Early BCG-Denmark and Neonatal Mortality Among Infants Weighing <2500 g: A Randomized Controlled Trial

Background. BCG vaccine may reduce overall mortality by increasing resistance to nontuberculosis infections. In 2 randomized trials in Guinea-Bissau of early BCG-Denmark (Statens Serum Institut) given to low-weight (LW) neonates (<2500 g at inclusion) to reduce infant mortality rates, we observed a very beneficial effect in the neonatal period. We therefore conducted the present trial to test whether early BCG-Denmark reduces neonatal mortality by 45%. We also conducted a meta-analysis of the 3 BCG-Denmark trials. Methods. In 2008–2013, we randomized LW neonates to “early BCG-Denmark” (intervention group; n = 2083) or “control” (local policy for LW and no BCG-Denmark; n = 2089) at discharge from the maternity ward or at first contact with the health center. The infants were randomized (1:1) without blinding in blocks of 24. Data was analyzed in Cox hazards models providing mortality rate ratios (MRRs). We had prespecified an analysis censoring follow-up at oral poliovirus vaccine campaigns. Results. Early administration of BCG-Denmark was associated with a nonsignificant reduction in neonatal mortality rate (MRR, 0.70; 95% confidence interval [CI], 0.47–1.04) and a 34% reduction (0.66; 0.44–1.00) when censoring for oral poliovirus vaccine campaigns. There was no reduction in mortality rate for noninfectious diseases, but a 43% reduction in infectious disease mortality rate (MRR, 0.57; 95% CI, 0.35–0.93). A meta-analysis of 3 BCG trials showed that early BCG-Denmark reduced mortality by 38% (MRR, 0.62; 95% CI, 0.46–0.83) within the neonatal period and 16% (0.84; 0.71–1.00) by age 12 months.Conclusion Early administration of BCG-Denmark in LW infants is associated with major reductions in mortality rate. It is important that all LW infants receive early BCG in areas with high neonatal mortality rates. Clinical Trials Registration. NCT00625482.