

## 14. IVI- NICED Collaborative Project

### 14.1 Randomised controlled evaluation of protection by Vi polysaccharide vaccine against typhoid fever in Eastern Kolkata

#### Objective:

1. To determine the protective effectiveness of the Vi polysaccharide vaccine following routine administration in a 1-dose schedule,
2. To estimate the cost-effectiveness of Vi vaccination, and
3. To monitor the safety and immunogenicity of Vi vaccine following administration through a mass vaccination campaign.

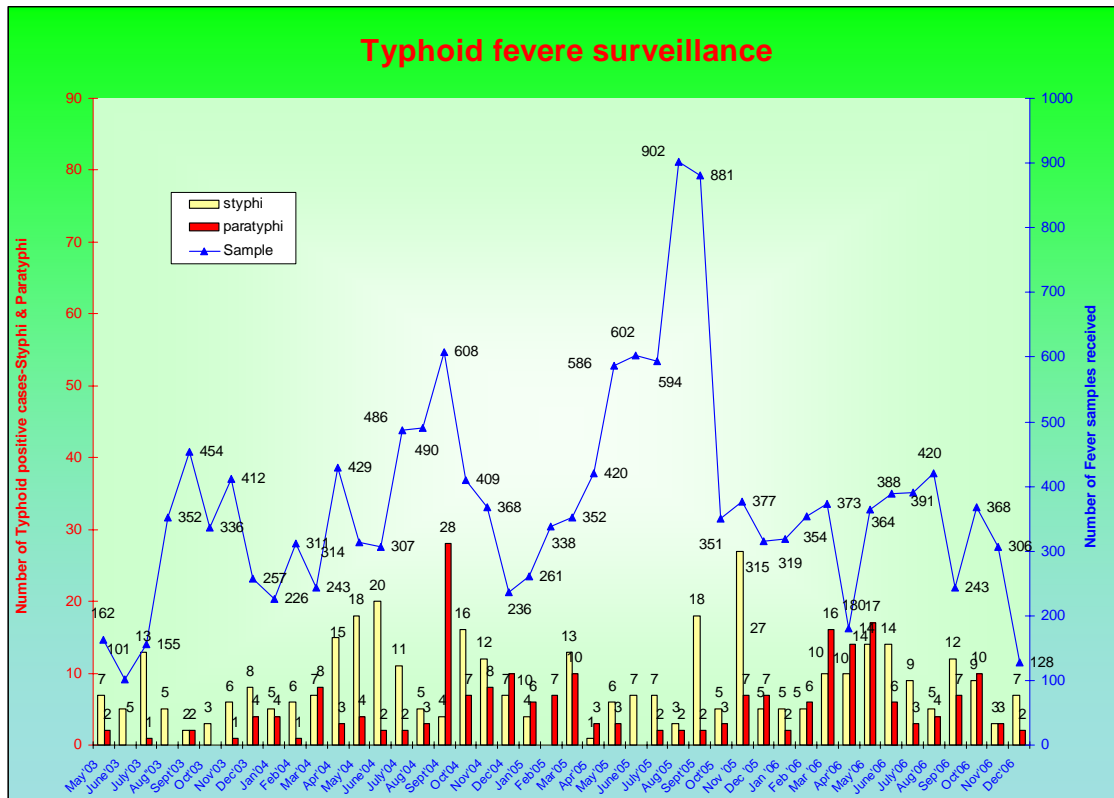
#### Ongoing activities:

In order to achieve this objective, we had selected the ward no.29 and 30 of Kolkata Municipal Corporation as the study site. In census survey, we covered 10,995 families of total 57,099 slum populations. The Identification card for each family including all family members in laminated form was distributed to each family. Satellite images of the study area were obtained and these were enhanced using an image processing software package (ERDAS Imagine, Atlanta, USA) to facilitate the digitization of houses in the study area. A ground survey was conducted to link each household identification number to a GIS number. The GIS was used to define clusters for the randomisation of the typhoid Vi and control vaccine during the effectiveness trial. We had set up 5-health outposts, each covering about 12,000 populations for passive surveillance of typhoid fever and also for diarrhoea for future cholera vaccine trial. Another 2 health outposts were also setup in the reference hospitals (Infectious Disease Hospital and B.C. Roy Children Hospital) for surveillance so that the case will not be missed from the study sites. During the surveillance period from May,03 to December,2007, a total number of 12,635 fever cases of more 3 days were reported and blood samples were taken. Out of those, number of positives for typhoid fever were 374 (3.0 %) and for Paratyphi-A 232 (1.8 %).

The mass typhoid Vi vaccination campaign was held in the study site from November 27 to December 31, 2004. Out of 60,615 individuals, 54,674 were considered eligible. During the vaccination, those who were considered not eligible were pregnant or lactating women, children < 2 years of age, those with a febrile illness or those travelling out of the study site. 37,686 individuals or 68.9% of 54,674 were immunized. The detailed vaccine coverage was given below.

	No. of individuals eligible for vaccination	No. of individuals vaccinated (%)
Ward 29	33,633	21,845 (65)
Ward 30	21,041	15,841 (75)
2 to ≤ 18 years old	19,007	14,395 (76)
18+ years old	35,667	23,291 (65)
Male	29,910	19,796 (66)
Female	24,764	17,890 (72)
Target population	54,674	37,686 (69)

Two years post vaccination surveillance for typhoid fever has been completed in December, 2007. The closeout census is also done. The graph depicts the fever surveillance during the whole period. Data analysis is going on for the vaccine effectiveness.



#### 14.2 A randomized controlled trial of the bivalent killed whole cell oral cholera vaccine in Eastern Kolkata, West Bengal, India

##### Objectives:

Our primary objective of the study was to estimate the efficacy of a two-dose primary regimen of the oral killed bivalent cholera vaccine when administered to residents at least 1 year of age in preventing culture-proven *V. cholerae* O1 diarrhoea episodes severe enough to require treatment in a health care facility.

##### The secondary objectives were:

- a. To estimate the efficacy of the vaccine in preventing:
  - Culture-proven *V. cholerae* O1 diarrhoea episodes associated with severe dehydration;
  - Episodes of acute watery diarrhoea associated with severe dehydration;
  - Episodes of acute watery diarrhoea severe enough to require treatment in a health care facility; and

- All the above endpoints stratified by age (less than 5 and over 5 years)
- b. To evaluate whether the vaccine induces acceptable serum vibriocidal responses in relation to the placebo group.

The existing area for typhoid vaccine trial and also extended area of ward 29 and ward no. 33 have been included for the study area for this vaccine trial to reach the sample size of 110,000 population. Initially, the census of the whole study area was done for exact number of population. The Geographical Information System work of the new area were also completed. All healthy, consenting, non-pregnant (as ascertained by history) residents at least 1 year of age of the study area were included in the trial. The individuals who were too weak to get out of bed to receive the vaccine; pregnant women (identified through verbal screening); and those less than 1 year of age were excluded from the trial.

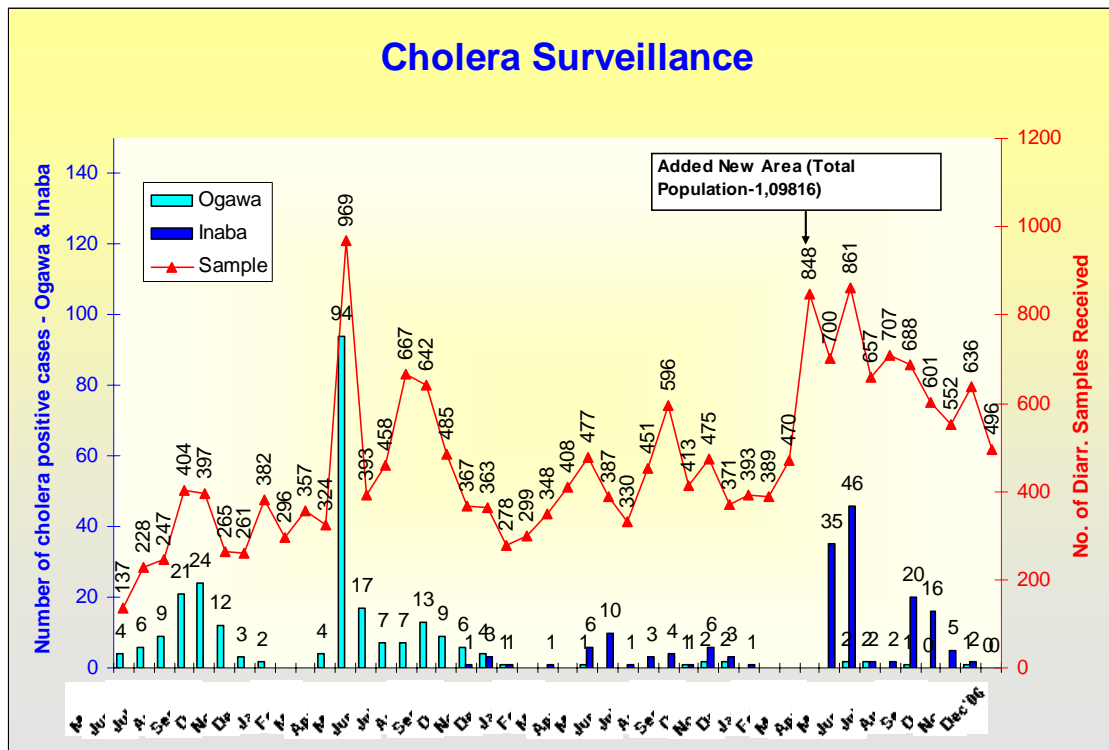
A total of 108,965 individuals were considered eligible for vaccination. The mass cholera vaccination campaign was held in the study site from July-September, 2007. During the vaccination, those who were considered not eligible were pregnant or lactating women, children < 1 years of age, or those travelling out of the study site. 69,308 individuals (64%) received single dose of vaccine but out of those single dose recipient, 67,061(61%) were fully immunised of two complete doses. Ward wise vaccine coverage given below:

#### **Cholera Vaccine Coverage of Phase- III Trial**

<i>Ward No</i>	<i>Eligible</i>	<i>No. who received at least 1st dose</i>	<i>No. who received both doses</i>
29	55,633	32,639 (59%)	31,347 (56%)
30	23,421	16217 (69%)	15917 (68%)
33	29,911	20452 (68%)	19797 (66%)
Total	108,965	69,308 (64%)	67,061 (61%)

Regarding the serious adverse events, no event was recorded as an attributable to vaccination. There was 11 cases of hospitalization during the first round, all are unrelated to vaccination, during the 2<sup>nd</sup> round there was 16 cases of hospitalization, not related to vaccination.

Post vaccination surveillance is going on. The diarrhoea surveillance was presented in graph.



### 14.3 Socio-behavioral and economic studies on typhoid fever and cholera

#### Objectives of the study:

1. To estimate the economic costs of cholera and typhoid fever in the community
2. To assess the cost effectiveness of vaccination (e.g., the cost per illness episode avoided, cost per life saved)
3. To evaluate the willingness to pay (private demand) for cholera and typhoid fever in the community

#### Ongoing activities:

We have completed a willingness to pay (WTP) approach to measuring the economic benefits of the vaccines for three reasons. First, WTP is the most comprehensive measure of the private benefits of disease prevention and encompasses at least two additional components of the economic benefits of disease prevention: (1) the avoided intangible costs of disease, like pain and suffering; and (2) the household's value of avoided risk. Second, the comprehensiveness of WTP is likely to be important for the diseases because of their reputation or susceptible populations. For instance, the dread associated with cholera and typhoid fever due to mortality would be reflected in larger WTP estimates. Third, since these vaccines have not been introduced in many countries, there is no evidence of the uptake and benefits that policymakers may expect by their adoption.

Private costs of illness (COI) measures the ex-post costs associated with an episode of illness, including both out-of-pocket expenditures and indirect costs (e.g., lost wages, costs of waiting time). Private cost of illness data is being collected using structured instruments

from subjects with laboratory confirmed cholera and typhoid fever. Respondents with cholera are being interviewed two times over a period of two weeks, while those with typhoid fever are being interviewed three times over a period of three months. The study covers duration of illness since the first symptom realized by patient including all sequence symptoms (sequelae) until cured. The costs include out-of-pocket expenditure such as cost of diagnosis, laboratory tests, medicines and indirect costs in terms of real income loss of patient or family members due to work absence (payment cut and/or cost of substitute labor). Institutional cost data was also collected and included recurrent and capital expenditures.

During cholera and typhoid fever (Vi) vaccination trials, two kinds of costs were collected. This included private cost of vaccination defined as expenditure incurred to receive a vaccine and vaccine delivery cost defined as the cost for providing and administering the vaccines. The private costs were collected from a sample of individuals who receive the vaccines using a structured survey instrument. Vaccine delivery cost including: personnel, equipment and supplies were calculated based on actual expenditure. Pre and post-cholera vaccine data collection has been collected. Data analysis is ongoing.

The socio-behavioural aspect of Cholera and Typhoid Fever Studies were also conducted in the same community. The objective of the study was to provide information for key policymakers regarding:

- 1) Local experiences and practices regarding cholera and typhoid fever demand for the new generation oral cholera vaccine and typhoid (Vi) vaccine.
- 2) Feasible strategies for the introducing the typhoid fever (Vi) and cholera vaccines into routine immunization programmes.
- 3) The study will also contribute to strategies for the implementation and removal of potential barriers to delivery and participation in the vaccination programme.
- 4) The data and related assessments of this research will be utilized to inform policymakers about population demand, perceived availability of local infrastructure for delivery, and enabling factors and barriers to programme delivery.

### **Ongoing activities**

The study included the qualitative rapid assessment and quantitative survey for the typhoid Vi vaccine and oral Cholera Vaccine. The quantitative survey was conducted into two parts one before the vaccine trial programme and then on the same population – after the vaccine trial programme. For both the vaccine trial programme there had been Refusals quantitative assessment. The Research study began in May 2004 with the qualitative rapid assessment on 40 respondents before the Typhoid Vi vaccine trial programme with semi-structured interviews with commune residents, commune leaders and healthcare providers. The interviews were recorded in the voice tape-recorder, and also recorded manually by the field survey specialists. This was followed by the pre Typhoid Vi vaccine household survey where 600 respondents were selected through random sampling and interviewed. The same sample respondents were interviewed again after the Typhoid Vi vaccine trial programme as Post Typhoid fever household Survey. 100 interviews were also conducted on the refusers, who did not participate in the Typhoid Vi vaccine trial programme.

The RAP Cholera was conducted from second week of May 2005 to third week of June 2005 in the similar manner that of Typhoid Vi vaccine trial. This was followed by pre –cholera vaccination Household Survey. Then data was collected from those respondents who did not participate in the Cholera vaccine trial programme.

#### **14.4 Multi Centre Severe Diarrhoeal Disease Burden and Etiology study – in collaboration with Centre for Vaccine Development, University of Maryland, USA**

##### **Objective:**

To estimate the population-based burden, microbiologic etiology and adverse clinical consequences of severe diarrhea among children 0-59 months of age in study sites in sub-Saharan Africa and South Asia to guide the development and implementation of vaccines and other interventions.

Slum population of wards 14, 31, 34, 58 and 59 has been identified for the study. Initial rapid survey was conducted in November 2006. This was followed by full census of the study area. A total of 1,16,000 populations in 46,000 families have been included. Data entry has been completed. Approximately 12,500 families with children less than 5 years of age have been identified and of this 1140 have been randomized for Health Care Utilization and Attitude Survey (HUAS). The survey has been initiated following intensive training of the field supervisors. This will be followed by a case control study to identify the causative organisms for diarrhoeal disease and also organisms found in the stool of healthy children. The study is in progress.

#### **14.5 Randomized Controlled Field Trial of a Probiotic (Yakult) to assess its role in the Prevention of Acute Diarrhoeal Diseases in Children- In collaboration with Yakult Central Institute for Microbiological Research, Tokyo, Japan**

##### **Objectives:**

###### *Primary objectives:*

To assess the impact of Probiotic (Yakult)

- a. in the prevention of acute Diarrhoeal diseases in children
- b. on nutrition and growth of the children

###### *Secondary Objectives:*

1. Reduction in duration, frequency of diarrhoea
2. Identification of pathogens causing diarrhoea
3. To examine composition of fecal Microflora

It is a double blind randomized controlled field trial involving 4000 children aged between 1 and 5 years in an urban slum of Kolkata, India. The study arm will receive Probiotic drink one bottle (65ml) daily (under supervision of a Health Worker) for 3 months and the control arm will receive a similar drink without the lactobacillus daily for 3 months. All the children will be followed up daily for 6 months for identification of acute diarrhoea cases. Stool samples will be collected from all diarrhoea cases and will be immediately transported to the laboratory of NICED for identification of established diarrhoeal pathogens. Measurements of

height, weight and mid-arm circumference will assess nutritional status of the children at the beginning of the study, at the end of 3 months and at the end of 6 months.

The study site has been selected as an impoverished urban area, encompassing Ward 66 of Kolkata Municipal Corporation in Eastern Kolkata . Households in the study area are densely grouped into premises. Each premise usually has a common latrine and water supply. The population is relatively stable with a household median number of years of residence of 35. Preparatory activities have been conducted in the study site. These include community mobilization; a baseline census of residents is being planned to be carried-out; setting-up of 5 health outposts within the wards (approximately one unit for every 10,000 population). In addition, community health workers (CHWs) who will visit each individual child in the study site once daily to administer the probiotic drink and also to find out about any diarrhoea episodes, hospitalization, or death using bound books pre-printed with the study children's names. The CHWs will encourage consultation for diarrhoea at any of the outposts and inform their field supervisor about hospitalizations and deaths.

### **Ongoing Activities:**

Rapid assessment of the population in the study area has been completed in early May 2007 for enumeration and identification of the households having children less than 5 years. About 5,161 families with 7,400 children within 0-5 year age group have been detected through rapid survey. Census survey is going on. The study is in progress.