

# ***Cholera vaccines: an update***

**Dipika Sur MD**

Consultant

Translational Health Science and  
Technology Institute, INDIA

Former Scientist 'G' ICMR

# ***Cholera is caused by poverty, lack of sanitation and clean water***

- Cholera as an issue of equity
  - Lack of clean water
  - Lack of sanitation
  - Lack of access to treatment
- High risk groups include:
  - Young children
  - Pregnant women
- With an estimated 100,000-120,000 deaths and a morbidity of 3.8-4.4 million annual cases, cholera is endemic in more than 50 countries globally

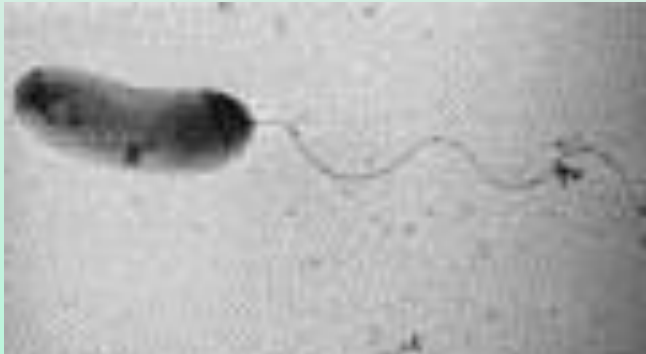


# *The disease*

- Cholera-ancient and dreadful disease characterized by uncontrolled purging of watery stools (colorless stool with flecks of mucus (“rice water”), fishy odor) leading to life-threatening dehydration, hypovolemic shock, acidosis, and – if left untreated – death. Otherwise healthy people can be dead in a few hours
- Is endemic but is also capable of causing severe epidemics and pandemics
- High household transmission
- Massive fluid replacement may be needed for treatment



# Organism



- Etiology:
  - *Vibrio cholerae* O1
  - *Vibrio cholerae* O139
- Enterotoxin consists of:
  - five binding (B) subunits
  - one active (A) subunit
- Humans only documented host but it is free-living in aquatic environment

# *Vibrio cholerae*

## CT Producing

Serogroups O1 and O139

Biotypes

Serotypes

Classical  
El Tor

Ogawa  
Inaba

Epidemic

## Non-CT Producing

Serogroups O2~ O206

(Non-O1, non-O139)

Non-epidemic

# ***Cholera Vaccines***

## ***Old parenteral cholera vaccine (Why discontinued?)***

- Killed whole cell vaccine – parenteral (2 doses, 2 wks apart)
- Efficacy of 30 to 50% for 3-6 months
- Did not prevent introduction of cholera into a country or interrupt transmission
- No value in controlling epidemics
- Could not prevent development of carrier state
- Undesirable side effects
- Gives false sense of security to recipients & health administrators
- General use was stopped in the 1970's

# ***New-generation oral cholera vaccines***



# LICENSED VACCINES FOR CHOLERA

Supplier	Crucell / SBL Vaccine	VABIOTECH (VietNam)	Crucell	Shantha Biotech
Vaccine	Dukoral	ORC-Vax	Orochol / Mutachol	Shanchol
Strain / Antigen	Killed <i>Vibrio cholerae</i> O1 strains (serotypes: Inaba & Ogawa; biotypes: El Tor & classical)+ rCTB	<i>Vibrio cholerae</i> O1 & O139 without CTB	<i>Vibrio cholerae</i> O1classical Inaba 569B strain (CVD103-HgR; expresses CTB)	Reformulated Bivalent <i>Vibrio cholerae</i> O1 & O139 without CTB
Adjuvant / Platform	Killed <i>Vibrio cholerae</i>	Killed <i>Vibrio cholerae</i>	Live attenuated <i>Vibrio cholerae</i> + CTB	Killed <i>Vibrio cholerae</i>
Administration Route	Oral	Oral	Oral	Oral
Formulation	Liquid	Liquid	Lyophilized	Liquid; new formulation
Presentation	2 unit-dose vials + 2 sachets of buffer	Multi-dose vials (buffer not required)	Double-chambered aluminum foil sachet containing CVD103-HgR and buffer	Single dose vial
Dosing Schedule	2-5yo: 3 doses (0, 1-2wks), revaccinate every 6 mo > 5yo: 2 doses (0, 1-2wks), revaccinate every 2 yrs	2 doses (0, 1-2wks)	Single dose	2 doses (1-2wks apart) revaccination expected every 5 yrs
Target Population for Licensure	≥ 2yo	≥ 1yo	≥ 2yo	≥ 1yo
Safety	No major safety concerns	No major safety concerns	No major safety concerns	No major safety concerns
Efficacy	85%-19% ;6mo-3yr	58%-41% ; 6mo-3yr	60-90%	66%; 5 yrs
Expected Duration of Protection	1 – 3 yrs	~3 yrs	~6mo	~5 yrs
Licensure Date (Location)	1991 (Sweden)	1997 (Viet Nam)	1993 (Switzerland)	2009 (India)
Estimated WHO Prequalification Date	2004	2016*	(no longer manufactured)	2011

\*As of June 2016, Viet Nam NRA has recognized by WHO and Vabiotech is up to GMP standards

# ***Oral killed whole-cell cholera vaccine developed in Sweden*** (rBs-WC)

- Consists of inactivated whole cells of *V. cholerae* O1 and the B-subunit of the cholera toxin (Dukoral™)
- Safety and protection demonstrated in large efficacy trials in Bangladesh and Peru
- 2 doses 14 days apart; protection 7 days after last dose; also effective against ETEC
- PE ~85% during first 6 months then to <50% for 3 years
- rBS-WC licensed in industrialized countries and mostly used by Western tourists

# ***Oral cholera vaccine produced in Vietnam***

## ***WC(no rBS)***

- Technology for production of WC-only vaccine transferred from Sweden to Vietnam in late 1980's
- Low-cost version of the killed whole cell vaccine (without the B subunit)
- Produced a protective efficacy of 66% in an outbreak in Vietnam
- Vaccine is licensed only in Vietnam
- A second-generation bivalent vaccine containing both serogroups O1 and O139 (developed in mid-90's) underwent safety and immunogenicity trial in Vietnam and Kolkata, India.

# ***Bivalent killed oral cholera vaccine contd...***

- ***Goal:*** To obtain a WHO recommendation and expand its use in public health settings globally
- ***Problems encountered:***
  1. Vietnam National Regulatory Authority (NRA) was not WHO approved
  2. Vaccine did not comply with WHO standards for production
- Vaccine needed to be reformulated
- Vaccine needed to be produced by a manufacturer in a country with WHO-approved NRA – following technology transfer, Shantha Biotechnics agreed to fill/finish and get necessary clearances

## ***Two potential problems identified***

1. Antigen quantification method was not accurate.
2. Removal of cholera toxin and no assay to detect residual toxin.

❑ Steps taken to improve safety and quality

### ✓ **Reformulation**

- Removed toxin hyper-producing strain and replaced with an equivalent serogroup (O1 Inaba).
- Increased the dose of the O1 Ogawa component.

### ✓ **Quality Control**

- Introduced an ELISA to quantify O antigen component of LPS.
- Introduced an ELISA to quantify residual cholera toxin.

## ***Bivalent killed oral cholera vaccine***

<b><i>Vaccine strains</i></b>	<b><i>Formulation 1 (1992)</i></b>	<b><i>Modified (1997)</i></b>	<b><i>Reformulated (2006)</i></b>
<b><i>V. cholerae O1 Inaba El Tor strain Phil 6973 formalin killed</i></b>	<b><math>2.5 \times 10^{10}</math> cells</b>	<b><math>5 \times 10^{10}</math> cells</b>	<b>600 Elisa units (EU) LPS</b>
<b><i>V. cholerae O1 Ogawa classical strain Cairo 50 heat killed</i></b>	<b><math>2.5 \times 10^{10}</math> cells</b>	<b><math>2.5 \times 10^{10}</math> cells</b>	<b>300 EU LPS</b>
<b><i>V. cholerae O1 Inaba classical strain 569B formalin killed</i></b>	<b><math>2.5 \times 10^{10}</math> cells</b>	<b><math>2.5 \times 10^{10}</math> cells</b>	<b>---</b>
<b><i>V. cholerae O1 Ogawa classical strain Cairo 50 formalin killed</i></b>	<b>---</b>	<b>---</b>	<b>300 EU LPS</b>
<b><i>V. cholerae O1 Inaba classical strain Cairo 48 heat killed</i></b>	<b><math>2.5 \times 10^{10}</math> cells</b>	<b><math>2.5 \times 10^{10}</math> cells</b>	<b>300 EU LPS</b>
<b><i>V. cholerae O139 strain 4260B formalin killed</i></b>	<b>---</b>	<b><math>5 \times 10^{10}</math> cells</b>	<b>600 EU LPS</b>

***Cluster- Randomized Placebo-Controlled  
Trial of Reformulated Bivalent Killed  
Whole Cell Oral Cholera Vaccine in  
Kolkata, India***

***(collaboration between International Vaccine  
Institute (IVI, Korea) and National Institute of  
Cholera and Enteric Diseases, (NICED, India)***

## ***Protective efficacy at end of 2,3 and 5 years***

<i><b>Age Group (yrs)</b></i>	<i><b>Protective Efficacy 2 years</b></i>	<i><b>Protective Efficacy 3 years</b></i>	<i><b>Protective Efficacy 5 years</b></i>
<b>1- &lt;5</b>	<b>53%</b>	<b>43%</b>	<b>42%</b>
<b>5- &lt; 15</b>	<b>88%</b>	<b>88%</b>	<b>68%</b>
<b>≥15</b>	<b>66%</b>	<b>61%</b>	<b>74%</b>
<b>Total</b>	<b>67%</b>	<b>66%</b>	<b>65%</b>



## ***Similar composition as Shanchol***

- **Eubiologics** - South Korea (Euvichol) applied for WHO- PQ
- **Incepta** - Bangladesh (Cholvax) – clinical evaluation ongoing non-inferiority study with Shanchol- expecting licensure in Bangladesh in 2016
- **Vabiotech** – (mORCVAX) Vietnamese National Regulatory Authority has now been recognized as functional by the WHO – will apply for WHO-PQ

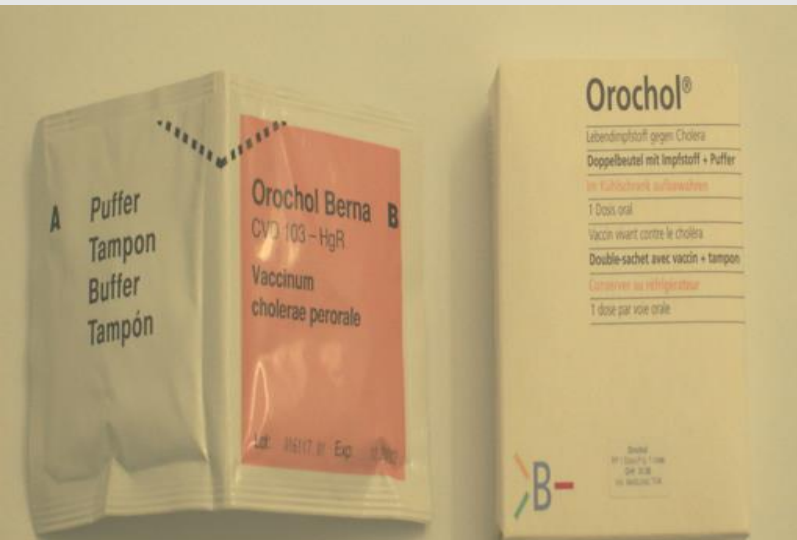
# ***Justification for single dose vaccine***

- In outbreak situations
- Logistics and feasibility
- Immense public health implications
- Could not be given in recent outbreaks because of licensed 2 doses
- Recently single dose study with Shanchol completed in Bangladesh- results awaited

# CVD 103-HgR single dose

(Orochol™, Mutachol™)

- Live attenuated oral cholera vaccine consisting of genetically manipulated classical *V.cholerae* O1 strain- available since 1994
- Showed great promise in human volunteer studies
- In a randomized, placebo-controlled, field trial in Indonesia, a single dose conferred 60% protection in first 6 months, but only 24% during the first year
- Did not confer significant long-term protection during the 4 years of observation.
- **Does not protect against O139**
- When rapid protection is necessary, CVD103-HgR was preferred as it confers protection within 7 days following single dose
- No longer manufactured- attempts being made to revive



# Available Oral Cholera vaccines

Killed Bivalent (O1 and O139) Whole Cell Oral Cholera Vaccine (OCV)

**Shanchol**  
 In Vivo Oral Cholera Vaccine  
 शॉनकोल

1.5ml single dose vial

SHANTHA  
 A MICROBIAL ALLIANCE  
 Company

Shanchol	शॉनकोल
Killed Bivalent O1 and O139 whole cell Oral Cholera Vaccine (OCV)	
Each oral dose (1.5 ml) of the vaccine contains	
Active Ingredients	Quantity
V. cholerae O1 Inactivated whole cells (strain 569B) (Formalin-killed)	800 Billion (10 <sup>10</sup> ) of non-replicating viable cells
V. cholerae O139 Inactivated whole cells (strain 569B) (Formalin-killed)	300 EU Dose
V. cholerae O1 Inactivated whole cells (strain 569B) (Formalin-killed)	300 EU Dose
V. cholerae O1 Inactivated whole cells (strain 569B) (Formalin-killed)	300 EU Dose
V. cholerae O139 Inactivated whole cells (strain 569B) (Formalin-killed)	300 EU Dose
Adjuvant	As a fluid carrier to form 0.5% Buffer
Buffer	Filled up to 1.5 ml



# ***Obstacles to cholera vaccine development and implementation***

1. Underestimation of the global cholera burden
2. Overestimation of the complexity of vaccine delivery
3. Underestimation of the potential benefit from vaccination

# ***WHO recommendations on cholera vaccination***

- Protection of population at risk in endemic areas
- Preplanned (pre-emptive) strategy for vaccination where disease is endemic or cholera outbreak imminent eg humanitarian crisis.
- Reactive deployment of vaccines in epidemics — to reduce mortality and limit spread of the disease
- Vaccination should be considered in conjunction with other control strategies.
- Vaccination should be considered in high-risk areas and population such as among refugees in primitive camps or urban slum dwellers and in resource poor settings.
- It is also recommended for travelers to high-risk areas.

# ***WHO recommendations on cholera vaccination***

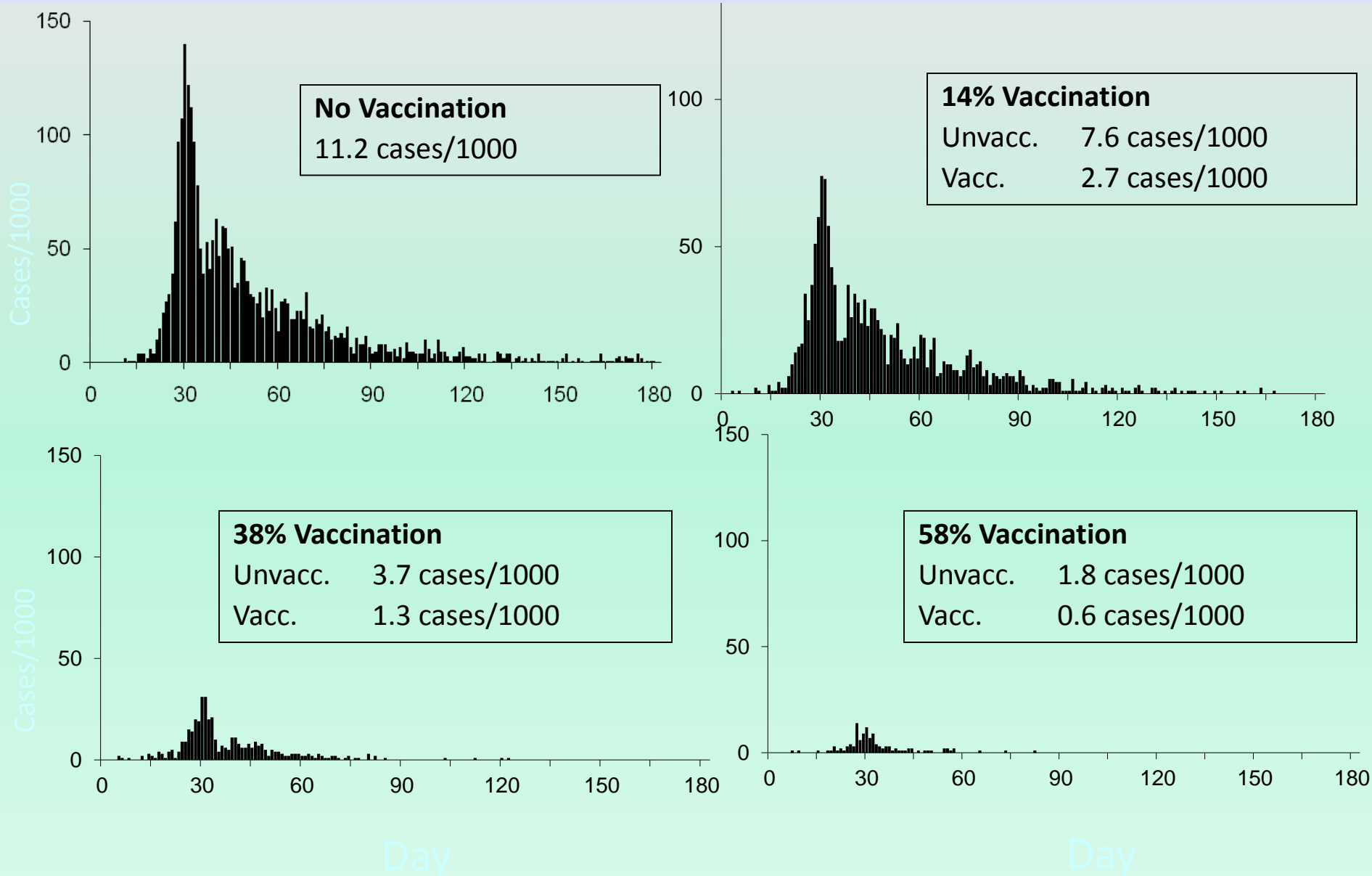
## **Groups to target for vaccination:**

- All age groups; priority to high risk age groups, if limited resources eg. pre school aged or school aged children
- Older age groups, if funding is available

## **Vaccine delivery strategy:**

- Periodic mass vaccination
- Schools, religious institutions and other community settings
- Routine vaccination schedules may be considered

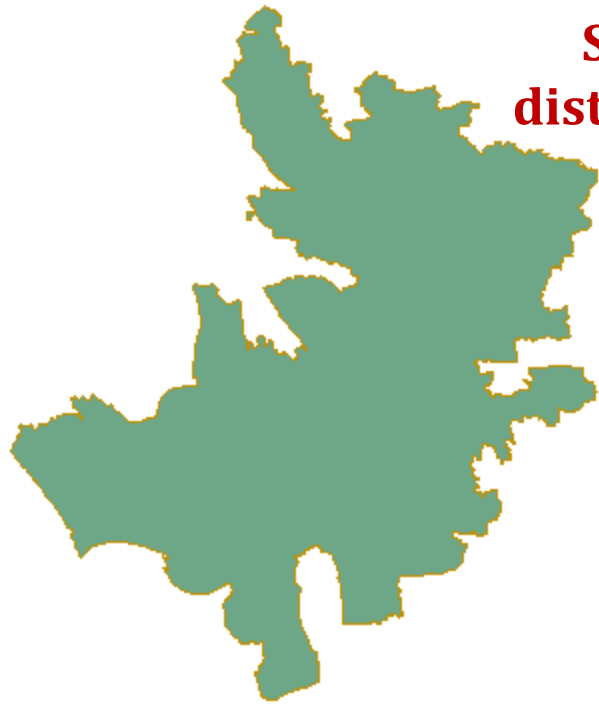
# Stochastic cholera transmission model





Mass Vaccination: 0 % Day 1

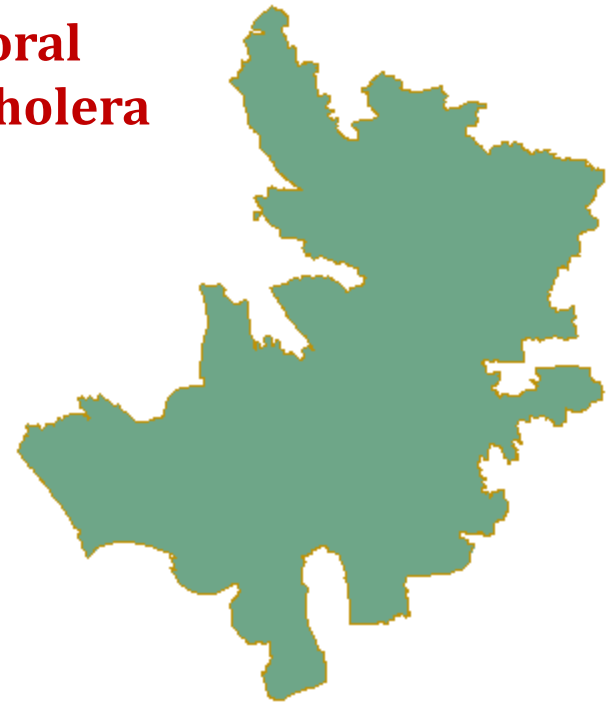
Red: Ill Yellow:Recovered



## Spatial-temporal distribution of cholera cases

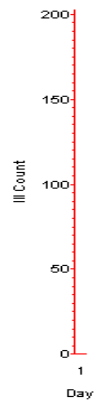
Mass Vaccination: 58 % Day 1

Red: Ill Yellow:Recovered



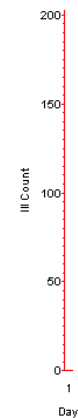
Epidemic curve: Day 1

Mass Vaccination:0 %



Epidemic curve: Day 1

Mass Vaccination:58 %



# Outbreak situations





# ***Post Cyclone Cholera outbreak***



Post AILA cyclone in Sunderban area, WVD iviay  
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***Thank you***

