit Miribel, the Director General of the Merieux Foundation presented the mission and activities of the Foundation – to fight infectious diseases in developing countries by developing and making available new and affordable approaches in the field of prevention, diagnostics and therapeutics. This meeting was part of the Foundation’s goal to share knowledge through training programs, scientific symposia and conferences. Welcoming remarks were also given by Bernard Ivanoff, the Foundation’s Scientific Director and main organizer of the meeting; Marie-Paul Kieney, Director of WHO’s Initiative for Vaccine Research (IVR); and John Clemens, Director General of the IVI.

In his keynote address, Dr. Tikki Pang, Director of the Research Policy and Cooperation unit at WHO/Geneva, provided an overview of the current issues, challenges and way forward regarding typhoid fever and its prevention. There have been several recent developments that together should create favorable conditions for the use of new-generation typhoid vaccines in developing countries. Recent articles in the literature point to the continual problem that typhoid poses to residents in endemic countries and to travelers, who are increasing in great numbers, as well as to the rise of antibiotic resistant typhoid in Asia, while the number of new antibiotics being produced continues to decline. New typhoid diagnostics and vaccines are also in development and, through the DOMI Program, more solid data on typhoid incidence and its economic impact have become available. Donor funding for immunization has and will continue to increase significantly through the GAVI Alliance and other innovative financing mechanisms. Among the remaining challenges to the greater use of typhoid vaccines in developing countries, however, are the relatively low visibility of typhoid fever and typhoid vaccine projects versus several other vaccine-preventable diseases; health system challenges in many developing countries, such as under-funding and lack of manpower, that could hamper typhoid vaccine introduction; and the lack of coordination among many vertical health projects often operating in the same country.

In discussing the way forward, Dr. Pang suggested several strategies to promote typhoid vaccination, such as working with regional tourism boards and the WTO, creating a dedicated initiative to promote typhoid vaccination, working with disease surveillance initiatives and networks to include typhoid fever surveillance, tying typhoid vaccination more to the Millennium Development Goal of reducing child mortality, and making the case with GAVI to support typhoid vaccination and to vaccine producers to provide low-cost vaccine to developing countries. A consensus strategy to make the case for typhoid vaccination to country policymakers needs to include the best scientific evidence (building upon data gathered from the DOMI program), and incorporate lessons learned from other programs, such as the need to develop local guidelines and the need to expand beyond government delivery systems. Based on the findings from the International Dialogue on Evidence-Informed Action for Health Improvement (IDEA Health) in 2006, packages of evidence for typhoid vaccination should be country-specific and include locally-generated data, involve local policymakers in their

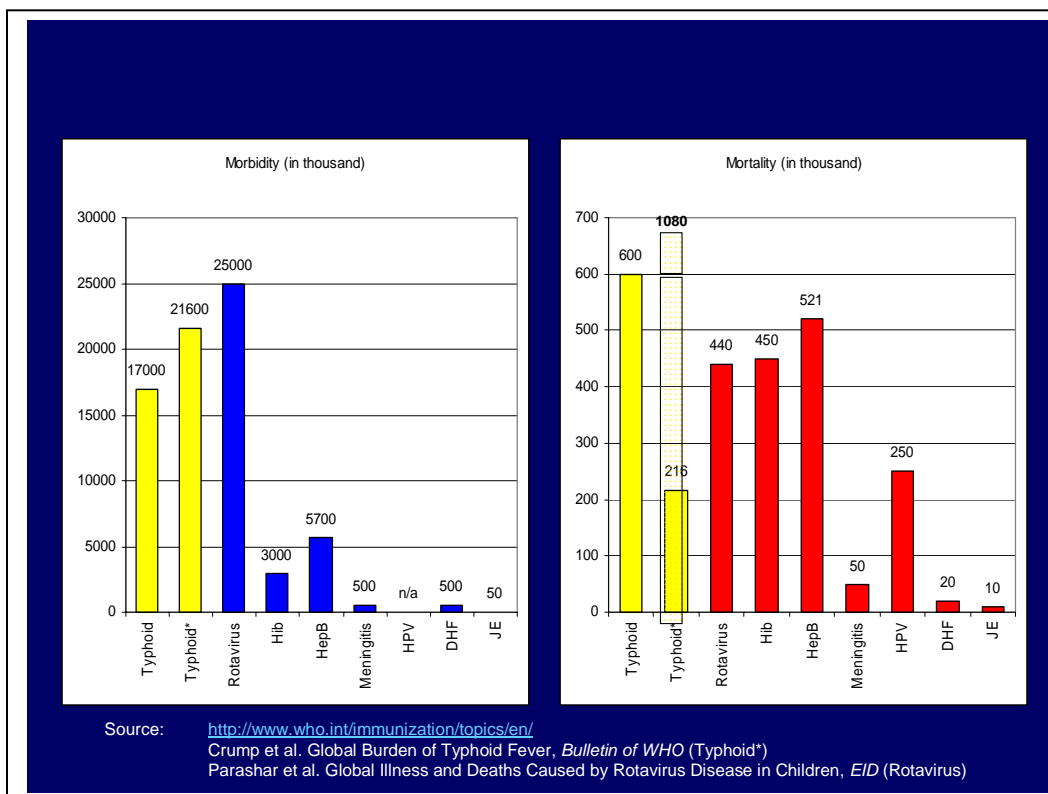
development and interpretation, contain simple language and be focused, as opposed to systematic reviews prepared today that local policymakers often find to be irrelevant, too complicated and not specific to their situation.

## **Session 1: Update on typhoid fever in Asia and the status of production of new-generation typhoid vaccines**

### **Overview of the magnitude, epidemiological patterns and economic consequences of typhoid fever in Asia (Leon Ochiai, IVI)**

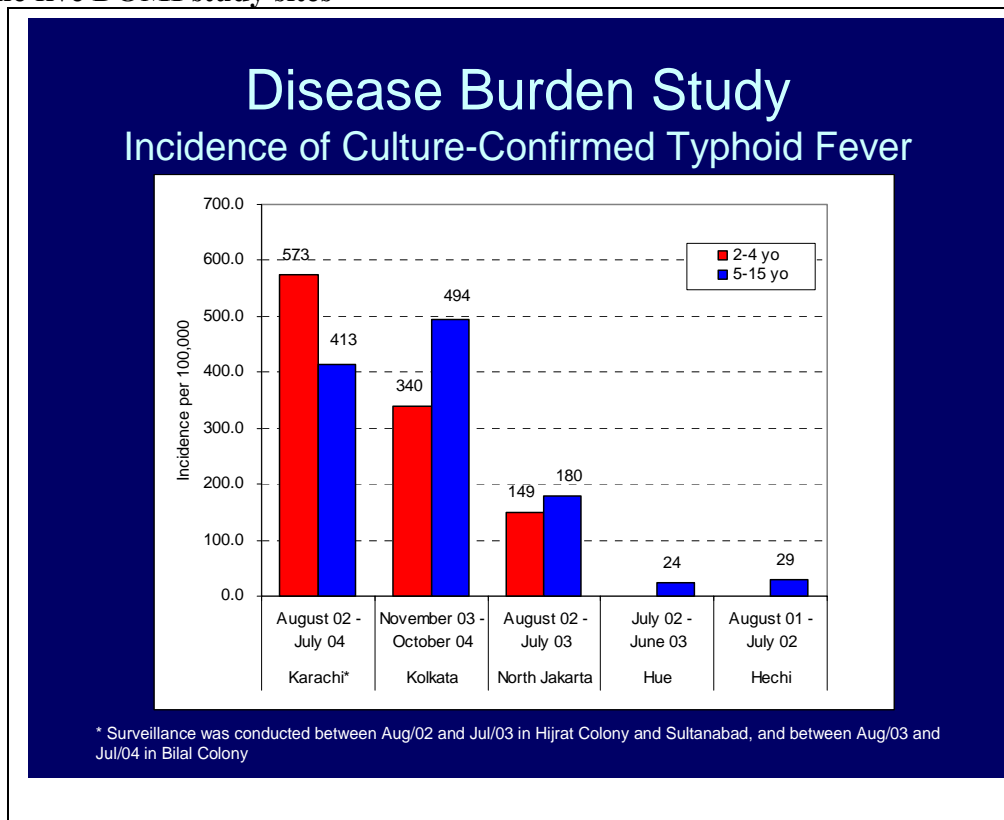
Global estimates of typhoid fever show 17-22 million cases each year and 216,000 – 600,000 deaths. All known countries with high incidence (>100/100,000 population per year) are in South and Southeast Asia and the Pacific Island region. Compared to other diseases for which new and under-utilized vaccines are being supported or considered for support by GAVI, typhoid incidence is amongst the highest – with only rotavirus having a higher estimated incidence (Figure 1). If one uses the lower mortality estimate of 216,000 annual deaths from Crump et. al. (*Bull WHO*, 2004), which is based on a conservative estimated case fatality rate of 1%, typhoid deaths approximate those from HPV disease (cervical cancer) and are greater than for several other vaccine-preventable diseases. Using the higher, often-quoted mortality estimate of 600,000 annual deaths or increasing the case fatality rate in the Crump analysis yields a higher annual mortality from typhoid fever than from rotavirus, Hib or hepatitis B.

**Figure 1: Global disease burden estimates of typhoid fever and other important diseases**



The Diseases of the Most Impoverished (DOMI) typhoid program was designed to obtain improved evidence for decision-making on the use of modern typhoid vaccines in developing countries. A coordinated series of multi-disciplinary studies, including prospective disease surveillance, vaccine effectiveness trials and demonstration projects (using the typhoid Vi polysaccharide vaccine), studies of the cost-of-illness and cost of Vi vaccination, and studies of population attitudes and beliefs regarding typhoid fever and demand for typhoid vaccination, took place in five study sites in Asia: slum areas in North Jakarta, Indonesia, Karachi, Pakistan and Kolkata, India; the city of Hue, Vietnam and a mixed rural/urban site in Hechi, Guangxi Province, China. A high disease burden was found among children in the three slum area sites – with rates of blood culture-confirmed typhoid of 180-494/100,000 among 5-15 year olds per year and 149-573/100,000 among 2-4 year olds (Figure 2). Assuming an estimated blood culture sensitivity of  $\approx 50\%$ , actual incidence is likely to be double these rates.

**Figure 2: Annualized laboratory-confirmed incidence rates of typhoid fever in the five DOMI study sites**



The cost of an episode of typhoid was found to \$146 - \$511 for hospitalized cases in the five study sites and \$51 - \$136 for all hospitalized and outpatient cases combined, with an average cost of nearly \$100 per case. Most costs were paid by the patients and their families, in the form of medical care and other direct costs and in indirect costs from lost wages due to missed work. High rates of multi-drug resistant typhoid was found in the Pakistan (65%) and Vietnam (22%) sites and rates of naladixic acid resistance – an indicator of reduced sensitivity to fluoroquinolones (e.g., ciprofloxacin) that are increasingly used in drug-resistant areas – ranged from 44% in Vietnam to 55-59% in Pakistan and India. Drug resistance can greatly increase the

cost of effectively treating typhoid (e.g., \$84-104 for a course of parenteral ceftriaxone at the Aga Khan Hospital in Karachi vs. \$3-5 for first-line antibiotics for non-resistant cases).

In addition to endemic typhoid, there have been a number of outbreaks occurring in recent years in different parts of the world, including Africa, Tajikistan and Haiti, some recording high case fatality rates.

In the discussion, several weaknesses in the Crump global estimates were pointed out, including the fact that they were mainly based on studies that were 20 or more years old, results from one or a few countries were extrapolated to an entire region – which the DOMI results indicate should not be done, and the estimated 1% case fatality rate used in the study is unrealistically low. Participants were interested in why incidence was so high among very young children in several sites and whether drug resistance is appearing in these patients as well (yes, according to the DOMI results). While one reason for the high rates was the small number of 2-4 year olds included in the study, the DOMI study Principle Investigator from India pointed out that there are many cases of typhoid in Kolkata in very young children, even among those under two years old, who were not included in the study.

### **Trends in antibiotic resistant typhoid fever and implications for treatment and prevention (John Wain, Wellcome Trust Sanger Institute, UK)**

With the rise in multi-drug resistant typhoid – which is resistant to all three first-line antibiotics (chloramphenicol, ampicillin and co-trimoxazole) – fluoroquinolone treatment has become the treatment of choice for typhoid fever in recent years. However, fluoroquinolone resistance has also been observed, and extensive studies have shown the complexity in its mechanism. Isolates that are sensitive to ofloxacin but resistant to nalidixic acid have been shown in Vietnam to have reduced treatment outcomes with ofloxacin. Further studies, however, showed that nalidixic acid screening alone is not a reliable way to determine low-level fluoroquinolone resistance.

Genetic studies have advanced our understanding of the mechanism of antibiotic resistance in *S. typhi*. Three chromosomal mutations are required for fluoroquinolone resistance. Plasmids encode antibiotic resistance and possibly more in terms of the organism's function and chromosomal mutations. Certain plasmids affect the bacterial load and enhanced survival in the macrophage. It has also been found that plasmids are well preserved when historical *S. typhi* isolates were examined. These findings underline the importance of maintaining partnerships between researchers and public health providers in order to understand the emergence of antibiotics resistant strains and to give the optimal treatment for resistant cases.

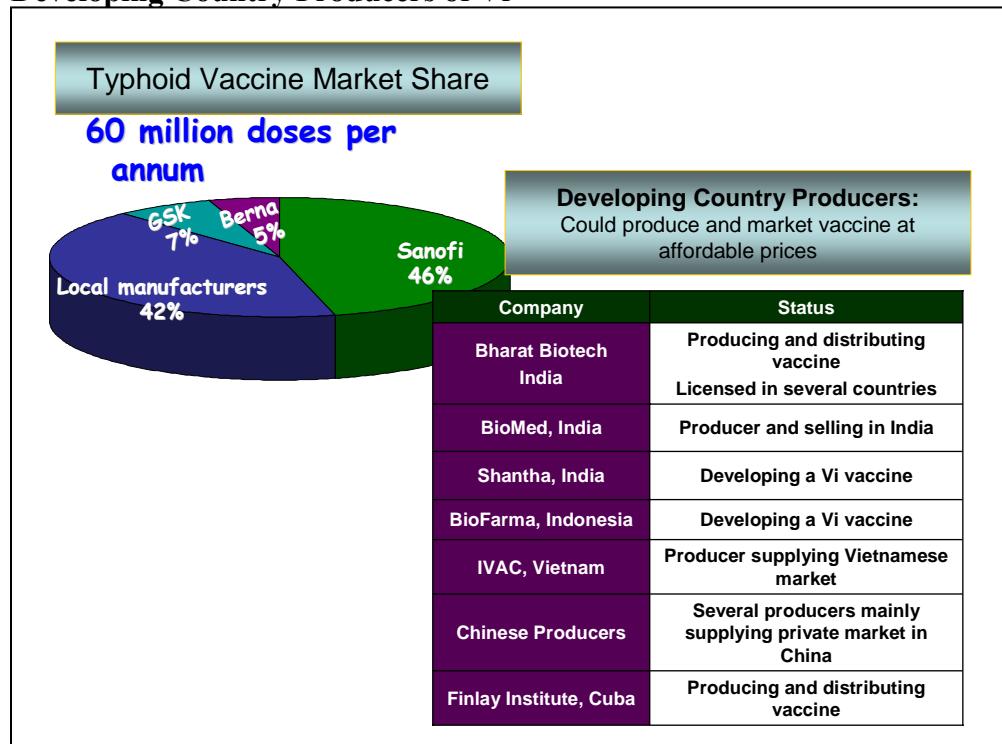
### **Production capacity and supply of typhoid fever vaccines for developing countries (Rodney Carbis, IVI)**

Two new-generation typhoid vaccines are currently available and found to be safe, though neither is yet used broadly in typhoid-endemic countries. Ty21a, derived from Ty2 and produced by a sole manufacturer (Berna Biotech of Switzerland), is a live attenuated oral vaccine requiring three doses spaced two days apart and is licensed in 56 countries for persons five years and above. The vaccine was found to provide 77% protection over seven years in its liquid

formulation and 62% over seven years in enteric coated capsules in field trials in Egypt, Indonesia and Chile, inducing both anti-*Salmonella* antibodies and a strong cell-mediated immune response. Vi polysaccharide vaccine, a single dose injectible vaccine, is a T-cell independent antigen that is poorly immunogenic in infants, and thus licensed for use in persons two years and above. It was found to provide 65 – 72% protection against typhoid after 17 – 21 months in field studies conducted in Nepal, South Africa and China. Developed by U.S. NIH and licensed in at least 92 countries, the vaccine has a number of producers, including several low-cost producers in developing countries. Other aspects of Vi that make it suitable for public health programs in developing countries are: its single-dose regimen, high heat stability (physicochemical characteristics remain unchanged after six months at 37°C), its simple production technology, high yields (with 1,000 liter fermentation yielding four million doses) and low production costs. Prices quoted by emerging producers for public sector use have been as low as \$0.50 per dose or less.

If typhoid vaccination is introduced into public health programs in endemic countries, the potential for a substantial supply of Vi to meet increased demand is high. While only an estimated 60 million doses of typhoid vaccines are currently sold per year (95% of that Vi), mostly to the private sector, there are several developing country producers either currently manufacturing or developing Vi vaccine (Figure 3).

**Figure 3. Current Market Share of New-Generation Typhoid Vaccines and Developing Country Producers of Vi**



A prototype Vi conjugate (exprotein A or rEPA) vaccine, developed by John Robbins' laboratory at U.S. NIH was found to provide 92% protection after 27 months when given in two doses to 2-5 year olds in Vietnam during a Phase III trial. In addition to providing greater protection than

the Vi polysaccharide vaccine, the conjugate should have the advantage of being effective in infants, allowing it to be included in the infant EPI schedule. A new, less expensive version of the vaccine, using diphtheria toxoid, is being developed at IVI in collaboration with Dr. Robbins' lab. The vaccine will not likely be licensed for at least seven more years, however. Mr. Carbis concluded that, since there will continue to be more than 21 million cases and more than 200,000 typhoid-related deaths per year with the current low levels of vaccination, and since the capacity to produce Vi must be established before producers can make Vi conjugate, it makes sense to establish a public sector market with Vi now and introduce the conjugate vaccine when it becomes available.

The discussion centered on the following:

- Whether and why it will take seven years before a Vi conjugate vaccine becomes available, especially since a Phase III trial of the rEPA vaccine already took place and since five Asian producers (two in India, two in China and one in Vietnam) are already developing conjugate vaccines and planning Phase I studies. However, the Vietnamese Phase III trial used a prototype vaccine and it can take years to develop an actual product, scale up and conduct all trials needed for licensure. John Clemens felt that seven years is actually a conservative estimate; Merck's HPV vaccine took ten years to get licensed after the technology to make the vaccine was well developed.
- The use of Vi as a possible booster (e.g., during school-aged years), following Vi conjugate vaccination during infancy. According to some participants, the conjugate may not require many booster doses, since protection has remained a high levels (89%) four years following the rEPA trial in Vietnam.
- The frequency of re-vaccination required with Vi: the standard response is every three years. Fewer boosters may be required, however, since the Vi trial in South Africa found an immune response in vaccinees 10 years after the trial.

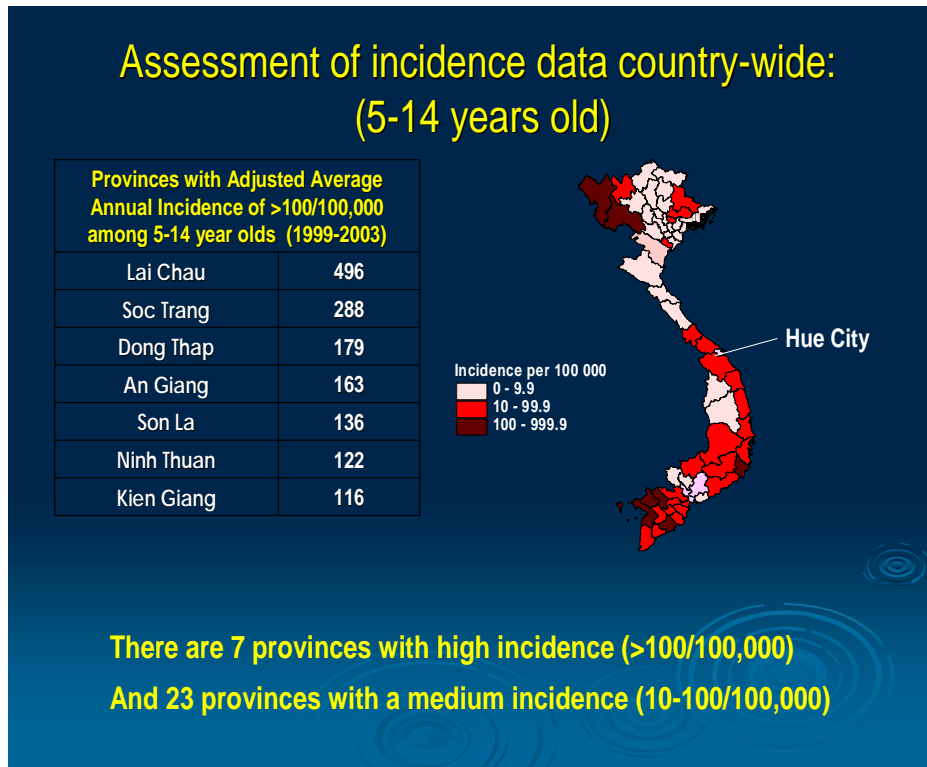
## ***Session 2: Recent experiences with typhoid vaccination using different delivery strategies***

### **Typhoid fever and typhoid vaccination in Vietnam (Dang Duc Anh, National Institute of Hygiene and Epidemiology, Hanoi) (presentation given by Luis Jodar in his absence)**

In response to a four-fold increase in typhoid fever incidence from 1991 to 1996 and to a sharp rise in antibiotic resistance, the Vietnamese government began Vi vaccination in 1997 in high-risk areas for 3-10 year olds. It is currently providing around one million typhoid vaccinations per year, which is considered inadequate to control typhoid effectively in the country. A comprehensive typhoid research program was developed through the DOMI Program to obtain data required by policymakers to make decisions about the future of typhoid control in the country. Much of the research took place in the city of Hue in central Vietnam, including a city-wide randomized, controlled Vi demonstration project for all students 5-18 years old. Key findings from the program include:

- Incidence among 5-18 year olds obtained through prospective passive surveillance in Hue involving all public and most private health facilities was moderate – 16/100,000 in terms of blood culture-confirmed incidence, with an adjusted rate of 33/100,000. The disease is quite severe, however, with 40% of lab-confirmed cases requiring hospitalization.
- Typhoid incidence varies greatly within the country. A meta-analysis using routine surveillance data and other studies shows incidence of 116 – 496 per 100,000 in seven provinces and moderate incidence (10-100/100,000) in 23 others (Figure 4)

**Figure 4. Typhoid incidence among 5-14 year olds by province in Vietnam, 1999-2003, based on meta-analysis**



- Average costs of confirmed typhoid cases were \$146 for hospitalized cases (with the government paying 70%), \$37 for outpatient cases, and \$68 for all cases combined.
- School-based immunization of Vi was found to be feasible in Hue and to cost ≈\$1.30 per child (vaccine + delivery costs)

**Vaccination of school-aged children with Ty21a live oral vaccine (video presentation by Myron Levine, Center for Vaccine Development, University of Maryland, USA)**

Ty21a, a live oral vaccine developed in the 1970s and licensed in many countries in the 1980s, is available in three formulations: enteric-coated capsules, liquid formulation (mixed with a buffer), and gelatin capsules. The vaccine doesn't express capsulated Vi polysaccharide, but does produce three types of immune response: 1) mucosal response (O and H antigens), 2) production

of serum antibodies; and 3) cell-mediated response. Six Phase III field trials of the vaccine have taken place: in Indonesia, Egypt and four in Chile. Lessons learned from the four Chilean trials, conducted in the 1980s in areas with high seasonal incidence of typhoid among 5-19 year olds, include:

- Efficacy is greatest with the liquid formulation, followed by the enteric capsules, and is long-term (at least five to seven years):
  - Liquid formulation: 77% efficacy at 1-3 years  
78% at 5 years
  - Enteric capsules: 67% efficacy at 1-3 years  
62% at 7 years
- School-based vaccination with Ty21a is practical, since large numbers of children can be vaccinated very quickly. Enteric capsules are especially practical for adolescents, but can't be swallowed by 7-8% of 6-7 year olds.
- A nested case control study shows that four doses provide the best protection (69%), but even three (51%) or two (44%) doses provide moderate protection.
- Disease surveillance in Santiago indicates some indirect protection from Ty21a in residents living in non-vaccinated areas contiguous to areas where vaccination took place;
- Pooled data from the Chile trials show moderate (49%) protection against paratyphoid B.
- Conclusion: We need to consider school-based vaccination with Ty21a as a practical public health tool that is currently available.

In the discussion, representatives of Berna Biotech, the producer of Ty21a ("Vivotif"), explained that most vaccine they produce is for the travelers' market, but that they could provide the vaccine to the public sector for a low price (e.g., ≈ \$0.50/dose) and could produce up to 50 million doses per year. While a key advantage of the vaccine is its long-term protection, the issue of its practicality (e.g., for Africa) was raised, since it requires a strict cold chain, a rigid schedule involving 3-4 doses, and it has bulky packaging.

### **Typhoid fever in childhood in Pakistan: the case for a school-based vaccination strategy (Zulfiqar Bhutta, Aga Khan University Hospital, Karachi, Pakistan)**

Hospital-based data have indicated that typhoid is an important disease in Pakistan. *S. typhi* has been found to be the most common cause of bacteremia in children with severe diarrhea coming to the emergency room at AKUH, and 70% of confirmed typhoid fever cases detected in Karachi occur in children under 16 years old. The disease has remained under the radar screen among government officials, however, in part because of the lack of national surveillance data and community-based studies for typhoid. Prospective surveillance through the DOMI Program was conducted in three slum areas of Karachi, selected as typical of slum areas throughout Pakistan and not overtly worse. The "augmented passive surveillance", which involved the establishment of project-specific clinics, weekly home visits by community health workers to check for febrile cases and refer them to the clinics, and the participation of private physicians in reporting cases and getting them lab-tested, found an overall incidence of blood culture-confirmed typhoid of around 400/100,000 among 2-15 year olds. Adjusted for blood culture

sensitivity of only 50%, the rates was nearly 800/100,000, and was highest among 2-4 year olds (1,146/100,000). Multi-drug resistance was found in 65% of the 127 isolates tested and naladixic acid resistance was found in 59%.

A community-based Vi vaccine demonstration project took place in the three slum areas for 2-16 year olds. In an effort to be programmatically realistic, the project mimicked the strategies of other EPI-led initiatives, in which vaccination takes place for only 2-3 days in each area, before moving on to a new area, instead of conducting more intensive vaccination in each location. The vaccination proved to be rather popular, with coverage rates of 74% achieved in two slum areas and 65% in the third, despite considerable out-migration. A total of more than 27,000 children were vaccinated. The successful campaigns required considerable logistical preparation and training, as well as intensive information dissemination activities, ranging from street information sessions to meetings of community and religious leaders, the distribution of printed IEC materials and announcements in mosques. Severe adverse events were found to be rare (3/12,830 children). The Vi demonstration involved a cluster-randomized controlled trial design (with the controls receiving hepatitis A vaccine) and surveillance for two years following vaccination, so that vaccine effectiveness rates can be obtained, once the codes are broken. Dr. Bhutta concluded that typhoid fever is under-appreciated in Pakistan and the experience in Karachi shows that mass typhoid vaccination campaigns in urban slums is feasible, can cover a large proportion of the population at risk, and can offer an effective strategy for reducing the overall typhoid disease burden in places like Karachi.

#### **Experience with school-based vaccination in a typhoid fever endemic area using Vi manufactured in China (Honghui Yang, Guangxi Province CDC, Nanning, China)**

Vi vaccine produced locally in China, with assistance from U.S. NIH, was licensed in 1996, following two randomized controlled trials involving 236,000 participants, which showed vaccine efficacy of 69-70% after 19 months. The health bureau of the Guangxi Autonomous Region, in Southeast China, decided to implement a Vi vaccination program in and around the typhoid-endemic city of Guilin for students of all ages, food handlers, and people living in and around areas where outbreaks occur. Re-injection takes place every three years. Students pay less than \$1.00 per dose for the vaccine, which is regulated by government price controls. From 1995-2006, more than 1.4 million doses were administered – with three-quarters going to students and one-quarter to food handlers and residents of outbreak areas. Coverage rates have varied broadly from year to year, but have averaged 60-70% for students over the 11-year period and 80-85% for the other target groups.

The impact on typhoid incidence has been dramatic – with a reduction among students from 55-60/100,000 during 1991-1994 (pre-vaccination) to 0.2-3.6/100,000 in 2003-2006 (Figure 5) – and similar reductions among adults. The overall incidence of enteric fever in the area has remained nearly the same, due to the concurrent increase in the incidence of paratyphoid A. The combined school-based and food handler immunization program has effectively controlled typhoid fever in both the school-age and general population in this area. In response to questions, Dr. Yang explained that Guangxi has a medium level of development and that water and sanitation improvements have been gradual over time. Paratyphoid A has increased more sharply in areas where the vaccination program has taken place, and has been found to be drug-sensitive.

**Figure 5. Data on Vi immunization and typhoid incidence pre- and post-vaccination among students in Guilin, China**

**Typhoid cases in students in Guilin, China, 1991 - 2006**

	<b>Pre-vaccination</b>	<b>Vaccination</b>		
<b>Year</b>	<b>1991-94</b>	<b>1995-98</b>	<b>1999-02</b>	<b>2003-06</b>
Vi dosage used	0	386,570	448,450	260,300
Case reported (Ty+Para A)	1,106	1,085	2,778	1,614
<i>S. typhi</i> isolated	44	44	7	1
<i>S. para</i> A isolated	0	12	571	259
Typhoid estimated (1/100,000)	1006~1106 (55.4~60.5)	716~955 (39.2~52.2)	7~111 (0.4~6.1)	1~65 (0.2~3.6)

**Experience with school-based Vi vaccination in Jakarta, Indonesia (Triono Soendoro, NIDHR, Jakarta, Indonesia)**

The incidence of typhoid fever is unknown in Indonesia, due to poor diagnosis, uneven reporting, and the fact that private physicians, who see the bulk of typhoid patients, rarely report the disease to the Government. One estimate based on surveillance studies showed 900,000 cases and more than 20,000 deaths throughout the country per year. Incidence is believed to be higher in urban versus rural areas. The DOMI surveillance study found adjusted incidence of nearly 500/100,000 among 6-14 year olds living in two slum areas of North Jakarta.

There is yet no official policy regarding typhoid vaccination, although the government has encouraged its use in certain situations, including in refugee camps following the tsunami, in which 5,000 people received Vi vaccine. Vaccination against typhoid has been recommended by both the national pediatric society (for children two and above) and the country's travel medicine association (for persons traveling to high-incidence areas). The DOMI Program was asked to evaluate the feasibility and costs of school-based Vi vaccination as a vehicle for typhoid control in the country, building upon the strong experience that Indonesia has with school-based DT and TT vaccination. A Vi demonstration project took place in two sub-districts of North Jakarta for 5,000 primary school children 6-11 years old in 18 schools. The project showed school-based

vaccination with Vi to be highly feasible, acceptable, safe and low cost in a low socio-economic urban area. A vaccination coverage rate of 91% was achieved, no serious adverse events were found, and the estimated cost of vaccine delivery through the schools was \$0.40 (or around \$1.00 including the cost of the vaccine, assuming it comes from an emerging producer or is produced locally).

In weighing the pros and cons of Vi use in high-risk areas of Indonesia, the “pros” include the fact that typhoid is clearly endemic in the country, children in North Jakarta were shown to be at high risk, and a safe, single-dose vaccine exists. The “cons” include: the need for more local incidence data, the relatively low perceived case fatality from the disease (1-2%), a vaccine efficacy of <80%, and the need to produce the vaccine locally to make it affordable. Based on the results of the DOMI Program, however, the Government is considering phasing in school-based Vi vaccination for 5-14 year olds in high-risk urban areas, starting with Jakarta and a few other cities. The plan assumes the use of a low-cost vaccine (such as one produced locally) and would involve cost-sharing, with local governments covering the delivery (operational) costs and donors helping to cover the vaccine costs. Expanded efforts to measure typhoid incidence in urban areas would be an important part of the plan.

The issues of how to measure the impact of mass vaccination and the need to have a longer term plan following initial catch-up vaccination of school children were raised during the discussion. An Indonesian participant suggested getting private physicians to report typhoid cases and examining school absenteeism rates pre- and post-vaccination as possible means of measuring impact.

### ***Session 3: Typhoid vaccine financing issues***

#### **The investment case for typhoid vaccination (Dale Whittington, University of North Carolina School of Public Health)**

The conventional approach towards analyzing whether a vaccine is a good investment measures the cost per DALY averted by vaccination, allocates interventions with the lowest cost/DALY saved until the public funds are gone, and assumes a top-down approach in deciding which health interventions to finance, with no voice from the people. This talk presented an alternative way to analyze vaccine investments, which incorporates the value of vaccination to people in terms of their willingness-to-pay as an economic benefit, as well as the benefits from lower treatment costs. This model assumes that if people are willing to pay for a vaccine and the economic benefits exceed the costs of the program, then the government should provide the vaccine, using some local financing. The model seeks to reduce as many typhoid cases as possible, while not requiring new public sector spending, and examines different financing policies – free vaccination for all, charging adults for vaccination to fully or partially subsidize vaccination of children, and charging both children and adults the same fee for vaccination.

This model was applied to a low-income neighborhood in Kolkata, India with high typhoid incidence in children, using actual data on disease incidence, cost-of-illness, cost of typhoid vaccination, and population willingness-to-pay/private demand for typhoid vaccination, obtained from the DOMI studies. The results (Figure 6) show that a policy in which children pay \$1.30

and adults pay \$4.00 for typhoid vaccination would prevent almost as many cases (70%) as would a policy of free vaccination for all. It would also be cost neutral to the Government and would have a cost/DALY avoided of \$700 – meeting the WHO definition of cost-effectiveness (cost/DALY avoided of less than the GNI/capital).

**Figure 6. Results of a cost-effectiveness analysis of typhoid vaccination incorporating willingness-to-pay benefits from a low-income area of Kolkata, India (Tiljala)**

	Adults subsidize children	Adult price = child price	Free vaccines
Child price	US\$1.3	US\$2.4	US\$0.00
Adult price	US\$4.0	US\$2.4	US\$0.00
Total number of vaccinations	23,400	28,400	66,000
Total costs of vaccinations	US\$63,300	US\$73,700	US\$151,000
Child (<5yrs) cases avoided	45	35	62
Child (5-14yrs) cases avoided	226	166	325
Adult cases avoided	51	95	242
Public COI Avoided	US\$6,000	US\$5,500	US\$11,700
Revenue from Vaccine Sales	US\$57,000	US\$68,200	US\$0
Program costs per case avoided	\$200	\$250	\$240
Program costs per DALY avoided	\$700	\$910	\$890
Total COI avoided / Program costs	0.13	0.11	0.12
[Public COI avoided + WTP] / Program costs	2.1	2.1	1.4

from Joseph Cook, 2007. "Are cholera and typhoid vaccines a good investment for a slum in Kolkata, India?" Draft PhD Dissertation, University of North Carolina at Chapel Hill

It was pointed out in the discussion that the cost-of-illness estimates in the DOMI studies were low because of the nature of the surveillance studies, in which typhoid cases were identified and treated earlier in the course of the illness than would normally be the case. Dr. Whittington stressed that he was not advocating user fees for vaccination, but that his research does show a higher demand for typhoid vaccination at the local level (through the willingness-to-pay findings) than has generally been believed.

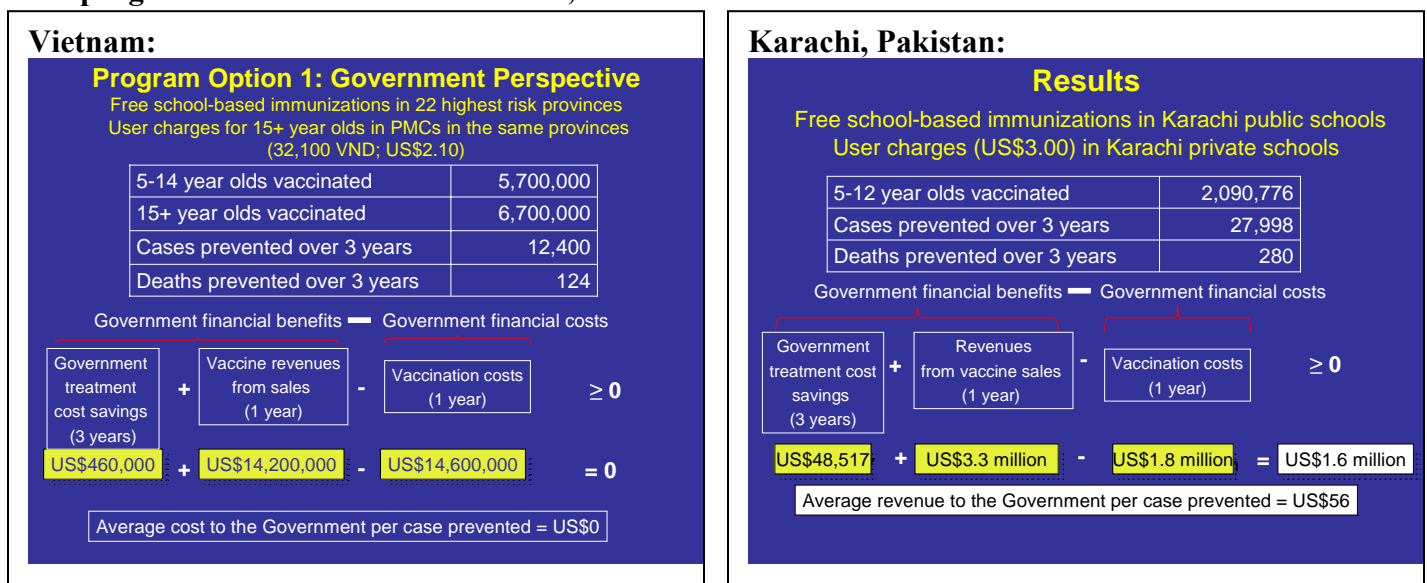
#### **Developing alternative vaccination program options to achieve financial sustainability: Vietnam and Pakistan (Luis Jodar, IVI)**

Economic analyses of different typhoid vaccination program options were carried out for Vietnam and Karachi, Pakistan, using data from the DOMI studies on typhoid disease burden, cost-of-illness, typhoid vaccination costs and private demand/willingness-to-pay for typhoid vaccination. The aim was to come up with programs that maximize the reduction in typhoid incidence, while at the same time being cost-neutral to the government and thus financially

sustainable. To achieve cost neutrality, the costs of vaccination would have to be offset by savings in treatment cost as a result of vaccination, plus revenues from the sale of the vaccine.

In Vietnam, the option that produced the best results consisted of free school-based immunization in the 22 highest-risk provinces – that account for 90% of typhoid incidence in the country – subsidized by vaccination to those 15 years old and above in Preventive Medicine Centers (PMCs) for a user fee (as is the current practice in the PMC vaccination clinics). A fee of \$2.10 at the PMCs would result in 39% of adults getting the vaccination, and, when coupled with treatment cost savings, would totally cover the cost of typhoid vaccination in the schools. The program would result in more than 12,000 typhoid cases prevented over three years (Figure 7).

**Figure 7. Results of the evaluation of financially-sustainable typhoid immunization programs for Vietnam and Karachi, Pakistan**



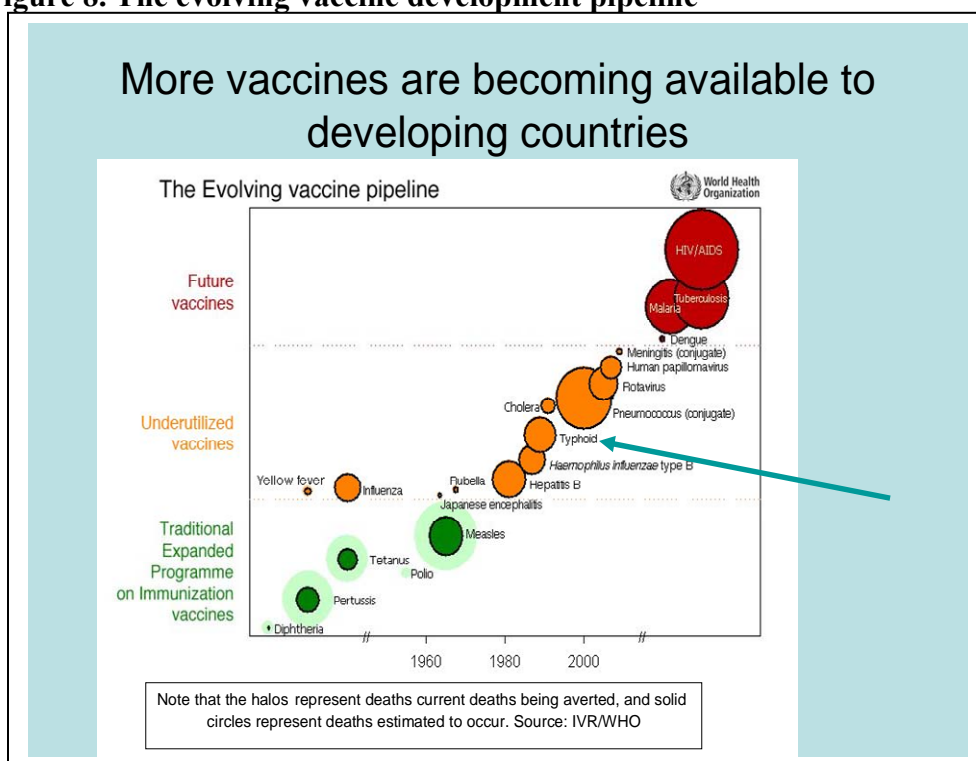
A similar analysis in Karachi, Pakistan examined options in which free school-based vaccination for all 5-12 year olds would be provided in the public schools, while private school children would be vaccinated in their schools for a user fee. Based on the private demand study results for typhoid vaccines, 90% of private school children in non-slum areas and 55% of those in slum areas would accept vaccination for a \$3.00 fee. This program would prevent nearly 28,000 typhoid cases over three years (a 50% reduction) and actually produce revenues for the Government (Figure 7). Reducing the private school fee to \$1.50 would result in cost neutrality.

Based on these results, both Vietnam and Pakistan have made plans to phase in school-based Vi vaccination and to pilot test the cross-subsidization schemes.

## Financing Typhoid Vaccines: A global overview (Lara Wolfson, Initiative for Vaccine Research (IVR), WHO)

More and more new vaccines are becoming available to developing countries and typhoid vaccines are in the middle of the group of under-utilized vaccines, in terms of the number of deaths that could be averted by vaccination and when they became available (Figure 8).

**Figure 8. The evolving vaccine development pipeline**



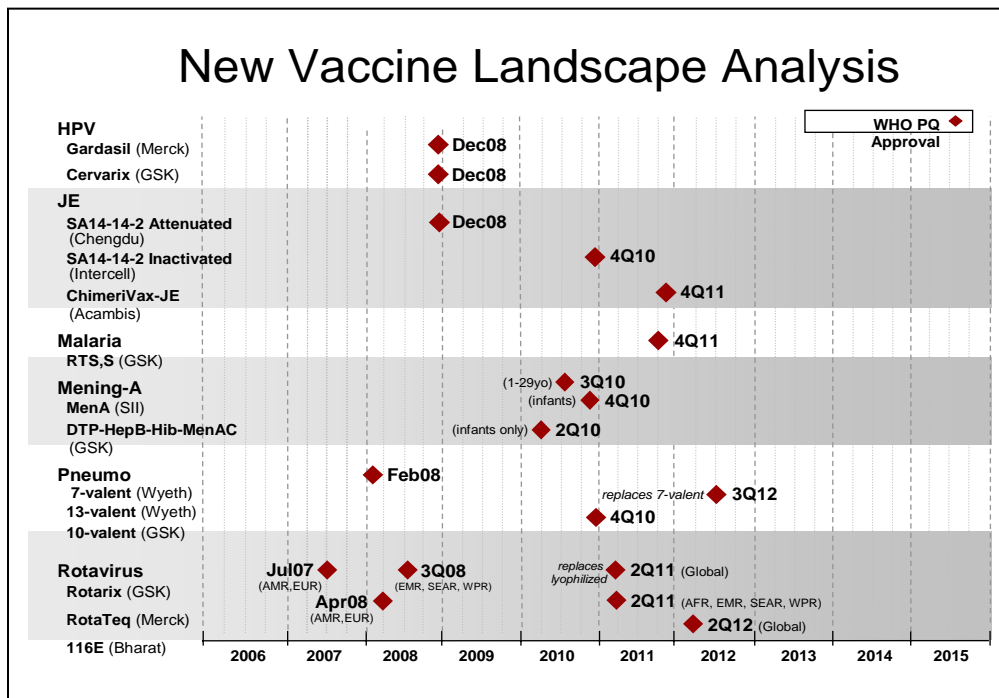
Overall funding for vaccination in GAVI-eligible countries has doubled from 2000 to 2005, reaching \$2.5 billion per year. Achieving the goals of the Global Immunization Vision and Strategy (GIVS), including increased measles coverage, and expanded introduction of vaccines such as Hib, hepatitis B, rotavirus and pneumococcal, will require \$4 billion per year and result in a funding gap of \$11-15 billion over the next 10 years. The projected gap doesn't include the introduction of vaccines against typhoid, cholera, TB, HIV/AIDS, HPV or malaria. To address this gap, the International Finance Facility for Immunization (IFFIm) was created in 2006, in which donors make commitments to fund immunization programs through GAVI for 25 years and bonds are issued against the donor commitments to front-load the flow of aid funds (provided over a 10-year period). This mechanism is expected to raise up to \$4 billion for immunization system improvements and the introduction of new vaccines through GAVI. Another new mechanism – Advanced Market Commitments (AMCs) – provide donor funds for research and development of new vaccines as well as for the purchase of the vaccines at a specified price, in return for producers committing to the price after donor funding ends.

Other possible mechanism to finance the immunization financing gap include: World Bank loan buy-downs (i.e., donor resources are used to lower or even eliminate the costs of loans, if performance targets are met), which have already been used for polio eradication in Pakistan and Nigeria, and various debt relief initiatives, such as the Heavily Indebted Poor Countries (HIPC) Initiative, which has enabled the MOH in Cameroon to greatly increase funding for EPI and human resources in recent years. In addition to external resources and mechanisms, a range of local solutions to funding new vaccine introductions also needs to be explored, such as social health insurance programs, user fees and cross subsidies, and raising additional tax revenues, such as sin taxes.

### The process for GAVI decision making for the introduction of new vaccines (Michel Zaffran, GAVI)

During Phase I (2000 – 2006), GAVI received commitments totaling \$2.2 billion in support for immunization programs – 81% of which was spent on four vaccines (hepatitis B, Hib, yellow fever and DTP). The introduction of hepatitis B has been especially successful, with an estimated 127 million children immunized with the vaccine through GAVI support. In Phase II (2007-2015) some co-financing for new vaccines will be required from the recipient countries, in the aim of countries achieving financial independence from GAVI by 2015. Recent developments also include the decision to approve \$200 million for the introduction of pneumococcal and rotavirus vaccines, and the new Advanced Market Commitment for the development of pneumococcal vaccines geared toward use in developing countries.

Figure 9. New vaccines expected to be WHO-pre-qualified in from 2007 - 2012



More and more new vaccines will soon become available; 18 new vaccines against Japanese encephalitis, HPV, meningitis A (conjugate), rotavirus, malaria and pneumococcal are expected to be pre-qualified by WHO in the next five years (Figure 9). In the recognition that introducing all of these vaccines, as well as other possible vaccines, including typhoid, will not be possible in GAVI-eligible countries, due to financial and programmatic constraints, GAVI is now undergoing a process to develop a strategy or roadmap for the support of immunization for the next 5-10 years. The new GAVI strategy may differ from the past in several important ways, including:

- Switching from a narrow to a broad focus: having countries decide among an array of vaccines to introduce instead of GAVI pre-selecting which vaccines it will support. This would, however, weaken GAVI's leverage in reducing prices by committing to large volume purchases;
- Supporting activities leading up to vaccine introduction, such as disease burden and cost-effectiveness studies, information dissemination and advocacy, and vaccine clinical trials and demonstrations.

The roadmap process will take place over the next year (to May 2008) in three phases, beginning with defining objectives (e.g., to save lives now and contribute to the MDGs or to focus on financial sustainability?), then screening a list of vaccines for possible support and requesting investment cases for those making this first cut (Phase II), and finally finalizing the roadmap and developing a detailed implementation plan (Phase III).

#### ***Session 4: Programmatic and introduction issues regarding typhoid vaccination***

##### **Policy and health system challenges for mass vaccination against typhoid fever (Peter Strebel, WHO)**

The WHO Position Paper on typhoid vaccines in 2000 recommended the replacement of the old inactivated whole-cell typhoid vaccines with new-generation Vi or Ty21a, and immunization of school-aged children and young adults where typhoid and/or antibiotic resistance is a significant problem, as well as for travelers to highly-endemic areas. The position paper did not provide guidance on program goals, timeframe or delivery strategies, such as routine vaccination vs. mass campaigns and targeting single cohorts vs. catch-up of older age groups. Many new disease control initiatives do not focus on a single strategy, but instead use a comprehensive approach that combines routine immunization with various supplemental immunization activities and other health interventions. For example, the Maternal and Neonatal Tetanus Elimination program combines routine infant immunization with the promotion of clean deliveries, adult boosters at first pregnancy, and mass catch-up campaigns for women of child bearing age. The Measles Initiative in 47 countries in Africa and Asia, has used a four-pronged approach – first immunization dose in infancy; second opportunity through routine vaccination or campaigns; surveillance; and case management with Vitamin A supplementation – to reduce measles deaths by 60% world-wide from 1999 to 2005 and by 91% in 19 African countries.

A UNICEF survey showed 16 developing countries with regular school-based immunization programs, but only two in South or East Asia – Indonesia and Nepal. Most programs center on the use of tetanus toxoid (in DT or TT) and do not cover children out of school. Important factors to take into account when considering school-based vaccination are school attendance rates and the need for special efforts to reach children not attending school.

Many factors need to be considered when planning a typhoid immunization program, including whether the goal is individual or herd immunity, which vaccine and schedule to select, which ages to target, what the risk of adverse events are, and what the cold chain requirements will be. Planners should also look for opportunities to integrate the program with other vaccination programs (e.g., measles, TT/Td), other child survival interventions (e.g., vitamin A or mebendazole), or as part of child health days (e.g., for <5s). It is also critical to examine the existing surveillance system in the country and what the surveillance needs will be to measure the impact of typhoid vaccination (e.g., lab testing).

### **School-based typhoid immunization: prospects and problems (T. Jacob John, Christian Medical College, Vellore, India)**

School-based typhoid vaccination demonstration projects, including the DOMI Vi projects in Pakistan, Indonesia and Vietnam, and the Ty21a trials in Chile, were successful, but the key challenge is how to continue and scale-up these programs once the research projects have ended. School-based vaccination is most appropriate when the following conditions are true:

- Disease incidence is high in school-aged children;
- There's a national or local policy to control the disease through vaccination;
- School-based vaccination is part of a larger disease control program (e.g., to include pre-school vaccination through the EPI, where needed, and food hygiene and water improvements)
- It is not perceived as a means to market vaccines, as has sometimes been the case in the past.

School-based vaccination needs to involve all key stakeholders – including the health and education systems, parents, the public and media, professional associations, and the children themselves (to understand and accept). Other factors to consider include:

- Immunizing children first with Vi and later with Ty21a;
- Conducting one-time catch-up campaigns for a large age group, followed by systematic vaccination of a smaller age cohort;
- Vaccinating other special groups, besides school children; and
- The need for location-specific, real-time incidence data through a function disease surveillance system, since the typhoid risk varies substantially within countries.

In the discussion, participants stressed the need to introduce vaccination in the context of overall typhoid control, to include the identification and treatment of carriers, measurement of water quality, and improving hygiene through education. The importance of presenting school-based vaccination as part of and not separate from a routine program was also discussed. It was also

noted that providing health interventions through the schools can actually present an opportunity to attract children not attending school, as has been the case in Pakistan with a school nutrition program, which has helped increase school attendance by 18-20% in target districts.

### **Typhoid vaccines: issues of economics and market potential (Krishna Mohan Vadrevu, Bharat Biotech, India)**

Bharat produces Vi vaccine, following technology transfer from the U.S. NIH. Vi is currently sold in the private sector in India (for \$3.40 - \$6.00/dose retail) and in Pakistan (for \$5.50 - \$6.60), but private sector sales are limited, generally do not reach beyond the elites and urban populations, and do not provide an adequate return on investment that is needed to ensure high GMP standards. Broader use of typhoid vaccines can only take place through public sector immunization. Supply and cost are not really issues, since there are a number of Vi producers, including several emerging producers such as Bharat, and prices recently offered to the public sector have been \$0.50/dose or less. However, public sector Vi introduction will require the involvement of global agencies, such as WHO, GAVI and UNICEF, since government investments are limited and since only such international groups have the credibility to create demand for the vaccine among governments and can ensure that the vaccine reaches the needy.

There are several mechanisms for a developing country supplier, such as Bharat, to work with others to supply needed vaccines for the public sector at low cost. These include:

- Providing bulk vaccine to producers in other countries to fill/finish locally, with restricted geographic licensing, as Bharat is currently doing with Vi in Pakistan (facilitated by IVI);
- Obtaining bulk vaccine from a multi-national company and fill/finishing it in a developing country, sharing marketing rights;
- Working with government or international R&D organizations, such as NIH and IVI, to obtain production technology of a vaccine (e.g., Vi conjugate), with the local producer committing to agreed-upon vaccine prices.

## ***Session 5: Recommendations from Working Groups***

Three Working Groups were formed to come to a consensus and develop recommendations on the steps required to expand the control of typhoid vaccination in endemic countries through the use of new-generation vaccines. Below are the recommendations of the three Working Groups.

### **I. Working Group I: Strategies and steps to take for the introduction and increased use of typhoid vaccines in developing countries (country perspective)**

Pilot introduction projects and data needs for policy makers: Program planners and typhoid researchers need to:

1. Implement all typhoid vaccine introduction programs in the context of efforts to improve sanitation and hygiene.

2. Make additional efforts to measure the disease burden in countries in order to identify high-risk groups and areas. This will require increasing the availability of microbiology labs capable of performing blood cultures, since the diagnosis of clinical enteric fever is insufficient to measure typhoid incidence and doesn't differentiate typhoid from paratyphoid. Increased typhoid disease burden studies will also help create a market for better point-of-use typhoid diagnostics, which are sorely needed.
3. Conduct additional vaccine demonstration and pilot projects, as required by policymakers, to test the feasibility of specific program aspects, such as the choice of vaccine, school-based vaccination, etc.
4. Involve the media in the dissemination of disease burden, vaccine and other data, since the media can be influential with policymakers.
5. Prior to implementing typhoid vaccine introduction, obtain the support of WHO and determine if there is population demand for the vaccination.
6. Evaluate existing Vi vaccination programs to provide country-level policymakers with critical data on the effectiveness of different vaccination strategies, including the Vi immunization program for pre-school children in Delhi State, India.

Vaccine regulation and production needs and issues:

7. Make the pre-qualification of typhoid vaccines by WHO an immediate priority, since the lack of WHO pre-qualified typhoid vaccines is a critical barrier to expanded introduction.
8. Encourage WHO to make a policy statement on the use of typhoid vaccination for outbreaks and emergency response.
9. Conduct studies to define and measure the potential market for new-generation typhoid vaccines, in order to encourage producers to scale up production and promote the vaccines.

**II. Working Group II: Development of an action plan to move the typhoid fever control agenda forward**

Working Group II focused on the steps required to present the case of typhoid vaccination to the WHO Scientific Advisory Group of Experts (SAGE), in the expectation that the SAGE will issue updated recommendations for typhoid vaccination. New recommendations from the SAGE since the 2000 position paper was written were seen as critical to the expanded introduction of typhoid vaccination for several reasons:

- a) There are considerably more data and a change in the landscape of new and under-utilized vaccines since the 2000 position paper (e.g., with the upcoming introduction of rotavirus and other vaccines);
- b) A SAGE recommendation increases awareness of the vaccine beyond the immediate interest groups to the broader global community, including WHO regional offices and health ministries;
- c) SAGE recommendations influence the position of other key organizations and thus it will be difficult to develop regional policies or to get a GAVI investment case accepted without a renewed and updated recommendation from the SAGE;
- d) A SAGE recommendation can serve as a catalyst for WHO pre-qualification of typhoid vaccines.

Typhoid vaccines have been included in the agenda for the next SAGE meeting in November 2007. The recommended steps to prepare for the SAGE meeting are as follows:

1. Establish a working group ( $\approx$  12 individuals) to prepare the documents to be presented and an agenda for the typhoid session of the SAGE. The intended outcome of the session will be for the SAGE to reach a consensus on the typhoid data presented and their meaning, to identify remaining gaps in data, and, over a longer term, to develop recommendations based on the information presented;
2. Develop a work plan and budget for the working group;
3. Prepare a new summary of the data on typhoid, which includes data on the effectiveness of mass Vi vaccination from the DOMI randomized controlled trials and which addresses other gaps in knowledge identified in the WHO position paper (e.g., vaccine efficacy in children < 5 years of age; defining high-risk areas, etc.); and
4. Convene a meeting of the Working Group several weeks before the SAGE meeting to review the data summary and prepare the presentations.

In the next one to two years, it will be critical for typhoid vaccines to be pre-qualified by WHO, since pre-qualification is required before GAVI can provide support for vaccine introduction.

### **III. Working Group III: Addressing policy and health system challenges for mass vaccination against typhoid fever**

1. The local or national introduction of typhoid vaccine needs to be preceded by a recommendation from the national government, even if implementation takes place at the local-government level.
2. **Choice of typhoid vaccines:**

- Typhoid vaccination in endemic countries should not wait until Vi conjugate vaccines become available (in seven years at the earliest).
  - Both Vi polysaccharide and the oral Ty21a are acceptable new-generation vaccines and the choice of vaccine should be left to the countries, based on cultural and social conditions and the capacity of the EPI.
  - Vi vaccine is preferred for outbreak control, since it has a single dose regimen (vs. 3-4 doses for Ty21a) and thus vaccination can be completed more rapidly.
3. **Vaccination schedule** (for Vi):
    - Vaccination of school-aged children (e.g., starting at age five) is recommended, although vaccination with Vi can be given from the age of two years. The age of vaccination should be based on age-specific incidence data from the country.
    - Re-vaccination with Vi should take place no sooner than every three years, where possible, during the school-aged years.
  4. **Delivery strategies:** Both school-based and community-based vaccination against typhoid have been shown to be feasible. The choice of delivery strategy should be left to the country and based on the local context. In areas where school attendance is low or where pre-school children are at high risk of getting typhoid, community-based campaigns or a combined strategy of school- and community-based vaccination should be considered. In some areas where school-based vaccination is negatively viewed as a marketing strategy, community-based vaccination may be preferable.
  5. **Financing:** Countries may want to consider a range of options for financing typhoid vaccination, including cross-subsidization (e.g., private schools subsidizing free public school vaccination), co-financing (imposing reasonable user fees, as in China), and shared financing between the local and federal governments. Vaccination should be provided free to those at highest risk and to the poor.
  6. It will be important to monitor the trends in typhoid incidence when introducing the vaccine, in order to evaluate its impact and to make adjustments in the program (e.g., ages of vaccination, frequency of or need for re-injection, etc.).

### ***Meeting summary and wrap-up***

Zulfiqar Bhutta provided a summary of the main information points and messages raised during the meeting:

- There is continued uncertainty in many countries of the typhoid disease burden, due to the lack of rapid, accurate diagnostics, the poor quality of surveillance and reporting systems and the likely under-reporting of the disease;
- Important new data are now available from the DOMI Program on population-based, age-specific incidence of typhoid and on the economic burden of the disease;

- We are running out of treatment options as multi-drug resistant and quinolone resistant *S. typhi* strains increase, at least in certain areas;
- Typhoid control needs to be included in the child survival agenda;
- Communities are not likely to accept vaccination alone as a means of controlling typhoid, and therefore improvements in water and sanitation systems must accompany typhoid immunization programs;
- Typhoid vaccination, especially for children, is relatively cost-effective – similar to anti-retroviral therapy for HIV and greater than dengue fever treatment;
- There are two safe, effective new-generation typhoid vaccines currently available at relatively low cost ( $\approx$ \$0.50/dose in the case of Vi). The cost can potentially be reduced further through technology transfer to additional emerging producers and through bulk purchasing. Vi conjugate is promising (including for use in infants), but will not be available for several years;
- Typhoid immunization has been demonstrated to be feasible and relatively popular in the DOMI Vi demonstration projects (with a coverage of near or greater than 70% in most settings);
- Several delivery strategies and combination of strategies could be considered for typhoid vaccination, including mass campaigns, routine EPI contacts, school-based vaccination and Child Health Weeks;
- There is now a broad range of financial options available for immunization and thus a positive climate for the financing of new vaccine introductions, such as typhoid.

Dr. Bhutta concluded that the following steps are needed to move typhoid vaccination from its phase of research and limited use to its broader implementation:

- The need for WHO, UN agencies, GAVI, child health organizations and industry to reach a consensus on typhoid disease burden estimates and on diagnostic and intervention strategies to recommend;
- The development of a formal WHO estimate of the global typhoid disease burden;
- The pre-qualification of typhoid vaccines by WHO;
- The involvement of the public health and policy communities in countries with high typhoid disease burden in the promotion of typhoid immunization to the global health community; and

- Presentation of the case for typhoid vaccination at the next WHO SAGE meeting, leading to updated SAGE recommendations concerning typhoid vaccine use and additional research needs.

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## ANNEX 1. Meeting Agenda

**Monday, April 2, 2007**

<b>17h30-18h15</b>	Registration	
<b>18h15-18h45</b>	Welcome Address	<b>B. MIRIBEL MP KIENY J. CLEMENS</b>
<b>18h45-19h15</b>	Keynote lecture: Overview of Global Problem of Typhoid Fever and Licensed Vaccines available as Public Health Tools	<b>T. PANG</b>
<b>19h45</b>	Welcome Dinner	

**Tuesday, April 3, 2007**

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### ***Session I: - Updates on typhoid fever in Asia (08h30-11h00)***

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**Chaired by: Henry WILDE**

<b>08h30-08h50</b>	Overview of the magnitude and epidemiological patterns and economic consequences of typhoid fever in Asia	<b>Leon OCHIAI</b>
<b>08h50-09h05</b>	<b>Discussion</b>	
<b>09h05-09h25</b>	Trends in antibiotic resistant typhoid fever and implications for treatment and prevention	<b>John WAIN</b>
<b>09h25-09h45</b>	<b>Discussion</b>	
<b>09h45-10h05</b>	Production capacity and supplies for developing countries	<b>Rodney CARBIS</b>
<b>10h05-10h20</b>	<b>Discussion</b>	
<b>10h20-11h00</b>	Coffee break	

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**Session II: - Recent experiences with typhoid vaccination using different delivery strategies (11h10-16h30)**

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**Chaired by: John Clemens, Samir Saha**

11h00-11h20	Typhoid fever vaccination in Vietnam	<b>Luis JODAR (for Anh DANG DUC)</b>
11h20-11h40	<b>Discussion</b>	
11h40-12h00	School-based typhoid vaccination in Chile (video conference)	<b>Mike LEVINE</b>
12h00-12h15	<b>Discussion</b>	
12h15-14h00	Lunch	
14h00-14h20	Experience with community based vaccination in a high-incidence urban area in Pakistan	<b>Zulfiqar BHUTTA</b>
14h20-14h40	<b>Discussion</b>	
14h40-15h00	Experience with school-based vaccination using Vi in a typhoid endemic area of China	<b>Honghui YANG</b>
15h00-15h15	<b>Discussion</b>	
15h15-15h45	Coffee break	
15h45-16h05	Experience with school-based Vi vaccination, Jakarta Indonesia	<b>Triono SOENDORO</b>
16h05-16h25	<b>Discussion</b>	

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**Session III: - Typhoid vaccine financing issues (16h25-18h00)**

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**Chaired by: May Montellano**

16h25-16h45	The investment case for typhoid vaccination programs	<b>Dale WHITTINGTON</b>
16h45-17h05	<b>Discussion</b>	
17h05-17h20	An investment case for typhoid fever vaccination in Vietnam and Pakistan	<b>Luis JODAR</b>

<b>17h20-17h40</b>	Financing options for typhoid fever vaccines global level	<b>Lara WOLFSON</b>
<b>17h40-17h55</b>	<b>Discussion</b>	
<b>17h55-18h15</b>	Pathways for GAVI decision making on vaccines to be supported for introduction	<b>Michel ZAFFRAN</b>
<b>18h15-18h30</b>	<b>Discussion</b>	
<b>19h00</b>	<b>Dinner</b>	

**Wednesday, April 4, 2007**

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***Session IV: - Programmatic and introduction issues (08h00-12h30)***

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**Chaired by: Claire Lise CHAIGNAT, Michael Favorov**

<b>08h00-08h20</b>	Policy and health system challenges for mass vaccination against Typhoid Fever	<b>Peter STREBEL</b>
<b>08h20-08h35</b>	<b>Discussion</b>	
<b>08h35-09h55</b>	Practical challenges for school-based typhoid fever vaccination	<b>Jacob JOHN</b>
<b>09h55-10h10</b>	<b>Discussion</b>	
<b>10h10-10h30</b>	Coffee Break	
<b>10h30-10h50</b>	Supply-pricing perspectives	<b>Krishna M. VADREVU</b>
<b>10h50-11h05</b>	<b>Discussion</b>	

## **ANNEX II. Participant List**

## **SPEAKERS**

BUTTHA, Zulfiqar  
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