CORRESPONDENCE

Single-Dose Cholera Vaccine in Response to an Outbreak in Zambia

TO THE EDITOR: Killed oral cholera vaccines (OCVs) are part of the standard response package to a cholera outbreak, although the two-dose regimen of vaccines that has been prequalified by the World Health Organization (WHO) poses challenges to timely and efficient reactive vaccination campaigns.[1] Recent data suggest that the first dose alone provides short-term protection, similar to that of two doses, which may largely dictate the effect of OCVs during epidemics.[2-4]

A cholera outbreak was detected in Lusaka, Zambia, in February 2016, after a period of 4 years without a reported case of cholera. An emergency reactive vaccination campaign was implemented in April 2016, targeting more than 500,000 persons who were at high risk for cholera in Lusaka (population, >2 million persons). The Ministry of Health, with support from Médecins sans Frontières and the WHO, decided to implement a single-dose campaign to quell the epidemic rapidly, in view of the insufficient number of vaccine doses that were available in the global stockpile to complete a two-dose campaign. In December 2016, when more doses became available, a second round of vaccination was organized and the second vaccine dose was offered to persons at risk.

We conducted a matched case–control study to quantify the short-term effectiveness of a single-dose OCV regimen (Shanchol) between April 25, 2016, and June 15, 2016. The study was approved by two institutional review boards, and written informed consent was obtained from all the participants (see the Supplementary Appendix, available with the full text of this letter at NEJM.org). Cases of cholera were confirmed by means of culture, polymerase-chain-reaction assay, or both. Age- and sex-matched controls were selected from among the neighbors of case patients with cholera.[5] We ascertained vaccination status by means of structured interviews using photographs of OCVs, and verified the information with the use of vaccination cards, when available. We calculated the vaccine effectiveness as (1−odds ratio)×100, using conditional logistic regression. We also conducted a bias-indicator study involving persons with noncholera diarrhea and matched controls.

We enrolled 66 persons with confirmed cholera and 330 matched controls. Vaccination with a single dose was associated with significant protection in both the crude and adjusted analyses (effectiveness in the adjusted analysis, 88.9%; 95% confidence interval, 42.7 to 97.8; P=0.009) (Table 1). The bias-indicator analysis included 145 persons with noncholera diarrhea and 725 matched controls. In that analysis, we found that

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

* In the main vaccine-effectiveness analysis, a person with a confirmed case of cholera was defined as any patient with acute watery diarrhea (at least three watery stools in a 24-hour period) with a positive culture, polymerase-chain-reaction (PCR) assay results, or both for *Vibrio cholerae* serogroup O1. In the bias-indicator analysis, a person with noncholera diarrhea was defined as a patient with a suspected case of cholera but with a negative cholera culture and PCR assay results. Inclusion and exclusion criteria for the controls and case patients, as well as the laboratory methods for confirmation of cholera, are provided in the Supplementary Appendix.

† Study staff asked participants during a structured in-person interview at their home whether they had been vaccinated. We considered a person to be vaccinated if the person reported having received the vaccine and if the date of diarrhea onset (or, for controls, the date of diarrhea onset in the matched case patient) was at least 7 days after the receipt of vaccine. For persons who reported having been vaccinated, the interviewer asked to see the vaccination card and took a photograph of it, if available. In the main analyses, vaccination status was based on oral reporting.

‡ The crude and adjusted estimates of vaccine effectiveness were obtained with the use of conditional logistic regression. The final adjusted model included variables that were potentially associated with the outcome and with exposure to cholera ($P<0.20$) and those that modified the vaccine effectiveness by more than 5% in the bivariate model (i.e., sharing the source of drinking water with a person with cholera or having a household member with cholera in the previous week). Living in a vaccination area was included as a stratification variable in the regression model.

§ The selection of variables for inclusion in the final regression model of the bias-indicator analysis was done with the use of the same criteria that were used in the main analysis. In the bias-indicator analysis, the vaccine effectiveness estimate was adjusted by frequencies of having treated drinking water and having soap available at home. Living in a vaccination area was included as a stratification variable in the regression model.

the odds of vaccination did not vary significantly between the two groups in the crude or adjusted analyses ($P=0.29$ in the adjusted analysis), which suggests the absence of selection bias.

Our results show the short-term effectiveness of a single dose of OCV delivered during an outbreak. Previous studies measuring the protection provided by a single dose of OCV were conducted in areas with recent exposure to cholera, which raises the possibility that single-dose regimens might act to boost natural immunity.[2,3,5] Our results indicate that single-dose regimens provide protection in populations with less exposure to cholera, such as those in Lusaka and much of sub-Saharan Africa, where multiyear lull periods are punctuated by explosive outbreaks. Although additional work is needed to determine the protection provided by a single-dose vaccine in young children and persons not previously exposed to cholera, the duration of protection provided by a single-dose regimen, and an appropriate interval for the administration of a second dose, our results support the use of single-dose regimens to improve responses during a cholera outbreak.

Eva Ferreras, M.Pharm., M.Sc.
Epicentre
Paris, France

Elizabeth Chizema-Kawesha, M.D., M.P.H.
Ministry of Health
Lusaka, Zambia

Alexandre Blake, M.D.
Epicentre
Paris, France

Orbrie Chewe, B.Sc.
Ministry of Health
Lusaka, Zambia

John Mwaba, M.Sc.
University Teaching Hospital
Lusaka, Zambia

Gideon Zulu, M.P.H.
Ministry of Health
Lusaka, Zambia

Marc Poncin, Ph.D.
Médecins sans Frontières
Geneva, Switzerland

Ankur Rakesh, M.B., B.S., M.P.H.
Anne-Laure Page, Ph.D.
Epicentre
Paris, France

Savina Stoitsova, M.Sc.
European Program for Intervention Epidemiology Training
Stockholm, Sweden

Caroline Voute, M.P.H.
Florent Uzzeni, M.D.
Hugues Robert, B.Arch., I.D.H.A.
Micaela Serafini, M.D.
Médecins sans Frontières
Geneva, Switzerland

Belem Matapo, M.Sc.
World Health Organization
Lusaka, Zambia

Jose-María Eiros, M.D., Ph.D.
University of Valladolid
Valladolid, Spain

Marie-Laure Quilici, Ph.D.
Institut Pasteur
Paris, France

Lorenzo Pezzoli, D.V.M., Ph.D.
World Health Organization
Geneva, Switzerland

Andrew S. Azman, Ph.D.
Johns Hopkins Bloomberg School of Public Health
Baltimore, MD

Sandra Cohuet, M.D., M.P.H.
Epicentre
Paris, France

Iza Ciglenecki, M.D.
Médecins sans Frontières
Geneva, Switzerland

Kennedy Malama, M.D., M.P.H.
Ministry of Health
Lusaka, Zambia

Francisco J. Luquero, M.D., Ph.D.
Epicentre
Paris, France
francisco.luquero@epicentre.msf.org

Supported by Médecins sans Frontières, by a grant to Drs. Azman and Luquero from the DOVE project at Johns Hopkins Bloomberg School of Public Health, and by Institut Pasteur.

Disclosure forms provided by the authors are available with the full text of this letter at NEJM.org.

1. Martin S, Lopez AL, Bellos A, et al. Post-licensure deployment of oral cholera vaccines: a systematic review. Bull World Health Organ 2014;92:881-93.
2. Qadri F, Wierzba TF, Ali M, et al. Efficacy of a single-dose, inactivated oral cholera vaccine in Bangladesh. N Engl J Med 2016; 374:1723-32.
3. Azman AS, Parker LA, Rumunu J, et al. Effectiveness of one dose of oral cholera vaccine in response to an outbreak: a case-cohort study. Lancet Glob Health 2016;4(11):e856-e863.
4. Azman AS, Luquero FJ, Ciglenecki I, Grais RF, Sack DA, Lessler J. The impact of a one-dose versus two-dose oral cholera vaccine regimen in outbreak settings: a modeling study. PLoS Med 2015;12(8):e1001867.
5. Luquero FJ, Grout L, Ciglenecki I, et al. Use of *Vibrio cholerae* vaccine in an outbreak in Guinea. N Engl J Med 2014;370:2111-20.

DOI: 10.1056/NEJMc1711583