WISH TO THANK

FONDATION MERIEUX
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Fig. 2. Geographical distribution of typhoid fever
In endemic areas schoolchildren and young adults are most frequently affected.

During recent decades typhoid fever has largely disappeared from industrialized countries, but remains a serious public health problem in several Asian regions of the former USSR, in parts of South and East Asia, Africa and South America.

According to conservative WHO estimates, 16 million cases occur each year, including about 600,000 deaths.

Asymptomatic intestinal carriers of *S. typhi* are common in endemic areas, and are important sources of infection.

Antimicrobial treatment of typhoid fever and of asymptomatic salmonella carriers has become increasingly complicated by the emergence of multidrug-resistant strains of *S. typhi*.

Vaccination of high-risk populations is considered the most promising strategy for the control of typhoid fever.

The old, heat-inactivated whole-cell vaccine showed protective efficacy rates that in controlled studies ranged between 51%-67%, but this vaccine is associated with frequent adverse reactions.
For this reason it has been replaced by newer typhoid vaccines in industrialized countries.

Decisions on whether or not to incorporate typhoid vaccination into large-scale immunization programmes should be based on detailed knowledge of the local epidemiological situation including data on age-specific incidence and possible subpopulations at particular risk, as well as on information concerning the sensitivity to relevant antimicrobial drugs of the prevailing *S. typhi* strains.

Ideally, cost-benefit analyses should be part of the planning process.

Immunization of school-age children is recommended in areas where typhoid fever in these age groups is a significant public health problem, and particularly where antibiotic-resistant *S. typhi* strains are prevalent.
Costs of Illness Due to Typhoid Fever in an Indian Urban Slum Community: Implications for Vaccination Policy

Rajiv Bahl, Anju Sinha, Christine Poulos, Dale Whittington, Sunil Sazawal

ABSTRACT

Data on the burden of disease, costs of illness, and cost-effectiveness of vaccines are needed to facilitate the use of available anti-typhoid vaccines in developing countries. This one-year prospective surveillance was carried out in an urban slum community in Delhi, India, to estimate the costs of illness for cases of typhoid fever. Ninety-eight culture-positive typhoid, 31 culture-positive paratyphoid, and 94 culture-negative cases with clinical typhoid syndrome were identified during the surveillance. Estimates of costs of illness were based on data collected through weekly interviews conducted at home for three months following diagnosis. Private costs included the sum of direct medical, direct non-medical, and indirect costs. Non-patient (public) costs included costs of outpatient visits, hospitalizations, laboratory tests, and medicines provided free of charge to the families. The mean cost per episode of blood culture-confirmed typhoid fever was 3,597 Indian Rupees (US$ 1 = INR 35.5) (SD 5,833); hospitalization increased the costs by several folds (INR 18,131, SD 11,218, p<0.0001). The private and non-patient costs of illness were similar (INR 1,732, SD 1,589, and INR 1,865, SD 5,154 respectively, p=0.8095). The total private and non-patient ex-ante costs, i.e. expected annual losses for each individual, were higher for children aged 2-5 years (INR 154) than for those aged 5-19 years (INR 32), 0-2 year(s) (INR 25), and 19-40 years (INR 2). The study highlights the need for affordable typhoid vaccines efficacious at 2-5 years of age. Currently-available Vi vaccine is affordable but is unlikely to be efficacious in the first two years of life. Ways must be found to make Vi-conjugate vaccine, which is efficacious at this age, available to children of developing-countries.
• The very conservative annual number of typhoid cases for the year 2000 is estimated at 17 million with 200 to 600,000 deaths.

• THIS IS A SIGNIFICANT NUMBER TO BE IGNORED.

• In virtually all endemic areas, the incidence of typhoid fever is highest in children 5-19 years of age, even if some reports mention an earlier age.
The Vi Polysaccharide Vaccine

- This vaccine is composed of purified Vi polysaccharide from *S. typhi*. It is administered subcutaneously or intramuscularly as 1 dose of 25 mg to individuals aged > 2 years.

- The vaccine confers protection 7 days after injection.

- Recommended storage temperature is between + 2 °C and + 8 °C.

- A randomized trial in Nepal involving persons aged 5-44 years showed 75% protection against culture-positive typhoid fever during the 20 months of active surveillance.

- In a recent study in South Africa, 55% efficacy was demonstrated 3 years after immunization of children aged 5-16 years.

- Ten years after vaccination, 58% still had >1mg ml-1 of anti-Vi IgG in their sera, a level frequently regarded as protective,
The Ty21a Vaccine

• This is a live attenuated strain of *S. typhi* Ty21a that was developed in the early 1970s by chemical mutagenesis. Protection is markedly influenced by the number of doses and their spacing.

• When the vaccine is given in 3 doses 2 days apart, protective immunity is achieved 7 days after the last dose.

• In endemic areas a booster dose is recommended every 3 years.

• Travelers from non-endemic to endemic regions are recommended a booster on a yearly basis.

• There are currently no field trial data to document the efficacy of this vaccine in children aged < 3 years.
WHO Position on Typhoid Vaccines

• The old, heat inactivated whole-cell vaccine may not always be manufactured according to international standards, whereas both the parenteral Vi-based polysaccharide vaccine and the live attenuated oral Ty21a vaccine are of assured quality and safety.

• The respective duration of protection is not fully established for any of these vaccines.

• Because of its considerable reactogenicity, the inactivated whole-cell vaccine should now be replaced by the less reactogenic and equally efficacious modern vaccines.

• Neither the Vi-based polysaccharide vaccine nor the Ty21a vaccine is licensed for children aged < 2 years, and with their current formulations they are not considered candidates for inclusion into large-scale vaccination programmes in this age group.

• However, while waiting for improved vaccines against typhoid fever, further assessment of the protective efficacy of the currently-licensed vaccines in the youngest age groups seems warranted.
National decisions concerning strategies to control typhoid fever should be based on thorough analyses of age specific incidence, on groups at particular risk of infection and on cost-benefit aspects of the planned control measures.

Immunization of school-age children and young adults is recommended in areas where typhoid fever in these age groups is a significant public health problem, and particularly where antibiotic-resistant *S. typhi* strains are prevalent.

Where appropriate the use of typhoid vaccines should be harmonized with the administration of tetanus and diphtheria vaccines.

It should be noted, however, that the vaccines do not provide complete protection and should not replace hygiene precautions.
WHO conservatively estimates the annual global incidence of typhoid fever at 0.3%, corresponding to about 16 million cases, of which approximately 600,000 end in death.

In some developing countries of Asia and Africa the annual incidence may reach 1% with fatality rates as high as 10%. About 70% of all fatalities from typhoid fever occur in Asia.

Hospital based data and passive surveillance studies in endemic areas have shown that the incidence of typhoid fever peaks between the ages of 5 and 12 years.

In children aged < 2 years the clinical course of the disease tends to be mild and the correct diagnosis may often be missed in this age group.
IVI’s Diseases of the Most Impoverished (DOMI) Program

$40 million effort funded by the Bill & Melinda Gates Foundation that was launched in 2000 to accelerate the development and introduction of vaccines against the diseases such as cholera, typhoid fever and shigellosis in endemic areas.

The main objectives of DOMI are to:

a) generate and disseminate evidence needed by policymakers for rationally introducing existing, licensed, new-generation vaccines against cholera and typhoid fever;

b) help assure an adequate and cost competitive vaccine supply of killed, whole-cell oral cholera and Vi polysaccharide typhoid vaccines by transferring production technologies to qualified producers in Asia and providing training in vaccine production and regulation;

c) help develop a consensus at national, regional, and international levels on the use of vaccines against diseases such as Typhoid.

The Program operates in 7 countries in Asia and 1 country in Africa.
The objectives of the DOMI Typhoid Program are to:

- Assure an adequate and cost-competitive supply of Vi PS vaccine by working with international producers, by assisting the transfer of production technologies to qualified producers in Asia, and by providing training in vaccine production and regulation.

- Bharat Biotech’s association with IVI in Pakistan

- Ensure that the pipeline of newer-generation experimental vaccines against typhoid is exploited by accelerating the development of new vaccine candidates and evaluating these in endemic settings.

- Help develop a consensus at the regional, national, and international levels on the use of vaccines against typhoid fever.
• Despite the availability of the modern typhoid vaccines since the late 1980s, as well as the recommendation of the World Health Organization in its 2000 position paper about typhoid vaccination, their use in public health programs in endemic countries has been quite limited.
Among the reasons for their limited use have been:

– the relative high cost of these vaccines produced by multinational producers;

– the reluctance of policymakers to introduce a vaccine outside of the infant immunization schedule of the Expanded Program on Immunization (EPI), since these vaccines are not effective in children under two years of age;
– a general skepticism about the cost-effectiveness and financial sustainability of introducing typhoid vaccines versus other interventions; and

– perhaps of greatest importance, the lack of reliable data on typhoid incidence in the vast majority of developing countries.

The last has resulted in likely under-reporting and low awareness of the magnitude of the problem among many national-level healthy policymakers.
The lack of accurate data and under-reporting, in turn, has been due to:

1) the inability of many health providers to accurately diagnose typhoid fever;

2) the lack of laboratory testing to confirm typhoid in many public health facilities in developing countries;

3) the reliance by many people on private providers or self-treatment with antibiotics, thereby bypassing the public health system; and

4) inadequate disease reporting systems in many typhoid endemic countries.
Economic Considerations

- The high and rising costs of treating typhoid fever, due to growing antibiotic resistance, and the economic costs to families resulting from loss of work to care for a child during long recovery periods, appeared to be key factors contributing to growing concern of policy-makers for the disease and interest in new-generation typhoid vaccines.

- The perceived need for typhoid vaccines appeared more urgent to policy-makers in countries that must import and pay high prices for ciprofloxacin.

- Suggested targets for typhoid vaccine included urban school-age children, slum residents, and soldiers.
Increased role of the private sector in the introduction and distribution of vaccines

- In developing economies, for vaccines such as typhoid Vi, there is a large demand among the middle class and urban dwellers.

- Policy-makers in these countries view private-sector distribution of vaccines as means to:
  
  - demonstrate public demand for a vaccine, which some national immunization programs increasingly require before considering public-sector use;
  
  - provide vaccines before the public sector is able to do so.
Increased role of the private sector in the introduction and distribution of vaccines

– Innovative strategies of distributing vaccine to large numbers of people in partnership with vaccine companies, medical associations, NGOs, and local governments have demonstrated that private-sector distribution can reach beyond small elites.
Increased role of the private sector in the introduction and distribution of vaccines

– ADOPT A CO-OPETITION MODEL.

– Bulk Vaccine Export >> Fill / Finish in Local demand regions (eg., Pakistan, Africa) with restricted geographic licensing

– Bulk Vaccine from an MNC Company >> Fill/Finish in a Developing Country (optimize costs) ; share Marketing Rights on Geographical considerations
– Licensure of Technology from Govt. Funded R & D Orgnzns such as NIH, IVI & Commitment of Vaccine Pricing/Profit.

– Specifically valid for Vi Conjugate vaccines.
Increased role of the private sector in the introduction and distribution of vaccines

- Collaborative public-private efforts have included large-scale immunization camps using discounted vaccine, school-based campaigns, and programs to distribute discounted vaccine at public-sector health facilities; and

- provide vaccines for free to the poor via the public sector, while encouraging those better-off to obtain the vaccine in the private sector. This 'dual channelling' approach was suggested in both India and Indonesia as a potential cost-containment strategy for the introduction of newer vaccines, such as new-generation enteric vaccines.
– In the case of new-generation enteric vaccines, cost-effectiveness data may be critical to inform vaccine-uptake decisions, given their moderate protection levels (e.g. ca. 70% for typhoid Vi) and the stated preference of many policy-makers for more permanent solutions, such as improvements in water and sanitation, over immunization. These data can most efficiently be gathered during vaccine demonstration projects.
Issues faced by Private sector in the introduction of vaccines

- Private Markets in Developing Countries do not give adequate ROI.
  – Desire to ensure high cGMP standards and attract global visibility needs reasonable ROI.
  – Demand Generation by private Companies, Marketing efforts cannot be adequate enough.
  – Governments in Developing Economies do not invest sufficiently.

SOLUTION : Intervention by Global Agencies such as WHO / GAVI / IVI / …
<table>
<thead>
<tr>
<th>Brands</th>
<th>Manufactured / Marketed by</th>
<th>Maximum Retail Price</th>
</tr>
</thead>
<tbody>
<tr>
<td>Typho-VI</td>
<td>BIOMED</td>
<td>3.98</td>
</tr>
<tr>
<td>TYPBAR</td>
<td>BHARAT BIOTECH</td>
<td>3.41</td>
</tr>
<tr>
<td>Typherix PFS</td>
<td>Glaxosmithkline</td>
<td>6.18</td>
</tr>
<tr>
<td>Shantyphi.</td>
<td>Shanta Biotech</td>
<td>4.52</td>
</tr>
</tbody>
</table>
### Available Typhoid Vaccines - Pakistan

<table>
<thead>
<tr>
<th>Brands</th>
<th>Marketed by (Manufactured by)</th>
<th>MRP (US $)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zerotyph Inj. (0.5 ml vial)</td>
<td>Amson (Boryung)</td>
<td>5.6</td>
</tr>
<tr>
<td>*Zerotyph Caps (3’s)</td>
<td>Amson (Boryung)</td>
<td>5.5</td>
</tr>
<tr>
<td>Typherix Inj. (0.5 ml PFS)</td>
<td>Glaxosmithkline</td>
<td>6.6</td>
</tr>
<tr>
<td>Typhim Vi Inj. (0.5 ml PFS)</td>
<td>Sind Medical Stores (Aventis)</td>
<td>6.6</td>
</tr>
</tbody>
</table>
## Steep Price Structures in Private Market

<table>
<thead>
<tr>
<th>Vaccine Dose</th>
<th>Typical Transfer Price (US $ / dose)</th>
<th>Retail Price (US $ /dose)</th>
<th>Patient Price (US $ / dose)</th>
<th>Cost Fact -or</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5 ml</td>
<td>0.55</td>
<td>3.30</td>
<td>3.0</td>
<td>5.5</td>
</tr>
<tr>
<td>2.5 ml</td>
<td>2.40</td>
<td>11.60</td>
<td>11.0</td>
<td>4.5</td>
</tr>
</tbody>
</table>
It appears that Supply and Cost of Typhoid Vaccine would not be a Constraint.

Projected vaccine costs could be around U$0.50 (max).

FINAL VERDICT: Creating awareness among policy makers and Global Funding Agencies
1- **Awareness**: Vaccine market is activity-driven due to lack of awareness. Typhoid vaccine is mainly used in urban areas among educated classes.

2- **Doctors’ obligations**: Dispensing segment contribute significantly towards vaccines uptake; thus incentives and obligations for doctors are patronized by all vaccines companies.

3- **Cost**: A major obstacle in typhoid vaccine uptake in some countries such as Pakistan.

4- **Mass vaccination campaigns**: A very useful tool to vaccinate masses directly after creating awareness.
1. Historically Vaccine Prices have become affordable after Technology capabilities increased in Developing Countries with high cGMP skills and infrastructure.

2. Even a well established Private Market in developing countries does not lead to widespread vaccine usage.

3. Hepatitis B is a primary example in India – a vaccine which is yet to be included in EPI Program.

4. Partnerships with “willing” Developing country manufacturers for “local” manufacture or at least “Fill/Finish” to control costs and circumvent geo-political issues.

UNICEF / GAVI & Other Funding Agencies Led Initiatives are the only answer to ensure cost effective vaccines would reach the needy.
1. Some of the suggestions being made:
   - Cross-subsidization
   - User-Fees
   - School going children 5 Yrs and above.

   Feasibility of adopting these ??

   2. What about children in age group 2 to 5 years
• It took around three years to develop the vaccine in collaboration with the National Institution of Health (NIH), USA, and is the first non-bovine-based typhoid vaccine in the world. The demand for the typhoid vaccine in India was through imports.

• The current market in India for typhoid vaccine is estimated at 50 million doses per annum (CII Report March 2007) and projected to go up to 100 million doses.

• However the demand estimation for the typhoid vaccine in India will be driven by increased awareness of prevention versus care.

• Bharat Biotech is committed to offer TYPBAR – our Typhoid vaccine at an affordable price for programs as required globally.
• We are also working on Vi – TT conjugate vaccines, which would soon be entering clinical trials.

• Other Indian Vaccine Manufacturers are also working on Typhoid conjugate vaccines.

• These would be available soon for Public markets at affordable prices.
“What might be overlooked, however, as life-sustaining drugs become available, is the fact that prevention is still by far the more compassionate and more cost-effective answer. Prevention does not replace treatment, but it does reduce the number of people whose lives will depend on expensive drugs with significant side effects.”

Vision: To be a leader in region-specific diseases.

Mission: Technology for the People in compliance with Global IPR.

Business Philosophy: Our Competitors are not other Companies but Infectious Diseases that we are trying to combat.
We are currently manufacturers of Hepatitis B, Typhoid and Rabies vaccines with HIB, Combination vaccines in pipeline.

From Bulk ....JE and OPV vaccines.

Major Programs on Rota Virus and Malaria vaccines (P.vivax and P.falciparum) thro PATH / MVI / EMVI.
WISH TO ACKNOWLEDGE INFORMATION SOURCES:

WHO Reports, IVI Reports,
Information from Partners in Pakistan
THANK YOU