

Benefits of routine immunizations on childhood survival in Tari, Southern Highlands Province, Papua New Guinea

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Background Non-specific beneficial as well as deleterious effects of childhood immunizations have been reported in areas of high mortality. This study aimed to determine the effects of diphtheria-tetanus-whole-cell-pertussis (DTP), BCG, hepatitis B, and measles vaccines on mortality in the highlands of Papua New Guinea (PNG).

Methods Demographic events for children born in 1989–1994 who were under monthly demographic surveillance in Tari were recorded from birth until age 2 years, out-migration, death, or the end of the study period. Data on BCG, hepatitis B, DTP, measles and pneumococcal polysaccharide vaccination were collected monthly from clinic records. To allow for different characteristics of immunized and non-immunized children, analysis included conditioning on a propensity score for vaccination, adjusting for differences in children's background characteristics.

Results In all, 101/3502 children (3%) who had at least one vaccine died between ages 29 days and 24 months were compared to 112/546 (21%) who had none. BCG was associated with lower mortality in the 1–5 month age group (hazard ratio [HR] = 0.17, 95% CI: 0.09, 0.34), measles vaccine with lower mortality at age 6–11 months (HR = 0.42, 95% CI: 0.17, 1.01), and pneumococcal polysaccharide vaccine with lower mortality at age 12–23 months (HR = 0.42, 95% CI: 0.19, 0.93). One or more doses of DTP was associated with lower overall mortality (HR = 0.27, 95% CI: 0.16, 0.44), particularly in the 1–5 month age group (HR = 0.19, 95% CI: 0.10, 0.34), and also in those who had had prior BCG (HR = 0.45, 95% CI: 0.22, 0.91).

Conclusion Routine immunizations are effective in reducing overall mortality in young children in an area of high mortality. In particular, DTP, whether considered separately or in addition to BCG, was associated with a lowering of overall mortality, in contrast to findings reported from Guinea-Bissau.

Keywords Childhood immunization, BCG, DTP vaccine, immunization programmes, measles vaccine, pneumococcal polysaccharide vaccine, mortality, Papua New Guinea, survival analysis, propensity score

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Vaccines included in routine childhood immunization programmes have generally been evaluated in areas of low mortality and then introduced into routine immunization programmes in developing countries. Routine immunization with diphtheria-tetanus-pertussis and oral polio vaccination have a direct impact on morbidity and mortality due to these diseases.¹ Studies in areas of high mortality found that measles vaccine improves childhood survival to a greater extent than the specific

protection it affords against measles.^{2,3} On the other hand, high-titre Edmonston-Zagreb measles vaccine was associated with an increased risk of death, particularly in females.⁴ While the efficacy of BCG (Bacille Calmette-Guérin) vaccination for prevention of tuberculosis remains controversial,⁵ it is regularly used in infancy to prevent tuberculous meningitis.

In view of differences in the epidemiology of disease between areas of high and low mortality and the problems associated with maintaining the cold chain required for delivery and storage of vaccines in remote areas, it is important to evaluate effectiveness of immunization programmes in non-industrialized countries. One such evaluation was an observational study of more than 15 000 women and their children living in rural areas of Guinea-Bissau. Kristensen and colleagues reported a reduction in mortality in young children following BCG and measles vaccination but a higher infant mortality associated with diphtheria-tetanus-whole-cell-pertussis (DTP) and oral polio vaccination.⁶ A non-significant increase in mortality in children receiving DTP was also reported in Senegal and Benin.^{2,7} Because of these findings and the dearth of studies evaluating the effectiveness of routine immunizations in non-industrialized countries, the World Health Organization (WHO) sought proposals to determine the effects of routine infant immunization on survival in areas of high mortality. We report here the results of an observational study undertaken in Tari, Southern Highlands Province, Papua New Guinea (PNG) aimed at determining the effects of DTP, BCG and measles vaccines on mortality in the first 2 years of life.

Subjects and Methods

Subjects and setting

This is a retrospective cohort study of all children born in Tari between 1989 and 1994.⁸⁻¹⁰ The Huli people live in scattered homesteads in the Tari Basin at 1300-1800 m above sea level. An unsealed all-weather road linking Tari to other parts of PNG was only completed in 1980. A recent survey found that 89% of women reported giving birth in a health facility.¹¹

Demographic surveillance

Huli reporters conducted monthly demographic surveillance continuously from 1971 until 31 March 1995.⁸⁻¹⁰ They each monitored 700-1400 people belonging to their own clan groups. Thus, in 1995, 37 reporters were monitoring >35,000 people to identify all pregnancies, births, deaths, migrations, marriages and divorces, with details entered monthly into computer files. Fortnightly reporter meetings enabled exchange of information about events occurring within the area under surveillance but outside individual reporters' assigned areas. Births away from clan ground and delays in monthly entry meant that children were often not recorded in the database until after 60 days. Migrations out of the Tari Basin for ≥ 2 months were also stored electronically. Only those children born under demographic surveillance and registered as such within 60 days of birth were included in this study to avoid bias towards surviving children.

The area under demographic surveillance has been divided into three regions:

- 1 The **eastern region** is densely populated and many people live near government and commercial services at Tari station.

People are generally healthier and have had more formal education than elsewhere in the area under surveillance.

- 2 The **northern region** is at higher altitude and more remote than other parts of the surveillance area, with fewer government services, unreliable road access, and poor soil.
- 3 The **western region** is at lower altitude than other parts of the surveillance area. Malaria is more prevalent here than in the other regions.

Infant mortality rates between 1991 and 1993 were 47, 75 and 85 per 1000 live births in eastern, northern and western regions, respectively, while mortality rates in children aged 12-23 months over the same time period in the three respective regions were 10, 9 and 16 per 1000 person-years.¹⁰

Determination of cause of death

Cause of death was determined by verbal autopsy supplemented by available information from health services. A Huli mortality clerk collected information from relatives on symptoms suffered during the terminal illness and what medical treatment was sought. Immunization history was not routinely collected. An epidemiologist coded the cause of death using a Classification of Symptom Complexes for Lay Reporters developed for population studies in PNG, based on the Ninth Revision of the International Classification of Diseases.^{10,12} Death due to acute lower respiratory tract infection (ALRI) was defined as cough and breathlessness for <3 weeks with or without fever and other symptoms. Between 1989 and 1993 ALRI accounted for 43% of deaths under 5 years. Measles mortality in children aged <5 years was 4/1000 person-years. Pertussis has rarely been recorded as a cause of death.¹⁰

Immunization

Nurses working out of Tari Hospital and five health centres held monthly fixed and mobile maternal and child health (MCH) clinics, independently of research activities. Scheduled mobile clinics were sometimes cancelled if no vehicle was available or if inter-clan fighting meant that either mothers or nursing staff were unable to travel. Thus clinics were disrupted in some parts of the Tari basin during 3 months of both 1993 and 1994 and for the last 2 months of follow-up in 1995. If a refrigerator was not functioning, vaccines were neither stored nor given. Dates of visits, immunizations and weights were recorded on clinic cards held by nurses and in child health books kept by mothers.

Some of the national immunization guidelines changed during the course of this study (Figure 1): from 1992 onwards DTP, pigbel and polio vaccinations were to start at a younger age (1 month) with one-month intervals between doses (doses 1, 2, and 3 abbreviated to DTP1, DTP2, DTP3, respectively).^{13,14} Pigbel vaccine consists of a toxoid aimed at preventing enteritis necroticans caused by the beta toxin of *Clostridium perfringens* type C.¹⁵ Measles vaccination was changed from a 1-dose to a 2-dose schedule at ages 6 and 9 months, but was to be given as young as age 3 months during an epidemic. Hepatitis B (Hep B) vaccine was introduced in Tari in 1991 but supplies were erratic. DTP, Hep B, or pigbel vaccines were to be withheld if a fever of >38°C was present.

The demonstrated efficacy of 23-valent pneumococcal polysaccharide (Pnc PS) vaccine in preventing death and severe ALRI in young children in Tari,^{16,17} led to an immunogenicity study¹⁸ and then an effectiveness study of Pnc PS vaccine

Vaccine	Calendar year							
	1989	1990	1991	1992	1993	1994	1995	
BCG	As near birth as possible							
DTP, Polio, Pigbel	← Ages 2, 4, 6 months →			← Ages 1, 2, 3 months →				
Measles	← Age 9 months →			← Ages 6 and 9 months ^a →				
Hepatitis B	← Birth, age 1 month and at least 2 months later →							
Pneumococcal polysaccharide	3–59 months ^b		← Given once, age 8–23 months →					

Figure 1 Vaccination schedule^{13,14}

^a Nurses were instructed to give measles vaccine from age 3 months during a measles epidemic.

^b Approximately 160 children were immunized in 1990 during an immunogenicity study.¹⁸

which was offered to all clinic attenders aged 8–23 months. For that effectiveness study, research staff collected immunization data recorded on cards held at clinics by MCH staff. Data were collected not only on Pnc PS immunizations but also on all other immunizations given between 1989 and 1995 to children attending MCH clinics in the area under demographic surveillance and in neighbouring areas. While the Pnc PS vaccine effectiveness study only formally began in 1991, in preparation for that study, routine monthly data collection of immunization records from health centres and Tari Hospital was in place from August 1989 and continuous until May 1995.

In order to link demographic to immunization data, reporters together with field supervisors recorded the unique demographic identity number and a seven-digit social number (identifying place of residence and position in family) on individual children's clinic-held cards as well as on the parent-held child health book. All clinic cards held at each health centre/hospital for all outreach clinics were brought into the office monthly for entry of details of immunizations and clinic visit dates. This included cards belonging to children who had died, since nursing staff kept their cards as well as those belonging to migrants or non-attenders for one year after their last attendance. The social number as well as visual display on computer monitor of the child's personal details provided cross-checks of identity. If no identity or social number was recorded on a clinic card, office staff gave demographic details to reporters to provide the identity number at future meetings. This was done repeatedly until identity and place of residence was established. Further error checks on immunization and clinic visit dates were performed regularly and overseen quarterly by one of the authors (DL). Following this intensive process of identification and error-checking, if there was no clinic card linked to a child on the demographic database, it was concluded that the child had not been vaccinated.

Data analysis

The cohort of children born alive between 1 January 1989 and 31 December 1994, who survived ≥ 28 days and who were under demographic surveillance within 60 days of birth were included. We excluded the neonatal period because data on

immunizations were based on MCH clinic records and those dying neonatally may have had incomplete data on BCG and Hep B vaccines given at or soon after birth. These vaccinations were recorded on clinic cards when the babies were brought for the first time to an MCH clinic. If a child died before the next scheduled MCH clinic or had never been taken to an MCH clinic, BCG or Hep B vaccines given soon after birth would never have been entered into the database. Such a misclassification bias could result in a falsely strong protective effect of these vaccines.

Background covariates available from the demographic database were: region, sex, birth order, year of birth, maternal age, death of an older sibling, birth interval from birth of previous sibling, and multiple births.

Mortality rates

Each person in the study contributed person-time to the vaccination status group that they were in at the time; thus, for example, until a child was vaccinated with BCG they accrued days in the unvaccinated group, then in the BCG only group until receiving DTP, when they would contribute person-time to the BCG + DTP group until death, or censoring at migration, 2 years of age or the end of the study period (31 March 1995). Deaths were similarly counted in the group to which children belonged at the time of death.

Survival analysis

As this was an observational study, vaccination status was not assigned at random. This was accounted for in the analysis by stratifying on a propensity score for any vaccination (the earliest of BCG, DTP, or measles).^{19,20} This propensity score adjusted for differences in background characteristics among the children in the study in a more efficient way than multivariate adjustment and incorporated numerous covariates and their interactions without concerns of over-fitting.²¹ Cox proportional hazards regression was used to estimate this propensity with all variables that were available for all children in the data set (region, twin status, sex, maternal age, birth order and date of birth), and their interactions, being used as covariates in this model.

The original formulation of propensity score methods²² was in terms of the probability of assignment to a particular non-randomized treatment (in this case, being vaccinated). In our

models, probabilities of vaccination were obtained by multiplying the underlying age-specific hazard rates that were obtained from the Cox model (i.e. the so-called baseline hazard rates) by the child-specific hazard ratios (HR) that were estimated by exponentiating the sum of the products of the coefficients and the child-specific values of each of the background variables that were used in the Cox model. These probabilities, or propensity scores, were then ranked by quintiles and used as strata in later modelling.

Further Cox models were then estimated with five vaccines (BCG, DTP, measles, pneumococcal, and Hep B) included as time-dependent covariates (i.e. each child was considered unvaccinated until the time of vaccination) and the outcome being death from any cause or censoring at first migration from the district or at the end of the study period, whichever was earlier. The quintiles of propensity score grouped subjects with similar probability of being vaccinated. While data existed on polio and pigbel vaccinations, these were not included in the models since immunization dates were highly correlated with those for DTP.

Most models thus included BCG, DTP, measles, pneumococcal and Hep B vaccinations, region, twin status, maternal age, birth order, date of birth, sex, together with 2-way interactions between each of the BCG, DTP and measles vaccinations and sex and region. Various, more complex, models were also fitted which included the above model plus combinations of the following: an interaction between BCG and DTP vaccinations which also modelled which order they were given in, BCG/DTP interaction terms crossed with sex, DTP dose-response (i.e. second and third DTP vaccination) and two-way and three-way interactions between DTP dose-response and sex and region.

Several other data sets were used. However, not all of the above models were applied to each of the data sets detailed below as reduced sample sizes in the restricted models made them unsuitable for some of the interaction models:

- A. For analysis of effect of all vaccines other than BCG, we included only those children on whom we had a record of BCG having been given before age 6 months i.e. those children identified on the demographic database whose clinic card had been seen by research staff. These analyses had the added advantage of also adjusting for access to health care or vaccination seeking behaviour that we were trying to take into account with our propensity scores.
- B. Models were estimated separately for ages 1–5, 6–11, and 12–23 months, in view of the rapid decline in mortality rates with age, the changes in cause-specific mortality, and the different relevant time periods for each of the different vaccines.
- C. In this analysis only the deaths due to ALRI were included, children dying from any other causes being censored at the time of death.
- D. Children <9 months who received DTP only or BCG followed by DTP, were followed up till date of measles vaccination or 9 months of age, whichever was earlier. This was included to investigate the suggestion that female children would be worse off in this set of circumstances.²³

In each case backwards elimination was used (with $\alpha = 0.05$) to find a 'best' model, with the vaccination

variables being protected from elimination. All analyses were done with and without stratification by propensity score quintile. All the 'best' models thus found are available from the authors and only a selection of primary interest are discussed below.

SAS version 8.01 was used for data analysis and manipulation.

Ethical approval

Ethical approval to carry out the study was given by the Medical Research Advisory Committee of PNG.

Results

Study population

A total of 6665 children were born between 1989 and 1994. The following were excluded: 1445 babies not under surveillance before age 60 days, 932 born outside the area under surveillance, 52 stillbirths, 117 who died aged <29 days, 12 who left the study before 29 days of age, 39 with uncertain vaccination dates, and 20 with unknown maternal age (because the babies had been adopted). Thus 4048 children were included in the survival analysis; 376 were excluded after their first migration, 2329 were censored at age 2 years, 213 died, and the remaining 1130 were censored at the end of the study period.

Characteristics of vaccinated and unvaccinated children

There were 3502 children who received one or more of the scheduled vaccines before age 2 years (87%) compared with 546 children (13%) who did not receive any vaccines (Table 1). The unvaccinated group accounted for 53% of deaths. In the unvaccinated group, 112 (21%) children died at a mean age of 121 days (median 89 days), 112 (21%) were censored at migration at a mean age of 203 days (median 121 days) and 234 (43%) were censored at the end of the study at a mean age of 267 days (median 210 days), leaving 88 other children with no record of vaccination by age 2 years (2% of children in the study). Among those children who received at least one vaccination, 101 (3%) died at a mean age of 291 days (median 256 days) and 264 (8%, mean age 351 days, median 327 days) were censored at migration, 2241 (64%) at the age of 2 years and 896 (26%, mean and median age 437 days) at the end of the study.

There were no significant differences between vaccinated and unvaccinated groups with regard to sex, region, birth order, recent birth spacing, the proportion with an older sibling who died, and twin status. More children born to women aged 24–34 years were unvaccinated compared with children born to either older or younger mothers ($\chi^2 = 12.4$, 2 d.f., $P = 0.002$).

A high proportion of the unvaccinated children (43%) were born in 1994 (Table 1). This is in part the result of incomplete follow-up due to the end of the study on 31 March 1995 and the relatively low vaccine coverage rates in younger children (Table 2). However, 85–89% of children born in 1989–1993 had been given at least one vaccine by 31 March of the following year compared with only 68% of those born in 1994. There was disruption to clinic activities for 3 months in 1994 as well as during February–March 1995 due to inter-clan fighting.

Table 1 Demographics and vaccine coverage among children aged ≥ 29 days

	Received ≥ 1 vaccines		No vaccines received		% Unvaccinated
	<i>n</i>	%	<i>n</i>	%	
No. of children in study	3502		546		13
Mean days in study	614		299		
No. of deaths	101	2.9	112	20.5	53
Mean/median age of death (days)	291/256		121/89		
Sex					
Female	1712	48.9	275	50.4	14
Male	1790	51.1	271	49.6	13
Region					
Eastern	1384	39.6	195	35.7	12
Northern	910	26.0	158	28.9	15
Western	1208	34.5	193	35.3	14
Year of birth					
1989	446	12.7	56	10.3	11
1990	522	14.9	54	9.9	9
1991	713	20.4	62	11.4	8
1992	685	19.6	70	12.8	9
1993	643	18.4	72	13.2	10
1994	493	14.1	232	42.5	32
Maternal age (years)					
≤ 23	735	21.0	102	18.7	12
24–34	1914	54.7	341	62.5	15
35+	853	24.4	103	18.9	11
Birth order					
1	749	21.4	121	22.2	14
2	666	19.0	110	20.1	14
3–5	1394	39.8	220	40.3	14
6+	693	19.8	95	17.4	12
Twin					
No	3439	98.2	530	97.1	13
Yes	63	1.8	16	2.9	20
Previous dead sibling^a					
None	1989	72.2	290	68.2	13
1+	764	27.8	135	31.8	15
Recent birth spacing^a (months)					
≤ 24	438	16.0	75	18.0	15
25–48	1818	66.5	270	64.7	13
49+	476	17.4	72	17.3	13

^a Excluding firstborn.

Excluding children born in 1994 made little difference to results from the survival analyses.

Vaccine coverage

By one month of age almost half the children were known to have been vaccinated with BCG and by age 84 days, more than half the children had received first doses of DTP, pigbel and

polio vaccines (Table 2). Of 3612 children still in the study at age 6 months, 3179 (88%) had received one or more vaccinations, 1322 (37%) had received BCG and three doses of DTP, while 433 (12%) had received no vaccines by age 6 months. Equivalent figures for age 12 months were 2925/3113 (94%), 2250 (72%) and 188 (6%), respectively. By the age of 12 months, 74% of children had received at least one dose of

Table 2 Coverage rates for BCG, pneumococcal polysaccharide (PncPS) vaccine and varying doses of DTP (DTP1, DTP2, DTP3), hepatitis B (Hep B1, Hep B2, Hep B3) and measles (mea1, mea2) vaccines by age

	Final age in days							
	28	56	84	120	182	270	365	730
No. of children ^a	4048	3990	3932	3804	3612	3357	3113	2329
BCG	0.48	0.61	0.68	0.74	0.80	0.84	0.87	0.92
DTP1 ^b	0.03	0.25	0.56	0.73	0.84	0.89	0.92	0.95
DTP2	0.00	0.01	0.13	0.38	0.65	0.79	0.86	0.93
DTP3	0.00	0.00	0.00	0.11	0.39	0.63	0.76	0.89
Hep B1	0.06	0.08	0.09	0.10	0.11	0.12	0.13	0.15
Hep B2	0.00	0.01	0.03	0.04	0.05	0.05	0.06	0.06
Hep B3	0.00	0.00	0.01	0.01	0.02	0.02	0.03	0.03
PncPS	0.00	0.00	0.00	0.00	0.01	0.16	0.55	0.83
Mea1	0.00	0.00	0.00	0.00	0.14	0.55	0.74	0.89
Mea2	0.00	0.00	0.00	0.00	0.00	0.08	0.23	0.40

^a Number of children in the study by final age in days shown in category, excluding those censored before the end of the period. For each vaccine type, numerator is number of children vaccinated by age in days shown in category, excluding those censored before the end of the period.

^b Since polio and pigbel vaccines were usually given at the same scheduled times as DTP, coverage rates for these vaccines are very similar.

measles vaccine and 55% had been given pneumococcal vaccine.

Patterns of mortality

Total mortality declined from 80/1000 person-years in the 1–5 month age group to 29/1000 person-years at 6–11 months and 12/1000 person-years at 12–23 months (Table 3). The postneonatal mortality rate was 43/1000 live births (31/1000 age 1–5 months, 12/1000 age 6–11 months). ALRI-specific mortality rates/1000 person-years were 52 (*n* = 84), 19 (*n* = 32) and 5.5 (*n* = 15), in children aged 1–5, 6–11 and 12–23 months, respectively. Diagnoses of pertussis and measles were assigned to 1 and 4 deaths, respectively. Mortality from acute abdominal causes (primarily gastro-enteritis) was highest in children aged 6–11 months, when it accounted for 15% of deaths. There were five accidental deaths and no deaths attributed to tetanus, tuberculosis, or diphtheria.

Mortality was generally highest among those who received neither BCG nor any DTP vaccine, intermediate among those who received BCG but no DTP and low among those who had both vaccines or DTP but no BCG (Table 3). Generally, mortality was higher in male than female children.

Survival analyses

A total of 4048 children were included in the full data set of children aged 29 days–23 months. Sub-analyses carried out on the 29 days–5 month, 6–11 and 12–23 month age groups included 4048, 3612 and 3113 children, respectively. The propensity score consistently stratified the probability of vaccination as well as mortality (Table 4). Thus, in individual strata, background characteristics of vaccinated and unvaccinated children were similar but mortality was higher in unvaccinated children. Table 5 shows the HR for immunizations and background variables after adjustment for vaccinations, dose response of DTP and background covariates. The model used in Table 5(a) includes the propensity score while results

shown in Table 5(b) are from the same model but excluding the propensity score. Table 6 shows the HR and 95% CI for immunizations other than BCG and for background variables, after adjustment for vaccinations, dose response of DTP and background covariates, in those children who had received BCG. Inclusion of the propensity score made no difference to results when considering only those children who had been given BCG. In nearly all models, mortality declined with increasing birth order.

Effect of DTP on mortality

Children receiving DTP vaccination had lower death rates. The protective effect of one or more doses of DTP vaccination was statistically significant except in the 12–23 month period (Table 5) and in the 6–11 month models for DTP 1 and 2 when adjusted for the propensity score (Table 5a). HR were very similar in models for ALRI-specific mortality. In general a dose response for DTP was not found. However, in the 6–11 month age group the protective effect from DTP vaccinations was only significant after the third dose (Table 5a). When restricted to children who had already received BCG (Table 6), in children aged 29 days–5 months, the HR for DTP doses 1, 2 and 3 were 0.48 (95% CI: 0.22, 1.09), 0.34 (95% CI: 0.13, 0.89) and 0.17 (95% CI: 0.04, 0.70), respectively. By 12 months of age, among those children who had received BCG (Table 6), only 28 out of 2280 children had not yet received DTP and none of them died, so no models could be fitted: the death rate in the no DTP group from 12–23 months was 0/1000 person-years (95% CI: 0, 208), in the DTP group it was 14/1000 person-years (95% CI: 10, 21).

Effect of BCG on mortality

Children who received a BCG vaccination were generally at lower risk of dying than those who did not receive BCG. However, when the effect was examined in different age groups, protection was confined to the first 6 months of life. In the whole data set the HR was 0.40 (95% CI: 0.25, 0.66), while the HR was 0.17 (95% CI: 0.09, 0.34) in the 1–5 month model

Table 3 Total mortality by age, sex and vaccination status for BCG and ≥ 1 doses of DTP

Vaccination status	Age at death						Rate/1000 person-years	Rate/1000 person-years	Deaths/person-days	Rate/1000 person-years	12–23 months		Rate/1000 person-years			
	29 days–5 months			6–11 months							No. of children ^a	Rate/1000 person-years		Deaths/person-days	No. of children ^a	Rate/1000 person-years
	No. of children ^a	Deaths/person-days	Rate/1000 person-years	No. of children ^a	Deaths/person-days	Rate/1000 person-years										
No BCG or DTP—Male	359	46/72 923	230.4	165	11/26 717	150.4	93	1/21 476	17.0	1/21 476	17.0	93	1/21 476	17.0		
No BCG or DTP—Female	347	46/71 362	235.4	163	5/28 677	63.7	108	4/27 623	52.9	4/27 623	52.9	108	4/27 623	52.9		
BCG only—Male	93	8/59 582	49.0	23	1/6667	54.8	14	1/3068	119.1	1/3068	119.1	14	1/3068	119.1		
BCG only—Female	96	4/56 663	25.8	32	2/7084	103.1	21	0/3785	0	0/3785	0	21	0/3785	0		
DTP only—Male	139	1/19 200	19.0	107	1/20 848	17.5	100	0/25 600	0	0/25 600	0	100	0/25 600	0		
DTP only—Female	143	0/18 114	0	107	2/20 562	35.5	101	0/24 067	0	0/24 067	0	101	0/24 067	0		
DTP before/with BCG—Male	347	4/32 302	45.2	424	4/68 407	21.4	382	2/138 870	5.3	2/138 870	5.3	382	2/138 870	5.3		
DTP before/with BCG—Female	339	5/32 188	56.7	411	1/66 089	5.5	368	1/128 627	2.8	1/128 627	2.8	368	1/128 627	2.8		
DTP after BCG—Male	1123	12/117 514	37.3	1111	11/188 179	21.4	991	14/315 132	16.2	14/315 132	16.2	991	14/315 132	16.2		
DTP after BCG—Female	1062	4/112 855	12.9	1069	11/180 357	22.3	935	11/306 692	13.1	11/306 692	13.1	935	11/306 692	13.1		
Total	4048	130/592 703	80.11	3612	49/613 587	29.17	3113	34/994 940	12.48	34/994 940	12.48	3113	34/994 940	12.48		

^a The total number of children is given for the beginning of each time period (Table 2); the number in each vaccination category is determined by their status at the end of the relevant time period or when censored (death, migration, end of study). Individual children contributed person-time at risk to more than one vaccination category within each age range if they were immunized during that age range and they could be in different categories in different age groups.

including the propensity score (Table 5a) and 0.39 (95% CI: 0.23, 0.68) excluding the propensity score (Table 5b).

Effect of measles vaccine on mortality

For measles vaccine, in children aged 6–11 months, the HR was 0.42 (95% CI: 0.17, 1.01) in the model that controlled for DTP dose-response (Table 5a) and 0.48 (95% CI: 0.18, 1.26) in children with prior BCG vaccination (Table 6). The HR was higher in other age groups.

Effects of pneumococcal polysaccharide and hepatitis B vaccines on mortality

The pneumococcal vaccine generally had a non-significant protective effect on mortality with an overall HR of 0.77 (95% CI: 0.39, 1.51) (Table 5a). However, in the 12–23 month age group there was a significant reduction in mortality, consistent with findings during the efficacy trial;¹⁶ the HR was 0.42 (95% CI: 0.19, 0.93). In the analysis restricted to children who had already received BCG the same significant HR was found in the 12–23 month age group (not included in Table 6).

In most models Hep B vaccination had a non-significant protective effect; for example, the HR was 0.69 (95% CI: 0.28, 1.71) in the DTP dose-response model over all ages (Table 5a).

Interactions between BCG and DTP vaccines and sex

There did not appear to be any appreciable or important vaccine interactions (Table 7). In general, the interactions suggested that receiving both vaccinations was very similar to receiving just one of either BCG or DTP.

As explored in Table 7, no significant two-way interaction between sex and BCG, DTP or measles vaccination was found in the many basic models tested. In none of the models was mortality greater in females than in males.

Effect of geographical region on mortality

Children living in the malarious western region were often found to be significantly worse off than those living in either northern or eastern regions, as reported previously:¹⁰ while vaccine coverage was similar (Table 1), survival was worse in the western region in the 1–5 month age group (Table 5). However, in many models the deleterious effects of the western region were offset by receiving either DTP or BCG vaccinations. For example, when considered over all age groups the western region had an HR of 1.96 if BCG vaccination had not been received (Table 5a) while survival in the western region was not significantly different to that in the northern or eastern region if BCG had been received.

Discussion

In the highlands of PNG, we have found that BCG, measles and DTP vaccines were independently associated with a non-specific reduction in overall mortality during the first 2 years of life. The reduction in mortality associated with BCG immunization was only during the first 6 months, while benefit from measles vaccine was only found during the second 6 months of life. Importantly, there was no deleterious effect of DTP immunization as reported in Guinea-Bissau;⁶ there were significant beneficial effects of DTP throughout the first year of life.

Table 4 Propensity score quintiles for vaccination with BCG, DTP or measles and mortality

Quintile group	Vaccination status	No.	Mean propensity score	Mortality %
Quintile 1	Vaccinated	439	0.17	1
	Not vaccinated	384	0.13	14
Quintile 2	Vaccinated	700	0.33	3
	Not vaccinated	123	0.30	26
Quintile 3	Vaccinated	766	0.51	3
	Not vaccinated	36	0.49	67
Quintile 4	Vaccinated	791	0.69	4
	Not vaccinated	3	0.63	100
Quintile 5	Vaccinated	806	0.86	3
	Not vaccinated	0	—	—

Methodological issues

The unvaccinated group in this population is a high-risk group with an overall mortality rate seven times that in the vaccinated group, and HR for vaccination will necessarily be very low in many comparisons. This makes it a good population in which to differentiate the effects of vaccines given at different times. However, the major concern is how much of the high risk can be attributed to lack of vaccination. This has been addressed in several ways.

This was an observational study and therefore prone to bias (with respect to selection, and hence comparability, of vaccinated and unvaccinated children and similarity of data collection methods between the two groups) and potential confounding (e.g. socioeconomic status, clinic attendance).²⁴ It

Table 5(a) Hazard ratios (HR) and 95% CI after adjustment for vaccinations, dose response of DTP, background covariates, and propensity score

Variable	Age							
	29 days–5 months <i>n</i> = 3937 ^a		6–11 months <i>n</i> = 3502 ^a		12–23 months <i>n</i> = 3008 ^a		29 days–23 months <i>n</i> = 3937 ^a	
	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
BCG	0.17	(0.09, 0.34)	0.88	(0.31, 2.51)	1.78	(0.36, 8.88)	0.40	(0.25, 0.66)
DTP 1	0.19	(0.10, 0.34)	0.41	(0.14, 1.22)	0.26	(0.02, 2.81)	0.27	(0.16, 0.44)
DTP 2	0.17	(0.07, 0.38)	0.39	(0.13, 1.19)	0.63	(0.11, 3.81)	0.35	(0.19, 0.62)
DTP 3	0.09	(0.03, 0.34)	0.27	(0.08, 0.84)	0.30	(0.05, 2.06)	0.24	(0.12, 0.48)
Measles vaccine	2.68	(0.34, 21.18)	0.42	(0.17, 1.01)	0.95	(0.30, 3.05)	0.94	(0.48, 1.84)
Pneumococcal vaccine	NA		1.27	(0.45, 3.55)	0.42	(0.19, 0.93)	0.77	(0.39, 1.51)
Hepatitis B vaccine	0.83	(0.26, 2.68)	0.57	(0.08, 4.25)	0.61	(0.08, 4.60)	0.69	(0.28, 1.71)
Mother’s age	—	—	0.57	(0.37, 0.88)	—	—	—	—
Birth order	0.67	(0.52, 0.86)	—	—	—	—	0.72	(0.59, 0.87)
Western region without BCG	1.89	(1.26, 2.85)	—	—	—	—	1.96	(1.36, 2.82)
Western region with BCG	0.87	(0.44, 1.71)	—	—	—	—	0.95	(0.62, 1.45)
Male	1.25	(0.88, 1.77)	1.42	(0.81, 2.51)	1.10	(0.56, 2.18)	1.24	(0.94, 1.62)

^a In the dose–response models, there are fewer subjects as those with errors in dates for 2nd and 3rd doses of DTP were excluded.

Table 5(b) Hazard ratios (HR) and 95% CI after adjustment for vaccinations, dose response of DTP and background covariates, without propensity score adjustment

Variable	Age							
	29 days–5 months <i>n</i> = 3937 ^a		6–11 months <i>n</i> = 3502 ^a		12–23 months <i>n</i> = 3008 ^a		29 days–23 months <i>n</i> = 3937 ^a	
	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
BCG	0.39	(0.23, 0.68)	0.96	(0.40, 2.29)	2.13	(0.46, 9.83)	0.56	(0.37, 0.86)
DTP 1	0.38	(0.21, 0.70)	0.35	(0.12, 1.01)	0.21	(0.02, 2.30)	0.38	(0.23, 0.62)
DTP 2	0.38	(0.17, 0.84)	0.33	(0.11, 0.93)	0.54	(0.09, 3.16)	0.47	(0.27, 0.82)
DTP 3	0.24	(0.07, 0.86)	0.23	(0.08, 0.68)	0.27	(0.04, 1.75)	0.36	(0.19, 0.68)
Measles vaccine	2.52	(0.32, 20.08)	0.44	(0.18, 1.06)	0.99	(0.31, 3.16)	0.88	(0.47, 1.67)
Pneumococcal vaccine	NA		1.32	(0.48, 3.64)	0.44	(0.20, 0.97)	0.8	(0.42, 1.54)
Hepatitis B vaccine	0.91	(0.28, 2.97)	0.58	(0.08, 4.29)	0.62	(0.08, 4.59)	0.7	(0.28, 1.72)
Mother’s age	—	—	0.58	(0.37, 0.89)	—	—	—	—
Birth order	0.66	(0.51, 0.85)	—	—	—	—	0.71	(0.58, 0.86)
Western region without BCG	2.04	(1.36, 3.07)	—	—	—	—	2.06	(1.43, 2.97)
Western region with BCG	0.92	(0.47, 1.81)	—	—	—	—	0.99	(0.65, 1.50)
Male	1.17	(0.83, 1.65)	1.42	(0.81, 2.51)	1.1	(0.56, 2.19)	1.21	(0.92, 1.58)
Twin	2.49	(1.10, 5.65)						

^a In the DTP dose–response models, there are fewer subjects as those with errors in dates for 2nd and 3rd doses of DTP were excluded.

Table 6 Hazard ratios (HR) and 95% CI after adjustment for vaccinations, dose response of DTP and background covariates, without propensity score adjustment, in children who had received BCG before age 6 months

Variable	Age					
	29 days–5 months <i>n</i> = 2788 ^a		6–11 months <i>n</i> = 2618 ^a		29 days–23 months <i>n</i> = 2788 ^a	
	HR	95% CI	HR	95% CI	HR	95% CI
DTP 1	0.48	(0.22, 1.09)	0.26	(0.05, 1.30)	0.45	(0.22, 0.91)
DTP 2	0.34	(0.13, 0.89)	0.42	(0.11, 1.61)	0.47	(0.23, 0.97)
DTP 3	0.17	(0.04, 0.70)	0.22	(0.05, 0.86)	0.26	(0.11, 0.59)
Measles vaccine	2.34	(0.30, 18.41)	0.48	(0.18, 1.26)	0.77	(0.39, 1.53)
Pneumococcal vaccine	—	—	0.88	(0.26, 2.97)	0.53	(0.26, 1.05)
Hepatitis B vaccine	1.03	(0.31, 3.42)	0.63	(0.08, 4.70)	0.74	(0.30, 1.85)
Mother's age	—	—	0.49	(0.28, 0.88)	0.73	(0.54, 1.00)
Date of birth (1992–1994 versus 1989–1991)	2.45	(1.22, 4.93)	—	—	1.72	(1.13, 2.61)
Male	1.77	(0.90, 3.47)	1.12	(0.52, 2.38)	1.41	(0.93, 2.14)

^a In the dose–response models, there are fewer subjects as those with errors in dates for 2nd and 3rd doses of DTP were excluded.

Table 7 BCG–DTP vaccine–sex interactions (in models without propensity score) in children who received BCG before age 6 months

Variable	HR	95% CI
BCG only—Female	1.00	—
BCG only—Male	1.50	(0.53, 4.22)
BCG and 1 dose of DTP—Female	0.50	(0.17, 1.46)
BCG and 1 dose of DTP—Male	0.62	(0.22, 1.73)
BCG and 2 doses of DTP—Female	0.38	(0.12, 1.19)
BCG and 2 doses of DTP—Male	0.79	(0.29, 2.14)
BCG and 3 doses of DTP—Female	0.27	(0.09, 0.79)
BCG and 3 doses of DTP—Male	0.32	(0.11, 0.93)
Measles vaccine	0.67	(0.33, 1.33)
Hepatitis B vaccine	0.72	(0.29, 1.79)
Date of birth (1992–1994 versus 1989–1991)	1.69	(1.11, 2.57)
Mother's age	0.73	(0.54, 0.99)

was therefore essential to consider all potential biases and aim to reduce their potential effects to a minimum.

Ongoing demographic surveillance over many years which was independent of the activities of MCH nurses ensured complete registration of births in the area. To avoid bias towards surviving children, only those born under demographic surveillance who were registered on the database within 60 days and who survived the neonatal period were included. We aimed to maximize the chances of complete registration of deaths as well as immunization by censoring children at time of first migration out of the area under demographic surveillance. Several additional steps were taken to ensure complete records of immunization. Data from clinic cards were entered on computer files monthly and reporters and their supervisors assisted in linking demographic and immunization records on a fortnightly basis. Collective knowledge of Huli staff gathered at regular meetings assisted in locating people who may have moved within the Tari Basin and hence attended different MCH

clinics. On several occasions we checked MCH cards from clinics in areas immediately adjacent to the area under demographic surveillance in the event that some mothers had taken their children to these clinics. In this way 10 children's records were identified. Children living ≥ 2 months in an adjacent area were censored from the study. Since MCH clinics were held at minimum time intervals of 4 weeks and all clinic cards were collected monthly, if a death had occurred we would have been able to check that child's card before MCH nurses might have discarded the card. Furthermore, MCH nurses kept all clinic cards for one year after a child ceased attending their clinic. Nevertheless we have no independent check that this always happened. If a mother took her child to a different clinic, the nurse would check the child's health book kept by the mother and record any previous immunizations on the clinic card. Whenever possible, mothers like to bring their children to the same clinic attended by others members of their clan group, since MCH clinics are important social events, a time when women can leave their gardening activities and meet with friends and relatives. If a nurse did not record an immunization on a clinic card then we would not have any record of it. However, such an event is unlikely since, generally, after checking immunizations listed on the child health book and clinic-held record card, she would write instructions for vaccination on the clinic card and hand the card to another staff member to administer vaccines according to written instructions. It is possible that occasionally an immunization was recorded on the card but for some reason was not given to the child.

While the same method was used to collect data on all immunizations given to all children in the study, the original study was designed to investigate the effectiveness of Pnc PS vaccine given at age 8–23 months. It is possible that during the setting up phase of the study, cards belonging to children who died young may not have been examined by the research team if discarded by MCH nursing staff before our first card collection. However, exclusion of children born in 1989–1990 made no difference to our results. Families of children who had no record of having received Pnc PS vaccine by age 2 years were

visited in order to record any missed Pnc PS vaccinations but health books were not checked for other immunizations. Unfortunately, the way results from these home visits were recorded does not provide satisfactory information on quality of our routine immunization data collection. Similarly, if a child died, we made a point of trying to determine Pnc PS immunization status. It is therefore likely that the most reliable data in this study are for Pnc PS vaccine; our findings of no significant reduction in mortality at 6–11 months of age (when more deaths were documented than in older children) but a HR of 0.42 at ages 12–23 months are entirely consistent with the results of the earlier randomized controlled trial when efficacy in prevention of death at age 12–23 months in Tari was 49%.¹⁶

Our main concern regarding bias was the potential differences in characteristics of clinic attenders (and hence vaccinees, since this was the only means of getting immunized) and non-attenders. The propensity score was used to adjust for potential differences in background characteristics between vaccinated and unvaccinated children in a time-dependent fashion so that comparisons between vaccinated and unvaccinated groups were always made independent of known factors leading to vaccination, including the child's age in particular. Thus bias due to known factors was removed, although of course we were unable to adjust for any unknown factors that could lead to vaccination. To allow more stringently for health service utilization, we also included an analysis restricted to BCG recipients, which confirmed protection afforded by DTP and a dose-response to DTP. With no propensity score, vaccines appeared somewhat less beneficial. Interestingly, the introduction of a propensity score into the model restricted to those with prior BCG made no difference to the HR, suggesting that the propensity score adjusted well for clinic attendance.

An additional explanation for high mortality (and hence low HR) in a small group of unvaccinated clinic attenders might be that, in some cases, sick children who are at greatest risk are brought to a clinic by their mothers in the hope of getting treatment, but these children never get vaccinated because of contraindications.

Comparison with other studies

The non-specific reduction in overall mortality associated with BCG in our study is consistent with the study in Guinea-Bissau.⁶ In The Gambia, BCG has been reported to induce a potent Th1-type response when given at birth.²⁵ We have found that BCG afforded maximum protection against death in the 1–5 month age group, a time when the immune system is still maturing. Had we been able to follow up reliably from birth, we might have shown even greater benefit, particularly during the neonatal period when mortality rates are high. This requires further investigation.

The HR for measles vaccine indicating protection against death in 6–11 month old children were also of the same order as reported elsewhere.^{6,26}

There are several reasons why our findings with respect to effectiveness of DTP might differ from those found in Guinea-Bissau. Our study population had different characteristics: lower infant mortality in Tari (68 compared with 121/1000 live births in Guinea-Bissau^{10,27}), higher birthweight (in the early 1980s, 15% of births were ≤ 2500 g²⁸ compared with 26% in a recent report from Guinea-Bissau²⁹), only one area with

mesoendemic malaria (the western region) compared with holoendemic malaria in the study area in Guinea-Bissau,³⁰ fewer deaths of older siblings (28%) in Tari compared with Guinea-Bissau (52%)⁶ and more supervised deliveries (estimated 89% compared with approximately 30% in Guinea-Bissau⁶). With respect to malaria endemicity, however, our data suggest that DTP and BCG protected children in both malarious and non-malarious regions of the Tari Basin.

Our methodology differed in that there was frequent (i.e. monthly) recording of vital events and immunization status. In Guinea-Bissau, immunizations tended to be given during the dry season while mortality was highest during the wet season. In Tari, immunization clinics were conducted monthly except for one month at the end or beginning of each calendar year or at times of clan fighting and there was no significant seasonal variation in total mortality. The poorer vaccine coverage among children born in 1994 compared with earlier years is in part attributable to a reduction in the number of clinics held as a result of clan fighting. Nevertheless it was still possible for research staff to go out and collect immunization data from health centres. In neither population do we know whether the vaccines were delivered under optimal cold-chain conditions. During the effectiveness study of Pnc PS vaccine in Tari (1991–1995), the research team assisted in ensuring optimum storage conditions of vaccines in health centres. It is also noteworthy that three additional vaccines (Hep B, pigbel and Pnc PS) were given in Tari but not in Guinea-Bissau. There is no way of distinguishing effects of DTP, pigbel and oral polio since these vaccines were usually given together; they may have had synergistic effects.

Conclusion

The limitations of observational studies are well known. In this study we have sought to address and adjust for known potential sources of bias and have found that routine childhood immunizations are effective in reducing mortality of young children in an area of high mortality. Further research is needed to understand mechanisms underlying possible non-specific effects of vaccines and interactions between vaccines. We need to ensure that appropriate vaccines can be delivered safely to those at greatest risk using optimum immunization schedules. Furthermore, monitoring systems must be in place that would detect potential unexpected effects of vaccines.

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KEY MESSAGES

- In an area of high mortality such as the highlands of Papua New Guinea, routine childhood immunizations are effective in reducing overall mortality in young children.
- Diphtheria-tetanus-whole-cell pertussis vaccine is not associated with increased risk of death.
- BCG has a protective effect against mortality.
- In an area of high mortality, pneumococcal polysaccharide vaccine, when given from the age of 8 months, is effective in reducing risk of death in children aged 12–23 months.
- The propensity score can be used to adjust for potential confounding of background characteristics.

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