Effect of national immunisation campaigns with oral polio vaccine on all-cause mortality in children in rural northern Ghana: 20 years of demographic surveillance cohort data

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Summary

Background Studies from Guinea-Bissau and Bangladesh have shown that campaigns with oral polio vaccine (C-OPV) may be associated with 25–31% lower child mortality. Between 1996 and 2015, Ghana had 50 national C-OPVs and numerous campaigns with vitamin A supplementation (VAS), and measles vaccine (MV). We investigated whether C-OPVs had beneficial non-specific effects (NSEs) on child survival in northern Ghana.

Methods We used data from a health and demographic surveillance system in the Navrongo Health Research Centre in rural northern Ghana to examine mortality from day 1–5 years of age. We used Cox models with age as underlying time scale to calculate hazard ratios (HR) for the time-varying covariate "after-campaign" mortality versus "before-campaign" mortality, adjusted for temporal change in mortality, other campaign interventions and stratified for season at risk.

Findings From 1996 to 2015, 75,610 children were followed for 280,156 person-years between day 1 and 5 years of age. In initial analysis, assuming a common effect across all ages, we did not find that OPV-only campaigns significantly reduced all-cause mortality, the HR being 0.96 (95% CI: 0.88–1.05). However, we subsequently found the HR differed strongly by age group, being 0.92 (0.75–1.13), 1.29 (1.10–1.51), 0.79 (0.66–0.94), 0.67 (0.53–0.86) and 1.03 (0.78–1.36) respectively for children aged 0–2, 3–5, 6–8, 9–11 and above 12 months of age ($p < 0.001$). Triangulation of the evidence from this and previous studies suggested that increased frequency of C-OPVs and a different historical period could explain these results.

Interpretation In Ghana, C-OPVs had limited effects on overall child survival. However, triangulating the evidence suggested that NSEs of C-OPVs depend on age of first exposure and routine vaccination programs. C-OPVs had beneficial effects for children that were not exposed before 6 months of age. These non-specific effects of OPV should be exploited to further reduce child mortality.

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Keywords: Oral polio vaccine campaigns; OPV; Non-specific effects of vaccines; Child mortality; Triangulation

Introduction

Many studies have shown that live vaccines have beneficial non-specific effects (NSE), that is they also reduce susceptibility to unrelated infections.[1–4] The World Health Organisation (WHO) reviewed the potential NSEs of Bacille Calmette-Guérin (BCG), diphtheria-tetanus-pertussis (DTP) and measles vaccine (MV) and concluded the evidence suggests that the live vaccines, BCG and MV, were associated with large reductions, around 40%, in overall mortality.[5,6] WHO's Strategic

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Research in context

Evidence before this study

During the last three decades numerous campaigns with the live oral polio vaccine (C-OPV) have been conducted in low- and middle-income-countries with the goal to ultimately eradicate wild poliovirus. However, in recent years studies from Guinea-Bissau and Bangladesh have suggested that C-OPVs are associated with 25–31% reduction in the mortality rates for children under three years of age.

Added value of this study

In rural Ghana, analysing data from 1996 to 2015 C-OPVs were associated with a non-significant 4% (95% confidence interval: -5-12%) reduction in the hazard comparing after vs. before C-OPV exposure in under-5-year all-cause mortality. However, key contextual factors differed in Ghana compared to previous studies. Children that we not exposed to C-OPV before 6 months of age had a beneficial effect of receiving C-OPV after 6 months of age, 22% reduction in mortality (5–35%). The estimate for the same historical period as previous studies (2004–2015), was associated with a non-significant reduction of 13% (−1 to 24%).

Implications of all the available evidence

Several studies support that C-OPVs have beneficial non-specific effects (NSEs). The present study did not show any overall beneficial effects of C-OPVs. However, triangulation of the evidence showed that the NSEs depend on age of exposure and routine vaccination. Understanding these causal structures is essential for future studies that investigate the beneficial NSEs of C-OPVs.

Advisory Group of Experts on immunization (SAGE) therefore recommended further research into the NSEs of vaccines. All live attenuated vaccines examined so far, including BCG, MV, and oral polio vaccine (OPV), have beneficial NSEs, and several randomised controlled trials (RCTs) have found 26–38% reductions in mortality not ascribed to the vaccine-targeted diseases.[7–10] WHO did not examine OPV but epidemiological studies and one RCT have documented beneficial NSEs of OPV.[8,11]

OPV is used in three different contexts: In the first month of life as a dose zero (OPV0) usually given with BCG; as three doses at 1.5–3.5 months of age co-administered with DTP and other routine vaccination; and in campaigns with OPV (C-OPVs) to eradicate wild poliovirus. Thousands of campaigns have been conducted for the last 25–30 years in low-income countries.[11] However, it is planned to remove OPV after eradication which could paradoxically have negative consequences by depriving children of beneficial NSEs.[12] We are therefore assessing the overall impact of C-OPVs in low and middle-income countries to get a better understanding of the extend C-OPVs have contributed to the decline in child mortality observed in the last decades.

We have previously used data from health and demographic surveillance systems (HDSS) in Guinea-Bissau and Bangladesh to document that C-OPVs, where OPV was administered alone, were associated with 25% and 31% lower mortality, respectively, when comparing the mortality after vs. before C-OPVs, adjusting for age, year, season, and other campaign interventions.[13,14]

We examined HDSS data for children under five years of age from the Navrongo Health Research Centre's HDSS in rural northern Ghana.[15] Our hypothesis was that C-OPV would significantly reduce all-cause child mortality.

Methods

Study design and setting

The study was conducted in the Kassena-Nankana East municipal and Kassena-Nankana West district in the Upper East region of northern Ghana. The study area covers 1675 km^2, close to the Burkina Faso border. It has one main hospital that serves as a referral hospital to nine clinics or health centers. Furthermore, there are over 30 Community Health Compounds, located mostly in rural communities and staffed by trained nurses, who provide basic health care as well as routine vaccinations.[15]

During the study period from 1996 to 2015, the HDSS field teams visited all households 3–4 times a year to document demographic events such as new births, deaths, and migrations. Educational attainment and household possessions are documented as part of the HDSS operations.

Vaccination data

Routine vaccination data from 1996 to 2015 collected by the Navrongo HDSS were used for the analyses (Supplementary File).[16] Between 1996 and 2010, vaccination data were collected once annually from health cards of children less than two years of age, except in 2001 when the HDSS failed to collect vaccination data. From 2011 to 2015, vaccination data were updated every four months for children aged three years or younger.

Campaigns

Information on campaigns has been summarized in Supplementary File. Navrongo did not have a particular programme for registering all campaigns. We have previously shown with data from Guinea-Bissau and Bangladesh that Rotary has the best information on C-OPVs.[17] We therefore used the Rotary data on C-OPVs in Northern Ghana. Data on other campaigns, in

particular vitamin A supplementation (VAS) and MV, were obtained from Navrongo HDSS, and by further checking the information from WHO, the grey literature and publications referring to campaigns in the period 1996–2015 (Supplementary File). We excluded campaigns that could not be confirmed by more than one source, except VAS campaigns that followed the usual pattern with VAS being administered in the second round of an OPV campaign consisting of two campaigns with one months' interval.

As in previous analyses, we implemented an intention-to-treat principle regarding campaign participation: Children were assumed to be exposed whenever they were eligible to a campaign,[13,18,19] i.e. campaign exposures were not changed by subsequent exposure. This ensures that campaign participation is independent of confounding factors, e.g., socioeconomic status. Campaign participation is usually very high, in Navrongo.[20]

We analysed OPV-only campaigns as the primary exposure as we have previously seen that OPV co-administered with other interventions, primarily VAS, did not have similar beneficial effects.[13,18,19] Any OPV campaign for children under 6 months of age was OPV-only, as OPV is the only intervention that has been administered under 6 months of age. We denote C-OPV-only as C-OPV for the rest of the article.

We analysed by birth year cohorts in the analyses over different time periods as these would better represent the effects of C-OPV over time in relation to the available vaccination coverage, rather than analyzing by calendar year.

Statistical analysis

The under-5 years mortality risk was calculated using the survival function by calendar year. Since we only followed children born in the study area, in 1996, the first year of the study, we only had infants, in 1997, there was only children under 2 years of age, etc. Since most events (campaigns and deaths) occurred in the first year of life, we present the results of the full data set from 1996. Since children only reached 5 years of age from 2000, we could only estimate the under-5 mortality from 2001 to 2015.

We examined mortality after and before C-OPV in Cox proportional hazards models with age as underlying time scale. Using age as the underlying time scale inherently differentiate between different mortality risk at different ages. All campaigns were included as time-varying covariates. The analyses included only children born in the HDSS area and alive during the first visit after birth by the HDSS team. The overall analysis up to 5 years of age assumed a common effect across all ages. We conducted two analyses, one which only included individual campaign interventions and adjusted for calendar year as a continuous trend within different age groups (0–5, 6–11, 12–23 and 24–59 months of age) and further included season (rainy: June–November, dry: December–April) with different baseline hazards functions. In the second and main analysis, we further included participation status for all campaign interventions. Proportional hazards were tested using the Schoenfeld residuals with the "*estat phtest*" Stata command. The proportional hazards assumption was not clearly (at $p < 0.05$). However, since the effects of C-OPV differed significantly between some of the age groups, all age group specific estimates were calculated from the full dataset by adding an interaction term with age group, i.e. "C-OPV#i.agegroup i.agegroup", in addition to the other covariates described above.

We used the data on vaccinations to calculate coverage and median age of vaccination for BCG and OPV0, as well as mean age of vaccination for DTP3 and MV.

We analysed the association of vaccination coverages and the effect of C-OPV by birth year cohorts in linear regression models. Since the effect of C-OPV varied substantially between individual birth year cohorts, we based the analysis on five-year birth cohorts for both the C-OPV effect and vaccination coverage. We present the estimated linear equation weighted by the mortality rate with 95% confidence band in plots, and provide r^2 and the p-value for test of association, i.e., slope coefficient = 0. We used point estimates for both C-OPV estimates and vaccination coverages.

Data was analysed using STATA version 17.0.

Triangulation methods

NSEs of vaccines are context-dependent and may depend on many factors.[4,21] The effect of a vaccine on all-cause mortality may therefore vary in different environments. It is therefore important that if the NSE effect of a vaccine is found to vary in different studies, potential explanatory factors are investigated. Explanatory factors identified in one study should be tested in previous studies and rejected if not confirmed. Thus, new explanatory factors should be compatible both with the present and the previous studies. This means that when all evidence is triangulated, the ability of the hypothesis to account for all existing data should increase with the inclusion of the explanatory factor.[21]

Ethics statement

The HDSS study was reviewed and approved by the institutional review board of the Navrongo Health Research Centre. Since HDSS requires frequent routine visits to households to update health and demographic information, verbal consent was deemed appropriate for monitoring of the demographic events. The HDSS field workers therefore sought verbal consent from household heads or any other adult member of the household.

Role of the funding source

The work was facilitated by a grant for DANIDA to organise a workshop to analyse the data on OPV

campaigns (21-EC03-SDU). Else og Mogens Wedell Wedellsborgs Fond travel grant (8-18-2) to SN to travel to Ghana. No funding body had any role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Results

Study population

Over the 20 years of the study, from 1996 to 2015, 75,610 children were followed for 280,156 person-years between day 1 and 5 years of age. This corresponds to 3.7 years of follow-up per child with 62% of all children followed and censored at 5 years of age. A total of 4968 deaths occurred. Under-5 mortality declined with 73% from 158 to 42 per 1000 newborns over the study period (Fig. 1).

OPV campaigns

During the study period 50 campaigns with OPV were conducted (Fig. 1 and Supplementary File). The effective interval between C-OPVs were 6 months, compared to 17 months in the previous studies from Bissau and Chakaria. This resulted in a large proportion of children having been exposed early in life to C-OPV in Navrongo, with 72% having been exposed to C-OPV before 6 months of age.

Overall effect of C-OPVs

In the overall analysis for all children under five years of age, where we assumed a common effect of C-OPV across all ages, C-OPVs were associated with a non-significant HR of 0.96 (95% confidence interval: 0.88–1.05) comparing time after-campaign vs. before-campaign (Table 1). The overall NNT to save one life with campaign-OPV-only was 352 neonates (95% CI: 324–383).

The estimates of the C-OPV effect tended to differ over calendar time. The first 5 birth year cohort having a HR of 1.00 (0.86–1.15) and the last five yielding a HR of 0.75 (0.54–1.06) (Table 2). Limiting the analysis to the comparable historic period to the studies from Bissau and Chakaria, i.e. between 2004 and 2015, yielded a HR of 0.87 (0.76–1.01) (data not shown).

Age of the child

The HR differed strongly by age group, being 0.92 (0.75–1.13) for children aged 0–2 months, 1.29 (1.10–1.51) in the 3–5 months age group, 0.79 (0.66–0.94) in the 6–8 months age group, 0.67 (0.53–0.86) in the 9–11 months age group and 1.03 (0.78–1.36) for children from one year of age ($p < 0.001$) (Table 1). Since other campaigns were only given after 6 months of age, we compared C-OPV and the other campaigns between 6 and 11 months (Table 3). C-OPV-only had a HR of 0.76 (0.66–0.88) and differed from the effect of C-OPV + VAS (HR = 1.12 (0.97–1.30); interaction test, $p < 0.001$) and C-VASs (HR = 1.84 (0.86–3.90); interaction test, $p = 0.02$) (Table 3).

Age of first C-OPV exposure

Among children that had not been exposed to C-OPVs before 6 months of age, 28% of children, the HR of C-OPV received after 6 months of age was HR of 0.78

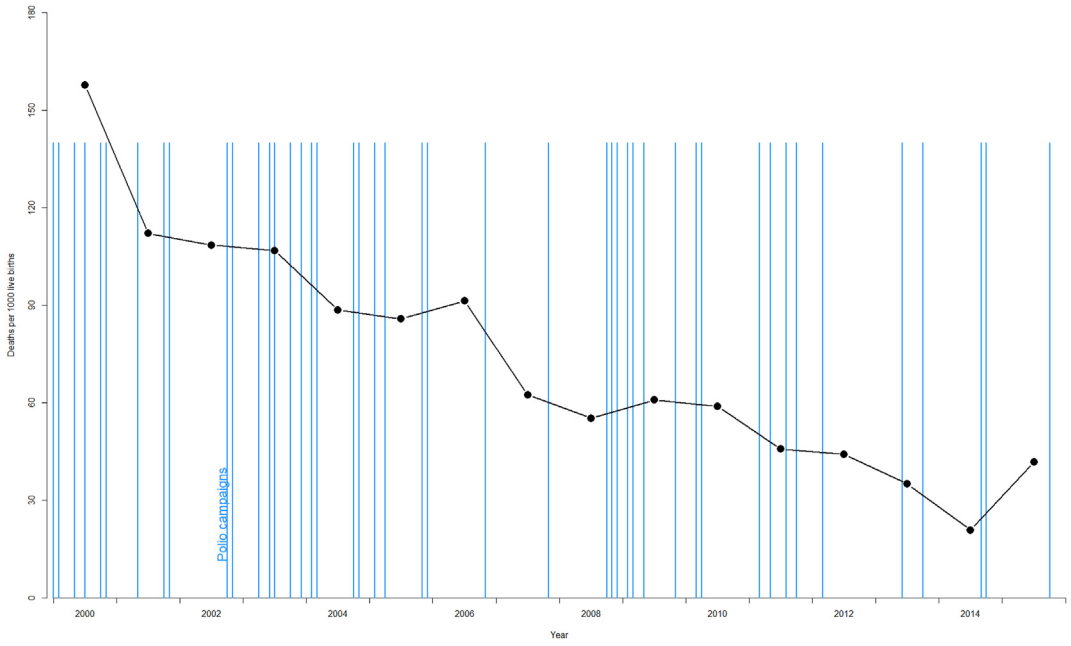

Fig. 1: **Under-5 mortality in Navrongo 2000–2015. The timing of OPV campaigns has been marked with vertical lines.**

Age group	Proportion exposed to oral polio vaccine campaigns (C-OPV) in age group	Rate per 1000 person-years (deaths/person-days)		Overall HR (after/before campaigns) (95% CI)[a]	Males HR (after/before campaigns) (95% CI)[a]	Females HR (after/before campaigns) (95% CI)[a]	p-value for same effect by sex
		After-campaign	Before-campaign				
Overall	95.4% (72,135/75,610)	15.31 (3985/95,076,335)	49.52 (983/7,250,537)	0.96 (0.88–1.05)	0.88 (0.78–1.00)	1.04 (0.91–1.18)	0.07
0–2 months	49.1% (27,004/54,989)	55.04 (146/968,853)	76.54 (351/1,674,884)	0.92 (0.75–1.13)	0.88 (0.66–1.17)	0.97 (0.73–1.29)	0.64
3–5 months	71.9% (49,765/69,188)	47.29 (459/3,545,317)	46.50 (285/2,238,700)	1.29 (1.10–1.51)	1.15 (0.92–1.45)	1.43 (1.14–1.79)	0.18
6–8 months	83.2% (58,158/69,873)	35.48 (462/4,755,931)	56.90 (216/1,386,561)	0.79 (0.66–0.94)	0.76 (0.59–0.99)	0.81 (0.63–1.03)	0.73
9–11 months	91.5% (62,823/68,693)	36.73 (546/5,430,156)	42.69 (79/675,958)	0.67 (0.53–0.86)	0.62 (0.44–0.86)	0.74 (0.52–1.06)	0.48
12–59 months	99.0% (67,057/67,766)	10.78 (2372/80,376,078)	14.90 (52/1,274,434)	1.03 (0.78–1.36)	0.89 (0.62–1.30)	1.21 (0.78–1.86)	0.29

[a]Full multivariable model: adjusting for age (underlying time), other campaigns (OPV + VAS (6–59 months), VAS (6–59 months), OPV + VAS + MV (9–59 months), VAS + MV (9–59 months), MV (9–50 months) and Meningitis vaccine (12–59 months)), year*age group and rainy/dry season.

Table 1: **Mortality rates (per 1000 person-years) and hazard ratios (HR) for after-campaign versus before-campaign overall and by sex in Navrongo health and demographic surveillance system (HDSS) data from 1996 to 2015.**

(0.65–0.95) (Table 4). The NNT to save one life with campaign-OPV-only in this group was 114 children (95% CI: 100–132).

Routine vaccinations

The coverage for routine vaccinations changed over the 20 years (Supplementary File). We have found previously that OPV0 given early is an important immune enhancer[22] and the overall effect of C-OPV between 0 and 11 months was strongly associated (p = 0.002) with the proportion of children receiving OPV0 within the first two weeks of life (Fig. 2, Supplementary File).

Triangulation of results

Two major contextual differences were found in the data from Navrongo compared to Bissau and Chakaria. First, the frequency of OPV campaigns and second the historical period. We compared the impact of these key parameters on mortality in the analyses from Navrongo, Guinea-Bissau,[13,18] and Bangladesh.[19] The difference in

Age group	Overall HR (after/before campaigns) (95% CI) [Proportion exposed to C-OPV in age group][a]			
	Birth years 1996–2000	Birth years 2001–2005	Birth years 2006–2010	Birth years 2011–2015
All children				
Overall	1.00 (0.86–1.15) [96.6%]	0.99 (0.81–1.22) [98.7%]	0.87 (0.70–1.09) [97.5%]	0.75 (0.54–1.06) [88.6%]
0–2 months	1.18 (0.86–1.60) [44.3%]	0.77 (0.55–1.09) [61.9%]	0.75 (0.42–1.32) [40.8%]	0.54 (0.23–1.28) [46.4%]
3–5 months	1.55 (1.23–1.96) [66.0%]	1.59 (1.08–2.34) [87.2%]	1.28 (0.77–2.14) [66.2%]	0.90 (0.53–1.52) [67.7%]
6–8 months	0.67 (0.53–0.86) [82.3%]	1.05 (0.63–1.73) [97.0%]	0.59 (0.37–0.93) [76.1%]	1.04 (0.52–2.06) [76.9%]
9–11 months	0.64 (0.46–0.90) [96.7%]	0.30 (0.15–0.58) [99.1%]	0.86 (0.48–1.55) [83.1%]	0.25 (0.10–0.60) [85.8%]
12–59 months	1.68 (0.23–12.24) [100.0%]	1.13 (0.36–3.60) [99.9%]	0.95 (0.65–1.40) [99.4%]	1.64 (0.22–12.4) [96.0%]
Males				
Overall	0.86 (0.70–1.05)	0.99 (0.74–1.34)	0.81 (0.60–1.10)	0.62 (0.38–1.01)
0–2 months	1.05 (0.66–1.65)	1.02 (0.62–1.66)	0.61 (0.29–1.28)	0.27 (0.06–1.24)
3–5 months	1.34 (0.95–1.87)	1.25 (0.74–2.11)	1.59 (0.77–3.30)	0.88 (0.41–1.92)
6–8 months	0.55 (0.38–0.79)	1.09 (0.55–2.15)	0.67 (0.34–1.30)	0.71 (0.27–1.88)
9–11 months	0.62 (0.39–0.98)	0.21 (0.09–0.47)	0.67 (0.31–1.45)	0.20 (0.05–0.81)
12–59 months	0.65 (0.09–4.90)	1.70 (0.23–12.41)	0.80 (0.48–1.33)	1.04 (0.13–8.29)
Females				
Overall	1.14 (0.94–1.39)	1.00 (0.74–1.33)	0.94 (0.68–1.31)	0.90 (0.56–1.45)
0–2 months	1.30 (0.85–1.97)	0.60 (0.36–0.98)	1.04 (0.42–2.60)	0.90 (0.30–2.71)
3–5 months	1.77 (1.28–2.45)	2.04 (1.15–3.63)	1.02 (0.49–2.11)	0.90 (0.44–1.84)
6–8 months	0.80 (0.57–1.11)	1.00 (0.47–2.11)	0.54 (0.29–1.04)	1.46 (0.53–4.01)
9–11 months	0.67 (0.42–1.09)	0.51 (0.16–1.64)	1.15 (0.47–2.79)	0.28 (0.09–0.87)
12–59 months	N/A	0.84 (0.20–3.51)	1.16 (0.66–2.04)	N/A

[a]Full multivariable model: adjusting for age (underlying time), other campaigns (OPV + VAS (6–59 months), VAS (6–59 months), OPV + VAS + MV (9–59 months), VAS + MV (9–59 months), MV (9–59 months) and Meningitis vaccine (12–59 months)), year*age group and rainy/dry season.

Table 2: **Mortality rates (per 1000 person-years) and hazard ratios (HR) for after-campaign versus before-campaign by five-year birth cohorts, overall and by sex in Navrongo HDSS data from 1996 to 2015.**

Type of campaign	Rate per 1000 person-years (deaths/person-days)		Overall HR (after/before campaigns) (95% CI)[a]	Overall HR (after/before campaigns) (95% CI)[b]	p-value for same effect as OPV-only
	After-campaign	Before-campaign			
OPV-only	36.14 (1008/10,186,087)	52.24 (295/2,062,519)	0.75 (0.65–0.86)	0.76 (0.66–0.88)	–
OPV + VAS	35.55 (285/2,927,757)	39.89 (1018/9,320,849)	1.12 (0.97–1.30)	1.12 (0.97–1.30)	<0.001
OPV + VAS + MV	73.90 (5/24,714)	38.78 (1298/12,223,892)	2.52 (1.04–6.09)	2.05 (0.83–5.05)	0.03
VAS-only	21.62 (7/118,244)	39.02 (1296/12,130,362)	1.75 (0.82–3.70)	1.84 (0.86–3.90)	0.02
MV-only	23.82 (5/76,668)	38.95 (1298/12,171,938)	1.16 (0.48–2.81)	1.27 (0.52–3.10)	0.27

VAS = vitamin A supplementation and MV = measles vaccine. [a]Univariate model: adjusting for age (underlying time), year*age group and rainy/dry season. [b]Full multivariable model: adjusting for age (underlying time), other campaigns (OPV + VAS (6–59 months), VAS (6–59 months), OPV + VAS + MV (9–59 months), VAS + MV (9–59 months), MV (9–50 months) and Meningitis vaccine (12–59 months)), year*age group and rainy/dry season.

Table 3: **Mortality rates (per 1000 person-years) and hazard ratios (HR) for after-campaign versus before-campaign between 6 and 11 months in Navrongo HDSS data from 1996 to 2015.**

early exposure between Ghana on one side and Guinea-Bissau and Bangladesh on the other was marked. In Navrongo the effective interval between OPV campaigns was 6 months compared to 17 months in Guinea-Bissau and Bangladesh. This significantly reduced the age of first C-OPV exposure compared with Guinea-Bissau and Bangladesh. Children that were not exposed to C-OPV before 6 months of age had a similar beneficial effect of C-OPV as in Guinea-Bissau and Bangladesh. The difference in the effect between the three studies was in the age group 3–5 months (Table 5).

Discussion

We observed an overall non-significant effect of C-OPV of 4% (–5 to 12%) in the hazard comparing time after vs. before C-OPV exposure in Navrongo in the analysis assuming a common effect across all ages. This clearly contradicted our initial hypothesis of a 25–31% reduction in mortality rate observed in Guinea-Bissau and Bangladesh.[13,18,19] The data from Navrongo differed significantly on several key parameters from Guinea-Bissau and Bangladesh. The frequency of C-OPV was much higher and data represented a different historical period. Triangulating the evidence from all three sites showed consistent patterns, that the effect of C-OPVs are dependent on both age of first exposure and routine vaccinations.

The Navrongo data set was large with nearly 5000 deaths covering the whole period from when C-OPVs were introduced in the mid-1990s.

Few HDSS sites have routinely collected information on dates of campaigns. With the passing of time and changes in staff, such information is likely to be lost. However, Rotary has collected very precise information on the timing of OPV campaigns.[17] The WHO information on C-OPVs and other campaigns, including VAS and MV, has been less precise.[17] However, we searched public health records, grey literature, and all published literature to obtain information on other campaigns. We are therefore fairly certain that the campaign information used is accurate, especially for the OPV campaigns.

We used essentially the same analytical model as used previously in Guinea-Bissau and Bangladesh.[13,18,19] As in previous analyses, the effect of C-OPV-only was stronger for males than females and had a better effect on survival than campaigns with OPV + VAS. After 6 months of age, C-OPV had beneficial effects similar to those found in Guinea-Bissau and Bangladesh for those that did not receive C-OPV before 6 months of age, HR = 0.78 (0.65–0.95).

There are several indications that C-OPV interacted with routine vaccinations. First, it has previously been shown, in an RCT[8,22,24–26] and several observational studies,[11] that OPV0 can have beneficial non-specific

Age group	Rate per 1000 person-years (deaths/person-days)		Overall HR (after/before campaigns after 6 months) (95% CI)[a]
	After-campaign	Before-campaign	
Overall	12.46 (735/21,554,038)	37.98 (347/3,336,953)	0.78 (0.65–0.95)
6–8 months	47.48 (45/346,198)	56.90 (216/1,386,561)	0.80 (0.57–1.14)
9–11 months	27.76 (77/1,013,035)	42.69 (79/675,958)	0.55 (0.39–0.77)
12–59 months	11.09 (613/20,194,805)	14.90 (52/1,274,434)	1.01 (0.74–1.38)

[a]Full multivariable model: adjusting for age (underlying time), other campaigns (OPV + VAS (6–59 months), VAS (6–59 months), OPV + VAS + MV (9–59 months), VAS + MV (9–59 months), MV (9–50 months) and Meningitis vaccine (12–59 months)), year*age group and rainy/dry season.

Table 4: **Mortality rates (per 1000 person-years) and hazard ratios (HR) for after-campaign versus before-campaign after 6 months of age for children that were not exposed to C-OPV before 6 months of age in Navrongo HDSS data from 1996 to 2015.**

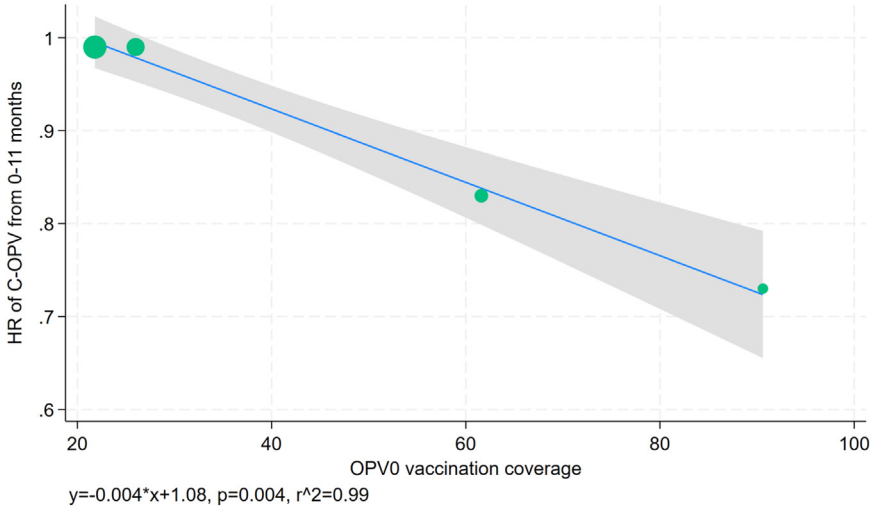

Fig. 2: **Scatter plot with linear trend for the association of OPV0 coverage and the HR of C-OPVs between 0 and 11 months of age by five-year birth cohorts and weighted by the mortality rate.**

immunological effects, particularly when given early.[8,22] It is therefore interesting that early administration of OPV0 was strongly linked to an overall beneficial effect of C-OPVs. As OPV0 coverage increased and the median age of OPV0 vaccination declined, the beneficial effect of C-OPV tended to increase in children under 1 year of age (Fig. 2, Table 4). Second, between 3 and 5 months, the overall effect was negative. This is the period when DTP vaccine is the predominant vaccine. We have previously observed that a vaccine with beneficial non-specific effects could interact negatively with subsequent DTP vaccine. For example, VAS may

Age group	Navrongo, Ghana		Bandim, Guinea-Bissau		Chakaria, Bangladesh	
	Proportion exposed to C-OPV in age group	Overall HR (after/before campaigns) (95% CI)[a]	Proportion exposed to C-OPV in age group	Overall HR (after/before campaigns) (95% CI)[a]	Proportion exposed to C-OPV in age group	Overall HR (after/before campaigns) (95% CI)[a]
Overall	95.4% (72,135/75,610)	0.96 (0.88–1.05)	80.3% (44,807/55,806)	0.78 (0.69–0.85)	61.9% (22,386/36,176)	0.69 (0.52–0.90)
0–2 months	49.1% (27,004/54,989)	0.92 (0.75–1.13)	23.7% (9159/38,631)	0.85 (0.65–1.11)	13.8% (2953/21,368)	0.64 (0.31–1.34)
3–5 months	71.9% (49,765/69,188)	1.29 (1.10–1.51)	40.9% (15,461/37,843)	0.68 (0.51–0.90)	28.0% (7038/25,098)	0.83 (0.48–1.44)
6–8 months	83.2% (58,158/69,873)	0.79 (0.66–0.94)	52.3% (19,610/37,493)	1.13 (0.86–1.48)	38.6% (10,127/26,220)	0.89 (0.45–1.77)
9–11 months	91.5% (62,823/68,693)	0.67 (0.53–0.86)	62.1% (23,065/37,122)	0.74 (0.54–1.01)	47.7% (12,391/25,966)	0.51 (0.21–1.25)
12–59 months[b]	99.0% (67,057/67,766)	1.03 (0.78–1.36)	87.6% (40,464/46,173)	0.70 (0.57–0.87)	66.4% (20,782/31,300)	0.55 (0.35–0.88)
Among children not exposed to C-OPV before 6 months of age						
6–59 months[b]	28.1% (19,423/69,188)	0.78 (0.65–0.95)	59.1% (22,382/37,843)	0.60 (0.44–0.81)	72% (18,060/25,098)	0.64 (0.42–0.99)
Intensity of exposure						
Rate of C-OPVs per year (campaigns/years)	2.5 (50/20)		1.8 (23/13)		1.6 (25/16)	
Interval between effective campaigns[c]	6.3 months		17.3 months		17.5 months	
Mean age at first OPV campaign (median, IQR)[d]	168 days (117, 65–216)		313.7 days (234, 88–474)		270.9 days (234, 117–363)	
Mean number of C-OPVs (median, IQR)[e]	6.7 (7, 3–9)		1.9 (2, 1–3)		2.4 (2, 0–4)	

[a]Full multivariable model: adjusting for age (underlying time), other campaigns (OPV + VAS (6–59 months), VAS (6–59 months), OPV + VAS + MV (9–59 months), VAS + MV (9–59 months), MV (9–59 months) and Meningitis vaccine (12–59 months)), year*age group and rainy/dry season. [b]6–35 months of age in Bandim and Chakaria. [c]Effective campaigns mean that they were likely to expose new children. The C-OPVs have often been organized as two campaigns with 1 month interval and they would therefore mostly expose the same children. We have therefore here only counted such campaigns as 1 effective campaign. There were 35, 9, and 11 effective campaigns in Navrongo, Bandim, and Chakaria. [d]Only calculated among children that received at least dose of C-OPV. [e]Calculated for all children followed.

Table 5: **Mortality rate ratios (MRR) for after-campaign versus before-campaign, and OPV campaign intensity in Navrongo, Ghana; Bandim, Guinea-Bissau; and Chakaria, Bangladesh.**

interact negatively with DTP vaccination[23] and similarly C-OPVs may have interacted negatively with DTP and early MV.[14] The present data could suggest that C-OPVs may also interact negatively with DTP-containing vaccines in the age group 3–5 months. Third, at 9–11 months, where measles vaccine (MV) would be the predominate vaccine, the effect of C-OPV was beneficial.

Unfortunately, information on routine vaccinations was not collected often in Navrongo, so it is difficult to test more specifically the potential age- and time-related interactions suggested by the data. To fully document these interactions with routine vaccinations, it would be necessary to have individual level data on vaccinations at the time of C-OPVs. Such data will have to be sought in future studies.

The Navrongo context contrasts with the contexts of previous C-OPV studies in two important aspects: the age of exposure to C-OPV and the underlying vaccination coverage. A negative effect for children under 6 months of age was not seen in previous studies, but it was clear that the effect of C-OPV was better after 12 months of age than in infancy. It may be important how common exposure was in the relevant age groups. As seen in Table 5, 72% of the Navrongo cohort was exposed before 6 months of age whereas only 41% and 28%, respectively, was exposed that early in Guinea-Bissau and Bangladesh. We propose that C-OPVs may interact with the non-live DTP-containing vaccines which are common in that age. The overall average effect of C-OPVs will thus be strongly affected by how many are exposed in the age group where there is a potential for negative interactions (Table 5).

Negative interactions with DTP have been seen in females. Hence, it is corroborating the hypothesis of negative interaction between C-OPV and DTP that the higher mortality after C-OPV in the 3–5 months age group was seen in females.

The Bissau and Bangladesh data set started in 2003 and 2004, respectively, at a time when the vaccination programme was better established. If we calculate the effect of C-OPVs for the similar historical period 2004–2015 in Navrongo, when routine vaccinations were high (Supplementary File), the HR (after/before campaigns) in Navrongo was HR = 0.87 (0.76–1.01), not very different from the estimates from Bissau and Bangladesh, and with a beneficial effect among males, HR = 0.80 (0.66–0.98).

Hence, the Navrongo analysis suggests that both the intensity of C-OPVs and the routine vaccination coverage are important contextual factors which may produce differences in the effect of C-OPVs in different settings.

It seems important to test a possible negative interaction between C-OPV and DTP vaccination at other sites which have experienced frequent C-OPVs. But also with routine OPV0, as shown in Supplementary File, and subsequent doses of OPV.

The limited effect of C-OPV was unexpected since previous studies have shown clear benefits of these C-OPVs. However, it was not a general limited effect. The effect was negative at 3–5 months of age and in particular during the period 1996–2005, representing a different historical period than previous studies. The effect was positive after 6 months of age, especially for children that had not been exposed to C-OPV before 6 months of age. These conclusions were supported by triangulation of the current and previous studies. The results support that C-OPV may have beneficial effects, but may vary based on context dependent factors. Understanding these causal structures is essential for future studies that investigate the beneficial NSEs of C-OPVs.

Contributors

PW and SN conducted the statistical analyses. The first draft was written by PW; all authors contributed to the final version of the paper. PW and SN accessed and verified the data and will act as guarantors of the study. All authors were responsible for the decision to submit the manuscript.

Data sharing statement

Through request to the authors.

Declaration of interests

Nothing to declare.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2023.102322.

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