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Stopping Oral Polio Vaccine (OPV) After Defeating Poliomyelitis in Low- and Middle-Income Countries: Harmful Unintended Consequences? Review of the Nonspecific Effects of OPV

Peter Aaby,[1] Sebastian Nielsen,[1,2] Ane B. Fisker,[1,2] Line M. Pedersen,[1,2] Paul Welaga,[3] Syed M. A. Hanifi,[4] Cesario L. Martins,[1] Amabelia Rodrigues,[1] Konstantin Chumakov,[5] and Christine S. Benn[2,6]

[1]Bandim Health Project, Indepth Network, Bissau, Guinea-Bissau, [2]Odense Patient Data Explorative Network, Institute of Clinical Research, University of Southern Denmark, Odense, Denmark, [3]Navrongo Health Research Centre, Navrongo, Ghana, [4]Health Systems and Population Studies Division, International Centre for Diarrhoeal Disease Research, Bangladesh, Dhaka, Bangladesh, [5]Office of Vaccines Research and Review, Center for Biologics Evaluation and Research, Food and Drug Administration, Silver Spring, Maryland, USA, and [6]Danish Institute of Advanced Science, Odense University Hospital, University of Southern Denmark, Odense, Denmark

Background. The live vaccines bacille Calmette-Guérin (BCG) and measles vaccine have beneficial nonspecific effects (NSEs) reducing mortality, more than can be explained by prevention of tuberculosis or measles infection. Live oral polio vaccine (OPV) will be stopped after polio eradication; we therefore reviewed the potential NSEs of OPV.

Methods. OPV has been provided in 3 contexts: (1) coadministration of OPV and diphtheria-tetanus-pertussis (DTP) vaccine at 6, 10, and 14 weeks of age; (2) at birth (OPV0) with BCG; and (3) in OPV campaigns (C-OPVs) initiated to eradicate polio infection. We searched PubMed and Embase for studies of OPV with mortality as an outcome. We used meta-analysis to obtain the combined relative risk (RR) of mortality associated with different uses of OPV.

Results. First, in natural experiments when DTP was missing, OPV-only compared with DTP + OPV was associated with 3-fold lower mortality in community studies (RR, 0.33 [95% confidence interval {CI}, .14–.75]) and a hospital study (RR, 0.29 [95% CI, .11–.77]). Conversely, when OPV was missing, DTP-only was associated with 3-fold higher mortality than DTP + OPV (RR, 3.23 [95% CI, 1.27–8.21]). Second, in a randomized controlled trial, BCG + OPV0 vs BCG + no OPV0 was associated with 32% (95% CI, 0–55%) lower infant mortality. Beneficial NSEs were stronger with early use of OPV0. Third, in 5 population-based studies from Guinea-Bissau and Bangladesh, the mortality rate was 24% (95% CI, 17%–31%) lower after C-OPVs than before C-OPVs.

Conclusions. There have been few clinical polio cases reported in this century, and no confounding factors or bias would explain all these patterns. The only consistent interpretation is that OPV has beneficial NSEs, reducing nonpolio child mortality.

Keywords. decline in child mortality; eradication; nonspecific effects of vaccines; OPV; oral polio vaccine; triangulation.

Poliomyelitis has nearly been eradicated with the extensive use of oral polio vaccine (OPV) in the routine Expanded Programme on Immunization (EPI) in low- and middle-income countries (LMICs) and in supplementary immunization campaigns conducted by the Global Polio Eradication Initiative. Over the past 10 years, >10 billion doses of OPV have been given to nearly 3 billion children worldwide.

The original trivalent OPV contained type 1, 2, and 3 polioviruses. Type 2 OPV was withdrawn in 2016. The current plan is to withdraw bivalent OPV when circulation of wild polioviruses has stopped. OPV can lead to vaccine-associated paralytic polio (VAPP, approximately 1 case in 2.7 million doses of OPV). Furthermore, with low population immunity, vaccine poliovirus strains may regain virulence, start transmission, and cause outbreaks of paralytic disease. These runaway strains are known as circulating vaccine-derived polioviruses (cVDPVs) [1]. If wild polioviruses are eradicated and only the specific effects of OPV are considered, stopping OPV would therefore be a rational decision. However, mounting evidence suggests that OPV has beneficial nonspecific effects (NSEs) against pathogens other than polioviruses.

Historically, there has been suggestions of beneficial NSEs of OPV [2–6]. In the 1950s, Sabin developed live OPV [2]. When first introduced in South America in the 1960s, reports suggested that OPV was associated with fewer diarrheal deaths because vaccine virus interfered with other enteric pathogens [3]. Based on large randomized clinical trials (RCTs) with >150 000 participants, Russian researchers reported that OPV and other

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Correspondence: Peter Aaby, DMSc, Bandim Health Project, Apartado 861, Bissau, Guinea-Bissau (p.aaby@bandim.org).

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nonpathogenic enteroviruses reduced influenza and respiratory morbidity 2- to 4-fold among healthy adults [5, 6]. In contrast, inactivated polio vaccine (IPV) has been associated with increased female child mortality [7].

When the World Health Organization (WHO) Strategic Advisory Group of Experts on Immunization commissioned a review of potential NSEs of vaccines for under-5 mortality, bacille Calmette-Guérin (BCG), diphtheria-tetanus-pertussis (DTP) vaccine, and measles vaccine (MV) were included [8], but not OPV. OPV vaccinations may soon stop. We therefore reviewed studies with mortality data to assess whether OPV might have beneficial NSEs on child survival in LMICs [9].

METHODS

In the EPIs in LMICs, OPV has been administered in 3 contexts: (1) with the 3 primary doses of DTP at 6, 10, and 14 weeks of age, and with the booster dose of DTP at 15–18 months of age; (2) at birth (OPV0), often together with BCG; and (3) as supplementary immunization campaigns with OPV (C-OPV). We reviewed the impact of OPV on child survival in these 3 contexts.

Search Strategy and Selection Criteria

We searched Medline (PubMed) and Embase for articles published until September 2021, and dealing with ("oral polio vaccine" or "OPV") and ("death" or "mortality") (Supplementary Figure 1). We included articles reporting observational studies, natural experiments, and RCTs, with no restriction on country or language. We excluded abstracts from conference proceedings (n = 21). We excluded articles dealing with other vaccines, health policies, and immunodeficiencies, and those without individual-level information on death/survival. We searched reference lists to identify other relevant studies.

The literature search would not necessarily find articles where OPV was mentioned or analyzed in the text but not in the abstract. We included 7 such articles where the impact of C-OPVs on outcomes in other trials were analyzed [10–16]. These articles were known to us because we had participated in the analyses (Supplementary Figure 1).

The research questions have been presented in the Supplementary Materials. Two authors (P. A. and C. S. B.) screened the abstracts of selected articles for eligibility. If the abstract suggested that a study had data on use of OPV and subsequent mortality, the full text of the article was read. There was no disagreement regarding the relevance of the selected studies.

Data Extraction

We extracted data from relevant studies on study objective, population, potential biases, use of OPV, length of follow-up, and survival for the 3 different contexts in which OPV has been used [10–38].

Data Analysis

We assessed possible biases of included studies in Supplementary Table 1. Since bias cannot be excluded in observational studies, we attempted to triangulate data from studies related to the same kind of issue, but with different approaches and different underlying biases [39] (Supplementary Materials).

When OPV and DTP are coadministered, separate estimates for OPV and DTP cannot be obtained. Hence, we focused on natural experiments without coadministration because OPV or DTP was missing.

We present all studies about OPV and mortality. Most studies analyzed the effect of OPV until a different vaccine type was given, and hence represent the effect of having OPV as the most recent vaccine. Some study cohorts were partly overlapping as explained in footnotes to the tables. When cohorts overlapped, we included the study with the largest number of children in the relevant meta-analyses.

Since C-OPVs appear to lower the child mortality rate, we examined how this affected the outcome in RCTs examining the impact of an intervention on mortality.

Meta-analysis estimates were obtained with the "meta" command in Stata. We have provided 95% confidence intervals (CIs). Fixed and random-effect estimates were the same.

RESULTS

Included Studies

The literature search provided 304 references, of which 20 were relevant (Supplementary Figure 1). Additionally, we included 7 studies that analyzed how C-OPVs affected the outcome in RCTs [12, 13, 15, 16] or observational studies [10, 11, 14] of child mortality. Forty-nine studies had no individual-level data about death, 88 dealt with other vaccines or antibody analysis or were conference abstracts, 113 were studies/reviews of health policy and vaccine coverage, 21 studies dealt with OPV in individuals with immunodeficiencies, and 13 were animal or plant studies. Most recent studies of OPV and mortality were from Guinea-Bissau; 5 studies analyzed data from India, Bangladesh, Burkina Faso, or Ghana [22, 31–34].

OPV at 6, 10, and 14 Weeks of Age

Routine OPV could be assessed in 3 studies in which children received OPV-only because DTP was missing (Table 1). OPV-only recipients had 3-fold lower all-cause mortality than recipients of DTP + OPV (relative risk [RR], 0.33 [95% CI, 0.14–0.75]) [17–20] in 2 studies when DTP and OPV were introduced in Guinea-Bissau in the 1980s. Twenty years later, DTP was missing for several months; the all-cause case fatality ratio (CFR) was 3-fold lower for hospitalized children who had received OPV1 only and not the recommended DTP1 + OPV1 [19].

Conversely, when OPV was missing, DTP-only-vaccinated compared with DTP-unvaccinated children had higher all-cause

Table 1. Relative Risks for Mortality Stratified by Most Recent Vaccination: Oral Polio Vaccine (OPV)–Only Vaccinated Compared With Diphtheria-Tetanus-Pertussis + OPV-Vaccinated Children[a]

Study	Study Design; Age Group	Mortality Rate per 100 PY (Deaths/PY) by Vaccination Status		RR (95% CI) of OPV-Only vs DTP + OPV
		OPV-Only	DTP + OPV	
Urban Bissau, introduction of DTP and OPV, 1981–1984 [17][b]	Natural experiment; children aged 3–35 mo	3.4 (4/116.8)	9.9 (69/696.1)	0.36 (.13–.98)[c]
Urban Bissau, introduction of DTP and OPV, 1981–1984 [18]	Observational study; Children aged 6–35 mo	1.7 (2/119.2)	6.2 (28/451.0)	0.27 (.06–1.12)[c]
Combined estimate	…	…	…	0.33 (.14–.75)
Study	Study Design; Age Group	Hospital Case Fatality (Deaths/Hospitalized) by Most Recent Vaccination		Relative Risk (95% CI) of OPV-Only vs DTP1 + OPV
		OPV-Only	DTP1 + OPV	
Urban Bissau, 2001–2002. Vaccination status at admission [19]	Natural experiment; children aged 0–59 mo; no MV	4/72	41/221	0.29 (.11–.77)[c]

Abbreviations: CI, confidence interval; DTP, diphtheria-tetanus-pertussis vaccine; DTP1, first dose of DTP; OPV, oral polio vaccine; PY, person-years; RR, relative risk.

[a]OPV in these periods would have been trivalent OPV.

[b]Mogensen et al [21] overlaps with reference [17] as it covers the same cohort but only in the age group 3–5 months, where the study was a natural experiment with limited selection bias.

[c]Reported, directly or inversed, in the original publication.

mortality (RR, 4.04 [95% CI, 1.93–8.45]) in the 2 available studies (Table 2). When DTP + OPV-vaccinated children were compared with DTP-unvaccinated children, the RR was 1.51 (95% CI, .88–2.58) (Table 2). Hence, using DTP-unvaccinated children as reference, mortality was 3-fold higher (RR, 3.23 [95% CI, 1.27–8.21]), for DTP-only compared with DTP + OPV.

The results were similar in the studies directly comparing DTP-only and DTP + OPV (Table 2). Between 3 and 8 months

Table 2. Relative Risks for Mortality for Children Vaccinated With Diphtheria-Tetanus-Pertussis (DTP) Vaccine Only or DTP + Oral Polio Vaccine

Study	Study Design; Age Group	RR (95% CI) by Most Recent Vaccination		RR (95% CI) of (DTP Only/No DTP vs DTP + OPV/No DTP)
		DTP Only vs No DTP	DTP + OPV vs No DTP	
DTP-only and DTP + OPV compared relative to DTP-unvaccinated children[a]				
Urban Bissau, 1981–1983[b] [17][c]	Observational study; children aged 3–8 mo	3.92 (1.78–8.62)[d]	1.15 (.55–2.38)[e]	3.38 (1.21–9.48)
Rural Bissau, 1984–1987[f] [20][g]	Observational study: children aged 3–8 mo	5.00 (.63–39.7)[d]	1.90 (.91–3.97)[d]	2.63 (.29–23.72)
Combined estimate	…	4.04 (1.93–8.45)	1.51 (.88–2.58)	3.23 (1.27–8.21)
Study	Study Design; Age Group	Mortality Rate per 100 PY (Deaths/PY) by Most Recent Vaccination		RR (95% CI) of DTP Only vs DTP + OPV
		DTP-Only	DTP + OPV	
DTP-only vs DTP + OPV compared directly[a]				
Urban Bissau, 1981–1983 [17][b]	Observational study; age 3–8 mo, before MV	28.4 (13/45.8)	9.5 (14/165.7)	3.38 (1.59–7.20)[c]
Urban Bissau, 1981–1983 [17]	Observational study; age 9–35 mo, DTP with MV or DTP after MV	20.7 (6/29.0)	2.9 (24/820.8)	6.25 (2.55–15.37)[c]

Abbreviations: CI, confidence interval; DTP, diphtheria-tetanus-pertussis vaccine; MV, measles vaccine; OPV, oral polio vaccine; PY, person-years; RR, relative risk.

[a]OPV in these periods would have been trivalent OPV.

[b]Children followed in the age group 3–8 months, before measles vaccination.

[c]Reference [17] provided data to both estimate the effect of DTP-only and DTP + OPV indirectly via comparison with children who received no DTP (first section) and directly (second section). It will be seen that the 2 estimates were essentially the same.

[d]Reported, directly or inversed, in the original publication.

[e]Calculated from rates in publication.

[f]Children aged 3–8 months at enrollment at a vaccination session, followed for 6 months until the next vaccination session.

[g]Reference [20] originally reported that the mortality ratio for DTP-vaccinated children in 1984 when OPV was not yet used was 5.09 (.63–39.9). When years later, we asked the statistician to produce the estimates for those who received DTP-only and DTP + OPV, respectively, the estimates were 5.00 (.63–39.7) and 1.90 (.91–3.97). We were not able to reconcile the difference between 5.09 (.63–39.9) and 5.00 (.63–39.7), but the 2 estimates are essentially the same.

of age, the RR was 3.38 (95% CI, 1.59–7.20) comparing DTP-only and DTP + OPV-vaccinated children [17]. When DTP-only or DTP + OPV was used after 9 months among children who received DTP with MV or DTP after MV, the RR (DTP-only/DTP + OPV) was 6.25 (95% CI, 2.55–15.37) [17].

OPV at Birth

Only 1 RCT of OPV0 with infant mortality as the main outcome has been conducted, comparing OPV0 + BCG vs BCG only. OPV0 was associated with 17% (95% CI, −13% to 39%) lower infant mortality. This estimate included follow-up after OPV campaigns. Censoring for C-OPVs, allocation to OPV0 + BCG vs BCG-only was associated with a 32% (95% CI, 0–57%) lower infant mortality until the C-OPVs (Table 3) [23]. OPV0 was particularly beneficial the first 2 days of life [23], as also seen in another observational study comparing periods with and without routine use of OPV0 [27]. In a small RCT among low-birth-weight (LBW) males who did not receive BCG at birth, randomization to OPV0 vs neonatal vitamin A supplementation (VAS) was also associated with 32% (95% CI, −54% to 79%) lower infant mortality [24].

Table 3. Randomized Controlled Trials and Observational Studies of Oral Polio Vaccine at Birth (Follow-up to Age 12 Months)[a]

Study	Study Design, Age Group	Mortality Rate per 100 PY (Deaths/PY)		HR (95% CI) for OPV0 vs No OPV0
RCTs				
Guinea-Bissau, urban, 2008–2011; before OPV campaigns [23]	RCT of BCG + OPV0 vs BCG + no OPV0; infant mortality	BCG + OPV0 2.6 (41/1567)	BCG 3.9 (60/1547)	0.68 (.45–1.00)[b]
Guinea-Bissau, urban, 2008; before OPV campaigns [24]	Newborn boys randomized to OPV0 or VAS[c]; infant mortality	OPV0 9.3 (10/108)	VAS 13.6 (14/103)	0.68 (.30–1.54)[b]
Observational studies				
Guinea-Bissau, urban, 2002–2004 [26]	LBW children randomized to BCG or no BCG; infant mortality	BCG + OPV0 5.4 (129/2376)	BCG 5.7 (22/386)	0.98 (.60–1.60)[b]
Guinea-Bissau, urban, 2007–2008 [27][d]	Children born at hospital; 99 received no OPV0 and 243 received OPV0; infant mortality	BCG + OPV0 10.3 (22/214)	BCG 16.7 (14/84)	0.55 (.28–1.08)[b]

Abbreviations: BCG, bacille Calmette-Guérin; CI, confidence interval; HR, hazard ratio; LBW, low birth weight; OPV, oral polio vaccine; OPV0, oral polio vaccine at birth; PY, person-years; RCT, randomized controlled trial; VAS, vitamin A supplementation.

[a]OPV in these periods would have been trivalent OPV.

[b]With the study design, it cannot be determined whether vitamin A was harmful or whether OPV stimulated a nonspecific immune response that provided some protection against infections (or both).

[c]Reported directly or inverse, as a mortality change in percentage in the original publication.

[d]No OPV campaigns in 2007–2008.

Occasionally, OPV0 has not been available, providing opportunities for "natural experiment" studies. Comparing children with and without OPV0, when OPV0 was missing in several periods, OPV0 had a significant negative effect for males [25]. However, the shortage of OPV0 was caused by EPI saving doses for later C-OPVs. Thus, children not receiving OPV0 were more likely to subsequently receive C-OPV than children who had received OPV0. Censoring for subsequent C-OPVs, "not having received OPV0" was no longer associated with a health benefit (Table 3) [26]. Furthermore, OPV0 was missing for 2 months in 2007–2008 for LBW children taking part in an RCT of BCG at birth vs delayed BCG; these children were compared with LBW children recruited 2 months before and 2 months after the period with no OPV0. There were no C-OPVs in the 2007–2008 period [27]. Receiving OPV0 was associated with a RR of infant mortality of 0.55 (95% CI, .28–1.08) (Table 3).

Other studies have suggested that having received OPV0 was associated with a lower mortality rate than having received no OPV0, but these studies have not adjusted for the potential biases explaining who received or did not receive OPV0 [36].

OPV Campaigns

Over the last 25–30 years, LMICs have had numerous C-OPVs to eradicate polio [28–31]. C-OPV is often coadministered with other childhood interventions, for example, VAS, deworming drugs or MV.

Community Studies

One study compared participants vs nonparticipants when the first C-OPVs were conducted in Guinea-Bissau in 1998 [28]. Adjusting for numerous background factors, C-OPV was associated with slightly lower mortality (RR, 0.81 [95% CI, .54–1.21]); the beneficial effect was particularly strong for children <6 months of age (RR, 0.09 [95% CI, .01–.85]).

Other studies did not have individual data on participation for all children, but since the coverage was high (>90%) [29, 30], intention-to-treat analyses were carried out, assuming that all study children received the proposed C-OPVs. In these studies, the hazard ratio (HR) compared the "after" campaign with the "before" campaign all-cause mortality rate (Table 4). Using data from urban Bissau (2002–2014), with 2834 child deaths and 100 594 person-years of follow-up, it was possible to evaluate the effect of 17 C-OPVs, adjusting for age, season, and time-trend in mortality [29, 30]. OPV-only campaigns were associated with 25% (95% CI, 15%–33%) lower mortality; each additional C-OPV was associated with 14% (95% CI, 8%–19%) lower mortality. Other campaigns with VAS-only, OPV + VAS, MV + VAS, or influenza A/H1N1 vaccine did not have beneficial effects [29]. Analyzing any C-OPV (ie, C-OPV-only or C-OPV + VAS), the estimated mortality reduction was 19% (95% CI, 9%–27%) [29]. In 1000 simulations with

Table 4. Oral Polio Vaccine (OPV) Campaigns: Change in Mortality Rate From Before OPV Campaigns to After OPV Campaigns

Study	Country; Reference	Study Design; Adjustments; Type of OPV	Age Group Covered	Mortality HR (95% CI) for After OPV Campaigns vs Before OPV Campaigns[a]
Community studies				
1	Guinea-Bissau, urban, 2002–2014 [29]	Total population. Age- and season-adjusted mortality rate comparing after vs before OPV-only campaign. Adjusted for other health campaigns; mOPV, bOPV, and tOPV were used in this period	1 d–35 mo	0.75 (.67–.85)[b]
2	Guinea-Bissau, rural, 2002–2003 [11]; study 2 partly overlaps with [10][c]	Observational study. Age- and season-adjusted mortality rate comparing after vs before any-OPV campaign; tOPV used in this period	0–11 mo	0.90 (.69–1.17)[b]
3	Guinea-Bissau, rural, 2011–2015 [12]	Observational study. Age-, region-, and vaccination coverage–adjusted mortality rate comparing after vs before any-OPV campaign; within a cluster RCT of MV for all vs restrictive MV vial policy; bOPV and tOPV were used in this period	9–35 mo	0.81 (.45–1.45)[b]
4	Guinea-Bissau, rural, 2017–2019 [13]	Observational study. Age-, region-, and vaccination coverage–adjusted mortality rate comparing after vs before any-OPV campaign; within a cluster RCT of MV campaign vs no campaign; bOPV used in this period	9–59 mo	0.72 (.55–.95)[b]
5	Bangladesh, rural, 2004–2019 [32]	Observational study. Age- and period-adjusted mortality rate comparing after vs before OPV-only campaign. Adjusted for other health campaigns; type of OPV not reported	1 d–35 mo	0.69 (.52–.90)[b]
	Combined estimate	…	…	0.76 (.69–.83)[d]
6	Burkina Faso, rural, 2012–2015 [31]	Observational study. Age-, season- and sex-adjusted severe morbidity rate (death, admissions) comparing after vs before any-OPV campaign; within an RCT of early MV; type of OPV not reported	4–35 mo	0.64 (.44–.94)[c]
Hospital case fatality studies				
7	Guinea-Bissau, hospital CFR, 2001–2008 [14]	CFR for any cause; children exposed before admission to any-OPV campaign or not exposed; tOPV used in this period	6 wk to 8 mo	0.72 (.58–.90)[c]
Partly overlapping studies				
8	Guinea-Bissau, urban, 2002–2014 [30]; study 8 is part of study 1	Participants in 7 RCTs. Age- and season-adjusted mortality rate comparing after vs before OPV-only campaign; mOPV, bOPV, and tOPV were used in this period	0–35 mo	0.81 (.68–.95)[c]
9	Guinea-Bissau, urban, 2002–2004 [26]; study 9 is part of study 1	Age-adjusted mortality rate comparing after vs before any-OPV campaign; tOPV used in this period	0–12 mo	0.33 (.19–.58)[c]

The campaign described in reference [28] compared mortality for those who received OPV and those who did not receive OPV during the campaign and did not compare mortality before and after a campaign.

Abbreviations: bOPV, bivalent oral polio vaccine; CFR, case fatality ratio; CI, confidence interval; HR, hazard ratio; mOPV, monovalent polio vaccine; MV, measles vaccine; OPV, oral polio vaccine; RCT, randomized controlled trial; tOPV, trivalent oral polio vaccine.

[a]Data for studies 6–9 are shown as HR (95% CI) for severe morbidity (death and hospital admissions).

[b]Reported, directly or inversed, in the original publication.

[c]One study [10], in which the mortality HR was 0.78 (95% CI, .64–.94) lower after OPV campaigns, was not included in this table. All campaigns were conducted at the end of the rainy season and it was therefore difficult to disentangle effects of OPV campaigns and season.

[d]Fixed and random-effect estimates are the same.

random fictive dates for C-OPVs, the average simulated C-OPV effect on mortality was null (HR, 1.00 [95% CI, .99–1.01]) [30]. Hence, the observed effect is unlikely to be due to the dates of implementing C-OPVs.

Other studies from Guinea-Bissau and Bangladesh have produced similar results. From 2004 to 2019, C-OPVs in Bangladesh were associated with a 31% (95% CI, 10%–48%) mortality reduction, and additional C-OPVs with 6% (95% CI, −2% to 13%) lower mortality [32]. The 5 community studies of all-cause mortality suggest that the rate was 24% (95% CI, 17%–31%) lower after C-OPVs (Figure 1, Table 4). If we excluded the 3 studies not found through the literature search, the rate was 26% (95% CI, 17%–34%) lower after C-OPVs. One community study in rural Burkina Faso analyzed hospital admissions and death as a combined outcome, and the rate was 36% (95% CI, 6%–56%) lower after C-OPVs (Table 4) [31]. A funnel plot did not suggest publication bias in the studies of C-OPVs and mortality or admissions (Supplementary Figure 2).

Hospital Studies

Lower mortality rates might also change the CFR at the hospital. At the main pediatric ward in Guinea-Bissau, children in the age group for DTP and OPV vaccinations (ie, 6 weeks to 8 months), who had been eligible for C-OPV before admission, had a lower CFR (11% [95% CI, 96/855]) for any cause than similar children who had not been eligible for C-OPVs prior to admission (16% [95% CI, 324/2089]); the CFR was

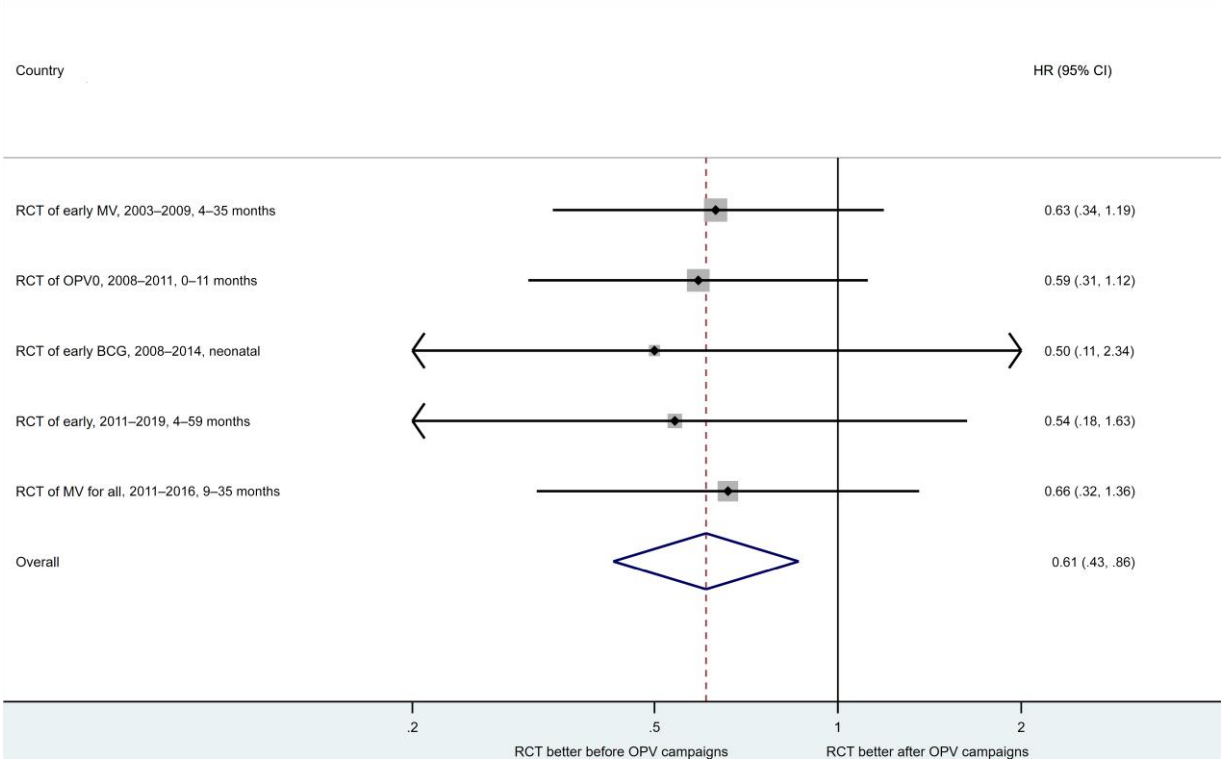

Figure 1. OPV campaigns: change in mortality rate from before OPV campaigns to after OPV campaigns. Abbreviations: BCG, bacille Calmette-Guérin; CI, confidence interval; HR, hazard ratio; MV, measles vaccine; OPV, oral polio vaccine; OPV0, oral polio vaccine at birth; RCT, randomized controlled trial.

28% (95% CI, 10%–42%) lower among children eligible for a C-OPV before admission [14].

Since the studies compared the outcome rate before and after C-OPVs, selection biases are unlikely to have played a major role (Supplementary Table 1). Other campaigns and routine vaccinations may have affected the results. The effect of OPV-only campaigns was 26% (95% CI, 17%–34%) [29, 32], whereas any-OPV campaigns were associated with a 19% (95% CI, 3%–33%) reduction in mortality (Table 4). Hence, the effect of C-OPVs may depend on how many campaigns were OPV-only.

Deduction: C-OPVs Affect Mortality Outcomes in RCTs

If C-OPVs reduce mortality (Table 4), this may affect the effect of other interventions. For example, RCTs to explore beneficial NSEs are based on the hypothesis that new vaccines strengthen the resistance toward other infections. However, C-OPVs during follow-up in RCTs might reduce the difference between the randomization groups. This is indeed what happened in the 8 RCTs that studied the NSEs of various interventions and had mortality or severe morbidity (death/hospitalization) as main outcome and where the effect was examined both before and after the C-OPVs (Figure 2, Supplementary Table 2). The randomized intervention had a stronger beneficial effect before the C-OPVs. After the C-OPVs, the hypothesized beneficial effect of the intervention had almost disappeared (Supplementary Table 2). In the 5 RCTs with mortality as outcome, the mortality reducing effect of the intervention was 39% (95% CI, 14%–57%) stronger before C-OPVs than after C-OPVs (Figure 2). If we excluded the 2 RCTs not found through the literature search [12, 15], the mortality reducing effect of the intervention was 40% (95% CI, 8%–61%) stronger before C-OPVs than after C-OPVs. Similarly, in the 3 RCTs with severe morbidity as main outcome, the morbidity-reducing effect was 19% (95% CI, −8% to 39%) stronger before C-OPVs than after C-OPVs (Supplementary Table 2). Hence, C-OPVs during follow-up reduced the difference between randomization groups.

DISCUSSION

Main Observations

OPV was associated with beneficial effects on survival in all 3 contexts: when OPV was given without DTP, when OPV0 was given at birth, and when C-OPVs were conducted. Furthermore, C-OPVs modified results in RCTs of the NSEs of other interventions. There has been limited or no clinical polio disease reported during the last decades [40], so effects are likely to be due to NSEs of OPV rather than specific poliovirus prevention.

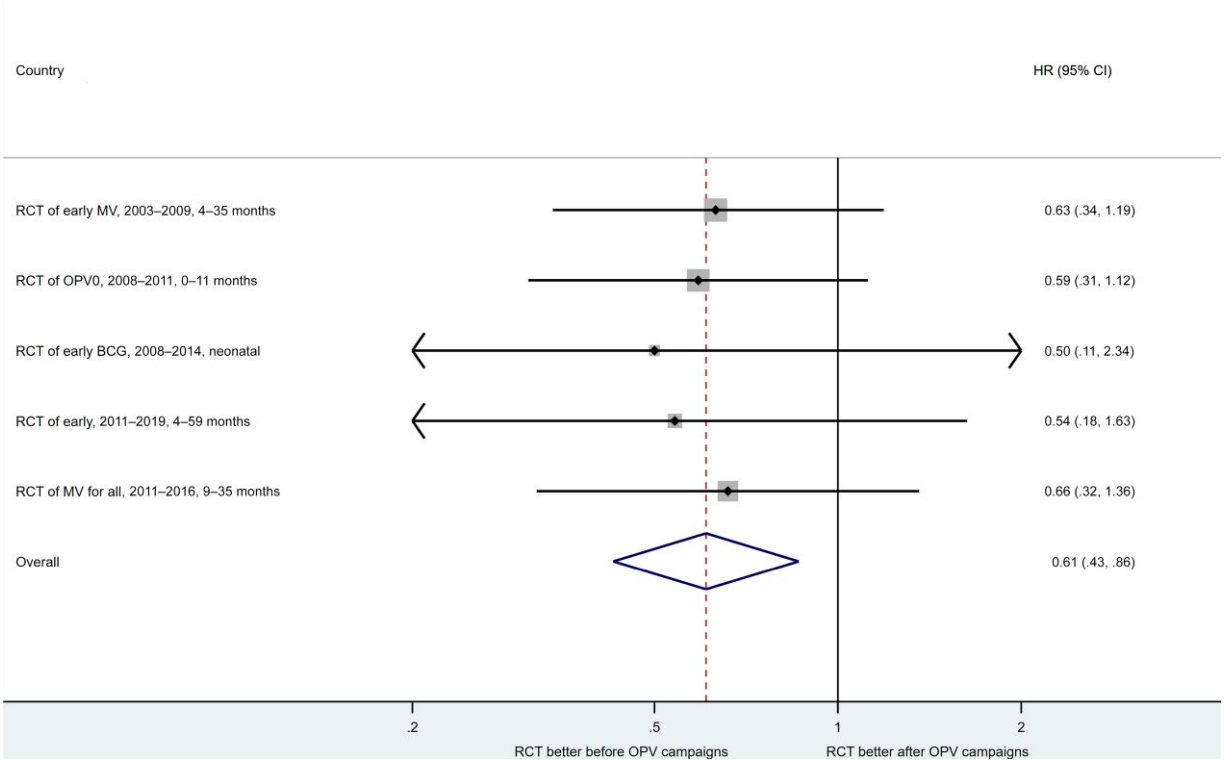

Figure 2. Impact of OPV campaigns on randomised controlled trials: effect better before or after OPV campaigns? Abbreviations: BCG, bacille Calmette-Guérin; CI, confidence interval; HR, hazard ratio; MV, measles vaccine; OPV, oral polio vaccine; OPV0, oral polio vaccine at birth; RCT, randomized controlled trial.

The WHO's review of potential beneficial NSEs on under-5 mortality suggested reductions of >40% for BCG and MV. Given the age profile for these vaccines, BCG was mostly compared with no vaccine and MV with children who had only received DTP. In the present analysis, OPV-only or OPV0 had similar strong effects. C-OPVs had a lower effect but covered a wider age range, including children who had received MV.

Strengths and Weaknesses

The majority of studies came from West Africa; however, studies from Bangladesh showed similar effects [32, 34, 41]. Most studies were natural experiments or RCTs, so adjustments for confounding factors are unlikely to remove the trends (Supplementary Table 1).

Noteworthy, OPV has been tested in real-life contexts, not in a purely experimental situation where there are no other vaccinations. In real life, there will always be other vaccinations. Hence, for instance, OPV-only has been compared with having DTP-only or DTP + OPV as the most recent vaccine, and it can be argued that it cannot be determined whether OPV-only is associated with lower mortality or DTP with higher mortality. However, the interpretation that OPV-only has beneficial effects is strongly supported by the RCT of OPV0, which indicated that OPV0 was associated with a 32% reduction in infant mortality [23].

It is a further strength that we were able to triangulate the OPV results by showing that OPV-only, DTP + OPV, and DTP-only had a continuum of effects. Furthermore, we tested the deduction that C-OPVs would reduce the effect of other interventions tested for NSEs in RCTs, because C-OPV would be given to all and thus blur the difference between intervention and control groups (Supplementary Table 2). If the primary results can predict other results, it is unlikely that the primary results are mainly due to bias.

Unfortunately, other groups have not examined these issues. We have collaborated with researchers holding datasets from Burkina Faso and Bangladesh and found similar associations in all 3 studies [31, 32, 34]. Hence, the OPV effects are not specific to Guinea-Bissau. Some studies used in Table 4 and Supplementary Table 2 were not found by the search but known to us as co-authors (Supplementary Figure 1); excluding these 7 studies did not change any of the conclusions [10–16].

Consistency and Contradiction With Previous Studies

The results were consistent for all uses of OPV. The results are strengthened by the historical studies showing that OPV may reduce nonpolio morbidity [3–6], and by more recent studies corroborating these morbidity findings. In Denmark, OPV was provided in 3 doses at 2, 3, and 4 years of age until 2001, and OPV was associated with 27% (95% CI, 13%–39%) lower

risk of hospital admissions for lower respiratory infections [9]. Two RCTs of OPV vs IPV in Bangladesh and Finland found that OPV reduced diarrhea and otitis media, respectively [9]. In Bangladesh, the mortality reduction associated with C-OPV was linked to prevention of fatal respiratory infections [41].

Previous studies of other live vaccines, BCG, MV, and smallpox vaccination, have suggested that the beneficial NSEs were stronger for females [35]. For OPV, several studies suggested a slightly stronger beneficial effect of OPV for males [23, 29, 30], but in Bangladesh the effect of OPV campaigns was also stronger for females [32].

Interpretation

The review produced consistent trends. First, though contrary to EPI policy, it was more beneficial to receive OPV-only than OPV + DTP and better to receive OPV + DTP than DTP-only (Tables 1 and 2). Second, the RCT [23] supported beneficial effects of OPV0 (Table 3). Third, in Guinea-Bissau, Burkina Faso, Ghana, and Bangladesh, C-OPVs were associated with a marked decline in the mortality rate even though clinical polio infection was absent (Table 4) [10–14, 29–32, 34, 35]. Fourth, boosting with C-OPV should have no additional beneficial effect since there was no clinical polio. However, as for other live vaccines [42], revaccination with OPV was associated with strong beneficial effects [29, 30, 32]. Fifth, C-OPVs reduced the effect of other interventions tested in RCTs (Supplementary Table 2). Sixth, other campaigns were not associated with similar beneficial effects [29, 30, 32].

It is impossible to identify a coherent set of confounding factors or biases which could explain that the OPV effect was not due to OPV per se but due to residual confounding. Hence, the triangulation of data supports that OPV has major beneficial NSEs. Immunological studies have shown that other live vaccines can fundamentally change the capacity of the immune system to fend off unrelated infections [43]. OPV may have similar effects on the immune system.

Implications: Stopping OPV?

All estimates point toward C-OPVs reducing overall mortality by at least 15%. Hence, the numerous C-OPVs may have been a major driver of the very large decline in mortality that has occurred in the last 20–25 years in LMICs [29–31, 34, 35]. There is no study of what happens when C-OPVs are stopped, and it is complicated to assess the effect because of other changes over time (eg in healthcare or interventions offered). However, while overall mortality declined during periods with frequent OPV campaigns, periods with no C-OPVs were associated with no further reduction in mortality, at least in Guinea-Bissau [29, 30].

The findings suggest that it is important to explore the feasibility and cost of continuing to use OPV or novel OPV (nOPV), the genetically stable strains of Sabin polioviruses [44], after the eradication of polio. The relative value of OPV, IPV, and nOPV for polio immunity should be considered (Supplementary Materials). Only 50 children in Guinea-Bissau [29] and 88 in Bangladesh [32] needed to be treated in C-OPVs to save 1 life, so administration of OPV is a very cost-effective way to reduce child mortality. However, if it is not possible to continue with OPV, and child mortality stops declining, we need to study ways of mitigating these effects. For instance, we need to examine whether other live vaccines can be used more liberally and not primarily for their disease-specific effects. For example, coadministration of BCG and DTP may reduce the negative effects of DTP [45], and MV campaigns might have effects similar to C-OPVs [46]. The beneficial NSEs of other live vaccines should be explored (eg, rotavirus, varicella, yellow fever, and live attenuated influenza vaccine), and we urgently need to explore whether nOPV provides similar beneficial NSEs as OPV. In the campaign to eradicate polio, the emphasis on stopping the use of OPV has been justified with the need to stop the risks of VAPP and cVDPV. However, if nOPV has limited risks of VAPP and cVDPV, the cost-effectiveness of continuing to use live nOPV may look very different.

CONCLUSIONS

When smallpox vaccine was removed globally (1980), the possibility that smallpox vaccine could have beneficial NSEs was not considered. Twenty years later, analyses revealed that smallpox vaccination was associated with major long-term health benefits in both Guinea-Bissau and in Denmark [47]. Adverse reactions caused by the vaccine were offset by these benefits, and the net result was improved health. Stopping smallpox vaccine may thus have had negative overall health consequences [47]. We might be about to repeat this mistake on a larger scale because far more young children have received OPV, often on multiple occasions, than received smallpox vaccination.

The coronavirus disease 2019 (COVID-19) pandemic in 2020 has had people reconsider many assumptions in the medical paradigm. For example, it has been suggested that the beneficial NSEs of live vaccines might be used to reduce severity of COVID-19 infection [46], and preliminary reports of RCTs of BCG and measles-mumps-rubella vaccines support this possibility [48]. The present work supports that we should consider the continued use of OPV, and investigate whether nOPV has the same beneficial NSEs as OPV without the risk of VAPP or cVDPV.

The discovery of the NSEs of vaccines and trained immunity, which makes children more resistant to different pathogens, obliges us to rethink how we use vaccines [49, 50]. Every decision on the introduction of new vaccines, or the withdrawal of old ones, should be made in a broad public health context to balance the protective effects that vaccines have against both

their target pathogen and unrelated infections. If we do not do this for OPV, removing OPV after defeating polio may have harmful unintended consequences that lead to an increase in child mortality.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Author contributions. P. A., S. N., A. B. F., L. M. P., P. W., S. M. A. H., C. L. M., A. R., and C. S. B. conducted studies of the impact of OPV on child mortality in low-income countries. P. A., S. N., A. B. F., and C. S. B. compiled epidemiological data. P. A. and S. N. analyzed data. P. A., K. C., and C. S. B. developed the idea and wrote the manuscript. The corresponding author had full access to all data and takes final responsibility for the decision to submit for publication.

Patient consent. Participants gave written or fingerprinted consent in all studies, and the studies received ethical approval as described in the original articles. The design of the studies conducted in Guinea-Bissau were approved by Comité Nacional de Ética na Saúde.

Data availability. Data are available upon reasonable request to the corresponding author.

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