ISPE (Vaccines SIG)-Brighton Collaboration Vaccine Journal Club

First Session (7 October 2020)

Nadja Vielot (UNC-CH)

Victoria Abbing (GSK vaccines)

Journal Club

Foreword

- First session as test run
- Hope for echoes for further interest
- Ensure continued optimization of sessions
- Choice of article for the first session
  - ✓Observational study
  - ✓Vaccine effectiveness estimation
  - ✓Instigate methodological discussions and insights

Paper overview

Alternative observational designs to estimate the effectiveness of one dose of oral cholera vaccine in Lusaka, Zambia. Ferreras E et al. 2020 Epidemiol Infect (Cambridge Univ Press)

Prior publication (NEJM 2018): *Single dose Cholera Vaccine in response to an outbreak in Zambia* (Letter to editor)

- Study Context
  - Lusaka, Zambia
  - Cholera outbreak: February 4 – June 15, 2016 (after 4 yrs of no reported cases)
- Intervention
  - Vaccine campaign, 1-dose OCV: April 9 – April 25, 2016
  - Deployed in high-risk areas (targeting 500,000 from >2M pop)
  - 1 dose due to insufficient stockpile for 2 doses
  - After doses became available in Dec 2016 2nd dose were given (high risk area)
- 2018 publication
  - Matched case –control : VE 88.9 (95%CI 42.7 ; 97.8)

3 study designs

Matched case control (MCC)

Test negative case control (TNCC)

Case-cohort (CC)

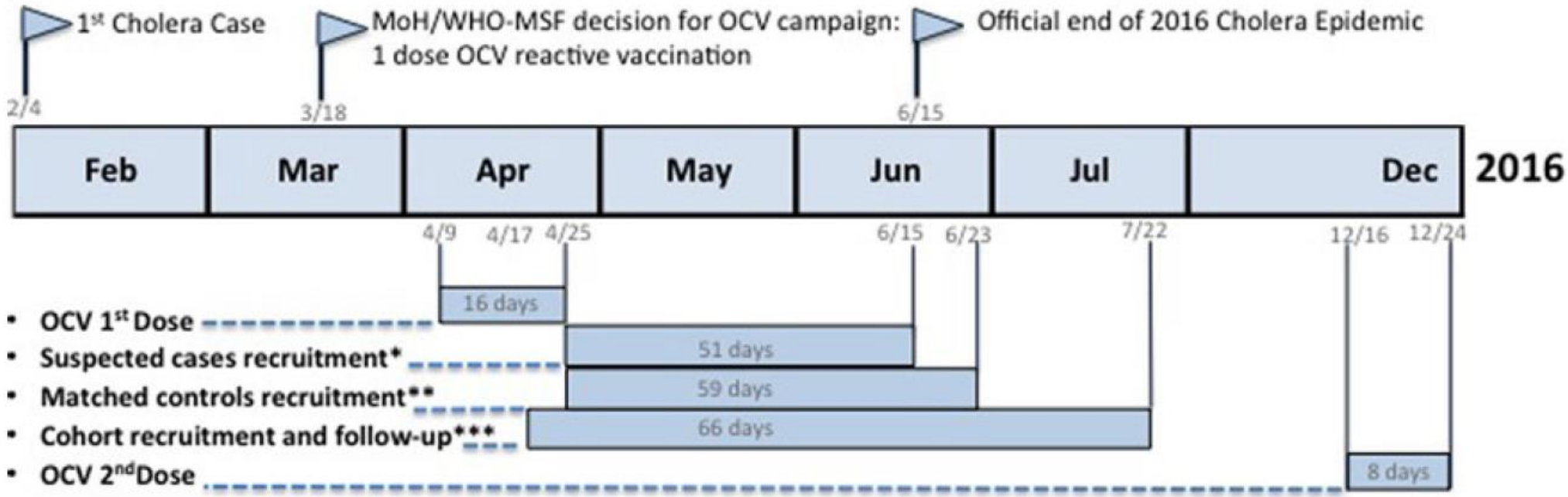

Fig. 1. Timeline, Lusaka, Zambia, 2016. *Test-negative; **case-control; ***case-cohort.

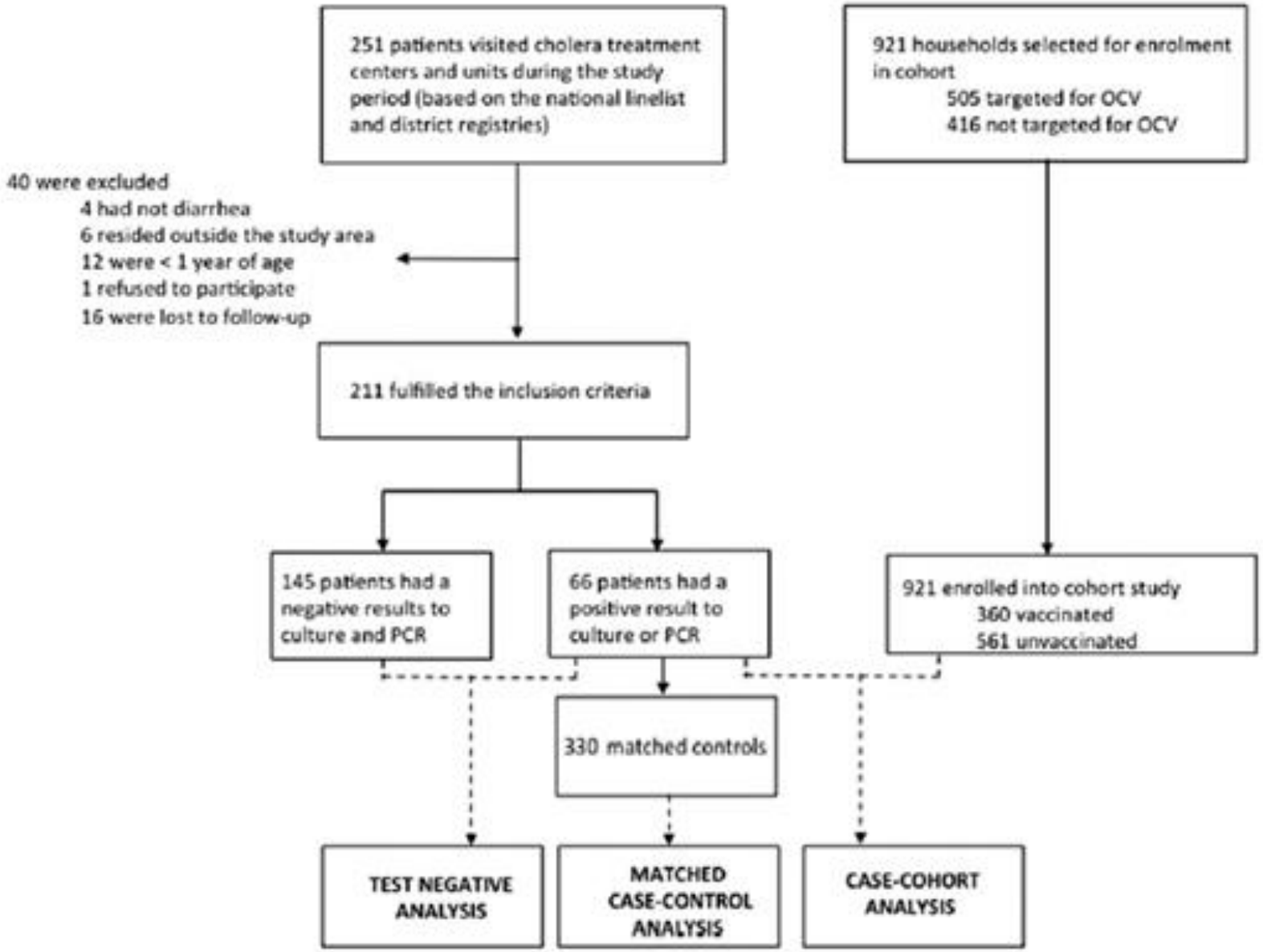

Fig. 2. Study flowchart.

3 study designs

Matched case control (MCC)

Test negative case control (TNCC)

Case-cohort (CC)

3 study designs

Matched case control (MCC)

Test negative case control (TNCC)

Case-cohort (CC)

Earlier publication (2018):
MCC same numbers
66 cases and 330 controls
Bias indicator analysis (next slide)

Table 1. Crude and adjusted VE estimates

	Vaccinated (single-dose)[a]	Unvaccinated	Crude VE		Adjusted VE	
	No. of participants (%)		(95% CI)	*P* value	(95% CI)	*P* value
TNCC analysis						
Cholera cases	3 (5)	63(95)	Ref		Ref	
Non-cholera diarrhoea cases	39 (27)	106 (73)	87.1% (62.4–97.0)	<0.01	80.2%[b] (16.9–95.3)	0.03
MCC analysis						
Cholera cases	3 (5)	63 (95)	Ref		Ref	
Matched controls	44 (13)	286 (87)	84.7% (27.0–96.6)	0.02	88.9%[c] (42.7–97.8)	<0.01
Case-cohort analysis						
Cholera cases	3 (5)	63 (95)	Ref		Ref	
Person time at-risk (in days)	48 765.6	18 826.0	86.7% (56.6–95.9)	<0.01	89.4%[a] (64.6–96.9)	<0.01

[a]Case-cohort: VE was adjusted by age, sex, number of children under 5 years of age living in the household, access to safe water and the place of defecation.
[b]TNCC: VE was adjusted by age, education level, frequency of treating the drinking water and contact (combined variable that considers those who had a household member with cholera in the previous week or shared the drinking-water source with a cholera patient as 'exposed'). Living in a vaccinated area was included as a stratification variable in the conditional logistic regression model.
[c]MCC: Adjusted by contact. Living in a vaccinated area was included as a stratification variable in the regression model.

Earlier publication (2018):
MCC same numbers
66 cases and 330 controls

Table 1. Crude and adjusted VE estimates

	Vaccinated (single-dose)[a]	Unvaccinated	Crude VE	Adjusted VE (95% CI)	*P* value
Ref					
80.2%[b] (16.9–95.3)				0.03	
Ref					
88.9%[c] (42.7–97.8)				<0.01	
Ref					
89.4%[a] (64.6–96.9)				<0.01	

Table 1. Crude and Adjusted Estimates of Vaccine Effectiveness against Cholera (Main Analysis) and Noncholera Diarrhea (Bias-Indicator Analysis).*

Analysis	Controls	Case Patients	Crude Estimate of Vaccine Effectiveness (95% CI)	P Value	Adjusted Estimate of Vaccine Effectiveness (95% CI)	P Value
	no. of participants (%)		%		%	
Main vaccine-effectiveness analysis						
Total no. of participants	330	66				
Unvaccinated participants	286 (87)	63 (95)	Reference		Reference	
Participants vaccinated with single dose†	44 (13)	3 (5)	84.7 (27.0 to 96.6)	0.02	88.9 (42.7 to 97.8)‡	0.009
Bias-indicator analysis						
Total no. of participants	725	145				
Unvaccinated participants	499 (69)	106 (73)	Reference		Reference	
Participants vaccinated with single dose†	226 (31)	39 (27)	22.8 (–19.7 to 57.5)	0.20	24.6 (–27.5 to 55.5)§	0.29

[a]Case-cohort: VE was adjusted by age, sex, number of children under 5 years of age living in the household, access to safe water and the place of defecation.
[b]TNCC: VE was adjusted by age, education level, frequency of treating the drinking water and contact (combined variable that considers those who had a household member with cholera in the previous week or shared the drinking-water source with a cholera patient as 'exposed'). Living in a vaccinated area was included as a stratification variable in the conditional logistic regression model.
[c]MCC: Adjusted by contact. Living in a vaccinated area was included as a stratification variable in the regression model.

Methods

Model selection for the multivariate analysis: Adjustment for confounder and effect modifier.

Missing variables (i) removing the entries (ii) dummy variable, (iii) multiple imputation. Adjusted VE reported were based on iii (choice?)

Spacial scale matching (to control for vacc uptake and infection risk) sensitivitiy analysis (excluding <150 m, <300m) → within 4% of the main VE estimates.

Confounders in the models based on bivariate analysis for each design

MCC matching by age group, neighborhood and calendar time

	TNCC	MCC	CC
Crude Vaccine Effectiveness (95% CI)	87.1% (62.4-97.0)	84.7% (27.0-96.6)	86.7% (56.6-95.9)
Table S5. Summary of the variables included in the multivariate models			
Variables included as possible confounders			
Age	x		x
Sex			x
Education level	x		
Frequency of treating the drinking water	x		
Household member with cholera in the previous week	x	x	
Shared the drinking water source with a cholera patient	x	x	
Nº of children under 5 years living in the household			x
Access to safe water			x
Place of defecation			x
Adjusted Vaccine Effectiveness (95% CI)	80.2% (16.9-95.3)	88.9% (42.7-97.8)	89.4% (64.6-96.9)

Discussion Points

- Rationale for re-assessment of VE after initial assessment in 2018
  - Single dose effectiveness to those not previously exposed to the infection
  - Duration of protection of single dose (possible?)
  - Appropriate interval for administration of 2nd dose (possible?)
- Case confirmation was culture , PCR or both. Non cases: negative cholera culture and PCR
- Exposure ascertainment (interview and Vx card check when possible)
- TNCC (balance between vaccinated and non vaccinated with respect to non cholera diarrhea), VE MCC ≅ TNCC (minimal healthcare seeking bias)
- Indicator bias in earlier analysis MCC
- No stratification of VE by age and severity of disease (couldn’t check for effect modification)

Discussion Questions

General

- Would have been nice to see a map of the vaccine coverage areas versus sampling areas

MCC

- age ranges are very wide and might lead to poor matching on cholera risk factors
- “would have sought treatment in a CTC”: how was this determined?
- Should they have controlled for the matching factors ? Age, sex, factors associated with proximity. Looks like the age distribution was changed by matching.
- Excluded controls might still be at risk for *cholera* diarrhea?

TNCC

- Vaccination was not associated with other-cause diarrhea, suggesting that vaccinated and non-vaccinated persons seek healthcare in equal proportions

CC

- The cohort was formed during the vax campaign but after the outbreak had already started. Was the cohort free of prevalent or recovered cases?

Observational designs

Basic requirement for robustness:
Disease identification and ascertainment
Vaccination status and ascertainment
Susceptibility to disease (at risk)

Matched Case Control	Test Negative Case Control	Case-Cohort
Strategy - Controls are selected from and representative of the source population - Controls can be selected at the time of the case (this study) or at the end of observation **Pros/Cons** - OR Can approximate risk ratio or rate ratio - Matching and selection can induce bias	**Strategy** - Controls selected from those who test negative for the disease **Pros/Cons** - More efficient in outbreak settings - Controls for healthcare utilization, catchment areas, geographical factors - Limited external validity - Classification dependent on test characteristics	**Strategy** - Select a random sub-cohort from the full cohort at risk - Use all cases and up-weight the non-cases **Pros/Cons** - More efficient than a cohort study - Can evaluate multiple outcomes in the same subcohort - Less precise than a cohort study