

# Addition of the Hepatitis B Vaccine in 1988 Increased the Rate of Type 1 Diabetes 1.62X in Children in New Zealand

Infectious Diseases  
In Clinical Practice 

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Classen David C.; Classen, John Barthelow  
Infectious Diseases in Clinical Practice: September-October 1997 - Volume 6 - Issue 7 - ppg 449-454  
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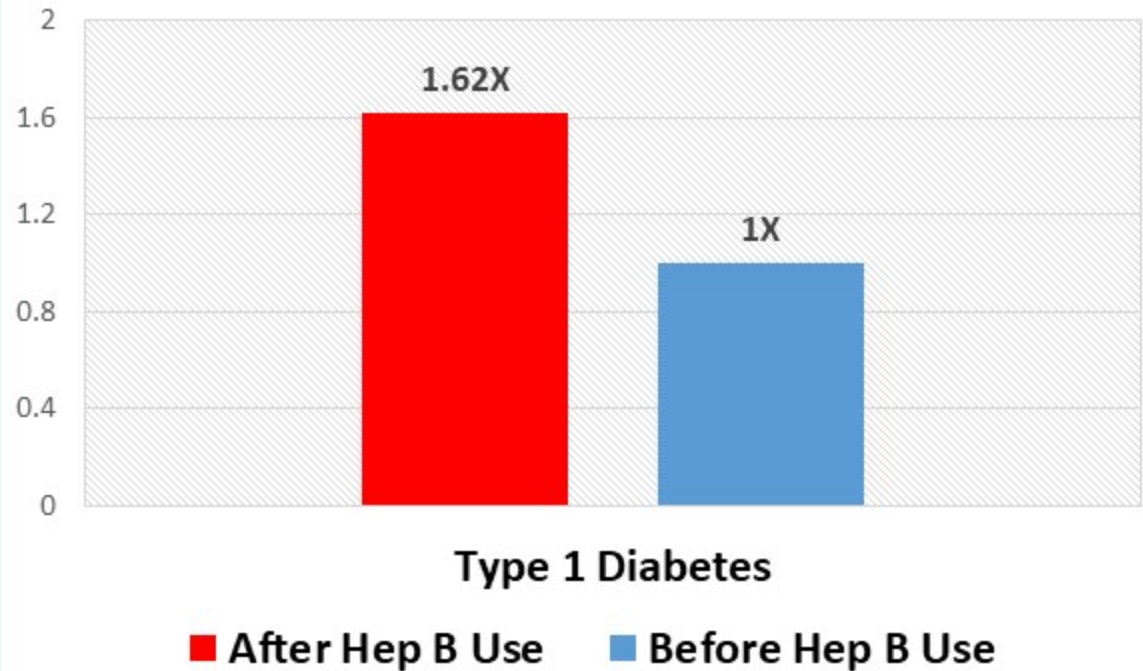
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HYPOTHESIS

THE TIMING OF PEDIATRIC IMMUNIZATION AND  
THE RISK OF INSULIN-DEPENDENT DIABETES  
MELLITUS

by David C. Classen and John Barthelow Classen

Incidence of Type 1 Diabetes in New Zealand Children Before and After the Introduction of the Hepatitis B Vaccine



**“The incidence of type I diabetes in persons 0-19 years old living in Christchurch rose from 11.2 cases per 100,000 children annually in the years before the immunization program, 1982-1987, to 18.1 cases per 100,000 children annually ( $P = .0008$ ) in the years following the immunization, 1989-1991.”**

# DTP Vaccination Increases Mortality by 2.45X in Girls Previously Receiving the BCG (Tuberculosis) Vaccine

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Trans R Soc Trop Med Hyg. 2016 Dec;110(10):570-581. Epub 2016 Nov 17.

**Is diphtheria-tetanus-pertussis (DTP) associated with increased female mortality? A meta-analysis testing the hypotheses of sex-differential non-specific effects of DTP vaccine.**

Aaby P<sup>1,2</sup>, Ravin H<sup>2,3</sup>, Fisker AB<sup>4,2,3</sup>, Rodrigues A<sup>4</sup>, Benn CS<sup>4,2,3</sup>.

Author information

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- 3 OPEN, Institute of Clinical Research, University of Southern Denmark/Odense University Hospital.
- 4 Bandim Health Project, InDEPTH Network, Apartado 881, Bissau, Guinea-Bissau.

Abstract

**BACKGROUND:** Ten years ago, we formulated two hypotheses about whole-cell diphtheria-tetanus-pertussis (DTP) vaccination: first, when given after BCG, DTP increases mortality in girls and, second, following DTP there is an increase in the female/male mortality rate ratio (MRR). A recent review by WHO found no convincing evidence that DTP increases mortality in females.

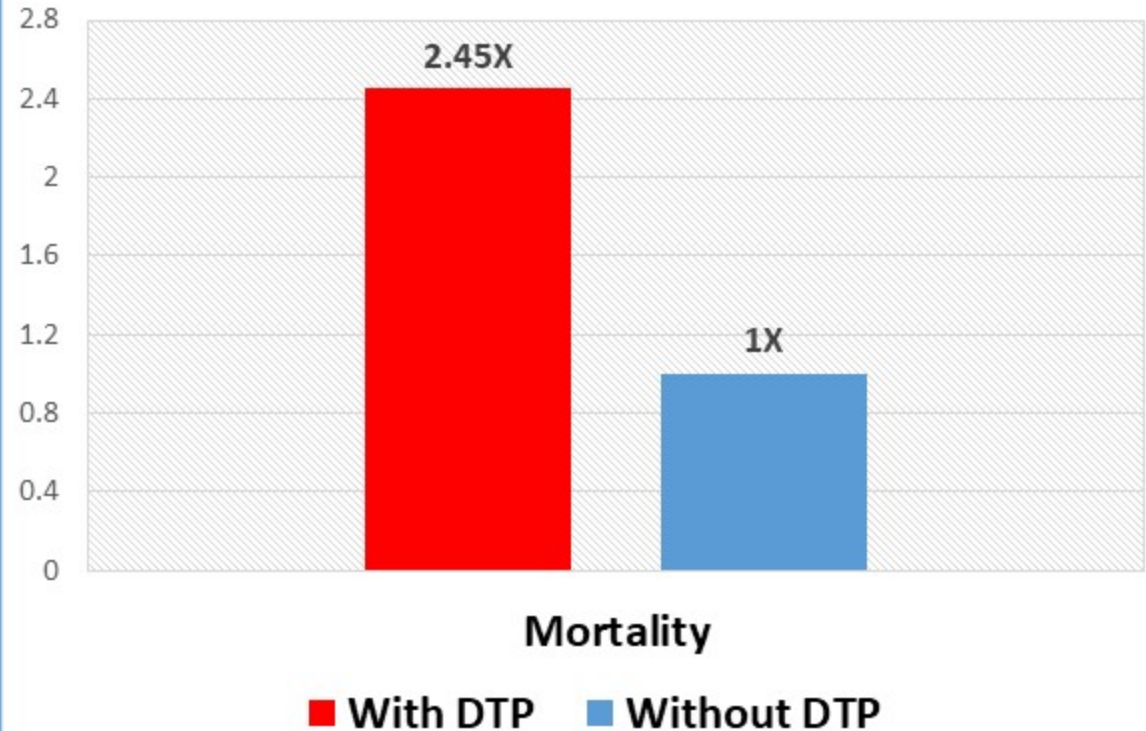
**METHODS:** We used previous DTP reviews as well as the recent WHO review for assessing the hypotheses. As pre-specified we excluded studies with survival or frailty bias; if children had received BCG and DTP simultaneously; and if the children had received neonatal vitamin A.

**RESULTS:** In seven studies of BCG-vaccinated children, DTP vaccination was associated with a 2.54 (95% CI 1.68-3.86) increase in mortality in girls (with no increase in boys [ratio 0.96, 0.55-1.68]). In 10 studies of BCG-vaccinated children, the female-to-male mortality ratio was 2.45 (1.48-4.06) times higher after DTP than before DTP. In 15 studies of children who had received DTP after previous BCG vaccination, mortality was 1.53 (1.21-1.93) times higher in girls than boys. The findings were similar in studies conducted before and after formulation of the hypotheses.

**CONCLUSIONS:** The two hypotheses were confirmed in the studies that fulfilled pre-specified criteria.

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## Mortality in BCG-Vaccinated Girls Receiving the DTP Vaccine



**“In seven studies of BCG-vaccinated children, DTP vaccination was associated with a 2.54 (95% CI 1.68–3.86) increase in mortality in girls (with no increase in boys [ratio 0.96, 0.55–1.68]). The ways in which the female and the male immune systems may respond differently to vaccinations in infants are only beginning to be studied.”**

# Higher Number of Vaccine Doses Prior to One Year of Age Increases Infant Mortality by 1.83X

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Hum Exp Toxicol. 2011 Sep;30(9):1420-8. doi: 10.1177/0960327111407644. Epub 2011 May 4.

**Infant mortality rates regressed against number of vaccine doses routinely given: is there a biochemical or synergistic toxicity?**

Miller NZ<sup>1</sup>, Goldman GS.

[Author information](#)

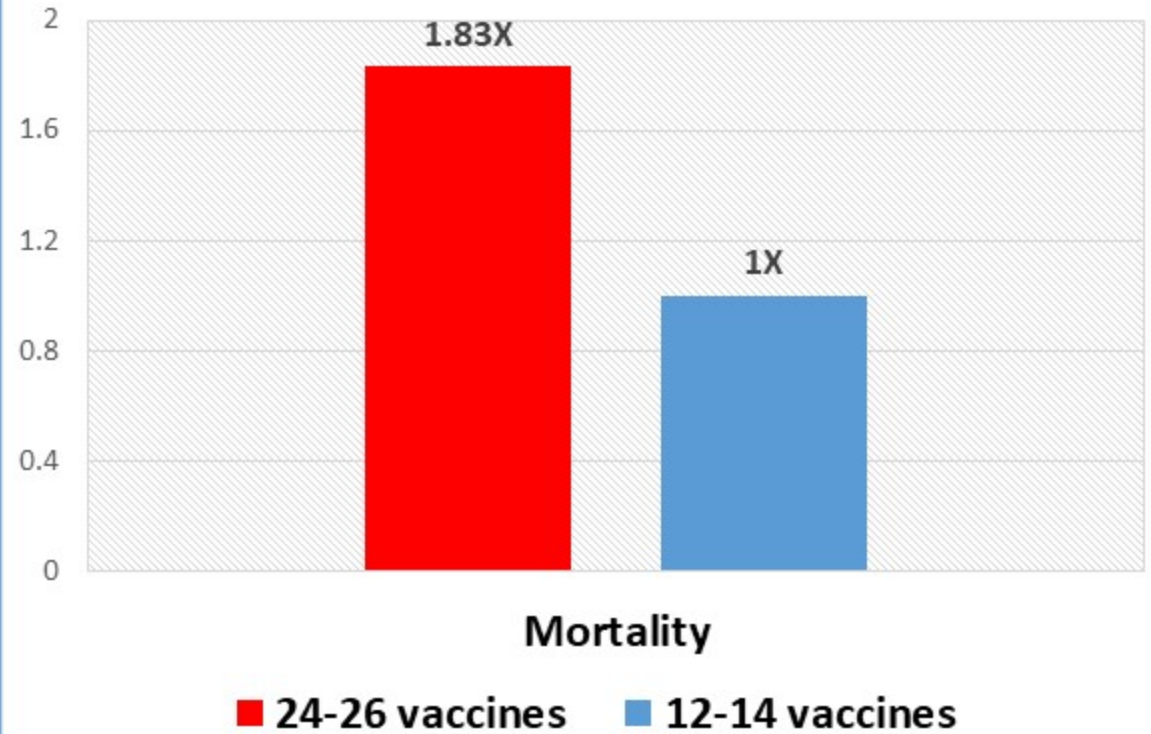
1 Think Twice Global Vaccine Institute, USA. neitzmiller@gmail.com [corrected]

**Erratum in**  
Hum Exp Toxicol. 2011 Sep;30(9):1429.

**Abstract**  
The infant mortality rate (IMR) is one of the most important indicators of the socio-economic well-being and public health conditions of a country. The US childhood immunization schedule specifies 26 vaccine doses for infants aged less than 1 year—the most in the world—yet 33 nations have lower IMRs. Using linear regression, the immunization schedules of these 34 nations were examined and a correlation coefficient of  $r = 0.70$  ( $p < 0.0001$ ) was found between IMRs and the number of vaccine doses routinely given to infants. Nations were also grouped into five different vaccine dose ranges: 12-14, 15-17, 18-20, 21-23, and 24-26. The mean IMRs of all nations within each group were then calculated. Linear regression analysis of unweighted mean IMRs showed a high statistically significant correlation between increasing number of vaccine doses and increasing infant mortality rates, with  $r = 0.992$  ( $p = 0.0009$ ). Using the Tukey-Kramer test, statistically significant differences in mean IMRs were found between nations giving 12-14 vaccine doses and those giving 21-23, and 24-26 doses. A closer inspection of correlations between vaccine doses, biochemical or synergistic toxicity, and IMRs is essential.

PMID: 21543527 PMCID: PMC3170075 DOI: 10.1177/0960327111407644  
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## Infant Mortality Based on Number of Vaccines Received Prior to One Year of Age



**“Using the Tukey-Kramer test, statistically significant differences in mean IMRs (infant mortality rates) were found between nations giving 12–14 vaccine doses and those giving 21–23, and 24–26 doses.”**

# One Dose of the DTP Vaccine Increases Infant Mortality by 1.84X

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BMJ. 2000 Dec 9;321(7274):1435-8.

**Routine vaccinations and child survival: follow up study in Guinea-Bissau, West Africa.**

Kristensen J<sup>1</sup>, Aaby P, Jensen H.

Author information

1 Bandim Health Project, Apartado 861, Bissau, Guinea-Bissau.

**Abstract**

**OBJECTIVE:** To examine the association between routine childhood vaccinations and survival among infants in Guinea-Bissau.

**DESIGN:** Follow up study.

**PARTICIPANTS:** 15 351 women and their children born during 1990 and 1996.

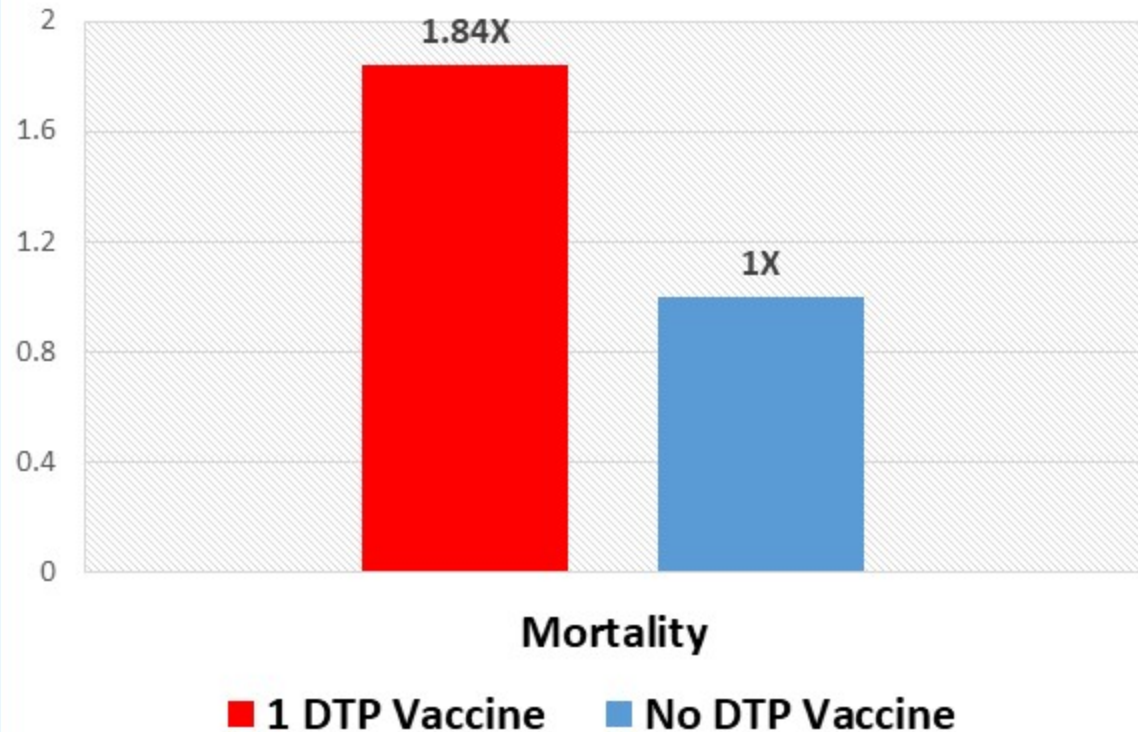
**SETTING:** Rural Guinea-Bissau.

**MAIN OUTCOME MEASURES:** Infant mortality over six months (between age 0-6 months and 7-13 months for BCG, diphtheria, tetanus, and pertussis, and polio vaccines and between 7-13 months and 14-20 months for measles vaccine).

**RESULTS:** Mortality was lower in the group vaccinated with any vaccine compared with those not vaccinated, the mortality ratio being 0.74 (95% confidence interval 0.53 to 1.03). After cluster, age, and other vaccines were adjusted for, BCG was associated with significantly lower mortality (0.55 (0.36 to 0.85)). However, recipients of one dose of diphtheria, tetanus, and pertussis or polio vaccines had higher mortality than children who had received none of these vaccines (1.84 (1.10 to 3.10) for diphtheria, tetanus, and pertussis). Recipients of measles vaccine had a mortality ratio of 0.48 (0.27 to 0.87). When deaths from measles were excluded from the analysis the mortality ratio was 0.51 (0.28 to 0.95). Estimates were unchanged by controls for background factors.

**CONCLUSIONS:** These trends are unlikely to be explained exclusively by selection biases since different vaccines were associated with opposite tendencies. Measles and BCG vaccines may have beneficial effects in addition to protection against measles and tuberculosis.

## Infant Mortality in Children Receiving 1 DTP Vaccine Versus No DTP Vaccines



**“One dose of diphtheria, tetanus, and pertussis vaccine was associated with a mortality ratio of 1.84 (1.10 to 3.10) and two to three doses with a ratio of 1.38 (0.73 to 2.61) compared with children who had received no dose of these vaccines.”**

# Early DTP Vaccination in Girls Increased Infant Mortality by 5.68X

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Arch Dis Child, 2012 Aug;97(8):685-91. doi: 10.1136/archdischild-2011-300648. Epub 2012 Feb 13.

**Early diphtheria-tetanus-pertussis vaccination associated with higher female mortality and no difference in male mortality in a cohort of low birthweight children: an observational study within a randomised trial.**

Aaby P<sup>1</sup>, Ravn H, Roth A, Rodrigues A, Lisse IM, Diness BR, Lausch KR, Lund N, Rasmussen J, Biering-Serensen S, Whittle H, Benn CS.

Author information

1 Bandim Health Project, Statens Serum Institut, Artillerivej 5, 2300 Copenhagen S, Denmark. p.aaby@bandim.org

**Abstract**

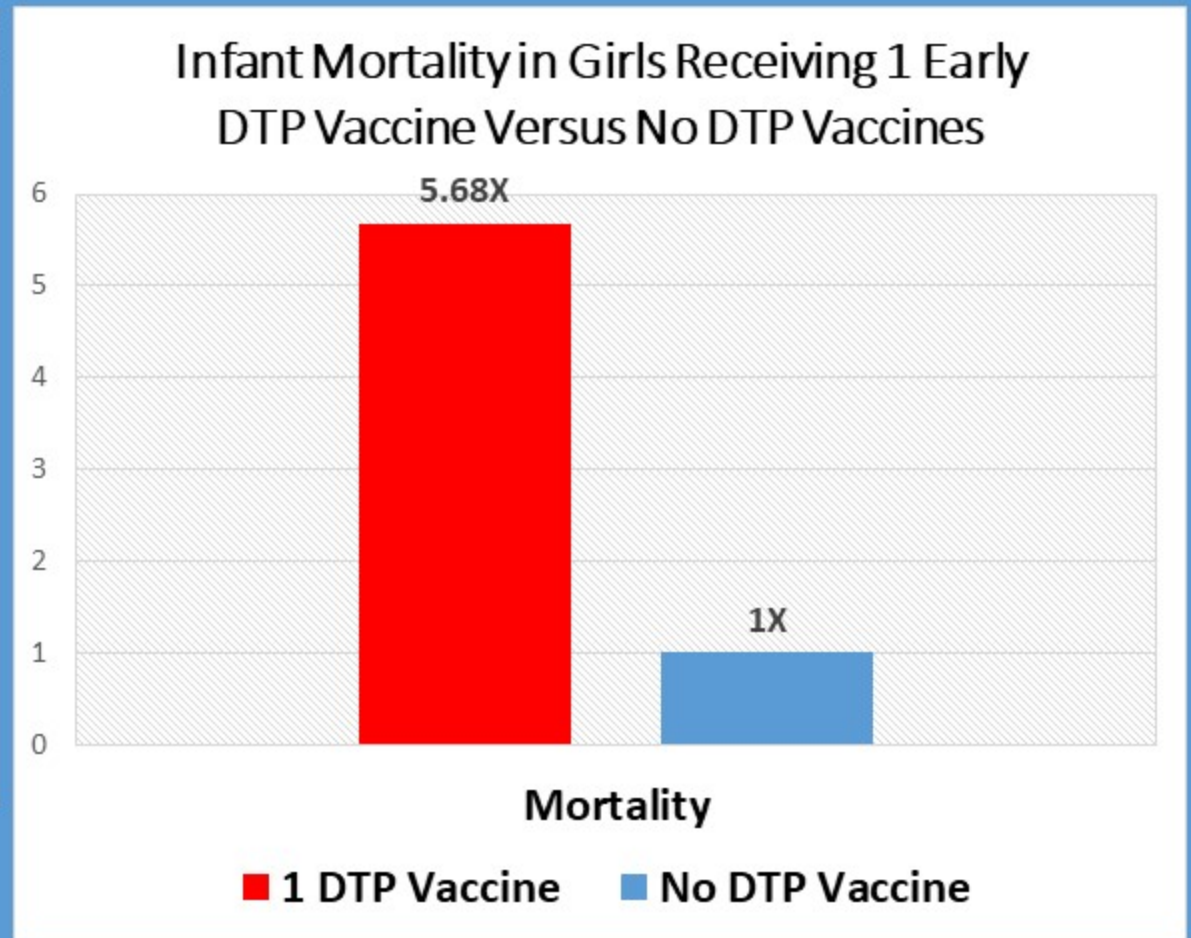
**BACKGROUND:** Studies from low-income countries have suggested that diphtheria-tetanus-pertussis (DTP) vaccine provided after Bacille Calmette-Guerin (BCG) vaccination may have a negative effect on female survival. The authors examined the effect of DTP in a cohort of low birthweight (LBW) infants.

**METHODS:** 2320 LBW newborns were visited at 2, 6 and 12 months of age to assess nutritional and vaccination status. The authors examined survival until the 6-month visit for children who were DTP vaccinated and DTP unvaccinated at the 2-month visit.

**RESULTS:** Two-thirds of the children had received DTP at 2 months and 50 deaths occurred between the 2-month and 6-month visits. DTP vaccinated children had a better anthropometric status for all indices than DTP unvaccinated children. Small mid-upper arm circumference (MUAC) was the strongest predictor of mortality. The death rate ratio (DRR) for DTP vaccinated versus DTP unvaccinated children differed significantly for girls (DRR 2.45; 95% CI 0.93 to 6.45) and boys (DRR 0.53; 95% CI 0.23 to 1.20) ( $p=0.018$ , homogeneity test). Adjusting for MUAC, the overall effect for DTP vaccinated children was 2.62 (95% CI 1.34 to 5.09); DRR was 5.68 (95% CI 1.83 to 17.7) for girls and 1.29 (95% CI 0.56 to 2.97) for boys ( $p=0.023$ , homogeneity test). While anthropometric indices were a strong predictor of mortality among boys, there was little or no association for girls.

**CONCLUSION:** Surprisingly, even though the children with the best nutritional status were vaccinated early, early DTP vaccination was associated with increased mortality for girls.

PMID: 22331681 PMCID: PMC3409557 DOI: 10.1136/archdischild-2011-300648



“Surprisingly, even though the children with the best nutritional status were vaccinated early, early DTP vaccination was associated with increased mortality.”

# Receipt of Both the BCG and DTP Vaccines Increased Infant Mortality in Girls by 2.4X

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Trop Med Int Health. 2005 Oct;10(10):947-55.

**Evaluation of non-specific effects of infant immunizations on early infant mortality in a southern Indian population.**

Moulton LH<sup>1</sup>, Rahmathullah L, Halsey NA, Thulasiraj RD, Katz J, Tielsch JM.

[Author information](#)

<sup>1</sup> Department of International Health, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD 21205, USA. lmoulton@jhsph.edu

**Abstract**

**OBJECTIVE:** The aim of this study was to assess the relationship between receipt of routine childhood immunizations and infant mortality before 6 months of age.

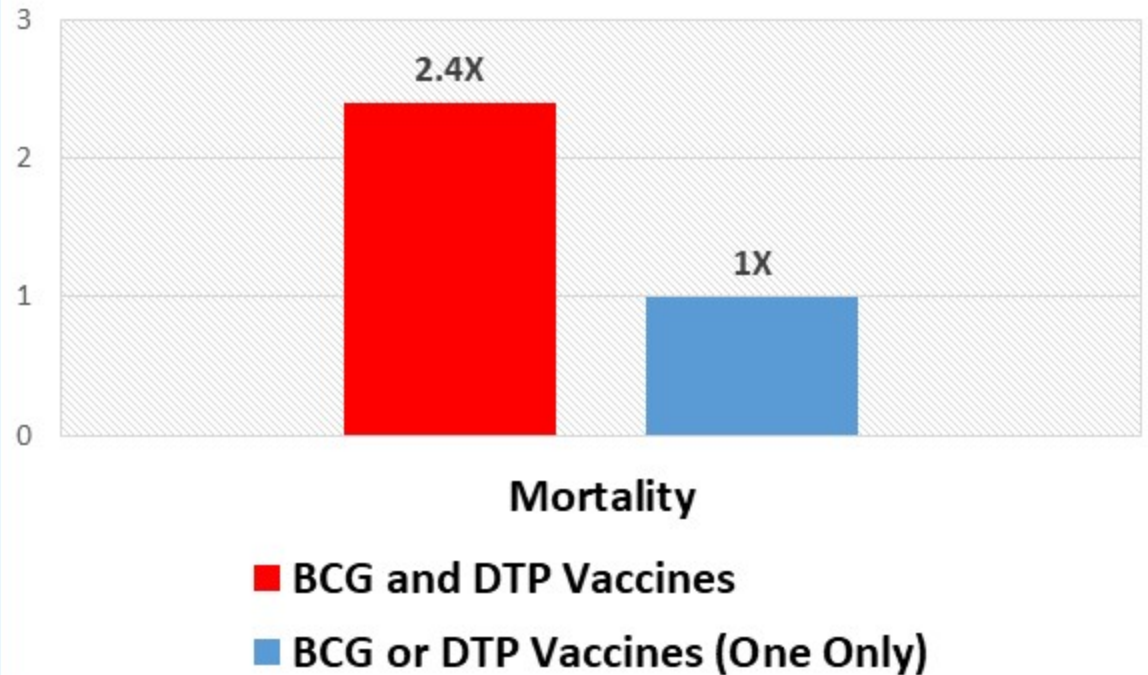
**METHODS:** This was an observational study of 10,274 infants, in a randomized trial of vitamin A supplementation, who received the study dose and survived to at least 1 week of age. The primary outcome was mortality before 6 months of age, analysed in Cox regression models as a function of vaccine receipt and gender.

**RESULTS:** Receipt of Bacille Calmette Guerin (BCG) or diphtheria, tetanus, polio (DTP) vaccine was associated with significant reductions of one-half to two-thirds of mortality hazards; among girls, those who received both BCG and DTP experienced higher mortality than those who received only one of the two vaccines (hazards ratio 2.4; 95% confidence interval 1.2-5.0).

**CONCLUSION:** The reduced mortality rate associated with receipt of BCG or DTP may be due to both biological and selection factors; the analyses regarding the combined effect of these vaccines and gender need to be replicated in other settings.

PMID: 16185228 DOI: 10.1111/j.1365-3113.2005.01434.x  
[Indexed for MEDLINE] [Free full text](#)

## Infant Mortality in Girls Receiving Both BCG and DTP Vaccines Versus One of the Vaccines Only



**“Among girls, those who received both BCG and DTP experienced higher mortality than those who received only one of the two vaccines (hazards ratio 2.4; 95% confidence interval 1.2–5.0).”**

# Receipt of the Second and Third Dose of the DTP Vaccine Increases Infant Mortality by 4.36X

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[Int J Epidemiol.](#) 2004 Apr;33(2):374-80.

### The introduction of diphtheria-tetanus-pertussis vaccine and child mortality in rural Guinea-Bissau: an observational study.

Aaby P<sup>1</sup>, Jensen H, Gomes J, Fernandes M, Lisse IM.

[Author information](#)

<sup>1</sup> Bandim Health Project, Apartado 861, Bissau, Guinea-Bissau. psb@mail.gtelecom.gw

**Abstract**

**BACKGROUND:** and objective Previous studies from areas with high mortality in West Africa have not found diphtheria-tetanus-pertussis (DTP) vaccine to be associated with the expected reduction in mortality, a few studies suggesting increased mortality. We therefore examined mortality when DTP was first introduced in rural areas of Guinea-Bissau in 1984-1987. Setting Twenty villages in four regions have been followed with bi-annual examinations since 1979.

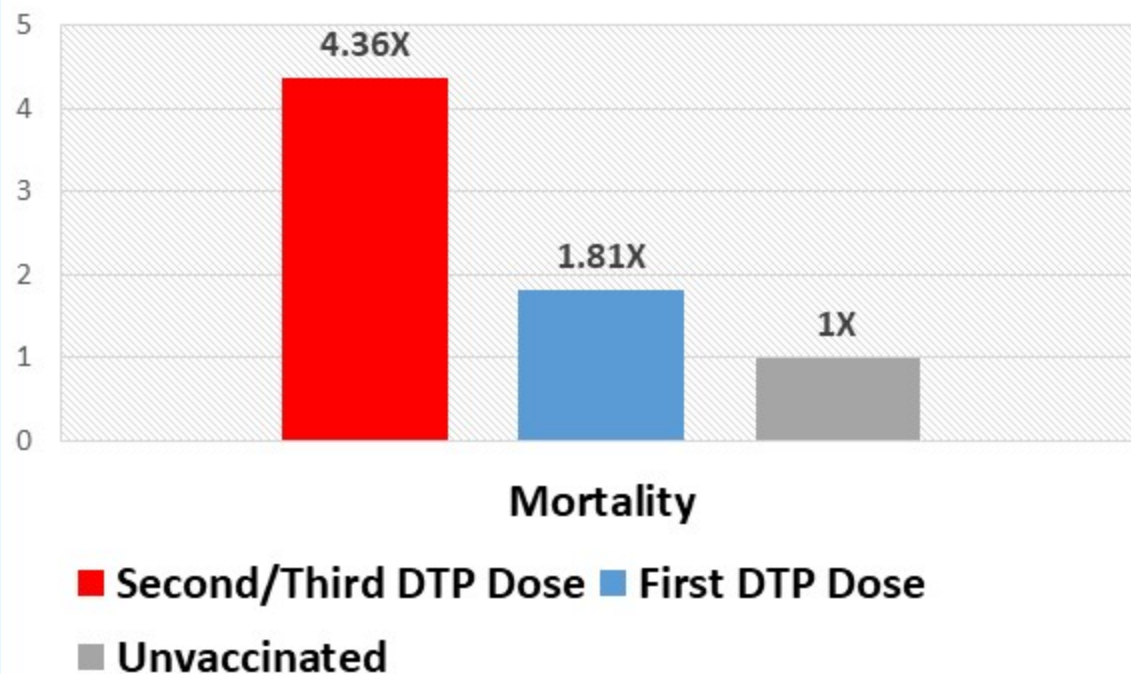
**SUBJECTS:** In all, 1657 children aged 2-8 months. Design Children were weighed when attending the bi-annual examinations and they were vaccinated whenever vaccines were available. DTP was introduced in the beginning of 1984, oral polio vaccine later that year. We examined mortality for children aged 2-8 months who had received DTP and compared them with children who had not been vaccinated because they were absent, vaccines were not available, or they were sick.

**MAIN OUTCOME MEASURE:** Mortality over the next 6 months from the day of examination for vaccinated and unvaccinated children.

**RESULTS:** Prior to the introduction of vaccines, children who were absent at a village examination had the same mortality as children who were present. During 1984-1987, children receiving DTP at 2-8 months of age had higher mortality over the next 6 months, the mortality rate ratio (MR) being 1.92 (95% CI: 1.04, 3.52) compared with DTP-unvaccinated children, adjusting for age, sex, season, period, BCG, and region. The MR was 1.81 (95% CI: 0.95, 3.45) for the first dose of DTP and 4.36 (95% CI: 1.28, 14.9) for the second and third dose. BCG was associated with slightly lower mortality (MR = 0.63, 95% CI: 0.30, 1.33), the MR for DTP and BCG being significantly inverted. Following subsequent visits and further vaccinations with DTP and measles vaccine, there was no difference in vaccination coverage and subsequent mortality between the DTP-vaccinated group and the initially DTP-unvaccinated group (MR = 1.06, 95% CI: 0.78, 1.44).

**CONCLUSIONS:** In low-income countries with high mortality, DTP as the last vaccine received may be associated with slightly increased mortality. Since the pattern was inverted for BCG, the effect is unlikely to be due to higher-risk children having received vaccination. The role of DTP in high mortality areas needs to be clarified.

## Infant Mortality in Children Receiving the First or Second/Third Dose of the DTP Versus Unvaccinated Children



**“The MR (mortality rate) was 1.81 (95% CI: 0.95, 3.45) for the first dose of DTP and 4.36 (95% CI: 1.28, 14.9) for the second and third dose.”**