STOP CHOLERA
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In Brief: Cholera and the Use of Oral Cholera Vaccines in Pregnant Women

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Introduction

Cholera in pregnant women has been linked to higher rates of miscarriages and stillbirths. When used effectively, oral cholera vaccines (OCVs) can prevent or control cholera outbreaks and manage endemic cholera. For this reason, the World Health Organization (WHO) listed pregnant women in its 2010 position paper on cholera vaccines as a group that is "especially vulnerable to severe disease and for which the vaccines are not contraindicated" and that therefore may also be targeted for cholera vaccination.[1] Pregnant women have been excluded from clinical trials of OCVs resulting in a lack of controlled data on their safety during pregnancy. As a result, the package insert of Shanchol, a killed whole-cell oral vaccine now being used in cholera-affected countries, states that the vaccine is not recommended for use in pregnancy, except under certain circumstances (see box). Interestingly, the package insert for Dukoral – a similar killed whole-cell oral vaccine that includes a component of the cholera toxin and is used mainly by travelers – states that the vaccine "may be administered during pregnancy and to lactating women."[2]

How are immunization program managers and policymakers planning cholera vaccination campaigns, supposed to process this conflicting information? Should they heed the more conservative OCV label and exclude pregnant women from the campaigns? Or should they include pregnant women based on the fact that no killed vaccines have been found to be harmful during pregnancy, and in fact, some (killed seasonal influenza vaccines and tetanus toxoid) are explicitly recommended for pregnant women? Or should pregnant women and women of child-bearing age be a priority target group for cholera vaccination because of the disease's elevated risk of harm to the unborn child?

Considerations for OCV use with Pregnant Women

This brief guides immunization program managers in making decisions about the use of OCVs with pregnant women by addressing the following questions:

1) Does cholera in pregnant women increase the risk of maternal or fetal death or other complications?
2) What is the evidence of the safety of killed OCVs during pregnancy and of killed vaccines in general?
3) Does vaccinating pregnant or lactating women against cholera offer additional protection to their fetuses or infants?
4) Do the benefits of vaccinating pregnant or lactating women against cholera outweigh potential risks of vaccination?

Excerpt: Shanchol package insert

"No specific clinical studies have been performed to evaluate the safety and immunogenicity of Shanchol in pregnant women and for the fetus. The vaccine is therefore not recommended for use in pregnancy. However Shanchol is a killed vaccine that does not replicate, is given orally and acts locally in the intestine. Therefore, in 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 risk in case of a medical emergency or an epidemic."

http://www.shanthabiotech.com/files/Shanchol Domestic Pack insert.pdf

Does cholera in pregnant women increase the risk of maternal or fetal death or other complications?

Evidence from several studies shows that there is a high risk that a pregnant mother will miscarry or have a premature delivery if she develops cholera. In one study conducted in the 1960s from Bangladesh, half of cholera patients in their third trimester of pregnancy had premature delivery.[3] Later studies from Senegal and Nigeria also found higher rates of fetal losses in women with cholera in their second or third trimester.[4, 5] More recently, the rates of fetal loss were lower in Haiti when women were treated in a specialized hospital, but these rates were still high.[6] The Haiti study clearly showed that severe dehydration due to cholera is a major risk factor for miscarriages and stillbirths (Table 1). Pregnant women who were severely dehydrated upon arrival at the hospital were nine times more likely to lose the infant than women who were mildly dehydrated.

Table 1. Rates of fetal losses (miscarriages and stillbirths) by level of dehydration among women in Haiti treated at a specialized cholera unit for pregnant women, 2010-20116

Dehydration level	No. pregnant women	Fetal losses		Adjusted relative risk
		No.	%	
None	136	4	2.9	9.4 (severe vs. mild dehydration) (p=0.005)
Moderate	110	11	10.0	
Severe	16	6	37.5	

The miscarriage or premature delivery is not due to an actual cholera infection of the fetus; rather, it is due a sharp, rapid reduction in blood volume (hypovolemia) in the woman due to dehydration. This leads to a lack of blood flow to the placenta which, in turn, leads to reduced blood flow and fetal asphyxia. These changes are further complicated by maternal acidosis (increased acidity in the blood and amniotic fluid), resulting from a loss of bicarbonate in the stool during cholera.

Theoretically, if proper hydration treatment was given to the pregnant woman, this complication would not occur, but often women are delayed in reaching a hospital. In the studies from Haiti and Bangladesh, nearly half of the fetal losses occurred before the pregnant woman reached the hospital, and the women were severely dehydrated or in shock when they arrived. In some settings, social factors appear to delay the decision to seek care at a hospital. For example, in Senegal, the average length of time between the onset of symptoms and arrival at a health facility was almost four times longer (43 vs. 11 hours) among pregnant women than in the general population and ranged from 1-8 days.[4]

In addition, treating pregnant women for cholera can be especially challenging – particularly in estimating dehydration levels towards the end of pregnancy, given that plasma volume is elevated in a normal pregnancy. As a result, clinicians may under-estimate the degree of dehydration in these women. Pregnant women with cholera therefore require earlier, more rapid and more intensive fluid replacement, as well as close monitoring of rehydration.

These factors highlight the need to prevent cholera in pregnant women, including specifically targeting them for cholera vaccination whenever cholera vaccine is being given to the community.

What is the evidence of the safety of killed OCVs during pregnancy and of killed vaccines in general?

To date, there have only been two studies that explored the safety of OCV use during pregnancy.

These studies – in Zanzibar (using Dukoral) and in Guinea (using Shanchol) – were both retrospective studies following mass cholera vaccination campaigns that identified all women who were pregnant during the campaigns through house-to-house visits, noting if they were vaccinated or not, and the outcome of their pregnancy. [7,8] Both studies found small and not statistically significant higher rates of miscarriages or stillbirths in vaccinated vs. non-vaccinated women. In Zanzibar, selection bias may have been a factor, as the vaccinated group was older, poorer and received less antenatal care – all confounding risk factors for fetal loss. Many years of post-marketing surveillance for Dukoral has found no safety concerns when given during pregnancy.

There is no scientific reason to believe that current OCVs (Shanchol and Dukoral) are unsafe in pregnant women. The vaccines are composed of killed bacteria, similar to those that enter our digestive system every time we eat cooked foods – thus, the bacteria are not able to replicate. The vaccines also act in the gastro-intestinal mucosa and do not enter the maternal or fetal circulation system. These factors make it highly implausible that oral cholera vaccines could harm a fetus. OCVs do not trigger systemic reactions such as fever, which have been linked to miscarriages in early pregnancy. Furthermore, there is no evidence that killed vaccines in general cause harm to fetuses. In fact, two such vaccines – tetanus toxoid and inactivated influenza vaccines – are now recommended by WHO specifically for pregnant women.

Does vaccinating pregnant women or new mothers against cholera offer additional protection to their fetuses or infants?

Studies indicate that mothers are major transmitters of cholera within their families, especially through their role as food preparers.[9] Thus, it is not surprising that a case-control study conducted during an OCV trial in Bangladesh found that vaccination of women was associated with a 47% reduction in severe cholera in their non-vaccinated children.[10] The lower rate in these children occurs because the vaccinated mothers do not transmit the disease as readily.

Do the benefits of vaccinating pregnant or lactating women against cholera outweigh potential risks of vaccination?

Below is a summary of the evidence of the risks and benefits of cholera vaccination in pregnant women using killed whole-cell based oral cholera vaccines:

Risks:	*Benefits:*
• No controlled trials of these vaccines have included pregnant women. However, available data from retrospective surveys of women vaccinated with OCV during pregnancy indicate no significant increase in adverse maternal or pregnancy outcomes in vaccinated as compared to non-vaccinated pregnant women. • Post-marketing surveillance data from manufacturers have found no evidence of elevated adverse events in pregnant women. • To date, there is no evidence that inactivated vaccines in general are harmful to pregnant women, their fetuses or newborns. In fact, two inactivated vaccines – influenza and tetanus toxoid – are, in fact, specifically recommended for all pregnant women by WHO and the U.S. Centers for Disease Control and Prevention (CDC). CDC also recommends acellular pertussis vaccination during pregnancy. The fact that OCV is administered orally should make it even safer than injectable killed vaccines.	• The vaccine can protect against cholera which causes severe dehydration. If cholera occurs, there is high rate of fetal loss. • Studies show that pregnant women with cholera often delay seeking health care so it is even more important to prevent cholera in this group who may not receive treatment in time to prevent complications. • In addition to the potential reduction in fetal losses by preventing cholera during pregnancy, vaccinating women before, during or just after pregnancy can reduce the risk the mother will transmit the infection to her children.

Conclusions

- Cholera presents a significant risk to the mother and unborn child.
- There is no evidence that the vaccine presents a risk to the mother or the unborn child.

Recommendations

- Pregnant women should receive OCV when vaccine is being distributed to their community. In fact, pregnant women should be encouraged to receive vaccine.
- Pregnant women should not be excluded from receiving OCV.
- There is no need to screen persons receiving vaccine for pregnancy status.
- Women in general should be targeted for vaccination to protect both themselves, their families and future children.
- Journalists should advocate for pregnant women and infants to be spared cholera infection by appropriate vaccination campaigns that adequately cover the population in need.

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[1] World Health Organization. Cholera vaccines: WHO position paper. Weekly Epidemiological Record 2010; 85:117-128.

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