No reason to change WHO guidelines on cleansing the umbilical cord

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20 years ago, neonatal survival was not on the global health agenda. In many low-income settings, infants died without recognition, causing untold grief. However, the past two decades have seen steady improvements in neonatal survival on a background of sustained advocacy, a culture of community-based trials, and improvements in quantity and quality of health care, health behaviour, and demand for services. Nevertheless, an annual 2·7 million newborn babies still do not survive their first month of life.[1] Focusing on one intervention to address this issue, two African trials in *The Lancet Global Health*[2,3] tested umbilical cord cleansing with antiseptic solution. Supporting evidence to date has come from randomised controlled trials in south Asia, which suggested that cleansing with chlorhexidine solution could reduce both periumbilical inflammation (omphalitis) and neonatal mortality.[4-6] In a previous Comment[7] we suggested that the putative effects might diminish at scale, that it would be good for families to do the cord cleansing themselves, and that evidence from high-mortality populations in Africa would be helpful. In the interim, a meta-analysis[8] estimated the combined risk ratio (RR) for neonatal mortality at 0·77 (95% CI 0·63–0·94).

Katherine Semrau and colleagues[2] did a cluster-randomised controlled trial in Southern Province, Zambia. Fieldworkers visited women antenatally within 24 h of delivery, and repeatedly during the newborns' first month of life. Families in the intervention group were given 4% chlorhexidine solution to apply 10 mL, using eyedropper bottles, once per day until cord separation, whereas families in the control group were encouraged to maintain dry cord care. Semrau and colleagues[2] reported no difference between allocation groups in the primary outcome of neonatal mortality rate (deaths [in the first 28 days post-partum] per 1000 livebirths; RR 1·12, 95% CI 0·88–1·44) or the secondary outcome of occurrence of omphalitis (diagnosed by erythema or purulent discharge; 0·73, 0·47–1·13).

Sunil Sazawal and colleagues[3] did a community-based, individually-randomised controlled trial in Pemba Island, Tanzania. Maternal–child health workers visited on the day of delivery and days 1, 4, 10, and 28; showed families how to care for the cord; and gave them 4% chlorhexidine solution to apply once per day, using 10 mL dropper bottles, until cord separation. The trial[3] began with three comparison groups—dry cord care, chlorhexidine treatment group, or control group using a placebo solution—but the control group was dropped in the second phase of the study. Sazawal and colleagues[3] reported no difference between allocation groups in

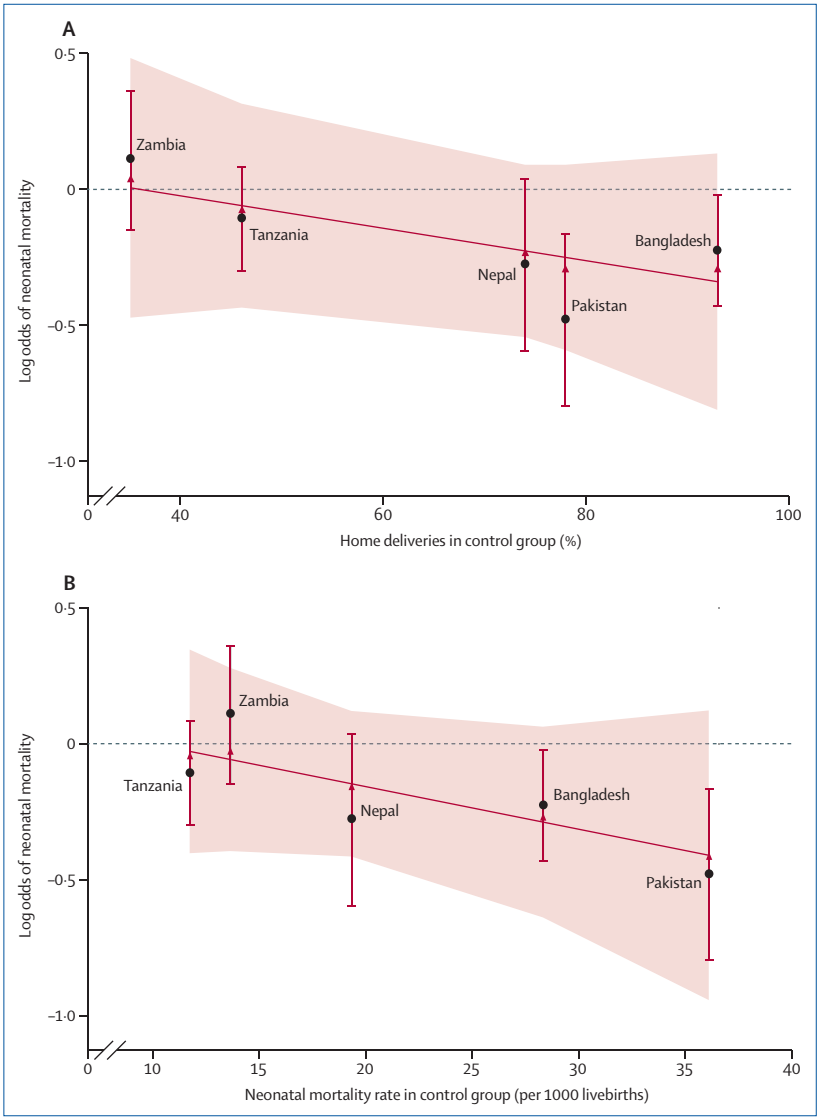

Figure: **Log odds of neonatal mortality associated with chlorhexidine cord cleansing, by proportion of home deliveries in control group (A) and neonatal mortality in control group (B)**
Data are from published findings of five trials.[2-6] Circles=point estimates of log odds. Bars=confidence intervals. Triangles=prediction including random effects. Shaded area=meta-regression CI.

neonatal mortality rates (RR 0·90, 95% CI 0·74–1·09), but babies in the chlorhexidine group had a lower risk of omphalitis than those in the dry cord care group (0·65, 0·61–0·70). Design and randomisation methods differed between the two studies, but follow-up was exceptionally successful: almost 100% of babies at 28 days in Zambia[2] and 97% in Tanzania.[3] On a spectrum of efficacy, the trials were pitched toward real-world conditions. The interventions were delivered by project staff, but mothers were encouraged to apply the treatment themselves. Whether or not they did so—and it seems likely that they did (98% compliance was reported in the Zambia study[2])—it was an intention-to-treat approach.

Two important issues affect our interpretation of these findings. First, many women chose institutional delivery (53% of deliveries were at hospitals in Sazawal and colleagues' trial, and 64% in Semrau and colleagues' trial[2]). The latest WHO guidelines[9] recommend application of chlorhexidine to the umbilical cord stump for the first week after birth, for infants born at home in environments with high neonatal mortality rates (>30 deaths per 1000 livebirths). Dry cord care is recommended after institutional births or home births in settings with lower neonatal mortality rates.[9] Chlorhexidine might be considered as a replacement for harmful applications to the cord stump,[9] but Cochrane reviews, a meta-analysis,[8] and these two new trials[2,3] have not supported an effect after hospital births.[10,11] Second, the neonatal mortality rates were lower than expected. The sample size for the Zambian study[2] was developed on the assumption that the neonatal mortality rate in the control group would be 29·0 deaths per 1000 livebirths. However, the observed rate was 14·4 deaths per 1000 livebirths. The Tanzanian study[3] assumed a control group neonatal mortality rate of 31 deaths per 1000 livebirths. The observed neonatal mortality rate was 11·7 deaths per 1000 livebirths. Both trials increased their sample sizes during implementation, yet confidence intervals around estimates of effects on neonatal mortality rates were nevertheless substantial. To address the issue of underpowering, the research groups combined their estimates in a random-effects meta-analysis, resulting in a relative risk estimate of 0·99 (95% CI 0·80–1·23) for neonatal mortality by day 28.

The three major drivers of newborn mortality are infection, preterm birth, and presumed intrapartum-related compromise. The implicit assumption is that antiseptic cleansing will prevent microbial invasion and reduce deaths from infection. However, as neonatal mortality rates decrease, the proportion of deaths explained by infection reduces in relation to the other two causes. What this means is that the yield in terms of reduction in all-cause mortality as a result of cord antisepsis is likely to be lower in settings with low neonatal mortality rates. To test our assumption, we used the published findings of the five trials[2–6] as a basis for conservative meta-regression. The figure shows the reduction in mortality associated with varying proportions of home delivery and neonatal mortality rates. Although not significant, the impression is that higher neonatal mortality rates (p=0·109) and a higher proportion of home deliveries (p=0·138) were associated with larger effects of cord cleansing on neonatal mortality rates.

Along with the individual trial findings, the figure is consonant with the current WHO guidelines[9] for cord care, to which we recommend no change. Cord cleanliness is part of the suite of hard-won improvements that accompany the increases in survival being seen worldwide. In settings in which neonatal mortality rates remain high, we recommend the kinds of programme that have been associated with reductions in all-cause mortality. These include improvements in institutional quality of care and efforts to improve community-based practices, both central to the 2014 Every Newborn Action Plan.[12]

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DO does not work with but has been a co-author of six publications in the past 5 years with Prof Robert Black, a named author of the paper from Tanzania. The publications were produced by large working groups and DO and TC both either contributed data from their research programmes or were members of a distributed expert group.

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