5th Meeting of the Initiative against Diarrheal & Enteric diseases in Asia –IDEA

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Country Situation Update: Bangladesh
Hanoi, Vietnam
7th March 2017

Cholera Epidemiology Update

Situation

According to the UN data 2008 entire population of Bangladesh is considered at risk of cholera, on advice from the country's cholera experts, because of frequent and widespread flooding

Cholera is endemic in Bangladesh, and outbreaks occur in a regular seasonal pattern

Case fatality without treatment 25-50%

Case fatality with treatment 1%

Cholera in Bangladesh and the Need for Prevention

Each year icddr,b admits around 120,000 diarrheal patients, of whom approximately 22,000 suffer from cholera- both children and adults

According to the IEDCR, DGHS of GoB estimates, there are 450,000 hospitalized cholera cases in the country. At least 4500 deaths occur annually

The 2% icddr,b hospital surveillance data shows that around 25% cholera patients are admitted annually which can go up to 40%

✓Cholera rates ~2.6/1000/year

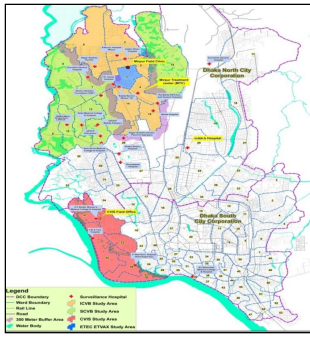
Cholera is a vaccine preventable disease

The added advantage of herd protection can be expected to decrease cases significantly globally- over 90% protection can be achieved

Oral cholera vaccine

icddr,b has been involved with cholera vaccine work since its inception

From 2011 onwards we have conducted studies in icddr,b with the affordable OCVs



Over 900,000 doses of OCV has been used in different studies in both urban and rural settings

Our studies have involved close collaboration with the Government of Bangladesh and the national immunization system, EPI

International partners have also played key roles

The target has been to vaccinate children and adults focusing on both men and women in the community and institution based programs

Introduction of Cholera Vaccine in Bangladesh

Major Objectives:

- To conduct and evaluate the feasibility and effectiveness of a mass cholera vaccination program and also behavior changes in decreasing the high incidence of diarrhea and cholera in a similar population in high incidence urban area.
- To establish a demographic surveillance system to monitor severe diarrheal illness attributable to cholera in target population.

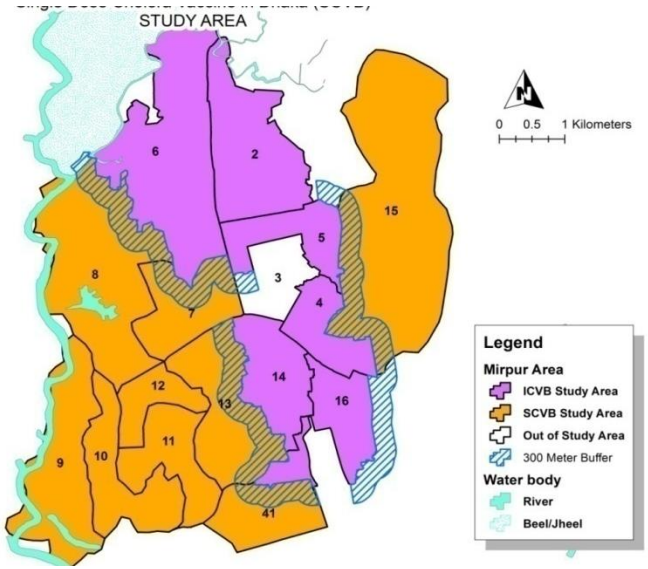
Study design:
Cluster randomized controlled trial

Sample size:
240,000 participants, aged 1 year and above excluding <1yr old children and pregnant women.

Study period: 2010- 2015

Study area: Mirpur, Dhaka (Ward: 2, 4, 5, 6, 14 & 16)

Vaccination Status: Dose1:141,878 & **Dose2:**123,694



Result: >37% of children and adults showed overall protective efficacy after 2 dose of cholera vaccine
>53% efficacy for severe cholera requiring hospitalization. (*The Lancet*; 2015)

Rural Oral Cholera Vaccine, Bangladesh

Study Title:

Impact evaluation of oral cholera vaccination in a rural setting using the national immunization system of Bangladesh.

Objectives:

Carry out cholera vaccination in one rural union in Keraniganj.

Evaluate the impact of vaccination in reducing cholera in the study area

Study design: Quasi experimental study to assess the feasibility of intervention with oral cholera vaccine and impact of the vaccine between intervention and non-intervention arm in a rural setting.

Sample size: 30,000 in each arm aging from 1 year and above (excluding <1 yr and pregnant women)

Study Site: Ruhitpur and Basta union in Keraniganj

Vaccination Status:

Census Population	Dose 1		Dose 2	
	Received	%	Received	%
34,263	29,134	85	26,740	78

Study Period: 2012 -2014

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Temperature stability of oral cholera vaccine Shanchol: Safety and immunogenicity profile in Bangladeshi participants

Sample size: Four groups (145 participants/group) of healthy adult participants aged 18-45 years (Group A; 2-8°C) or at elevated temperatures (Group B, 25°C; Group C, 37°C; Group D, 42°C)

Output: OCV is stable at elevated temperature.

Outcome: The vaccine at higher temperature does not alter vibriocidal antibody responses

Impact: Vaccination costs and decreased logistical challenges to vaccine delivery can be expected

ELSEVIER

Vaccine
Volume 34, Issue 13, 18 March 2016, Pages 1551–1558

The oral cholera vaccine Shanchol™ when stored at elevated temperatures maintains the safety and immunogenicity profile in Bangladeshi participants

Single Dose Cholera Vaccination, Bangladesh

Objective:

To evaluate protective efficacy of a single dose regimen of oral cholera vaccine Shanchol against culture-proven *V. cholerae* O1 diarrhea detected in all treatment settings serving the catchment population from 7 days to 6 months, from 7 days to 12 months and from 7 days to 24 months after dosing and also safety of the vaccine assessing 28 days after dosing

Study Design:

two-arm individually randomized double-blind placebo-controlled trial (Single Dose Cholera Vaccine Study, Bangladesh-SCVB)

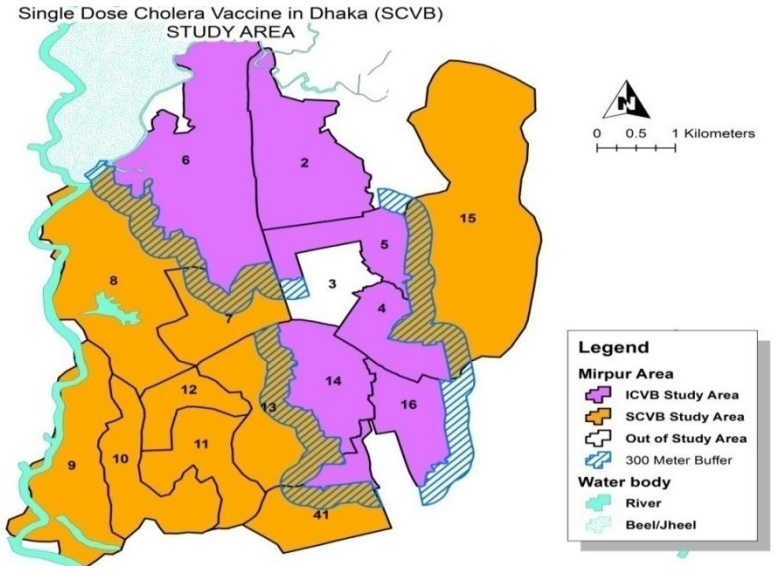
Study participants

204,438 (aging from 1 year and above excluding <1 yrs of children and pregnant women)

Study site- Mirpur (7- 13, 15 & 41)

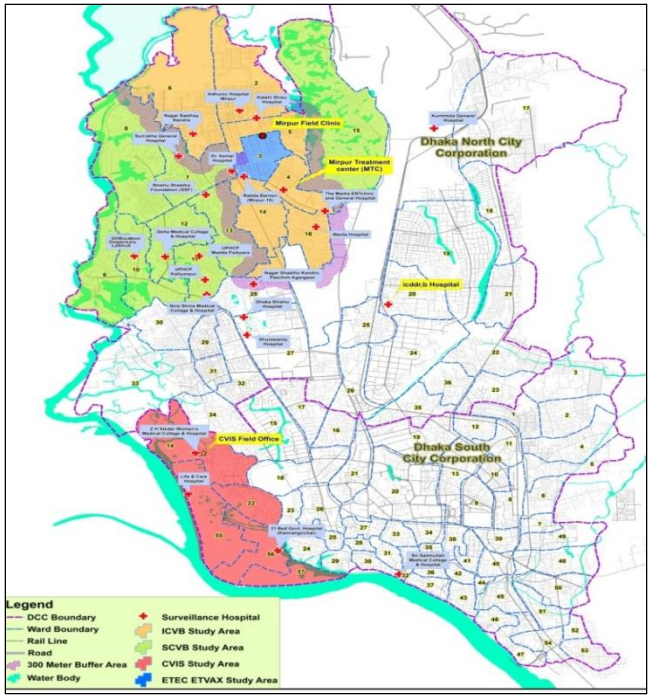
Vaccinated population: 205,661

Study Period: 2014 -2016



Result: Protective efficacy (Total) of single dose OCV for 6 months is 40% for all participants. Highest PE was observed among 5-<15 years (63%).Lowest PE efficacy was calculated among Less than 5 years (16%). (NEJM, 2016)

Cholera Vaccine Investment Strategy



Objective:

To evaluate the feasibility, efficiency and impact of a two-dose regimen of the oral cholera vaccine (OCV) **Shanchol™ delivered to children aged 1-14 years residing in urban slums**, leveraging a targeted mass immunization delivery platform used for MR vaccines in Bangladesh.

Design: Observational design based on the contrast of persons who do and do not get vaccinated according to public health practice.

Study participants: Children aged 1- 14 years old

Study Site: Kamrangirchar (Ward no 55, 56 and 57)
Hazaribagh (Ward no 22)
Part of Rayerbazar (Ward no 14)

*****Using a approach deployed by the Government of Bangladesh in countrywide campaign of Measles Rubella (MR) vaccination.

Vaccination Period and Population		
Dose	Time	Vac. Pop
1st	23 Jan- 04 Feb, 2016	75,170
2nd	06 Feb- 18 Feb, 2016	66,487

Duration of OCV protection from different studies

- 2 doses of OCV has been considered to give protection 53 % for 2 years (Qadri et el. 2015, lancet)

- Single dose Protective efficacy of single dose OCV for 6 months is 40% for all participants. 63% PE was observed 5-<15 years . (Qadri et el. 2016, NEJM)

- 2 doses of OCV has been considered to give protection 65% for 5 yrs (Sur et el. 2013, lancet)
- Indirect herd protection raises the efficacy of OCVs to much higher

Mapping country capacities

Local production of OCV

Transfer of Technology to Bangladesh

The OCV stockpile was established by WHO in 2013 with 2-3 million doses available per year

Based on increasing demand of OCV stockpile~it is extrapolated that about 40 million doses will be needed for control of epidemic and endemic cholera

Two oral cholera vaccine technology has been transferred by the:

1. International Vaccine Institute
2. Wellcome Trust Hilleman Laboratories

to

Incepta Vaccine Ltd in Bangladesh

Cholvax produced in Bangladesh is similar to Shanchol

V. cholerae O1 Inaba El Tor strain Phil 6973 formalin killed	600 ELISA units (EU) of Lipopolysaccharide (LPS)
V. cholerae O1 Ogawa classical strain Cairo 50 heat killed	300 EU of LPS
V. cholerae O1 Ogawa classical strain Cairo 50 formalin killed	300 EU of LPS
V. cholerae O1 Inaba classical strain Cairo 48 heat killed	300 EU of LPS
V. cholerae O139 strain 4260B formalin killed	600 EU of LPS

Cholvax Study in Bangladesh

Study Title: A randomized observer-blinded controlled non-inferiority trial to evaluate the safety and immunogenicity of locally manufactured inactivated bivalent whole cell-oral cholera vaccine (WC-OCV) 'Cholvax' in healthy Bangladeshi adults and children

icddr,b : Fahima Chowdhury, John Clemens *et al*

IVI : Laura Digilio Jean-Louis Excler, Samuel Teshome et al

Objective: To evaluate and compare the safety and immunogenicity of locally produced Cholvax with Shanchol

- To evaluate the immunogenicity and safety of Cholvax in healthy adults and children in Bangladesh.

Study design: Randomized, observer blinded controlled non-inferiority trial

Study period: 2016-2017

Study participants: 2052

Cohort 1 (18-45 y) = 868

Cohort 2 (6-17 y) = 736

Cohort 3 (1-5y) =448

Study area: Mirpur, Dhaka

Study initiated in May 2016 and follow up to day 42 completed in November 2016; analysis is ongoing at present

Cholvax has been found to be safe with no vaccine related adverse events

Entire study period (day 0 to day 42)		Test Group		Comparator Group	
		Number of AEs	Number of Participants (%)	Number of AEs	Number of Participants (%)
Solicited AE	(day 0 to day 7)				
By age cohort	Adults (n=434)	39	31 (7.14%)	42	29 (6.68%)
	Adolescent children (n=373)	12	9 (2.41%)	10	9 (2.41%)
	Younger children (n=219)	46	35 (15.98%)	42	31 (14.16%)
Unsolicited AE					
By age cohort	Adults (n=434)	3	3 (0.69%)	2	2 (0.46%)
	Adolescent children (n=373)	7	7 (1.88%)	6	6 (1.61%)
	Younger children (n=219)	5	5 (2.28%)	3	3 (1.37%)
SAE		**0**	**0 (0.00%)**	**0**	**0 (0.00%)**

Serum vibriocidal antibody titers to *V. cholerae* O1 Inaba and Ogawa among Cholvax and Shanchol vaccine recipients Primary objective (PP Analysis)

All ages	Post first vaccine dose (Seroconversion rate)			Post second vaccine dose (Seroconversion rate)		
	Test Group (N=1007)	Comparator Group (N=1002)	Test - Comparator† (Lower limit of one-tailed 97.5% CI)	Test Group (N=1007)	Comparator Group (N=1002)	Test – Comparator† (Lower limit of one-tailed 97.5% CI)
Inaba	83.12	83.33	-0.22 (-3.49)	82.92	83.93	-0.87 (-4.11)
Ogawa	79.94	78.04	1.60 (-1.96)	80.64	77.35	3.13 (-0.38)

† Adjusted for age strata in the model. The Test vaccine is non-inferior to the Comparator vaccine if the lower limit of the seroconversion rate difference is equal to or greater than pre-defined non-inferior margin of -10%

The single strain OCV- Hillchol

Hillchol Vaccine	Composition	LPS Amount
HL-OCV- A **HL-OCV- B**	*V. cholerae* O1 recombinant Hikojima strain - MS1568 (Formaldehyde-inactivated)	600/µg/ml 900 µg/ml of total O1 LPS content

Wellcome Trust Hilleman Laboratories
Goteborg University, Sweden

Technology transfer to Bangladesh

Hillchol Study

Study Title: A phase I/II dose-escalation study to evaluate safety, tolerability and immunogenicity of '2-dose primary series' single strain (Hikojima serotype) inactivated Oral Cholera Vaccine formulations (two formulations based on total O1 LPS content), in sequential age descending population of healthy adults and children

Objective: The objective of this study is to determine most safe and immunogenic formulation for new oral cholera vaccine HL-OCV, and comparing with licensed OCV Shanchol

Study design: Randomized, Open labeled study

Study period: 2016-2017

Study participants: 840

Study area: Mirpur, Dhaka;

Three cohorts:

Adults (n=360),

Children and Adolescent (n=240)

Younger children (n=240)

We have completed the 'Adult Cohort' between 17th July to 28th August 2016;
Adolescent Cohort' has been completed 19th Feb 2017;
Child cohort to follow soon

OCV in Bangladesh plans from 2017 onwards

Inclusion in the Project Implementation Plan (PIP) and Operational Plan (OP) of Bangladesh: 2017-2021

Oral Cholera Vaccine (OCV) has been included for priority population in OP of Communicable Disease Control (CDC), DGHS under Diarrhoea Prevention and Control Program. It will be executed after approval from ECNEC

Advocacy meeting: (5th January 2017)

Meeting was chaired by of Hon'ble State Minister, MoH&FW. Hon'ble Secretary, DG- DGHS and other representative from different stakeholders were present in the meeting

All opined to include OCV as a part of integrated strategy for control and prevention of cholera in high risk population in Bangladesh

- **V**accine will be implemented through GoB Operational Plan
- Funding sources being identified

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Challenges for the use of OCV and way forward

Strengthen ***countrywide surveillance*** to identify high risk areas for cholera

Licensure of Cholvax in Bangladesh

Marketing by local companies

Secure ***funds*** for OCV vaccination in Bangladesh

Cholvax needs to be **WHO prequalified** for global use and for entry into the OCV stockpile

Plan ***OCV introduction*** in Bangladesh- start as demonstration projects in high risk areas such as Dhaka and Chittagong

Acknowledgement

BILL & MELINDA GATES foundation

Government of Bangladesh

FONDATION MÉRIEUX

Ministry of Health and family Welfare

IEDCR

- **Non-government organizations- BPA**
- **International Partners-**

International Vaccine Institute

Gavi, the Vaccine Alliance

World Health Organization

UNICEF

Cholera vaccination Team

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