



Published in final edited form as:

Lancet Infect Dis. 2017 May ; 17(5): 469–470. doi:10.1016/S1473-3099(17)30055-5.

Pregnant women should not be excluded from cholera vaccination campaigns. Commentary for Safety of a killed oral cholera vaccine (Shanchol) in pregnant women in Malawi: An observational cohort study by Ali M, et al.

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Cholera is a serious dehydrating diarrheal disease caused by toxigenic serogroups (O1 and O139) of *Vibrio cholerae*, which is spread by fecal contamination of water and food. It is a disease of poverty and is closely linked to poor sanitation and lack of clean water.¹ It has been estimated that cholera affects as many as 2.8 million and kills approximately 91,000 persons annually.² Children aged <5 years have the greatest incidence of disease in endemic areas. Among pregnant women, cholera can cause serious complications, namely fetal loss, with rates varying from 2% to 36%.^{3–4} Three vaccines have been prequalified by the World Health Organization: Dukoral™,^{5,6} a monovalent oral killed vaccine based on whole cells of *V. cholerae* O1 and recombinant cholera toxin B subunit, Shanchol and Euvichol, both bivalent oral killed vaccines based on serogroups O1 and O139.^{5,7–9} The range of protective efficacy for Dukoral™ and Shanchol at 4–6 months, 1 year, and 2 years after vaccination are 86%–66%, 62%–45%, and 77%–58%, respectively.⁵ For Euvichol efficacy was 65% after 5 years for > 5 year olds.¹⁰

Pre-licensure and post-marketing studies of these vaccines have demonstrated favorable safety profiles.^{5–10} In addition, a limited number of safety evaluations have been conducted in pregnant women during cholera outbreaks that suggest these vaccines are safe during pregnancy.^{11,12} However, pregnant women have not generally been included in studies intended to assess the safety of these cholera vaccines. In an observational cohort study by Ali et al. Shanchol was used in the setting of a 2015 cholera outbreak in Malawi.¹³ The authors assessed the risk of pregnancy loss in 316 pregnant women compared to 327 pregnant women not exposed to the vaccine.¹³ The authors found the vaccine was not associated with an increased risk of stillbirth or neonatal mortality. Although there was no increased risk of spontaneous abortion (SAB) in vaccinated women, few of the enrolled women received the vaccine during the first trimester. Moreover, the rate of SAB was well below the national background rates (15%) of SAB in both study groups. The study also

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Authors contributions: All authors contributed to the design, development and writing of the manuscript. PLM conceptualized the idea, led the writing and was the primary author of the manuscript. PLM and LS contributed as maternal subject matter experts, collected and compiled relevant external information, and prepared the manuscript.

found no increased risk of birth defects in pregnant women exposed to the vaccine. However, the small number of first trimester exposures limits the significance of this finding. Additionally, this study was not powered to assess for the risk of birth defects, which are rare events.

Only two other studies, both retrospective cohorts, have assessed the safety of cholera vaccines in pregnancy. Hashim et al.¹¹ assessed the safety of Dukoral™ among 196 pregnant women in Zanzibar and compared pregnancy and infant outcomes to 955 unvaccinated pregnant women. They found no statistically significant differences in SABs, infant deaths or infant abnormalities among both groups.⁸ In a second study, Grout et al.¹² assessed the safety of Shanchol in 1,543 pregnant women in Guinea. Among 1,312 and 272 vaccine exposed and unexposed fetuses from these pregnancies, no statistically significant differences were found in the rate of pregnancy loss, infant deaths or malformations.¹² In both studies, the rate of SAB in vaccinated and unvaccinated groups was well below the expected background rate for this condition in the populations studied.

In an ideal study design, pregnant women would have been randomly assigned to receive the cholera vaccine or a placebo. However, pregnant women are considered special populations in clinical research, with specific regulations to protect the pregnant woman and her fetus.¹⁴ For this reason, there are ethical considerations for administering the vaccine in a clinical trial. However, since pregnant women are at higher risk of morbidity and mortality from disease, there are also ethical considerations in withholding a potentially life-saving vaccine during a cholera epidemic. Although the study by Ali et al.¹³ adds important safety information about Shanchol in pregnant women, there continue to be gaps in knowledge on the safety of this vaccine in pregnancy, specifically, if administered during the first trimester. Future studies will need to further clarify the safety of cholera vaccines in first trimester exposed pregnant women by including more women exposed to the vaccine during the first trimester, and by actively capturing data on early losses which may be missed or not reported.

In areas endemic for cholera, pregnant women are at risk of severe diarrheal disease which can result in dehydration and pregnancy loss.^{1,4} Although good sanitation measures (clean water and sewage systems) are ideal, these measures are beyond the reach of many areas, especially during cholera outbreaks. The available cholera vaccines recommended by WHO offer an additional preventive approach and based on current available data they can be safely used during pregnancy.

Acknowledgements

We thank CDC's Immunization Safety Office staff whose work allowed this activity to be conducted. This commentary is a US Government-initiated project and received no external funding. The findings and conclusions in this Article are those of the authors and do not necessarily represent the official position of the CDC.

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