International Vaccine Institute Research Updates 2020

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IVI Cholera Program Strategy and Projects

Goals	Program Objectives	Current Projects
Ensure OCV Supply	Continue Supporting Manufacturers	• Critical Reagents • BIBCOL (new tech transfer to India) • **Reformulation of OCV (OCV-S)**
Improve Cholera Vaccine	Improve Vaccine Efficacy (Especially in <5 y.o.) And Flexibility of Use	• Euvichol CTC Label • **Pre-Clinical Development of Cholera Conjugate Vaccine (CCV)**
OCV Use & Introduction	Generate Evidence to Support Endemic Country Introduction & Use in Support of Global Roadmap	• CSIMA-Malawi • **MOCA- Mozambique** • ECCP-Ethiopia • ECHO-Nepal • ECHO-Mozambique

Reformulation of OCV

Rationale

OCV contains 5 distinct components:

- Redundant heat and formalin inactivated O1 Inaba and Ogawa
- Vibrio cholera O139

➢ ***Could a simplified formulation containing only two current components, O1 Inaba (El Tor) and O1 Ogawa (classical), and inactivated by a single method (formalin), be equally effective?***

➢**Anticipate 20% reduction in costs and 38% increase in production capacity**

Reformulation of OCV (in partnership with EuBiologics)

Technical Expert Group Meeting Jan 2020 =>

- Consensus that **two-component** vaccine should achieve an **equivalent protective immune response to O1** serotypes of *V. cholerae*
- Agreed that the **O139 component** provides **no cross-protection to O1**, and little public health value as O139 has limited circulation

Regulatory Consultations =>

- Acceptable rationale for change, and acceptable clinical development plan

Test formulations => Feasible, process validation in process at EuBiologics

Clinical trial => May-June 2021

Regulatory submission => 2023

Cholera Conjugate Vaccine (CCV)

- Conjugate vaccines elicit long lasting T-cell dependent immune responses in young children, often with a single dose
- An injected vaccine with a long duration of protection can be cost effectively incorporated into EPI, reducing the burden of repeated vaccination campaigns, and building population immunity from infancy up in endemic populations

CCV => (Ed Ryan- Mass General Hospital, Harvard University) Purified OSP from *V. cholerae* O1 Inaba El Tor strain PIC018 conjugated to a recombinant tetanus toxoid heavy chain fragment (rTTHc)

- Protectively immunogenic in preclinical animal models
- A COG analysis suggested a cost of 0.42 USD per dose

- IVI/MGH/EuBiologics-> Manufacturing process transferred to EuBiologics as partner for CTM production (RIGHT Fund)
- Pre-clinical Tox study underway (Wellcome Trust)
- IND Filing expected June 2021

OCV effectiveness research and challenges

Se Eun Park, PhD

International Vaccine Institute

GTFCC OCV Working Group Annual Meeting

10 December 2020

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Cuamba District | Baseline household survey

Niassa Province
Cuamba District

Baseline Survey
573 households
Cuamba District
in 2018

WaterAid

Collaboration with WaterAID

Population of 264,572 in Cuamba District

Cholera outbreak in Dec 2014-2015: over 8,835 cholera cases & 65 deaths by mid-2015 in Mozambique

Over 100-200 suspected cholera & 2,000 diarrheal cases almost every year in Cuamba

Year	Cases	Deaths	CFR (%)	IR (100,000)
2010	133	14	10.5	63.4
2011	123	8	6.5	56.9

Cholera situation Cuamba 2010-2011 (Source: MOH)

Year	Cases	Deaths
2012	223	3
2013	344	5
2014	0	0
2015	202	6
2016	0	0

Cholera situation Cuamba 2012-2016 (DPS Niassa)

Toilet
80% of surveyed households with latrine (traditional latrines)
10% without any latrine

Waste disposal
49% without garbage disposal system
38% dispose garbage in pits
5% burn garbage

Knowledge on cholera & cholera prevention
5.2% never heard of cholera
94.8% heard of cholera

Household water and WaSH practice

70% with hand washing facility
59% of household handwashing facility in kitchen or near toilet
75% use soap or ash to wash hands
78% wash raw food before cooking/eating
78% clean utensils before serving food
66% use covered container to store drinking water

OCV (Euvichol-Plus) vaccination campaign and coverage

Pre-emptive mass vaccination campaign (Aug 2018)

2-dose Euvichol-Plus with each round conducted over 5-6 days (15-day dose interval)

Fixed posts & mobile teams: mixed vaccination strategy to improve accessibility and coverage

- 1st round 194,581 people vaccinated -> administrative coverage = 99%
- 2nd round 194,325 people vaccinated -> administrative coverage = 99%

Two Stage Cluster Coverage survey

First coverage survey after 1st round:
572 households

Final coverage survey:
714 households

60.4% (±3.4%) estimated to have received full two-doses of OCV

		First Round	Second Round	Full Two Doses
Age (years old)	1- 4	81.1±4.5%	72.2±6.9%	64.4±7.3%
	5-14	86.4±3.1%	71.3±5.8%	65.2±6.1%
	≥15	67.6±3.3%	65.2±4.8%	55.7±5.0%
Sex	Male	76.3±2.9%	77.8±3.9%	57.3±4.6%
	Female	75.4±3.2%	67.7±5.0%	64.4±5.1%
Total	-	**75.9±2.2%**	**68.5±3.3%**	**60.4±3.4%**

Jucunu Chitio et al (to be published)

Preliminary findings

Surveillance & VE research design

Healthcare facility-based prospective surveillance

Enrolment of cholera and diarrheal patients (Inclusion criteria):

Suspected cholera
- Acute watery diarrhea* or severe dehydration
- Acute watery diarrhea* with or without vomiting

OR

Diarrhea
- Acute bloody diarrhea (dysentery)
- Persistent diarrhea

AND

Live in surveillance catchment area (Cuamba district)

AND

Informed consent obtained

***AWD case definition used:**
- -Passage of 3 or more loose or watery stools in any 24-hr period within 3 days prior to presenting to HCF
- -1 or 2 loose or watery stools with any sign of dehydration
- -Severe dehydration from acute watery diarrhea

Stool or rectal swab – cholera RDT & culture

Minimum sample size of 45 cholera cases (1:4 case-control)

Test negative design with hospital-controls

Assuming 70% VE with 80% power when 80% coverage in vaccination campaign

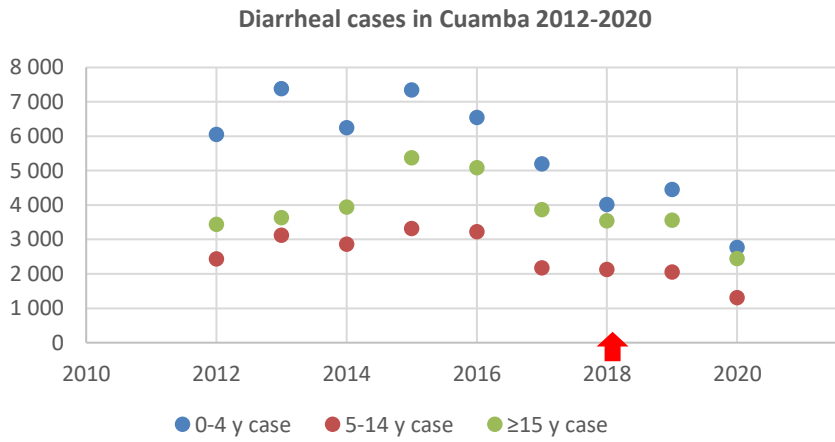
Cholera outbreaks in Cuamba 2010-2020 (source: MOH/DPS Niassa)

Year	Cases	Deaths	CFR (%)	IR (100,000)
2010	133	14	10.5	63.4
2011	123	8	6.5	56.9

Year	Cases	Deaths
2012	223	3
2013	344	5
2014	0	0
2015	202	6
2016	0	0
2017	0	0
2018	0	0
2019	0	0
2020	0	0

Diarrhea cases in Cuamba 2012-2020 (source: MOH/DPS Niassa)

Year	0-4 y		5-14 y		≥15 y	
	case	death	case	death	case	death
2012	6,054	11	2,438	1	3,443	3
2013	7,379	22	3,123	4	3,639	4
2014	6,249	12	2,862	40	3,940	1
2015	7,349	16	3,318	3	5,379	7
2016	6,546	6	3,230	0	5,091	1
2017	5,196	0	2,174	0	3,873	0
2018	4,019	0	2,132	0	3,541	0
2019	4,456	0	2,058	0	3,563	0
2020	2,773	0	1,317	0	2,447	0



OCV vaccine effectiveness & impact of vaccination

Paucity of data on OCV vaccine effectiveness

- Safety and efficacy (66 to 85%): inferred herd immunity up to 5 years (two-doses, Shanchol) (*Pape JW et al, N Engl J Med* 2014; 370: 2067–9)
- Euvichol non-inferiority trial in the Philippines: in adults (82% vs 76%) and children (87% vs 89%) (*Baik YO et al, Vaccine* 2015; 33: 6360–5)
- Matched case-control study in Guinea 2012: 86.6% effectiveness (two-doses, Shanchol) (*Luquero FJ et al, N Engl J Med* 2014; 370: 2111–20)
- Test-negative case-control study in Odisha, India 2011: protective effectiveness of 69% (two doses) and 33% (single dose, Shanchol) (*Wierzba TF et al, Vaccine* 2015; 33: 2463–9)
- Case-cohort study in Juba, South Sudan 2015: 80.2% unadjusted short-term protection (single-dose Shanchol in outbreak response), 87.3% adjusted vaccine effectiveness (*Azman AS et al, Lancet Glob Heal* 2016; 4: e856–63)

Challenges of vaccine effectiveness study

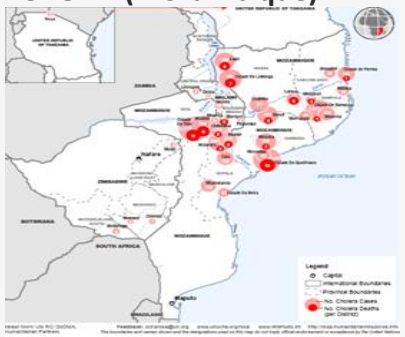
- Minimum sample size requirement for cholera cases post-vaccination of OCV
- Cholera outbreak pattern – natural variability in cholera epidemiology
- Setting-up a prospective surveillance system in a research naïve and remote setting
- WaSH interventions (comprehensive integrated approach recommended)

Considerations for impact of vaccination

- Cholera incidence with and without vaccination
- Same population pre- and post-vaccination
- Non-mobile population, similar susceptibility to cholera, persistent cholera
- Cholera case detection and reporting for data comparability
- Interpretation of confounding and biases

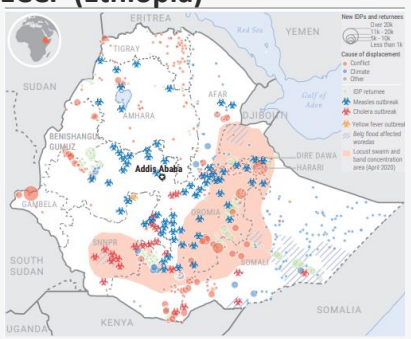
Preemptive OCV vaccination
Prospective cholera and diarrheal disease surveillance
Retrospective acute watery diarrhea/cholera data
Vaccine effectiveness and impact assessment
Site-specific cholera risk factors
Cholera healthcare seeking
Transmission and carriage
Support cholera control policy dialogue

ECHO-M (Mozambique)



Map: OCHA Reliefweb. Mozambique.

ECCP (Ethiopia)



Map: OCHA. Ethiopia: Humanitarian Snapshot. 2020

THANK YOU

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