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Oral Killed Whole Cell Vaccines:

review of available evidence of vaccine effectiveness and safety across different settings and age groups

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Acknowledgments: Kashmira Date, Dominque Legros

MEDECINS SANS FRONTIERES

2010 WHO position on OCV safety and protection

"The available oral cholera vaccines are safe and provide sustained protection of >50% that lasts for 2 years in endemic populations"

New evidence generated since 2010

- Safety
- Safety among pregnant women
- Vaccine protection

SAFETY OF ORAL CHOLERA VACCINES

2010 SAGE Recommendation on OCV Safety

- Currently licensed cholera vaccines are safe in all groups aged >1 year; for Dukoral, in all groups aged >2 years

- New data remains consistent with this statement

OCV Clinical Trials for Safety Outcomes Included in GRADE Review

- In the prior review (2010) only 3 studies evaluated safety on Shanchol/ORCVAX, however new evidence is available, with 5 RCT demonstrating safety of Shanchol
  - **Sur D, Lopez AL, Kanungo S et al. Efficacy and safety of a modified killed-whole-cell oral cholera vaccine in India: an interim analysis of a cluster-randomised, double-blind, placebo-controlled trial. Lancet 2009; 374: 1694-1702.**
  - **Qadri et al. Efficacy of a Single-Dose, Inactivated Oral Cholera Vaccine in Bangladesh. N Engl J Med 2016: 374: 1723-32.**
  - Qadri F, Ali M, Chowdhury F et al. Feasibility and effectiveness of oral cholera vaccine in an urban endemic setting in Bangladesh: a cluster randomised open-label trial. Lancet 2015; 386:1362-1371.
  - Saha A, Chowdhury MI, Khanam F et al. Safety and immunogenicity study of a killed bivalent (O1 and O139) whole-cell oral cholera vaccine Shanchol, in Bangladeshi adults and children as young as 1 year of age. Vaccine 2011; 29(46): 8285-8295.
  - Desai, Sachin N. et al. A Randomized, Placebo-Controlled Trial Evaluating Safety and Immunogenicity of the Killed. Bivalent, Whole-Cell Oral Cholera Vaccine in Ethiopia. Am. J. Trop. Med. Hyg 2015, 93(3): 527–533
- One additional RCT using Euvichol (same formulation as Shanchol) produced by Eubiologics
  - Baik YO, Choi SK, Olveda RM et al. A randomized, non-inferiority trial comparing two bivalent killed, whole cell, oral cholera vaccines (Euvichol vs Shanchol) in the Philippines. Vaccine 2015; 33(46): 6360-6365.

Safety Data from Phase IV Surveillance

- More than 40 campaigns implemented in Africa, Asia and the Americas
  - Primarily using Shanchol, but recent campaigns have used Euvichol (eg. Haiti or Somalia, around 2 million doses distributed)
  - Reports on AEFI from several campaigns
    - Low frequency (eg. Guinea: 48 patients spontaneously reported AEFI (15 per 100,000 vaccinated))[1]
    - Most AEFIs reported classified as mild: nausea, diarrhea, vomiting
    - Low number of SAE investigated, none of them attributable to OCVs

1. Luquero et al. First outbreak response using an oral cholera vaccine in Africa: vaccine coverage, acceptability and surveillance of adverse events, Guinea, 2012. .PLoS Negl Trop Dis. 2013 Oct 17;7(10):e2465.

Summary of Evidence on Vaccine Safety

What is the evidence that the currently available killed, whole-cell oral cholera vaccines (kOCVs) are safe among non-pregnant individuals (Dukoral ≥ 2 years old, Shanchol/Euvichol/mORCVax ≥ 1 year olds)?

Currently licensed kOCVs are safe

SAFETY IN PREGNANT WOMEN

General WHO Recommendations on Vaccination During Pregnancy

- Global Advisory Committee on Vaccine Safety
  - There is **no evidence of adverse pregnancy outcomes** from the vaccination of pregnant women with **inactivated** virus, **bacterial** vaccine, or toxoid. Therefore, **pregnancy should not preclude women from immunization with these vaccines**, if medically indicated.
  - **The benefits of vaccinating pregnant women generally outweigh the potential risks**, if they are at high risk of being exposed to a particular infection and the disease would pose a risk for the woman or her unborn child, and if the vaccine is unlikely to cause harm.
- It is well established that cholera during pregnancy increases the risk of pregnancy loss and maternal death

Prior Recommendation from the 2010 WHO Position Paper on OCV

- Groups that are especially vulnerable to severe disease and for which the vaccines are not contraindicated may also be targeted, such as pregnant women and HIV-infected individuals

- No specific studies published on pregnancy outcomes after kOCV intake

Current recommendation from the manufacturers

- *Dukoral*
  - *"The vaccine may be administered during pregnancy and to lactating women"*
- *Shanchol*
  - *"No specific clinical studies have been performed to evaluate the safety and immunogenicity of Shanchol in pregnant or lactating women and for the fetus.* ***The vaccine is therefore not recommended for use in pregnancy or during lactation****. However, Shanchol is a killed vaccine that does not replicate, is given orally and acts locally in the intestine. Therefore,* ***in the theory, Shanchol should not pose any risk to the human fetus****.* ***Administration of Shanchol to pregnant or lactating women may be considered after careful evaluation of the benefits and risks in case of a medical emergency or an epidemic****"*

Review of the Scientific Evidence: Safety of kOCV in Pregnant Women

- Four new observational studies including pregnancy outcomes
  - Hashim et al. (Zanzibar): Dukoral
  - Grout et al. (Guinea): Shanchol
  - Ali et al. (Malawi): Shanchol
  - Khan et al (Bangladesh): Shanchol, nested in a RCT
- Five different outcomes evaluated: any adverse event, congenital malformation, neonatal deaths, miscarriage and stillbirth
- Similar results for all outcomes : risk-ratio close to 1 (i.e. no risk) and non-significant p-value in individual and pooled analysis
- Similar limitations: difficulties to capture pregnancy loss in the first trimester

Summary of evidence on vaccine safety in pregnant women

What is the evidence that the currently available killed, whole cell kOCVs are safe in pregnancy?

Currently licensed kOCVs are safe for use during pregnancy

VACCINE PROTECTION

Prior Statement from the 2010 Position Paper

- *What is the evidence for protective efficacy/effectiveness of currently licensed cholera vaccines (DukoralTM and ShancholTM /ORCVaxTM/) in endemic settings during the first two years following immunization?*

- High level of scientific evidence that the currently licensed cholera vaccines offer significant protection against cholera during the first two years after vaccination

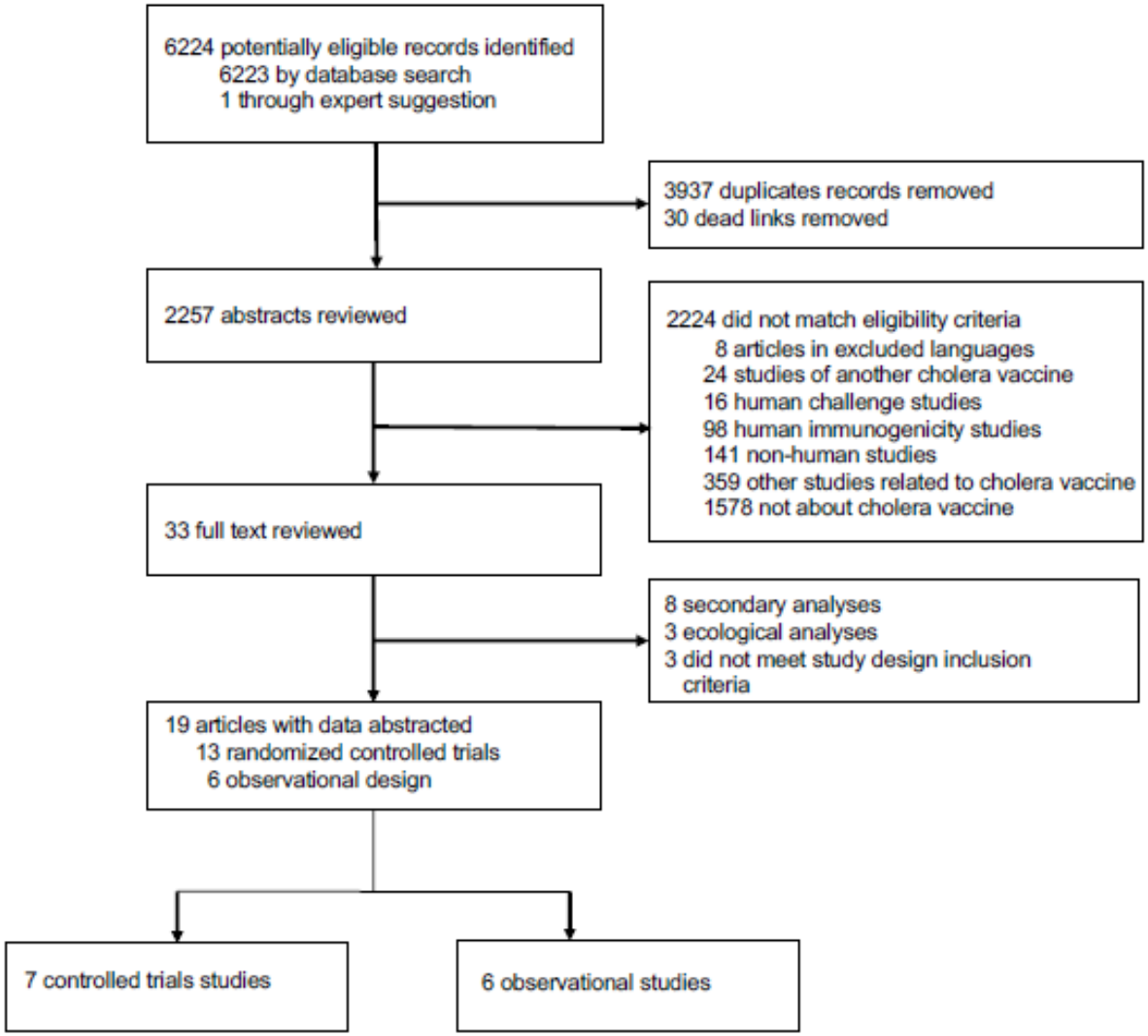
New Evidence on Vaccine Protecion

- Additional efficacy and effectiveness studies:
  - 5 new RCT evaluated (including immunogenicity), 3 of them efficacy trials
  - 5 new observational studies measuring effectiveness
- Some factors determine differences between studies
  - Type of study: RCT vs observational studies
  - Number of doses
  - Age group
  - Time since vaccination
  - Location where the study was implemented (natural exposure)

Systematic Review and Meta-analysis

- Inclusion criteria
  - Randomized clinical trial, case-control, cohort, case-cohort designs
  - Measure of direct (or total) protection
  - Primary analysis (e.g., no re-analyses of studies)
  - Medically-attended confirmed cholera case
- Searched standard databases for estimates of protection
- Two reviewers independently assessed and categorized each abstract and some were flagged for full text review according to inclusion criteria
- The reviewers independently extracted data from all papers eligible into standardized data collection form (protection by number of doses, duration, age-group, and severity)

Systematic Review and Data Abstraction



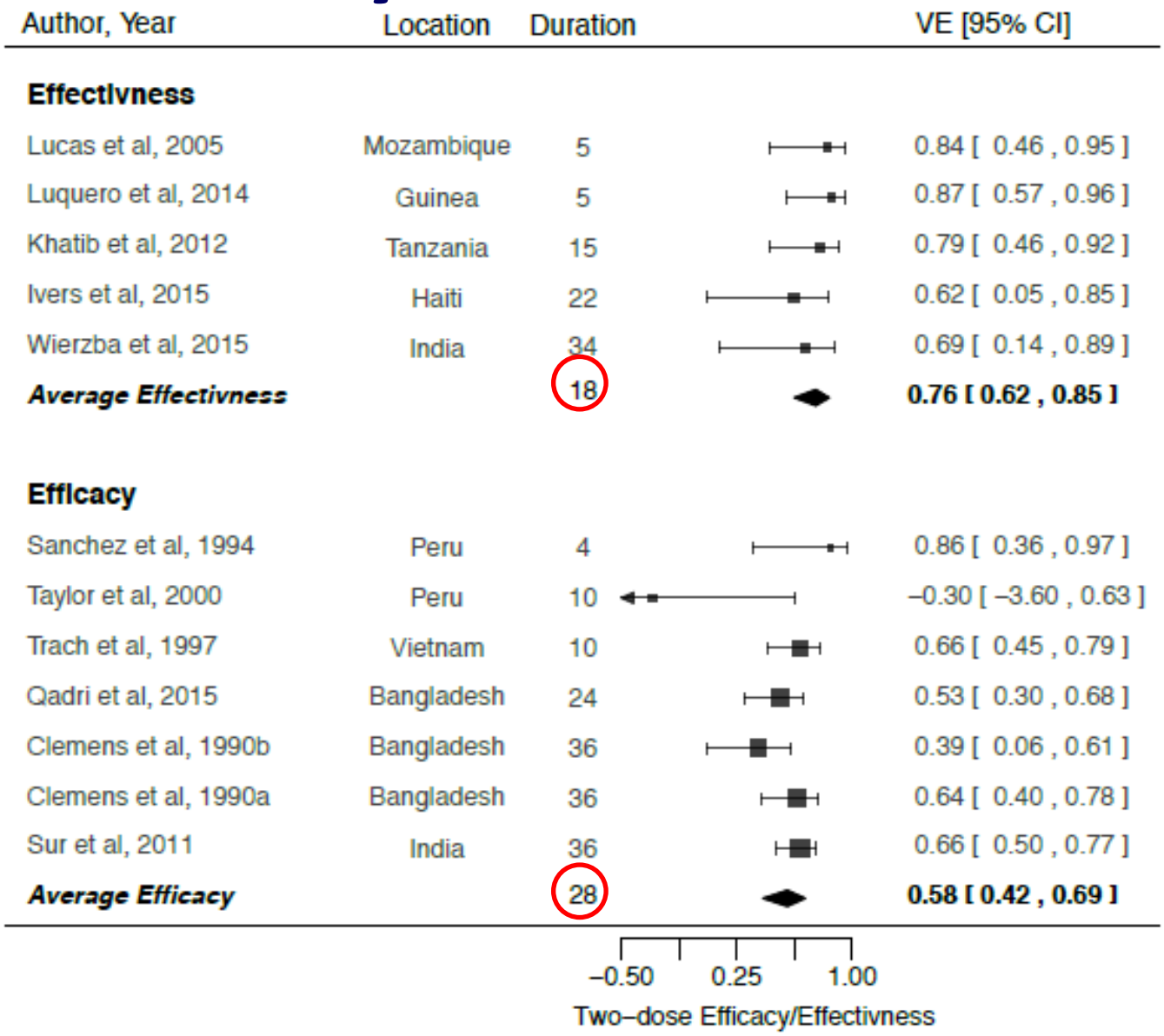
Summary of the RCT

Continent	Location	Study Design	Vaccine	Duration of Estimate(s)	Doses	Study Population	Number of Cases
Asia	Kolkata, India	Cluster Randomized Placebo-Controlled Trial	WC	2-, 3-, and 5-years	2	All non-pregnant individuals ≥1 years old	168
South America	Lima, Peru	Individually Randomized Placebo-Controlled Trial	WC-BS	2-years	3	All individuals nonpregnant 2-65 years old	7
South America	Lima, Peru	Individually Randomized Placebo-Controlled Trial	WC-BS	5-months	2	Male military recruits 17-65 years old	16
Asia	Matlab, Bangladesh	Individually Randomized Placebo-Controlled Trial	WC/WC-BS	6-months, 1-, 3-, and 5-years	3	Children 2-15 years old and all women >15, non-pregnant	81/68
Asia	Dhaka, Bangladesh	Cluster Randomized Trial	WC	2-years	2	All non-pregnant individuals ≥1 years old	139
Asia	Dhaka, Bangladesh	Individually Randomized Placebo-Controlled Trial	WC	6-months	1	All individuals ≥1 years old, nonpregnant	101
Asia	Hue, Vietnam	Household Randomized Trials without Placebo	WC	10-months	2	All individuals ≥1 years old	117

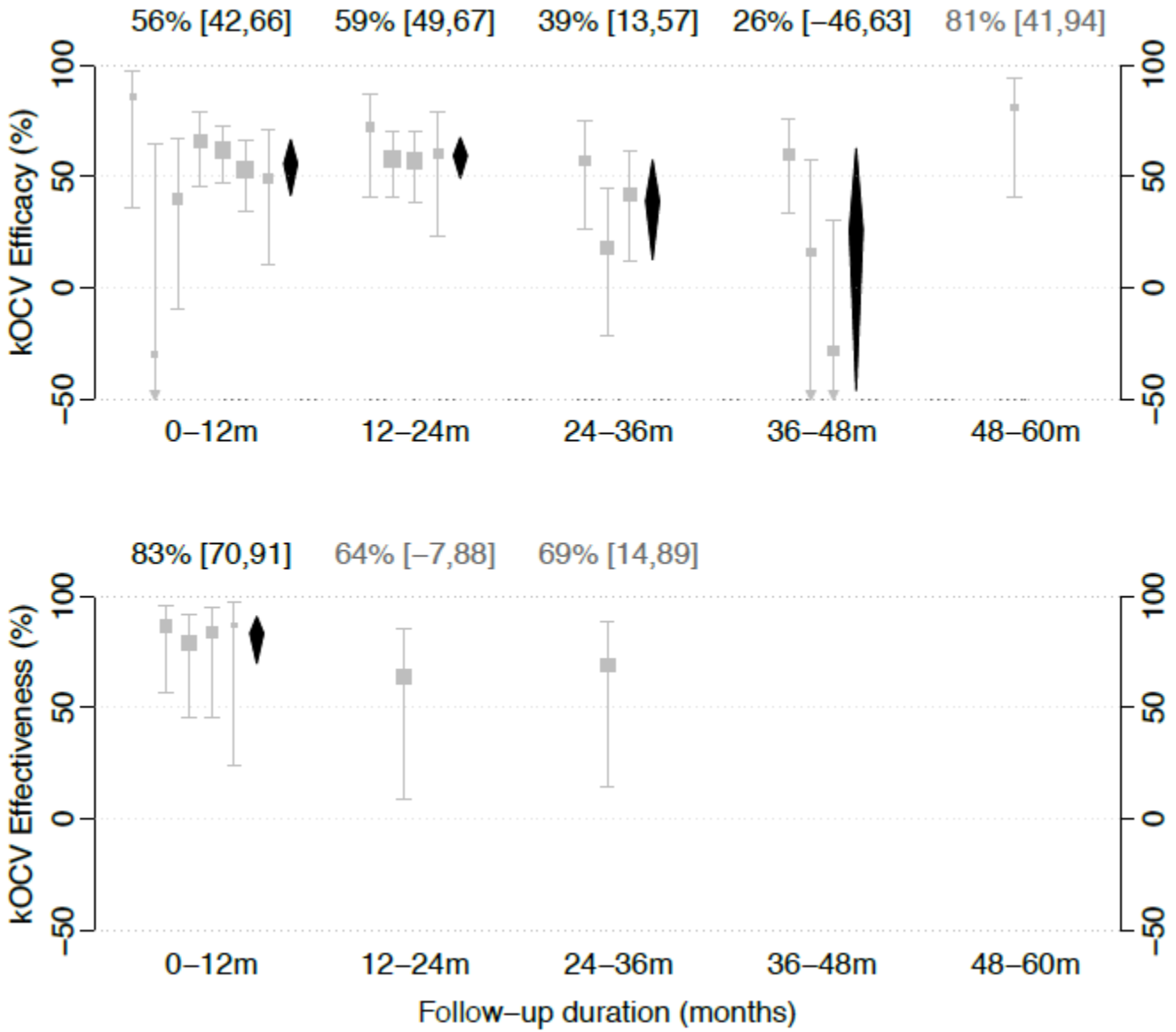
Summary of the Observational Studies

Continent	Location	Study Design	Vaccine	Duration of Estimate	Doses	Study Population	Number of Cases
Asia	Puri District, India	Case-Control	WC	3-years	2	All non-pregnant individuals 1 and older seeking care at health facilities	35
North America	Artibonite Department, Haiti	Case-Control	WC	2-years	2	All individuals 1 year and older seeking care at health facilities	44
Africa	Boffa and Forecariah Districts, Guinea	Case-Control	WC	4-months	2	All individuals >1 seeking care at health facilities	26
Africa	Zanzibar, Tanzania	Cohort	WC-BS	15-months	2	All non-pregnant healthy individuals 2-year and older	39
Africa	Beira, Mozambique	Case-Control	WC-BS	4-months	2	All non-pregnant healthy individuals 2-year and older	88
Africa	Juba, South Sudan	Case-Cohort	WC	2-months	1	All individuals 1-year and older	34

Efficacy vs Effectiveness

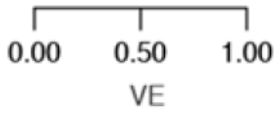


Duration of Vaccine Protection

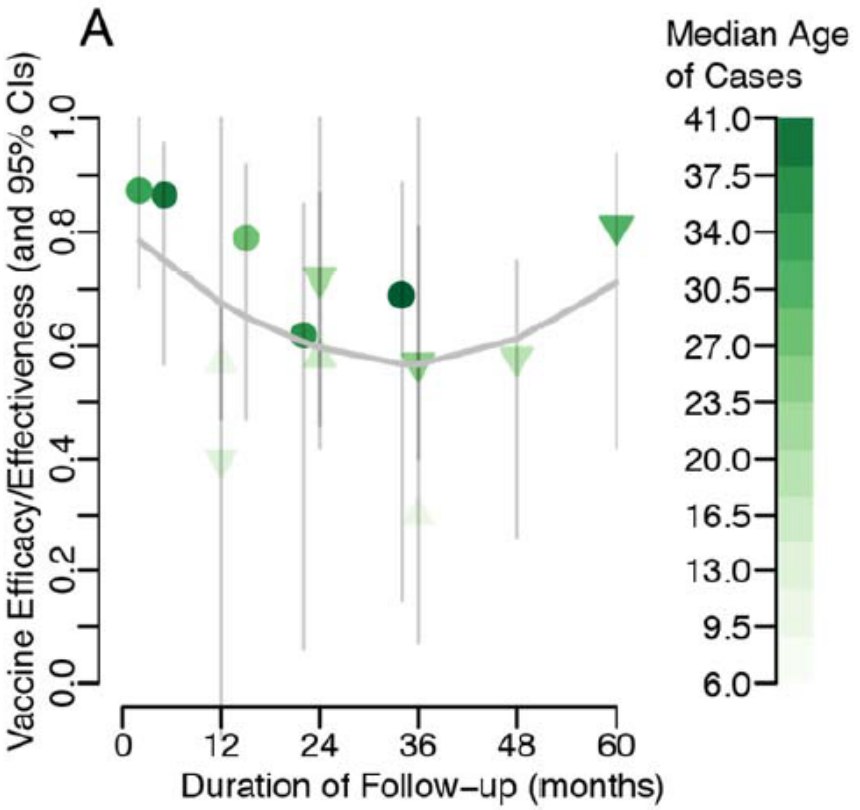


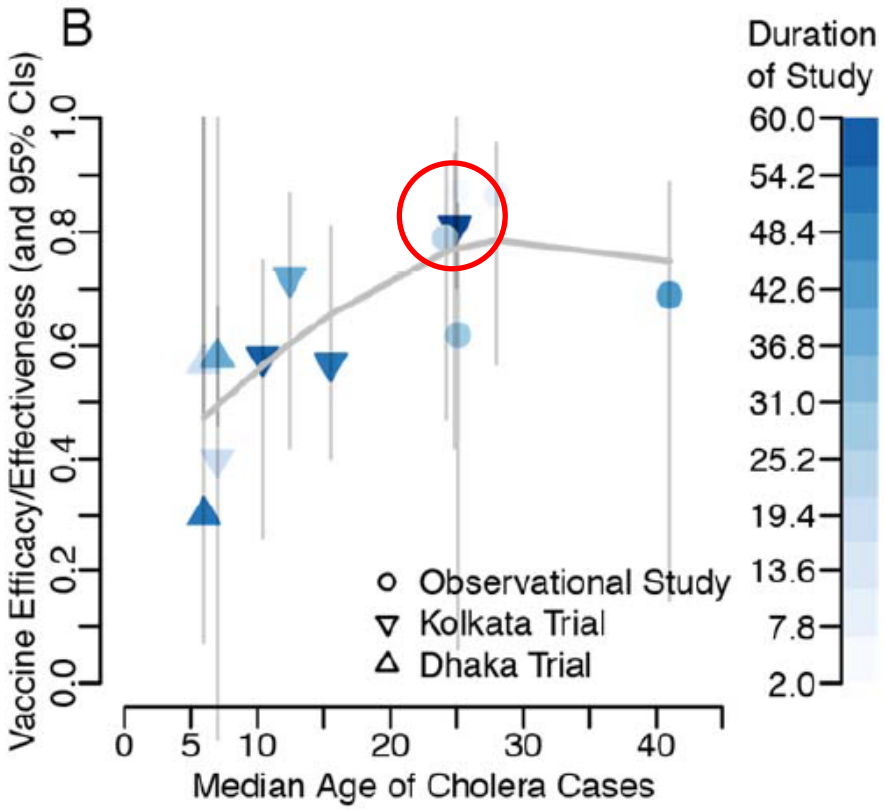
Effect by Age Group

Author, Year	Location	Duration	VE [95% CI]
<5 Years Old			
Trach et al, 1997	Vietnam	10	0.68 [0.14 , 0.88]
Qadri et al, 2015	Bangladesh	24	0.44 [−0.36 , 0.77]
Clemens et al, 1990b	Bangladesh	36	0.23 [−0.04 , 0.43]
Clemens et al, 1990a	Bangladesh	36	0.26 [−0.01 , 0.46]
Sur et al, 2011	India	36	0.43 [−0.02 , 0.68]
Average Efficacy		**31**	**0.30 [0.15 , 0.42]**
≥ 5 Years Old			
Sanchez et al, 1994	Peru	4	0.86 [0.36 , 0.97]
Trach et al, 1997	Vietnam	10	0.66 [0.42 , 0.80]
Qadri et al, 2015	Bangladesh	24	0.56 [0.31 , 0.72]
Clemens et al, 1990b	Bangladesh	36	0.68 [0.57 , 0.76]
Clemens et al, 1990a	Bangladesh	36	0.63 [0.51 , 0.72]
Sur et al, 2011	India	36	0.61 [0.31 , 0.78]
Average Efficacy		**34**	**0.64 [0.58 , 0.70]**



Effect by Age Group and Time Since Vaccination





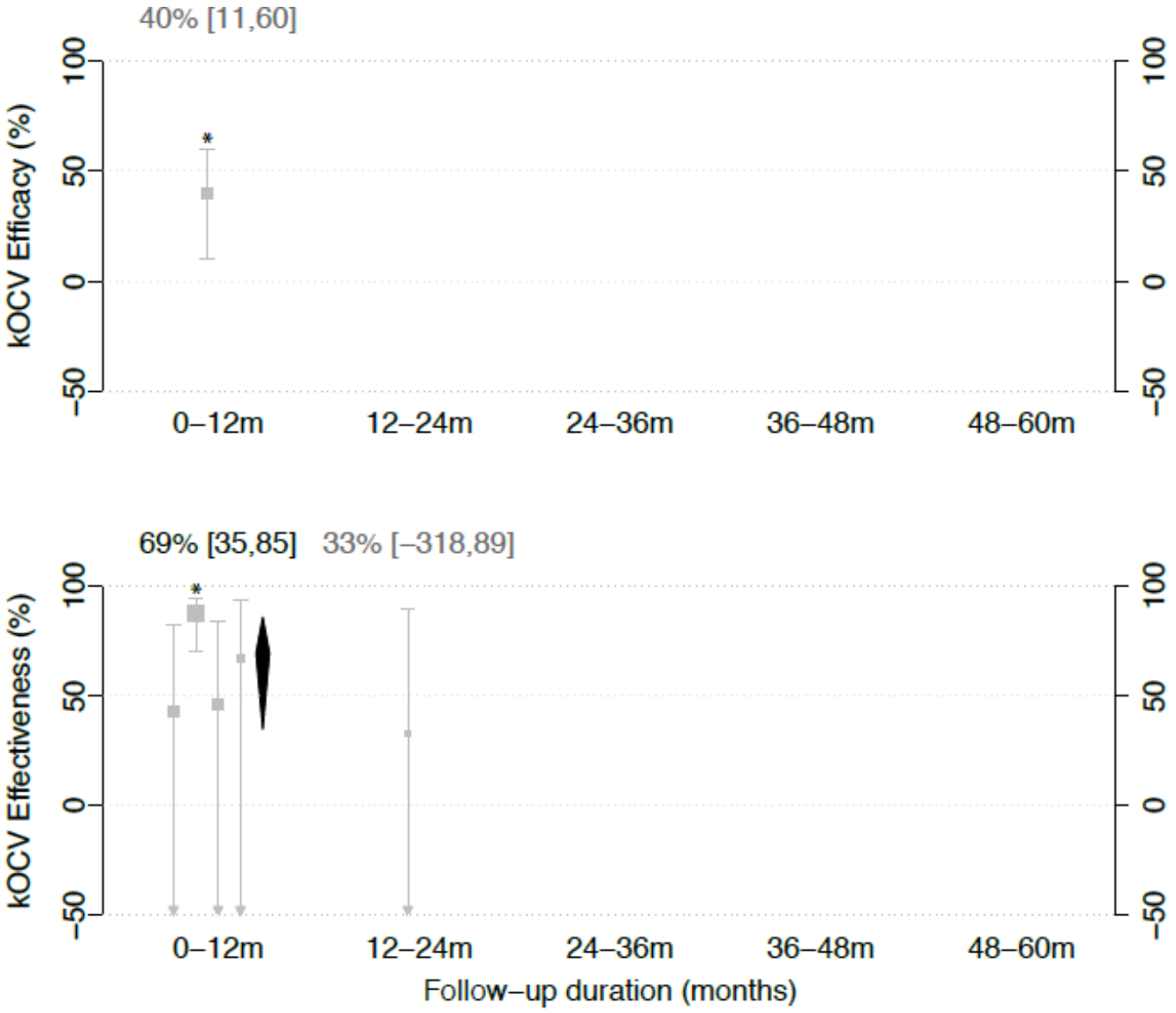
Location Where the Study Was Implemented

Author(s)	Country	Duration	Design	VE
Asia				
Trach et al, 1997	Vietnam	10	Randomized	0.66 [0.45 , 0.79]
Sur et al, 2011	India	36	Randomized	0.66 [0.50 , 0.77]
Qadri et al, 2015	Bangladesh	24	Randomized	0.53 [0.30 , 0.68]
Clemens et al, 1990b	Bangladesh	36	Randomized	0.39 [0.06 , 0.61]
Clemens et al, 1990a	Bangladesh	36	Randomized	0.64 [0.40 , 0.78]
Weirzba et al, 2015	India	34	Observational	0.69 [0.14 , 0.89]
Average VE				0.59 [0.50 , 0.67]
Americas				
Sanchez et al, 1994	Peru	4	Randomized	0.86 [0.36 , 0.97]
Ivers et al, 2015	Haiti	22	Observational	0.62 [0.05 , 0.85]
Average VE				0.72 [0.31 , 0.89]
Africa				
Khatib et al, 2012	Tanzania	15	Observational	0.79 [0.46 , 0.92]
Lucas et al, 2005	Mozambique	5	Observational	0.84 [0.46 , 0.95]
Luquero et al, 2014	Guinea	5	Observational	0.87 [0.57 , 0.96]
Average VE				0.83 [0.68 , 0.91]

0.00 1.00

By geography, 2-dose Efficacy/Effectivness

One vs Two Vaccine Doses



One Dose Protection

- Single RCT: efficacy estimate of 40% at 6-months (though 63% against severely dehydrating cholera)
- Effectiveness data from African and Haiti suggests similar levels of protection between 1- and 2-doses in the short term (p=0.31)
- New data from short-term effectiveness study (Epicentre/MSF) in Zambia consistent with these results: VE=84.7% (95% CI: 27.0 to 96.6)

Summary on Vaccine Protection

What is the evidence for protective efficacy, effectiveness, and duration of the currently available killed, whole cell kOCVs during the first 5 years following immunization among individuals ≥ 1 year old?

- Currently available oral cholera vaccines with a 2-dose schedule are efficacious and effective for at least 3 years
- Currently available kOCVs are effective for at least 5 years (only 2 studies)
- Currently licensed oral cholera vaccines are efficacious and effective for at least 6 months for a single dose

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