World Health Organization

# Technical Note

## Evidence of the risks and benefits of vaccinating pregnant women with WHO pre-qualified cholera vaccines during mass campaigns

## November 2016

### Background

Three oral cholera vaccines (OCVs) are currently pre-qualified by WHO: Dukoral®, Shanchol™, and Euvichol® All are oral killed whole-cell (WC) vaccines that provide sustained protection of >50% for at least two years in endemic populations, induce an immune response relatively quickly (7-10 days after the 2nd dose) and have a good safety profile. Shanchol™ has demonstrated longer term protection – 65% over five years – as compared to Dukoral®.[1] On the other hand, Dukoral® has been shown to provide better short-term protection against cholera, particularly among children 2-5 years old and also confers significant short-term protection against ETEC (≈50% for three months).[2,3] Shanchol™ and Euvichol® have the same formulation and comparable safety and immunogenicity profiles.[4] Both are reformulated versions of Dukoral® without the B subunit of the cholera toxin (no need for buffer).[5] All three vaccines have a two-dose regimen with doses given between one and six weeks apart (three doses for Dukoral® in children aged 2–5 years).

### Summary of current WHO recommendations concerning OCVs[6]

Given the availability of 3 WHO pre-qualified OCVs and data on their efficacy, field effectiveness, feasibility and acceptance in cholera-affected populations, immunization with these vaccines should be used in conjunction with other prevention and control strategies in areas where the disease is endemic. It should also be considered in areas at risk for outbreaks. Vaccination should not disrupt the provision of other high-priority health interventions to control or prevent cholera outbreaks.

*OCV use during emergencies (humanitarian crisis and cholera outbreaks)*

Vaccination should be considered by local health authorities to help prevent potential outbreaks [e.g., during crisis situations] or the spread of ongoing outbreaks to new areas. Depending on the local infrastructure, vaccination should be considered as an additional control measure, following a clear identification and thorough assessment of the actual risk of cholera in the areas to be targeted and a thorough investigation of the current and historical epidemiological situation

*OCV use in endemic settings*

Cholera control should be a priority in areas where the disease is endemic. In cholera-endemic countries, vaccination should be targeted at high-risk areas [so called “hotspots”]

and population groups. Vaccination should be one of the components of a comprehensive approach to control cholera, which should include long-term plans for the development of water and sanitation systems.

*Use during pregnancy*

According to the 2010 WHO Position Paper on cholera vaccines[4], preschool-aged and school-aged children are the primary targets for cholera vaccination in many endemic areas. However, the paper also specifically mentions pregnant women as a group that is "especially vulnerable to severe disease and for which the vaccines are not contraindicated", and thus a possible target for vaccination as well.

## Current documentation from producers of WHO pre-qualified OCVs concerning their use during pregnancy

*Dukoral® documentation*

The Dukoral® package insert states that "The vaccine may be administered during pregnancy and to lactating women."[7] However, the Dukoral® product monograph states the following: "The effect of Dukoral® on embryo-fetal development has not been assessed and animal studies on reproductive toxicity have not been conducted. No specific clinical studies have been performed to address this issue. The vaccine is therefore not recommended for use in pregnancy. However, Dukoral® is an inactivated vaccine that does not replicate. Dukoral® is also given orally and acts locally in the intestine. Therefore, in theory, Dukoral® should not pose any risk to the human fetus. Administration of Dukoral® to pregnant women may be considered after careful evaluation of the benefits and risks."[8]

*Instructions from the Shanchol™ package insert[9]*

"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 women may be considered after careful evaluation of the benefits and risk in case of medical emergency or an epidemic."

*Instructions from the Euvichol® package insert[10]*

"No specific clinical studies have been conducted to evaluate the efficacy and safety of Euvichol in pregnant and lactation women. Therefore, the vaccine is not recommended for use in pregnancy."

*Clarification of the producers' documentation*

The documents from producers do not state that the vaccine is contraindicated during pregnancy. The phrase "the vaccine is …. not recommended for use in pregnancy" refers to the fact that a specific recommendation for its use during pregnancy has not been made

due to a lack of data on the use of the vaccine in pregnant women. Thus, none of these 3 vaccines is contraindicated in pregnant women.

### The risk associated with cholera in pregnant women

The rates of fetal loss among pregnant women with cholera who are in their second or third trimester have ranged in studies from 8% to 33%,[11,12,13,14] while stillbirth rates alone (third trimester losses) among these women in recent studies in Haiti and Senegal were found to be 5.5 times and 1.8 times higher than estimated national stillbirth rates, respectively.[8,9] Two of the studies, from Haiti and East Pakistan (now Bangladesh), also showed that severe dehydration in pregnant women with cholera significantly increases the risk of stillbirths or miscarriages – up to nine times in the study in Haiti.[8,11]

Studies show that pregnant women with cholera often delay seeking health care – by on average four times longer than in the general population in the study in Senegal.[9] Nearly all women in their third trimester who lost their fetuses in the study in East Pakistan conducted in the 1960s were near death when they arrived at the hospital.[11] In addition, in some studies, a substantial portion of pregnant women with cholera – 48% in Haiti – lost their fetuses before arriving at the hospital. This is likely due to both the delay in seeking health care among pregnant women and the fact that the fetuses appeared to die early in the course of the disease.

Estimating the degree of dehydration in pregnant women is difficult, especially towards the end of pregnancy, due to a normal increase in the volume of the mother's plasma. As a result, clinicians may under-estimate the degree of dehydration. Treating cholera in pregnant women is therefore more challenging than in other patients and requires earlier and more intensive fluid replacement, as well as close monitoring of rehydration.

In conclusion, cholera is more severe in pregnant women because of an increased risk of fetal complications and premature delivery, associated with delays in seeking care and difficulties in patient management.

### The risk associated with vaccinating pregnant women with killed OCVs

No controlled trials of WHO pre-qualified OCVs have included pregnant women. However, available data from two retrospective surveys of women vaccinated with OCV during pregnancy – conducted in Guinea in 2012[15] and in Zanzibar in 2010[16] – do not reveal any significant increase in adverse maternal or pregnancy outcomes in vaccinated as compared to non-vaccinated pregnant women. Post-marketing surveillance data for Dukoral®, as well as surveillance data conducted during the efficacy trial of Shanchol™, also have not indicated any elevated adverse effects in pregnant women, though there have been relatively few reports of their use during pregnancy. Similar considerations can be made for the safety profile of Euvichol®, which has the same formulation as Shanchol™.[5]

There is to date no evidence that killed vaccines in general are harmful to pregnant women, their fetuses or newborns and most are not contraindicated during pregnancy. In fact, two –

influenza and tetanus toxoid vaccines – are specifically recommended for all pregnant women by WHO and the U.S. CDC, while the CDC also recommends pertussis vaccination during pregnancy. The fact that OCV is administered orally should, in theory, make it even safer than injectable killed vaccines.

### Potential benefits of vaccination of pregnant women with OCVs

Shanchol™ has been shown to provide 74% protection to adults (age 15 and older) over a five-year period.[17] While there are little data on the efficacy of killed OCVs in pregnant women, a retrospective cohort study in Guinea following mass vaccination with Shanchol® showed that, among women who became pregnant after the vaccination campaigns, cholera incidence was significantly lower in women who had been vaccinated during the campaigns than those who had not.[12] The randomized, non-inferiority trial comparing Euvichol® and Shanchol™ conducted in the Philippines showed that a two dose schedule with Euvichol® induces a strong vibriocidal response comparable to that elicited by Shanchol™.[5]

In addition to the likely reduction in fetal losses by preventing cholera during pregnancy, vaccinating women before, during or just after pregnancy can reduce the risk of cholera in their infants or young children. This is due to the important role of mothers in transmitting the disease to their children and to the herd effects of vaccinating adults in reducing the risk of cholera in children too young to receive the vaccine. In a reanalysis of data from the clinical trial of killed whole-cell oral cholera vaccines in Bangladesh, in which only women and children two years and above were vaccinated, the risk of cholera in non-vaccinated children under two years of age living in areas with high vaccination coverage was less than half the rate among children under two living in areas with low vaccination coverage.[18]

### Conclusion

OCVs are only being supplied to populations deemed to be at high risk of cholera. In these situations, based on the analysis of the risks and benefits, the GTFCC considers that there are considerable benefits, and very few risks, from including pregnant women in a vaccine campaign. The GTFCC will continue to monitor information about safety of OCV during pregnancy.

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