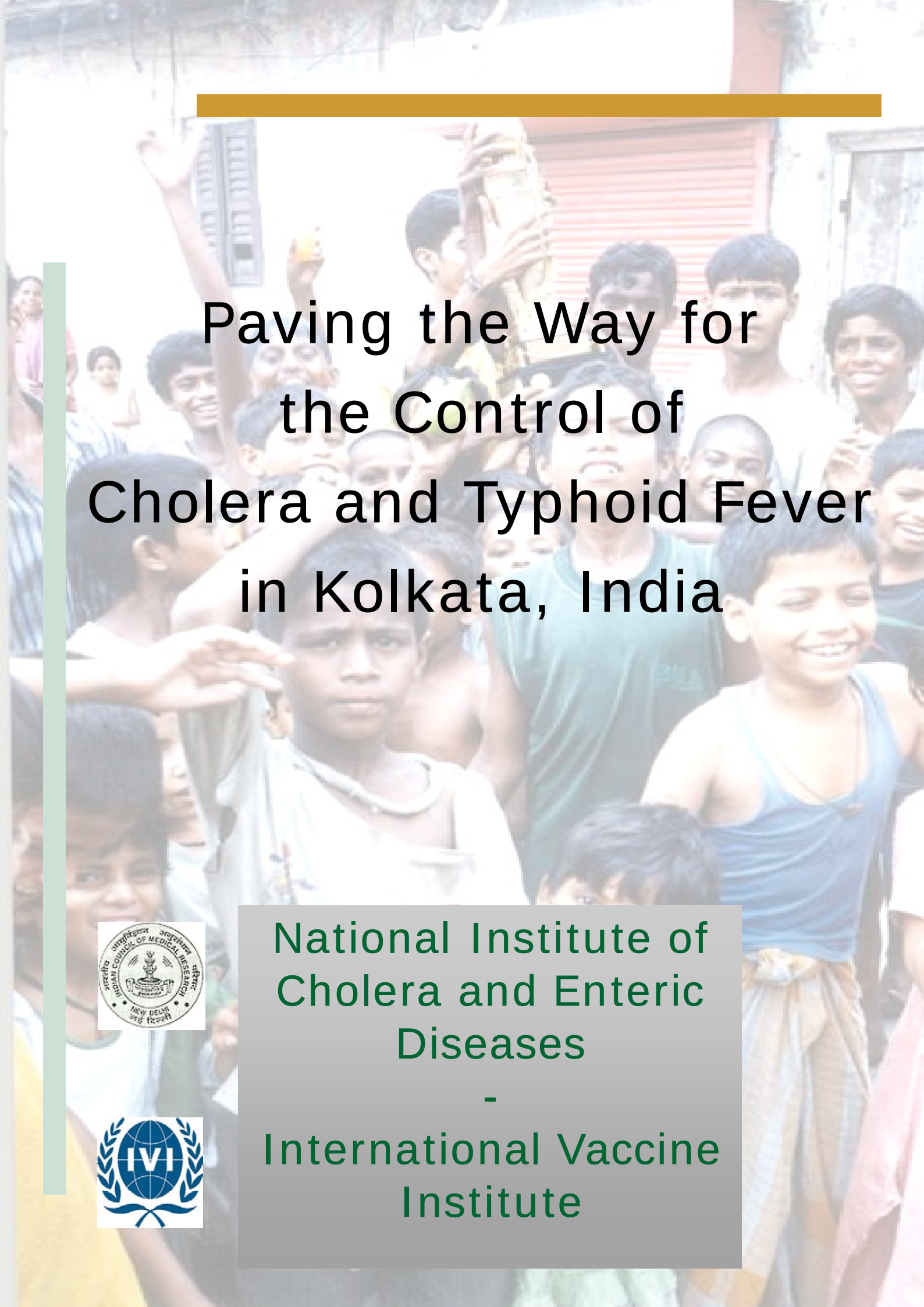
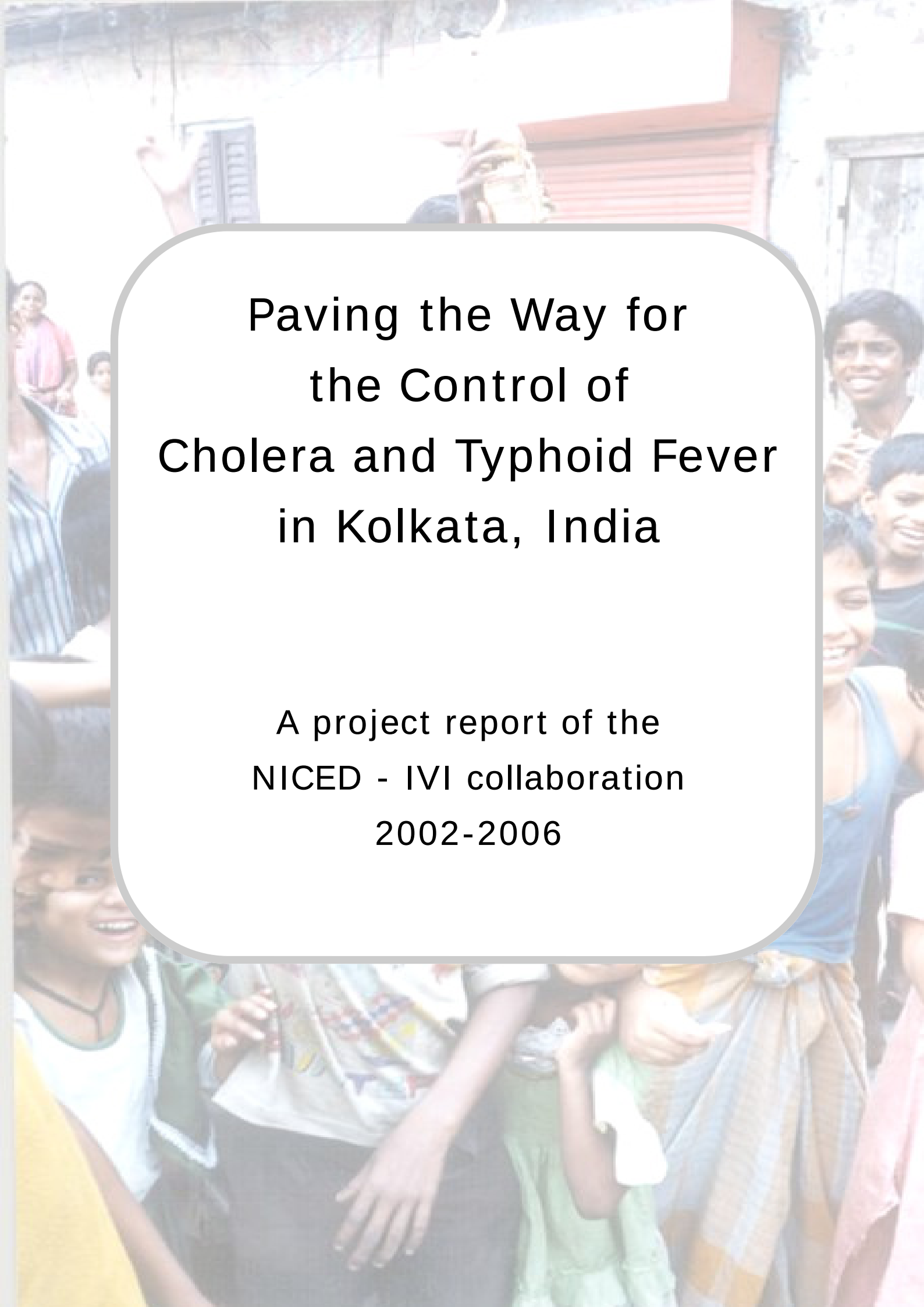


Paving the Way for the Control of Cholera and Typhoid Fever in Kolkata, India

National Institute of Cholera and Enteric Diseases

-

International Vaccine Institute



Paving the Way for the Control of Cholera and Typhoid Fever in Kolkata, India

A project report of the
NICED - IVI collaboration
2002-2006

Acknowledgements

Paving the Way for the Control of Cholera and Typhoid Fever in Kolkata, India:
A project report of the NICED - IVI collaboration, 2002-2006

We wish to thank the hundreds of project staff in Kolkata who have made the NICED - IVI collaborative project a success. We also wish to thank Ms. Eunyoung Kim and the administrative staff of IVI, who help the project run smoothly from behind the scenes.

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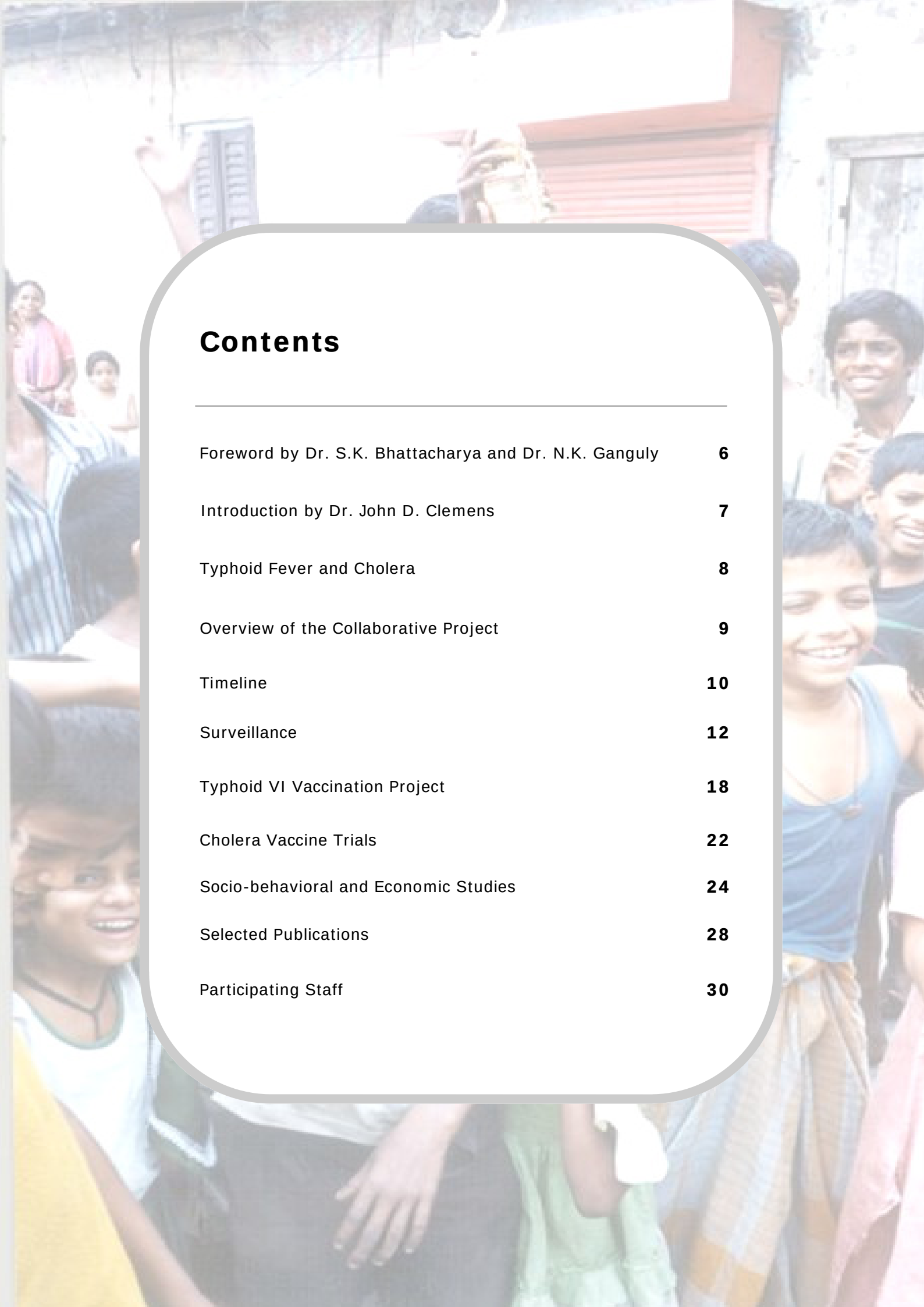


Contents

Dr. S.K. Bhattacharya

The collaborative research work between NICED, Kolkata and IVI, Seoul has been highly successful and has achieved its objectives and goals. This project is giving useful information for the prevention and control of Typhoid fever and Cholera. A number of research papers have been published already in international journals of repute. The dedication and cooperation of the scientists of NICED and IVI have been the key for the success of the project.

The guidance received from Prof. N.K. Ganguly, Director General, ICMR, New Delhi, and DR. John D. Clemens, Director General, International Vaccine Institute, Korea is gratefully acknowledged.

S. K. Bhattacharya

Director

National Institute of Cholera and Enteric Diseases

Kolkata

L to R: Dr. N.K. Ganguly, Dr. S.K. Bhattacharya, Dr. John Clemens

Dr. N.K. Ganguly

I am aware that collaborative project between NICED, Kolkata and IVI, Seoul is being implemented successfully. Myself and ICMR will extend all support and cooperation for this important project. I thank Dr. John D. Clemens, Director General, IVI, for his keen interest and personal involvement in this project.

I wish the project a grand success.

Prof. N.K. Ganguly

Director General

Indian Council of Medical Research

New Delhi

Dr. John Clemens

Dear Colleagues,

For the past several years, the International Vaccine Institute (IVI), located in Seoul, Korea, has had the privilege to coordinate the Diseases of the Most Impoverished (DOMI) Program, supported by the Bill and Melinda Gates Foundation. DOMI is working in 7 countries of Asia and 1 country of Africa to accelerate the introduction of new generation vaccines against cholera, shigellosis, and typhoid fever, through research and capacity-building.

Within India, The National Institute of Cholera and Enteric Diseases, one of the world's great centers of expertise in research on diarrheal diseases, is DOMI's principal partner organization. For the past four years, NICED and IVI scientists have worked together in poor areas of Kolkata on several challenging and important projects to accelerate the introduction of new generation typhoid and cholera vaccines into programs for the poor.

The results of the collaboration have been phenomenal. A field site for population-based studies among over 100,000 slum-dwellers has been created. The field site includes ongoing demographic surveillance as well as surveillance for febrile and diarrheal diseases among all members of the target population. The surveillance for febrile and diarrheal illnesses is being accomplished through a highly successful cooperative system entailing special study health outposts, referrals from private practitioners, and local hospitals. NICED's outstanding laboratories are evaluating clinical specimens with state of the art microbiological techniques. As well, a model computerized data entry and management system is maintaining databases for the surveillance in a real-time fashion. And the entire study area has been mapped with computerized geographical information system techniques that are providing important geographic insights into patterns of disease and medical service delivery.

This robust research infrastructure is supporting two ongoing cluster-randomized trials, one of Vi polysaccharide vaccine against typhoid, being conducted in ca. 38,000 participants, and the other of killed oral cholera vaccine, which succeeded in enrolling nearly 70,000 participants.

Supplementing this epidemiological and clinical trials work has been a program of socio-behavioral and economic studies to provide critical information to Indian vaccine policymakers on population demand for cholera and typhoid vaccines, costs of cholera and typhoid illnesses, and the cost-effectiveness of vaccinating against these two infections.

The legacy of this work will extend beyond the current trials of cholera and typhoid vaccines. Already, the study site is being considered for future studies of several other vaccines.

This successful collaborative program of work would not have been possible without the enduring support and mentorship of Dr. N. Ganguly, Director-General of the Indian Council of Medical Research, and the leadership of Dr. S.K. Battacharya, Director of NICED. We at the IVI have been honored to have had the opportunity to work with these two remarkable professionals.

Sincerely,

John Clemens, M.D.

Director-General

International Vaccine Institute

Seoul

Typhoid Fever and Cholera

Typhoid Fever & Cholera

Typhoid fever is a major cause of morbidity, especially in developing countries like India. It is estimated that 18.6 million cases occur in South Asia, a large portion of the global incidence of 21.6 million cases[1]. Typhoid fever is both a waterborne and food-borne gastrointestinal infection, with incidence approaching one percent of the population annually in some endemic areas. The disease primarily affects school-age children and is most prevalent in urban areas. A case typically lasts several weeks and can lead to serious complications such as gastrointestinal hemorrhage, perforation of the gut, and shock. Treatment has been complicated by the emergence of multi-drug resistant strains. Vaccination of high-risk populations is considered the most promising public health strategy for control of typhoid fever.

Cholera, a waterborne and highly infectious bacterium, is also a serious health problem worldwide, with a total of 131,943 cases and 2,272 deaths reported to the World Health Organization (WHO) in 2005[2]. The true figures are likely to be much higher due to underreporting and other limitations of surveillance systems. In addition to high morbidity and mortality, cholera outbreaks cause economic and social disruption. In spite of simple and accessible oral hydration treatment, small children and the elderly are particularly vulnerable to the extreme dehydration of severe cholera.
Establishment of adequate personal hygiene, food safety and sanitation are the long-term public health solutions for cholera prevention, but in the meantime, there is an urgent need for efficient vaccines to control this life-threatening disease.

... the GAP in access has WIDENED between WEALTHY and POORER countries...

Vaccines for enteric diseases are some of the most promising public health tools for children and adults in areas where these diseases are endemic. Despite major breakthroughs in the development of such vaccines, the gap in access has widened between wealthy and poorer countries. In addition, vaccine research and development agendas are tailored to the needs of wealthier countries. To help shift this balance, the Diseases of the Most Impoverished Program, funded by the Bill and Melinda Gates Foundation, was established to encourage vaccine development and promotion in developing countries.

[1]Crump et al – WHO bulletin, Global burden of Typhoid Fever

[2]Cholera 2005- WHO, Weekly epidemiological record

Below: Scenes from the study site

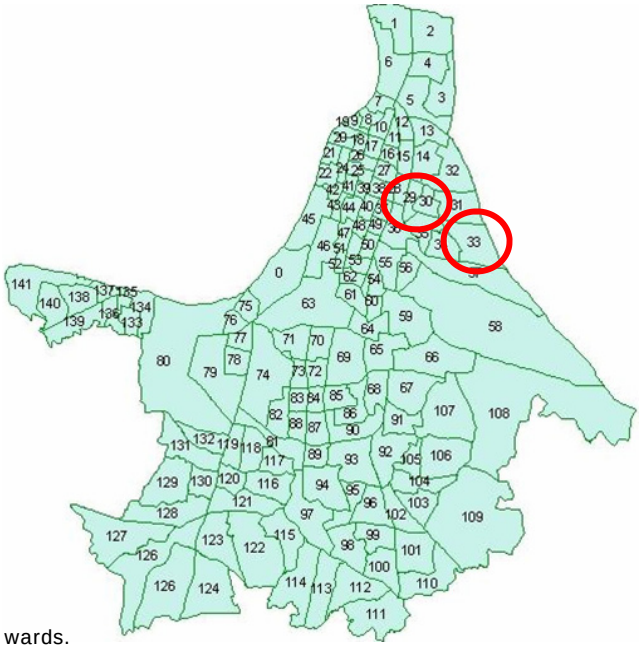
Overview of the Collaborative Project

As part of the Diseases of the Most Impoverished (DOMI) program, the International Vaccine Institute (IVI) has been working in different countries to undertake research in order to accelerate the development and introduction of vaccines against cholera, typhoid fever and shigellosis. Field sites have been developed to assess various aspects of these enteric diseases and determine the acceptability and effectiveness of vaccination in the population. India is endemic for both cholera and typhoid. A field site in the city of Kolkata in West Bengal was established to measure the burden of these diseases and to conduct an efficacy trial of a killed whole-cell oral cholera vaccine and an effectiveness trial of the typhoid Vi vaccine. The research activities are being conducted by the National Institute of Cholera and Enteric Diseases (NICED), an established centre of excellence in basic and applied research in the field of enteric and other infectious diseases.

The IVI-NICED collaboration commenced when both national and World Health Organization (WHO) clearances for surveillance of typhoid fever and cholera in eastern Kolkata, West Bengal, India were granted in August 2002. The over-all goal of the project is to generate accurate epidemiologic, socio-behavioural, and economics data on typhoid fever and cholera in impoverished slum populations of eastern Kolkata and to implement this data for field trials of vaccines against these two diseases. It was envisioned that data from this project may be used in the planning and implementation of programs to control typhoid fever and cholera in Kolkata, and that the data may be extrapolated to areas with similar demographic characteristics.

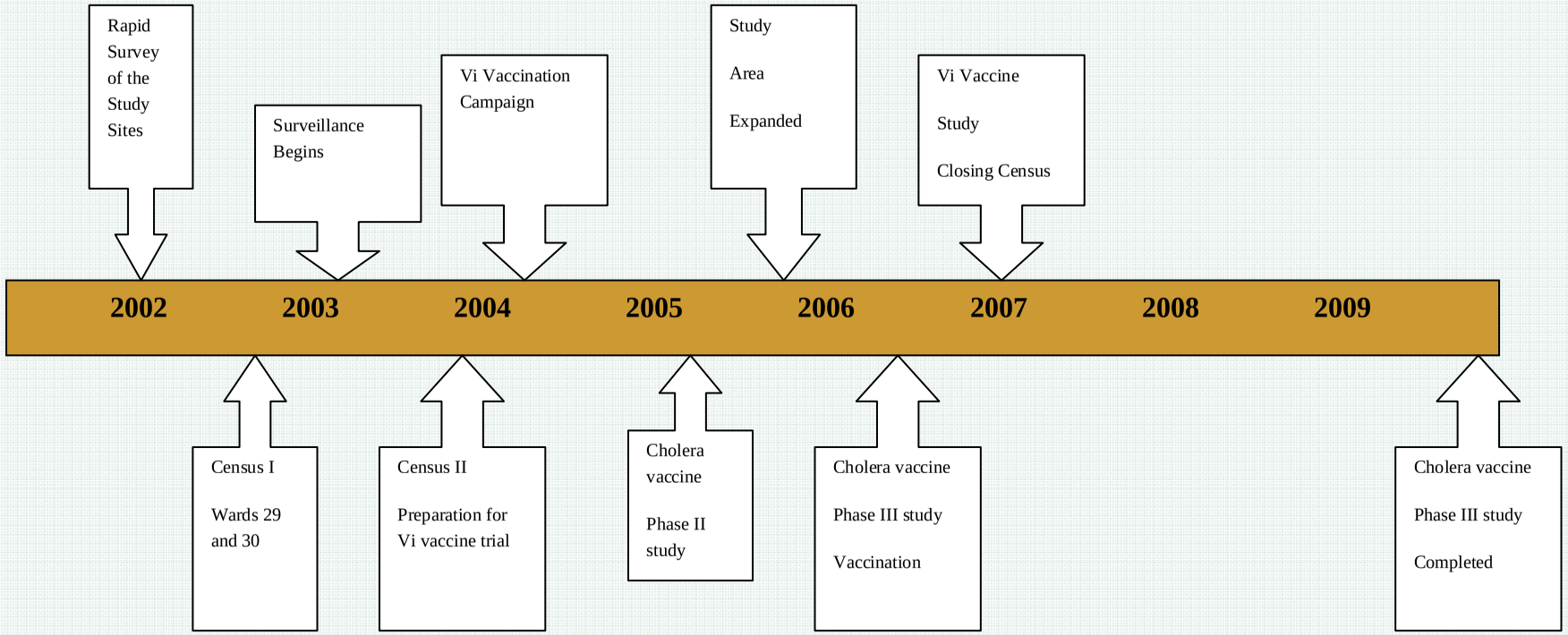
Project site and population

Kolkata is the third largest city in India. With its 13 million residents packed into 1,450 square kilometres, it is one of the world's most densely populated metropolitan areas. The study site, 0.7 square kilometres in size, was already in maps from 1856 as an impoverished residential area known as Narkeldanga. Today, the study site encompasses *bustees*, which are legally recognised and registered slums. In the study area, the streets are narrow with little space between houses, piped municipal water supply is intermittent, and several households share one or two latrines and water taps. Most sewage is collected in open gutters which overflow when it rains. Kolkata has three seasons, the cool dry months from November to February, the hot dry period from March to May, and the monsoon season from June to October.



Right: Map of Kolkata showing the different wards. Wards 29, 30 and 33 (in red circle) are the areas included in the collaborative project.

NICED – IVI Collaborative Project



Timeline

2002:

August to December - Rapid survey of the sites

2003:

January to March - A baseline census (Census I) of the selected sites, Wards 29 and 30 of the Kolkata Municipal Corporation

April - Surveillance for cholera and later typhoid fever piloted

May- Surveillance officially launched

2004:

February to March - A second census was performed prior to the typhoid Vi vaccine effectiveness trial. Clearances from the local community and different international, national, and local government units were obtained prior to the planned mass typhoid vaccination campaign. The cooperation of the local media, opinion leaders and the local police were tapped in order to mobilize the community.

November to December- The typhoid Vi vaccination campaign

2005:

August to November - Cholera vaccine phase II trial conducted

2006:

February - Study area expanded for phase III study of cholera vaccine added

April - New health out posts operational

July to September - Vaccination for the phase III trial cholera vaccine

2007:

January to February- Typhoid study closing census

Ongoing to 2009:

Cholera phase III study continues

Right: Children in Ward 29

Objectives

- To determine the incidence of cholera and typhoid fever in preparation for an effectiveness trial of the typhoid Vi vaccine and efficacy trial of the killed whole-cell oral cholera vaccine in a population with a high burden of these two diseases.
- To estimate the age- and sex-specific incidence of treated typhoid fever and cholera in impoverished slum dwellers in five police station areas of eastern Kolkata, West Bengal, India;
- To identify major risk factors for typhoid fever and cholera;
- To determine the antimicrobial susceptibility patterns of *Salmonella typhi* and *Vibrio cholerae*.
- To establish a surveillance system for treated typhoid fever and cholera in the study population in preparation for trials of typhoid fever and cholera vaccines.

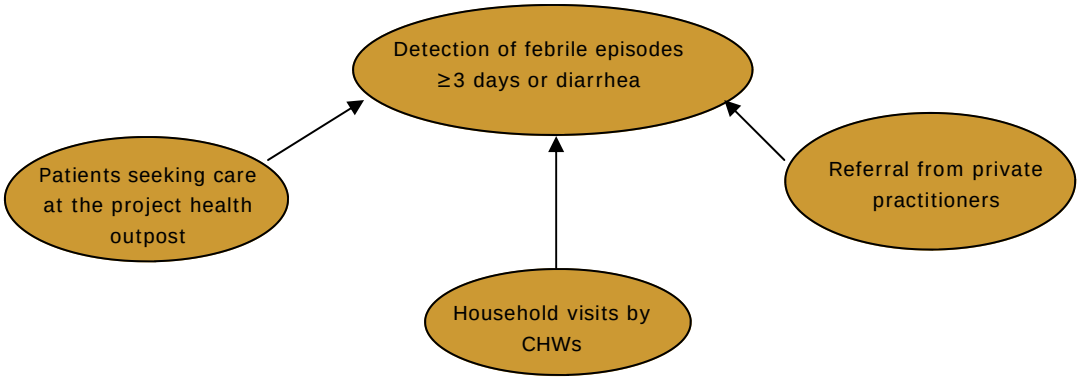
Rapid Assessment and Baseline Census

The census was preceded by an intensive campaign to publicize the study. Between January and March 2003, 57,099 residents belonging to 11,089 households were recruited in a house-to-house baseline census in order to collect relevant socio-economic, demographic, and healthcare utilization information. About 62% of the individuals enrolled live in ward 29, whereas 38% reside in ward 30. More than 99% of the residents recruited from ward 30 are Hindus whereas in ward 29, more than 67% of the residents are Muslims.

During the census, a unique number was assigned to each household and to each individual living in the household. Following the census, all eligible individuals were issued an ID card with a unique ID number. The *de jure* population were registered as the target population for this study. This population included the normal residents with no plans to move in the next 3 years who usually live in the household but who may be absent during the census.

57, 099

residents were recruited in a house-to-house census in early 2003



Above: Schematic Diagram of Surveillance System

Health care facilities / Field Activities

In order to achieve the objectives, a healthcare facility-based surveillance system was developed and implemented as a part of this collaboration. In this system, the Infectious Diseases Hospital in Beliaghata and the BC Roy Children's Hospital are referral facilities. In addition, five project medical outposts (one per approx. 12,000 population) were established to conduct passive surveillance of cases that come directly or are referred for diarrhoea or fever of 3 days or more. The 5 community health outposts are open from 8 am to 8 pm, while the hospital outposts are open 24 hours every day.

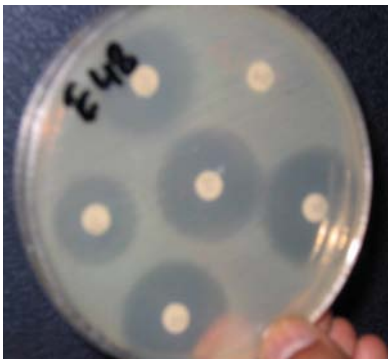
5 MEDICAL OUTPOSTS were created to conduct passive surveillance.

All registered medical practitioners in the study area are requested to refer all residents of the study area with diarrhoea or fever of 3 days or more to the 5 field outposts or to the Infectious Diseases Hospital or BC Roy Children's Hospital, for enrolment in the surveillance system and diagnostic tests. Residents of the community are encouraged to seek medical care in the 5 field outposts or in the two hospital outposts. Project medical teams based at the 2 hospital or the 5 project medical outposts enroll, interview, examine, and obtain blood for serology and culture or rectal swab for laboratory investigations from all consenting study participants presenting with fever or diarrhoea. Once specimens are obtained, the participants are then referred to the appropriate hospital for further evaluation and admission (if moderate to severe) or to private practitioners for further care (for mild cases). All laboratory results are provided to patients and their physicians, free of charge. The project provides Oral Rehydration Salts and funding of antibiotics and other medications.

Monthly visits by the community health workers (CHWs) to participating households are performed in order to encourage study participants to visit the health outpost facilities and to ascertain and follow-up hospitalisations of household members. One community health worker is responsible for approximately 5,000 study participants.

Above: (Left) Infectious Disease Hospital, Beliaghata (Middle) BC Roy Children's Hospital (Right) Two project medical outposts.

Surveillance



Above: (Left) Inoculated BACTEC blood culture bottles (Right) susceptibility testing of *Salmonella* by Kirby-Bauer disk diffusion technique

Laboratory

Blood cultures are obtained using BACTEC bottles (Becton Dickinson, Franklin Lakes, NJ, USA). Rectal swabs are obtained and placed in Cary-Blair transport medium prior to transport to the laboratory in NICED where they are processed.

For the detection of *Salmonellae*, blood is inoculated into BACTEC bottles and incubated at 37^{o}C for 7 days and visually examined for growth every day. Bottles are subcultured on MacConkey agar (Difco, USA) on days 1, 2, 4 and 7 or when turbidity is detected. Suspected non-lactose fermenting colonies are screened using KIA, SIM, Urea agar, and Citrate. Colonies giving biochemical reactions suggestive of Salmonellae are confirmed serologically by slide and tube agglutination test with specific O and H antisera (Becton Dickinson, Franklin Lakes, NJ, USA). *Salmonella* isolates are preserved in glycerol stock at –70^{o}C and verified at a reference laboratory (University of Oxford-Wellcome Trust Clinical Research Unit , Ho Chi Minh City, Vietnam). Recently, through a grant from the Japan International Cooperation Agency (JICA), an automated BD BACTEC blood culture system machine was made available and put to use starting in April 2005. Serologic testing of typhoid fever is also performed. Collected sera from suspected cases are separated by clot centrifugation and stored at 4^{o}C until testing. Widal, Typhidot and Tubex tests are performed based on the manufacturer's recommendation.

Between April 29, 2003 and December 8, 2006, a total of 16,468 blood samples have been collected and tested for *Salmonellae* at the NICED laboratories.

For the detection of cholera, the rectal swabs are placed in Cary-Blair transport medium, kept at room temperature and transported to NICED. From the Cary-Blair media, specimens are plated directly onto thiosulfate citrate bile salt sucrose (TCBS) agar (Eiken Chemical Company, Tokyo, Japan). The specimens are also incubated in alkaline peptone water (pH 8.6) for 6 to 8 hours at 37°C then plated onto TCBS. After overnight incubation at 37°C, suspected colonies on the TCBS plates are tested biochemically and confirmed by agglutination with polyvalent O1 and monovalent Ogawa and Inaba antisera (Difco Laboratories, USA). Non-agglutinating strains are tested with antiserum to *Vibrio cholerae* O139 strain.

A total of 20,166 rectal swabs have been collected and tested for cholera between April 21, 2003 and December 9, 2006.

To improve clinical care, malaria diagnosis was incorporated in the laboratory activities. A drop of blood is used to prepare a thin blood film on a single slide and stained with Leishman stain. At least 100 high power microscopic fields of the thin film are examined to identify Plasmodia. *Plasmodium* species are confirmed by a senior malariologist.

16,468 blood samples were tested for *Salmonellae* and 20,166 rectal swabs were tested for cholera.

Follow-up Activities

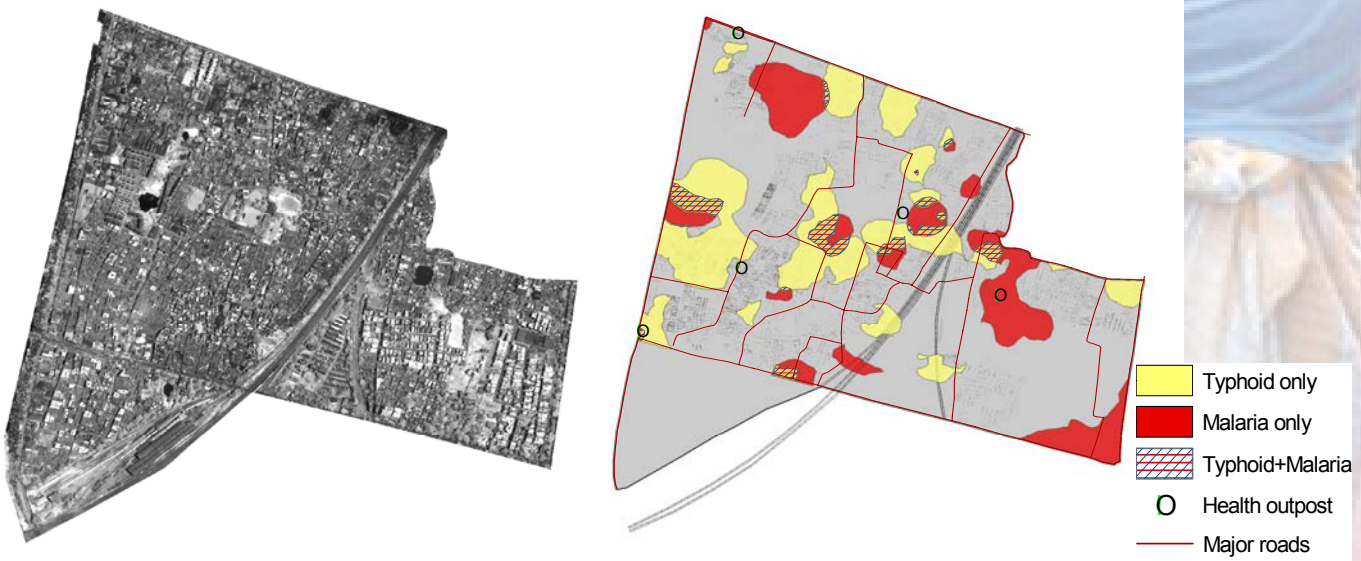
Results from the laboratory are transmitted to the field outposts to identify patients for follow-up. Follow-up visits are undertaken to allow confirmation of the identification of the patient, to assess clinical progress and typhoid fever-related disability. Culture proven typhoid fever cases are visited 7, 14, 30, and 90 days after onset of illness. Follow-up questionnaires are used. Patients testing positive for *V cholerae* 01 or O139 are visited at home by study personnel within 48 hours of the availability of the culture result. When a member of the study population dies, verbal autopsies are performed in order to ascertain the cause of death.

Data management

The census and clinical report forms are double-entered into custom-made data entry programs using FoxPro software (Microsoft, Seattle, Washington, USA). The individual identification number assigned to each subject on enrolment is used to link the surveillance to the census data and the GIS maps. Data management programs included error, range, and consistency check programs.

Geographic Information Systems

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. Spatial patterns of diseases (disease maps) and the relation of a disease with environmental factors (health facilities, high population density, social and economic conditions, etc.) are determined utilizing spatial analytical techniques. Several spatial variables (distance from the nearest health facilitates, rivers, putative sources of risk, herd immune areas, etc) can be computed using the GIS data, and can be used to determine potential confounders in the analysis of risk factors for diseases.



Above: (Left) Satellite picture of the study site wards 29 and 30, and (Right) a map with high disease incidence areas hilighted

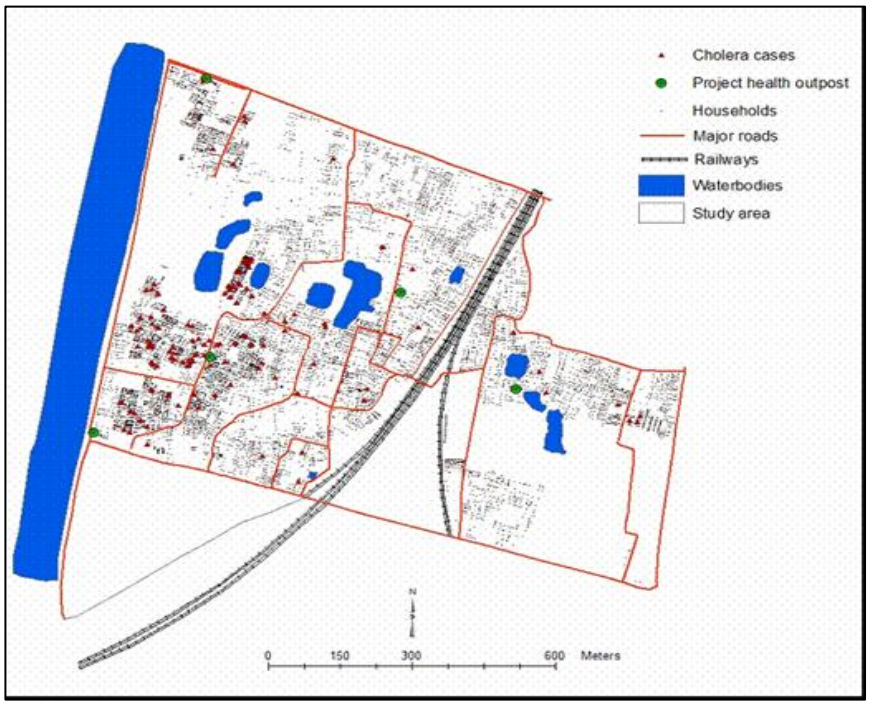
Key Findings

Healthcare Use

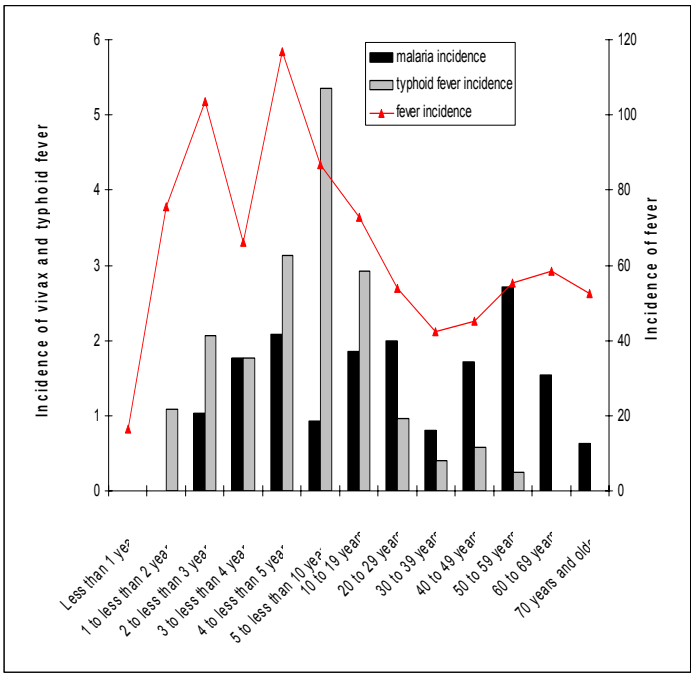
- As part of the diarrhea-surveillance project, structured interviews were held during the census and healthcare-use survey. Of 57, 099 subjects, 428 (0.7%) reported a diarrhea episode sometime during the four weeks preceding the interview.
- The strongest independent factors for reporting a history of diarrhea were having another household member with diarrhea and age less than 60 months.
- The first choice of treatment by the 428 subjects was self- or parent-treatment (35%) or consulting a private allopathic practitioner (35%). The other choices, from most common to least common, are as follows: pharmacy, hospital, homeopathic practitioner, aryurvedic practitioner and other traditional healers.

Burden of Cholera

- Of 62, 329 individuals under surveillance for one year, there were 3, 284 diarrhea episodes detected, of which 3,276 (99%) had stool samples collected. Culture-confirmed cholera was found in 126 (4%) of the samples collected. 19 (15%) were children under the age of 2, 29 (23%) had severe dehydration, and 48 (38%) were hospitalized.
- Risk factors for cholera were found to be: another household member with cholera, young age, and lower educational level.



Right: Geographic location of households of cholera cases in the study site from 1 May 2003 to 30 April 2004



Above: Incidence (per 1,000-population per year) of fever episodes, malaria, and typhoid fever cases by age group, January 1 to December 31, 2004

Malaria and Typhoid Fever Burden

- In a population of 60,452, 3,605 fever episodes were evaluated over a 12 month period. The blood film of 93 febrile patients contained *Plasmodium (90 P.vivax, 2 P.falciparum, 1 P.malariae)*. The blood cultures from 95 patients grew *Salmonella enterica* Serotype Typhi.
- Malaria patients were found to be significantly older (mean age 29.2 years) compared to patients with typhoid fever (14.9 years; $p<0.001$) but had similar clinical features on presentation (e.g. nausea, vomiting, abdominal pain).
- A household member with malaria was a highly significant risk factor for malaria.
- Three socio-economic risk factors; illiteracy, low household income, and living in house not built of bricks, were associated with an increased risk for malaria.
- Having a household member with typhoid fever and no soap for hand washing were highly significant risk factors for typhoid fever.

Vi Vaccination Project

Objectives

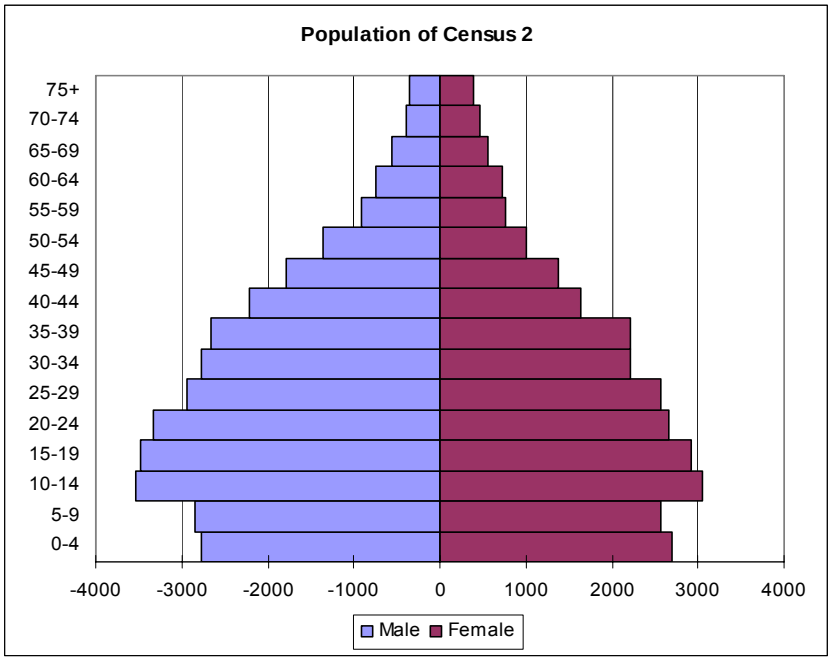
- To demonstrate the effectiveness of the parenteral typhoid Vi polysaccharide vaccine.
- To assess the potential use of typhoid vaccines in public health programs in disease endemic countries.

Initiation

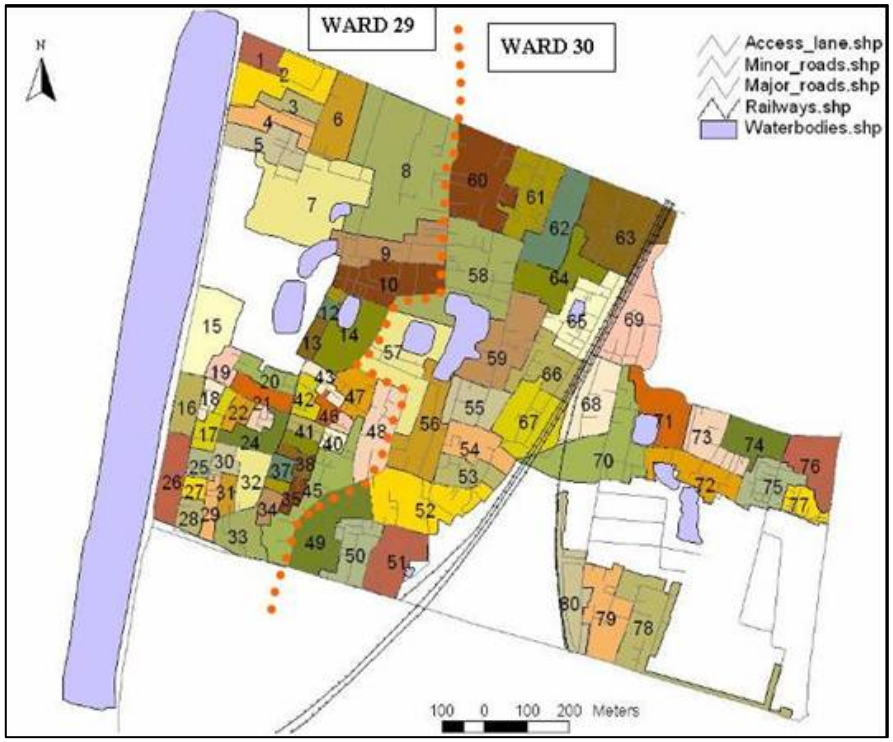
The national and IVI-IRB clearances for the typhoid Vi vaccination project were granted in early 2004. After a certification visit on July 2004 by IVI director Dr. John Clemens and DOMI microbiology consultant, Dr. John Wain, the site was prepared for the forthcoming mass vaccination. The local Kolkata Municipal Corporation clearance was obtained in addition to those of the police department and local opinion leaders. The local media was involved in mobilizing the community to participate in the mass immunization.

Pre–Vaccination Census

From February to March 2004, a census was performed prior to the planned vaccination in order to update the population data. During the second census, 60,615 individuals were included (increased from 57,099). There were 7.5% new entrants into the study.



Above: Age pyramid of study population during census 2, by sex



Above: GIS map showing geographic features of the study site that was used for cluster randomisation in the typhoid Vi vaccination demonstration project

The Vaccine

Older-generation, killed whole-cell vaccines were abandoned due to their reactogenicity. There are two new-generation typhoid vaccines that promise protection without significant side effects: the live, attenuated oral vaccine, Ty21a, and the injectable subunit vaccine, Vi polysaccharide (Vi PS). For use in developing countries, the Vi PS has several advantages: it is consistently effective in field trials in areas with high typhoid incidence, can be administered in one dose, and it has less strict cold-chain requirements. Finally, the production technology is simple enough to transfer to producers in typhoid-endemic regions, such as India.

Why use Vi PS in developing countries?

- Consistently effective in field trials in areas with high typhoid incidence
- One dose regimen
- Feasible cold chain requirements
- Production technology is simple enough to transfer to local producers

Typhoid Vi Mass Vaccination

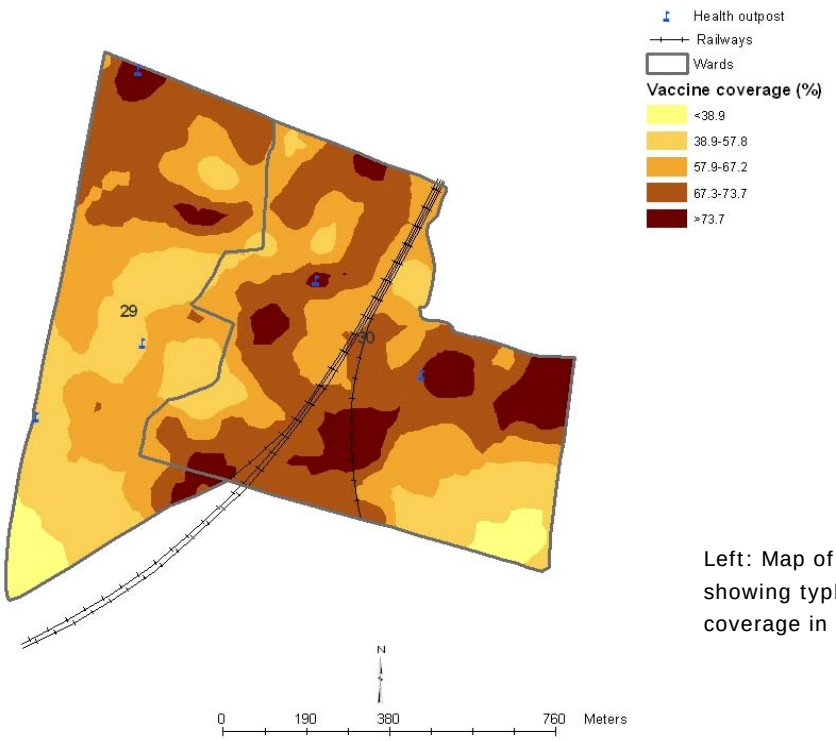
The design of the project was cluster randomised double-blinded controlled trial. The study site was divided into 80 clusters (geographically contiguous entities) and randomised to receive either the typhoid Vi polysaccharide vaccine or active control, inactivated Hepatitis A vaccine. The mass vaccination 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 69% of 54,674 were immunized.

Right: Community mobilization through press interviews

	No. of individuals eligible for vaccination	No. of individuals vaccinated (%)
Ward 29	33,633	21,845 (65)
Ward 30	21,041	15,841(75)
≤ 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)**

Left: Typhoid Vi Vaccine coverage of Wards 29 and 30 in Kolkata

Above: Scenes from the vaccination



Left: Map of study area showing typhoid Vi vaccine coverage in %

Post-vaccination Surveillance

To determine the protective effectiveness of the Vi vaccine against typhoid fever, the disease surveillance system to enroll febrile patients from the study site was established since April 28, 2003. In the typhoid fever surveillance area, there are 5 outposts providing primary health care and serving as a referral post for laboratory assessment of typhoid fever from the private sectors. Additionally, there are outposts in the two government hospitals in the area. The surveillance will continue for 2 years post-vaccination until January 2007.

Vi Vaccination Project

Cholera Vaccine Trials

Objective

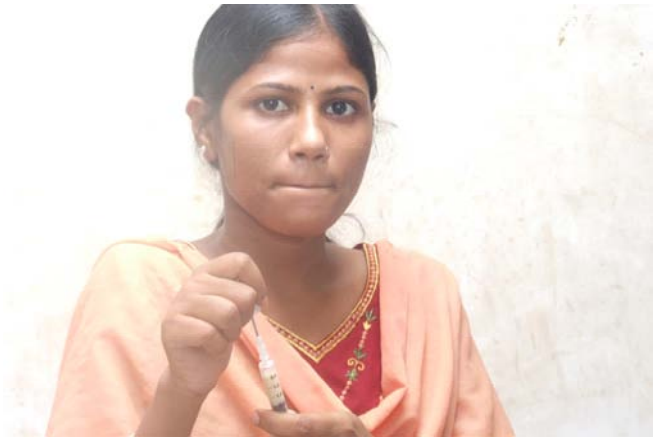
- To evaluate the reformulated killed oral bivalent cholera vaccine for licensure in India and in other countries.

The Vaccine

Starting in the mid-1980s, after a technology transfer from Prof Jan Holmgren, Vietnamese scientists at the National Institute of Hygiene and Epidemiology (NIHE) in Hanoi developed and produced an oral, killed cholera vaccine for the country's public health programs. The first generation monovalent (anti-O1) cholera vaccine was produced at $0.10 per dose. Subsequently, killed O139 whole cells were added to the vaccine in response to the emergence of epidemic cholera caused by this serogroup. A study found the bivalent vaccine to be safe and immunogenic in adults and children over 1 year of age.

Since licensure in Vietnam, over 9 million doses have been given safely. The producer, the Company for Vaccine and Biological Production No. 1 (VABIOTECH) in Hanoi, is working towards WHO Good Manufacturing Practices (GMP) certification. IVI has helped VABIOTECH reformulate the vaccine in order to comply with WHO requirements. This vaccine has undergone a phase II trial among Vietnamese adults where it was found to be both safe and immunogenic.

For the phase III study of the reformulated vaccine in Kolkata, IVI has facilitated an agreement for technology transfer between VABIOTECH and Shantha Biotechnics of India so that the oral killed bivalent vaccine will be available in India in the future.



Above: A vaccinator prepares to administer the vaccine.

Phase 2 study

A safety and immunogenicity trial of the killed whole-cell oral cholera vaccine in 100 adults and 100 children was performed in Kolkata.

The randomised double-blind placebo controlled study enrolled 100 adults aged 18-40 and 100 children aged 1 – 17 years. Subjects were given 2 oral doses of either cholera vaccine or *E. coli* K12 placebo. Active surveillance was performed for 3 days for adverse events, with passive surveillance for adverse events continuing until the end of participation, on day 28. Immunogenicity was determined by blood samples tested for vibriocidal antibodies both prior to vaccination and 28 days after the first dose.

Preliminary results show that the vaccine is safe among adults and children. There were no significant differences in adverse events reported among the placebo and vaccine groups. No serious adverse event was associated with the vaccine. The vaccine was found to be immunogenic among adults and children alike.

Cholera Vaccine Trials

Phase 3 study

A large randomised controlled trial of the killed whole-cell oral cholera vaccine is ongoing in wards 29, 30 and 33 in Kolkata. The study area was expanded to include all of ward 29 and ward 33, with a total population of 109, 816. A baseline census was performed in the new areas, and four new health outposts were established. Surveillance began in the new area in April of 2006.

Above: A child enters the vaccination center with his ID card in hand.

The study population covered 3950 premises which were randomised to receive either placebo or oral cholera vaccine. Prior to randomisation, the groups were stratified by ward and size of premise based on risk factors identified through the previous two years of surveillance in wards 29 and 30.

The first dose was given from July 27 to August 13, 2006. After an interval, the second dose was given between August 27 and September 10, 2006. Coverage estimates are that 69, 298 individuals participated in the first round and 67,061 (98%) of the first dose recipients took both doses. The estimated overall coverage was 62% of the geographic population.

The outpost-based surveillance of culture confirmed cholera cases will continue for 3 years post-vaccination.

Above: (Left) Vaccination supervisors receive announcements for the day. (Right) Vaccination supervisors, some of the hundreds of project staff who made the vaccination possible.

Future Plans

Completion of the 3 years follow-up will be made possible with the new Cholera Vaccine Initiative (CHOVI) grant from the Bill and Melinda Gates Foundation. In order to expand the use of the bivalent killed oral cholera vaccines in the international setting, further studies on alternative dosing regimens and the use of the vaccine in younger age groups are planned. At the same time, IVI will continue to work on the transfer of the cholera vaccine technology to Shantha Biotechnics.

Socio-behavioral and Economic Studies

Sociobehavioral and Economic Studies

Objectives

- To provide important information for: understanding health practices, demand for vaccine and perceived susceptibility to cholera and typhoid fever
- To develop economic data regarding: willingness to pay for vaccine, cost of illness, and vaccine delivery cost
- To assess the use of the new generation oral cholera vaccine and Vi vaccine for broader public health delivery
- To contribute to strategies for the implementation and removal of potential barriers to delivery and participation
- To inform policy makers about population demand, perceived availability of local infrastructure, as well as enabling factors or barriers to program delivery

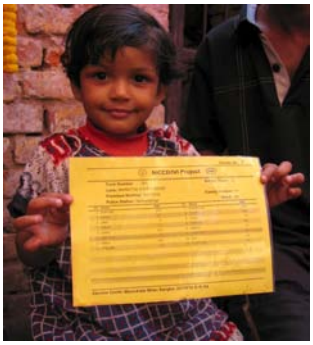
The socio-economic studies are integrated into the ongoing surveillance of cholera and typhoid fever, the typhoid Vi mass vaccination, and the cholera mass vaccination. The general study design of the socio-behavioral component includes two phases. The first phase is a qualitative rapid assessment. The second phase is a pre- and post-vaccination survey. The general study design of the economic component includes willingness to pay, cost of illness and vaccine delivery cost surveys as well as policy analysis. The research is a collaborative effort between the IVI Social Science Task Force for the DOMI Program and the Kolkata social science team.

Qualitative Rapid assessment

The rapid assessment involved short-term data collection, small samples and an interview guide on specific topics. The rapid assessment provided in-depth information on community attitudes and responses regarding typhoid fever, cholera, and vaccine use. This data facilitated the construction of pre and post -vaccination household surveys in relation to local socio-cultural terminology and practices related to typhoid fever, cholera and use of vaccines. These data will assist with the quantitative data analysis. In addition this information provides compelling and comprehensible real world information for discussions with policy makers to promote the introduction of cholera and typhoid (Vi) vaccines.

Right: Children in the study site

Socio-behavioral and Economic Studies



Pre- and post-vaccination survey

The pre- and post- vaccination surveys were conducted with approximately 600 to 800 individuals randomly selected from the census of the study area. The same individuals also receive a post-vaccination interview as a means of assessing pre-post changes, e.g., in preventive behaviours, knowledge and attitudes regarding vaccination and issues related to participation in the vaccination trial.

The quantitative pre-vaccination survey provides a generalizable database and builds on the data collected from the rapid assessment. The quantitative survey is based on the key policy related issues that are guiding this research.

The typhoid pre-vaccination survey began in June 2004 with the cholera pre-vaccination survey beginning in December 2005. These surveys were essential for planning the mode of information dissemination and the conception of what information about the vaccine community residents would want to know in order to decide whether to participate in the vaccination trials. The post- vaccination survey has been completed for typhoid fever, and the cholera post-vaccination survey is underway. These latter surveys provide critical information on experiences and attitudes regarding the vaccine and participation in the vaccination projects which is important for planning and implementing vaccination programs in the future.

Above: (Top) A child with her typhoid vaccination ID card (Bottom) A woman participates in the cholera study while her family waits for their turn.

600 - 800 people participated in the pre– and post– vaccination surveys for the typhoid vaccine

Cost of illness study

Private costs of illness (COI) studies measure the costs associated with an episode of illness. Private cost of illness data are collected using structured instruments from subjects with laboratory-confirmed cholera and typhoid fever identified through the surveillance project. Respondents with cholera are interviewed two times over a period of two weeks, while those with typhoid fever are interviewed three times over a period of three months. The study covers duration of illness since the first symptom realized by the patient and including all sequence symptoms (sequelae) until cured. The costs include out-of-pocket expenditures 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 are collected from the five project outposts set up for surveillance of cases and two referral hospitals in the study site. This includes current and capital expenditures.

All culture proven *V. cholerae* and *S. typhi* and *paratyphi* cases and 200 Widal positive typhoid cases are included in the study.

Illness-related

Out of Pocket Expenditures

cost of diagnosis

lab tests

medicines

real income loss

private expenditures for obtaining care

Willingness-to-pay for a vaccine study

A willingness to pay (WTP) approach is used to measure the economic benefits of the typhoid and cholera vaccines. The “private demand” data collection examines how much individuals and households would be willing to pay for cholera and typhoid fever vaccines. There are two principal reasons why policy analysts would want to know such WTP information. First, WTP information is a direct measure of the *ex-ante* economic benefits that individuals perceive from obtaining a vaccine. In this context, *ex-ante* economic benefits refer to the fact that the individual obtaining the vaccine does not know whether or not he would subsequently become infected with the disease. The *ex-ante* economic benefits thus derive from the fact that a vaccination provides an individual with a reduction in the risk of contracting the disease, and the private demand studies attempt to measure the benefits the individual perceives from this risk reduction. The WTP estimates can therefore be used as one measure of economic benefits in a cost-benefit analysis or cost effectiveness analysis of alternative vaccination strategies. Willingness to pay data was collected as pre-vaccination surveys for both the typhoid and cholera vaccine studies. Analysis of the data is underway.

Socio-behavioral and Economic Studies

Left: Children in ward 29

Vaccine delivery cost surveys

During typhoid fever (Vi) vaccine mass vaccination two kinds of costs were collected. These included private cost of vaccination defined as expenditures incurred to receive a vaccine and vaccine delivery cost defined as the cost for providing and administering the vaccines. The private cost data were collected from a sample of individuals who received the vaccines using a structured survey instrument. Vaccine delivery costs including personnel, equipment, and supplies, was calculated based on actual expenditure. Analysis of the data is underway. Similar data were collected during the cholera mass vaccination.

Policy Assessment

To inform policymakers about the need for and cost-effectiveness of immunization programs against cholera and typhoid fever, it is critical to present cohesively assembled data on disease burden, vaccine efficacy and effectiveness, and the economic costs and benefits of vaccination programs. A comprehensive analysis of all the data collected will be presented to policymakers to enable them to assess the desirability and feasibility of vaccination programs against the typhoid fever and cholera.

Analysis of economic data

There will be a series of analyses conducted using the willingness to pay data. First, there will be estimation of a demand relationship that shows projected vaccine uptake at different prices. Such a relationship is essential for forecasting market penetration at different prices, likely revenues that could be collected if different prices were charged, and estimating who would buy vaccines at different prices (i.e., demand of various socio-economic groups). Cost of illness analysis will involve estimation of the average cost of treating an episode of cholera or typhoid fever. Vaccine delivery cost analysis will involve estimating the cost per person fully immunized. The results of these analyses will be used to estimate the benefits and cost effectiveness of vaccination (e.g., the cost per illness episode avoided, cost per life saved) and the costs and cost-effectiveness of different vaccine delivery strategies.

Selected Publications

Surveillance

Sur D, Manna B, Deb AK, Deen JL, et al. Factors associated with reported diarrhoea episodes and treatment-seeking in an urban slum of Kolkata, India. *J. Health Popul Nutr* 2004; 22: 130-8.

Sur D, Deen JL, Manna B, Niyogi SK, Deb AK, Kanungo S, Sarkar BL, Kim DR, Danovaro-Holliday MC, Holliday K, Gupta VK, Ali M, von Seidlein L, Clemens JD, Bhattacharya SK. The burden of cholera in the slums of Kolkata, India: data from a prospective, community-based study. *Arch Dis Child* 2005/Nov; 90(11): 1175-81.

Sur D, von Seidlein L, Manna B, Dutta S, Deb AK, Sarkar BL, Kanungo S, Deen JL, Ali M, Kim DR, Gupta VK, Ochiai RL, Tsuzuki A, Acosta CJ, Clemens JD, Bhattacharya SK. The malaria and typhoid fever burden in the slums of Kolkata, India: data from a prospective community-based study. *Trans R Soc Trop Med Hyg* 2006/Aug; 100(8): 725-33.

Dutta S, Sur D, Manna B, et al. Rollback of *Salmonella enterica* serotype typhi resistance to chloramphenicol and other antimicrobials in Kolkata, India (letter). *Antimicrobial agents and chemotherapy* 2005; 49:1662-3.

Shanta Dutta, Dipika Sur, Byomkesh Manna, Bhaswati Sen, Alok Kumar Deb, Jacqueline L. Deen, John Wain, Lorenz Von Seidlein, Leon Ochiai, John D. Clemens and Sujit Kumar Bhattacharya. Evaluation of new-generation serologic tests for the diagnosis of typhoid fever: data from a community-based surveillance in Calcutta, India. *Diagn Microbiol Infect Dis* 2006/ Aug; [Epub ahead of print].

Typhoid Fever

Acosta CJ, Galindo CM, Ali M, Elyazeed RA, Ochiai RL, Danovaro-Holliday MC, Page AL, Thiem VD, Jin Y, Park JK, Lee H, Puri MK, Ivanoff B, Agtini MD, Soeharno R, Simanjuntak CH, Punjabi NH, Canh do G, Sur D, Nizami Q, Manna B, Bai-qing D, Anh DD, Honghui Y, Bhattacharya SK, Bhutta Z, Trach DD, Xu ZY, Pang T, Donner A, Clemens JD. A multi-country cluster randomized controlled effectiveness evaluation to accelerate the introduction of Vi polysaccharide typhoid vaccine in developing countries in Asia: rationale and design. *Trop Med Int Health* 2005/Dec; 10(12): 1219-28.

Dutta S, Sur D, Manna B, Bhattacharya SK, Deen JL, Clemens JD. Rollback of Salmonella enterica serotype Typhi resistance to chloramphenicol and other antimicrobials in Kolkata, India. *Antimicrob Agents Chemother* 2005/Apr; 49(4): 1662-3.

Ochiai RL, Wang XY, Seidlein L, Yang J, Bhutta ZA, Bhattacharya SK, Agtini M, Deen JL, Wain J, Kim DR, Ali M, Acosta CJ, Jodar L, Clemens JD. Salmonella paratyphi A rates in Asia. *Emerg Infect Dis* 2005/Nov; 11(11): 1764-6.

Basu, P. Vaccines on trial. *Nature* 2005/Jul 28; 436: 484.

Bahl R, Sinha A, Poulos C, Whittington D, Sazawal S, Kumar R, Mahalanabis D, Acosta CJ, Clemens JD, Bhan MK. Costs of illness due to typhoid fever in an Indian urban slum community: implications for vaccination policy. *J Health Popul Nutr* 2004/Sep; 22(3): 304-10.

Poulos C, Bahl R, Whittington D, Bhan MK, Clemens JD, Acosta CJ. A cost-benefit analysis of typhoid fever immunization programmes in an Indian urban slum community. *J Health Popul Nutr* 2004/Sep; 22(3): 311-21.

Socio-behavioral and Economic Components of Cholera and Typhoid Fever Studies

Deroeck D, Clemens JD, Nyamete A, Mahoney RT. Policymakers' views regarding the introduction of new-generation vaccines against typhoid fever, shigellosis and cholera in Asia. *Vaccine* 2005/Apr; 23(21): 2762-74.

Acosta CJ, Galindo CM, Deen JL, Ochiai RL, Lee HJ, von Seidlein L, Carbis R, Clemens JD. Vaccines against cholera, typhoid fever and shigellosis for developing countries. *Expert Opin Biol Ther* 2004/Dec; 4(12): 1939-51.

Deen JL, von Seidlein L, Clemens JD. Multidisciplinary studies of disease burden in the Diseases of the Most Impoverished Programme. *J Health Popul Nutr* 2004/Sep; 22(3): 232-9.

Kaljee LM, Pack R, Pach A, Nyamete A, Stanton BF. Sociobehavioural research methods for the introduction of vaccines in the Diseases of the Most Impoverished Programme. *J Health Popul Nutr* 2004/Sep; 22(3): 293-303.

Above: Ward 29 at dusk

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Dr. Byomkesh Manna, Assistant Director

Dr. Swapan Kumar Niyogi, Deputy Director (Senior Grade)

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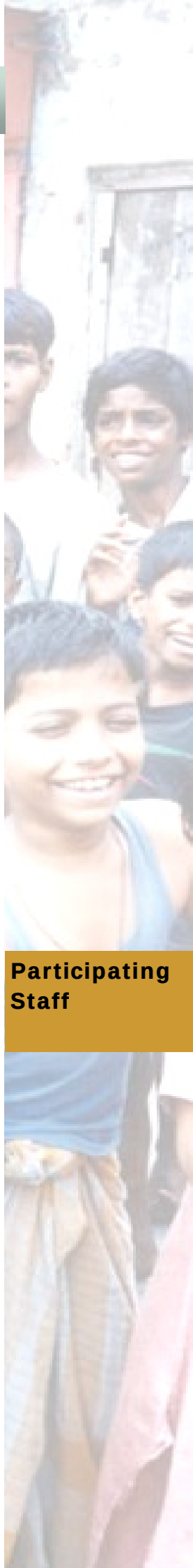

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