VIVA Research Center for Vitamins & Vaccines

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Dear SAGE,

In 2013-2014, SAGE reviewed the potential non-specific effects (NSEs) on child mortality of BCG, diphtheria-tetanus-pertussis vaccine (DTP) and measles vaccine (MV) and concluded that NSEs warrant further study. Oral polio vaccine (OPV) was not included in the review.

The purpose of this letter is to suggest that SAGE reviews the potential NSEs of OPV before OPV is removed.

The present letter argues that:

I. OPV campaigns reduce the general mortality rate in high mortality communities
II. OPV has beneficial NSEs reducing child mortality in randomised controlled trials (RCTs)
III. Co-administration of DTP and OPV reduces the negative NSEs of DTP vaccine
IV. Compared with OPV, IPV is not likely to have beneficial NSEs

The points are primarily based on some recent publications and some still unpublished studies from our field site in Guinea-Bissau, so they are not commonly known, but we have shared the overall results with you below. Do not hesitate to let us know if you want us to send the unpublished papers.

Please note that if just one point is true, the removal of OPV may lead to increases in child mortality in low-income countries. It must be in the best interest of public health and the vaccine community to refute these possibilities, and if that cannot be done to consider how to remedy the situation. In other words, what can be done if eradication of OPV increases child mortality or halters the decline in child mortality?

I. OPV campaigns reduce the general mortality rate in high mortality settings

Over the last 20 years, there have been numerous OPV campaigns in most low-income countries. A graphic presentation of campaigns in Ghana is seen in Figure 1.

To our knowledge, only one study compared mortality of participants and non-participants in OPV campaigns (1). This study was carried out when the first OPV campaign was conducted in Guinea-Bissau in February-March 1998. Adjusting for numerous background factors, campaign-OPV was associated with 19% (-21-46%) lower mortality (1).

The effect was not statistically significant, but the observation has now been corroborated in larger studies:

A study of the effect of OPV campaigns within seven RCTs (2):

Using data from seven RCTs conducted in urban Bissau between 2002 and 2014 (Figure 2), we analysed 17 OPV campaigns in Guinea-Bissau. As the coverage was very high, we conducted intention-to-treat analyses assuming that all eligible children received the vaccine. Within each RCT, using Cox models, we estimated the mortality rate ratio (MRR) comparing "after-campaign" mortality versus "before-campaign" mortality (Figure 3).

With the 1244 deaths and 33,822 person-years (pyrs) from all seven RCTs it was possible to adjust for age, possible seasonal effects and changes in mortality rate over time. Campaign-OPV was associated with a 19% (95% CI=5-32%) mortality reduction. Each additional OPV campaign reduced mortality by 13% (4-21%). In the same model, no beneficial effect was found for the other campaigns with vitamin A supplementation (VAS), MV and H1N1 vaccine. We also conducted 1000 simulations with random fictive OPV campaign dates; the average simulated OPV campaign effect on the mortality rate was 1.00 (0.99-1.01) (2).

Interestingly, the OPV campaigns modified the results of the randomised comparisons within the RCTs (Appendix, Table S1).

A study of the effect of OPV campaigns within the Bandim Health Project urban study area (3):

We subsequently extended the analysis to include all children aged 1 day to 3 years of age in the urban study area in the period from 2002 to 2014 (3). With 2818 deaths and 100,202 pyrs the study was considerably larger than the first study described above. The reduction in mortality for after-campaign/before-campaign for OPV-only was 25% (15-33%) (3). No other campaign had similar beneficial effects, including OPV+VAS campaigns. Thus, all other campaigns differed significantly from the effect of OPV-only-campaigns. Effects did not differ significantly for trivalent (MRR=0.76 (0.67-0.86)), bivalent (MRR=0.89 (0.72-1.11)) and monovalent (MRR=0.79 (0.62-1.01)) strains of OPV. With each additional campaign-OPV, the mortality rate declined by 14% (8-19%).

With follow-up to 3 years of age, the number needed to treat (NNT) with campaign-OPV to save one life was as low as 47 neonates (3).

We register vaccination status at admission to the paediatric ward at the main hospital in Bissau and examined whether OPV-campaigns affected the hospital case fatality. The study was conducted between May 2001, when registration of vaccination status started, and until January 2008, when the hospital registration system changed. DTP-vaccinated hospitalised children aged 6 weeks to 8 months of age (the DTP age group), who had been eligible for an OPV campaign before admission, had significantly lower case fatality ratio (13% (96/755)) for any cause than similar children who had not been eligible for an OPV campaign (15% (323/2089)) before admission. Hence, the case fatality ratio at the hospital was 27% (10-41%) lower after the OPV campaigns (7).

A study of the effect of OPV campaigns within the Bandim Health Project rural study area:

In rural Guinea-Bissau, we studied the effect of measles vaccine status on mortality in the age group 6-36 months and the same time we examined the possible effect of OPV campaigns (8). As seen in Table 1, among measles-vaccinated children, the MRR for after-OPV-campaign versus before-OPV-campaign was 0.68 (0.50-0.92) and among measles-unvaccinated children the MRR was 0.84 (0.66-1.06), for an overall effect of 0.78 (0.64-0.94) (8). Hence, the OPV campaigns reduced the general mortality rate by 22% (6-36%) in 6-36 month-old children in the rural areas.

Table 1. Mortality rates before and after OPV campaigns in rural Guinea-Bissau, 1999-2006

	MR per 1000 PYRS (deaths/PYRS)		MRR for After-campaign versus before-campaign mortality
All children (number of observations)	Before OPV campaigns (31,730 observations) #	After OPV campaign (13,937 observations)#	
Measles unvaccinated	73.2 (215/2938)	46.8 (57/1217)	0.68 (0.50-0.92)
Measles vaccinated	47.2 (345/7315)	38.4 (96/2497)	0.84 (0.66-1.06)

Notes: # Children were visited at home in 100 village clusters in the 5 most populous regions of Guinea-Bissau. Vaccination status was based on inspection of the vaccination card. The children were followed to the next visit or for a maximum of 6 months.*estimated in a Cox model, age as underlying time scale, stratified by cluster

Studies from rural Ghana have also shown that there have been major reductions in the general mortality rate after campaigns (see Appendix, Tables S2 and S3).

Hence, all the results suggest that campaign-OPV has lowered the general mortality rate in the community. Since campaign-OPV has been given to all children under five years of age, the numerous campaigns have potentially had major effects on overall mortality in the community. Figures 2, 4 and 5 show how mortality has declined very dramatically in urban Bissau (Figure 2),

rural Bissau (Figure 4) and rural Ghana (Figure 5) in the last 15-20 years. With the data we have presented, it is likely that OPV campaigns have been one of the main drivers of this development.

II. OPV has beneficial NSEs reducing child mortality in RCTs

We have conducted the first RCT of OPV-at-birth (OPV0) with mortality as the main outcome (11). As seen in the Appendix, Table S1, the overall effect was a 17% (-13-39%) reduction in infant mortality, but when the analysis was restricted to the period before the children received campaign-OPV, allocation to OPV0+BCG versus only BCG was associated with a 32% (0-57%) reduction in infant mortality, the beneficial effect being particularly strong for boys (11). In another small RCT among low-birth-weight males, who do not receive BCG at birth in Guinea-Bissau, allocation to OPV0 versus neonatal vitamin A supplementation (NVAS) was also associated with a 32% (-54-70%) reduction in infant mortality; the RCT had limited power because it was stopped due to a cluster of deaths among children who had received NVAS (16). Hence, in these two RCTs, the effect of OPV0 was a reduction of 32% (3-52%) in infant mortality. There has been no polio in Bissau throughout this period so the effect is clearly not due to the specific disease-protective effects of OPV.

III. Co-administration of DTP and OPV may reduce the negative NSEs of DTP vaccine

A number of natural experiments have allowed for comparison of the effect of OPV relative to DTP. These natural experiments arose because DTP was unavailable or because OPV was administered alone. In 2002, DTP was missing for several months in Guinea-Bissau. We compared the hospital case fatality of children who had only received OPV and children who had received the recommended combination of OPV and DTP. The case fatality for any cause was 3-fold higher for children who had received OPV and DTP rather than OPV-only (Table 2) (17).

Table 2. Hospital case fatality of DTP+OPV-vaccinated and OPV-only vaccinated children

Bissau main hospital 2001-2002	Hospital case fatality (deaths/admitted)		Case fatality ratio (DTP1/OPV)#
Vaccination status	DTP1+OPV	OPV only	
Age 1-59 months	41/221	4/72	3.45 (1.30-9.09)

Notes: # age-adjusted; adjustment for other background factors did not change the results (18)

When DTP and OPV vaccines were first introduced in Bissau in the early 1980s, there were periods where OPV was administered alone. As seen in Table 3, among both infants and older children, DTP (+/-OPV) was associated with 7-fold higher mortality than having received OPV-only, the combined HR being 7.06 (1.72-28.9) (19,20)

Table 3. Mortality rates and hazard ratios (HR) for DTP and OPV-only vaccinated children as most recent vaccination#

	Mortality rates (deaths/person-years)		
	DTP (+/- OPV)	OPV only	HR for DTP vs OPV only
Urban Bissau, 1981-84 3-11 months##	12.4 (49/394.3)	1.8 (1/57.0)	7.30 (1.01-52.9)
Urban Bissau, 1981-84 12-35 months##	6.8 (20/295.1)	1.1 (1/87.6)	6.81 (0.91-51.07)
Combined			7.06 (1.72-28.9)

Notes: # Adjusted for age group; ## Vaccinations were administered in relation to routine 3-monthly nutritional surveillance. The children were at risk from when DTP (+/-OPV) or OPV-only had been administered and until they received subsequent vaccinations.

Hence, compared with receiving DTP(+OPV), OPV-only may be associated with lower mortality. It is therefore important to examine what might happen if OPV is no longer given routinely with DTP, as will be the situation when OPV has been removed. In two studies of the introduction of DTP in Guinea-Bissau, there were periods where OPV was not available and the children therefore received DTP-only (21,22). In the two studies (Table 4), the negative effects of DTP compared with DTP-unvaccinated children was significantly worse when DTP-only (without OPV) was given (HR=8.1 (2.6-25)) than in the periods where DTP and OPV were co-administered (HR=2.2 (1.2-4.2)).

Table 4. Hazard ratio (HR) for mortality of DTP-only or DTP+OPV-vaccinated compared with DTP-unvaccinated children

Introduction of DTP and OPV	HR DTP-only vs DTP-unvaccinated	HR DTP+OPV vs DTP-unvaccinated
Urban Bissau, 1981-83 (22)	10.0 (2.6-39)	3.52 (1.0-12.9)
Rural Bissau, 1984-1987 (21)	5.00 (0.6-40)	1.90 (0.9-4.0)
Combined	8.1 (2.6-25)	2.2 (1.2-4.2)

Thus, OPV seem to reduce the negative effects of DTP. If that is true, the unfortunate implication may be that once OPV is stopped, the negative effects of DTP will be more pronounced and visible. It should be remembered that all available studies suggest that DTP-containing Penta has the same negative effects as the DTP vaccine (14,15,23,24).

IV. Compared with OPV, IPV is not likely to have beneficial NSEs

OPV has been compared with IPV in two small RCTs (25,26). Compared with IPV recipients, OPV-recipients had fewer episodes of otitis media between 6 and 18 months of age in Finland, the reduction in risk being 24% (6-41%) (25). In a small RCT in Bangladesh, children were randomised to OPV or IPV at 9 months just one week before measles vaccination. The OPV vaccinated children had fewer days with diarrhoea and fewer episodes between 9 and 12 months of age (26).

Surprisingly few studies have examined the effect of IPV on child survival. A PubMed search does not suggest that any other group has examined the possible impact of IPV on child survival; hence, no study has shown that IPV has beneficial effects on child survival. We used IPV as a comparator vaccine in four RCTs of early measles vaccine before 9 months of age. In these RCTs, the female-male MRR among children randomised to IPV was 1.52 (1.02-2.28) (27). This excess mortality in girls relative to boys changed as soon as the children received MV after 9 months of age (27).

We have also documented in trials of high-titre measles vaccination (HTMV) in Senegal, The Gambia and Guinea-Bissau that children who received DTP-IPV or IPV after HTMV had a female-male MRR of 1.93 (1.33-2.81) whereas the MRR was 0.96 0.69-1.34) for those who did not (28). Hence, IPV may be associated with negative NSEs for females as we have also documented for other inactivated vaccines (DTP, HBV, Penta, RTS,S) (2,24,29,30,31).

Conclusions

Our data suggest that OPV has beneficial effects beyond prevention of poliovirus infection. These NSEs were apparent when OPV is administered during nation-wide campaigns, when OPV is administered at birth, and when OPV is administered as a routine vaccination with DTP. IPV does not have positive NSEs, and may have negative effects for females.

Several RCTs ought to be conducted to examine the potential beneficial NSEs of OPV before OPV is completely phased out: First, it should be possible to conduct cluster-randomised trials of the overall effect on child survival of OPV campaigns. Second, in many settings very few infants receive OPV at birth, so RCTs of the effect of OPV0 could be conducted (8). Third, before IPV replaces OPV, trials should compare the effect on all-cause mortality of the old OPV schedule with an IPV-based schedule (25,26).

Such trials should help define the possible extent of the problem and serve as a basis for studying ways to remedy the situation. For example, could a more liberal use of MV campaigns remove the need for OPV campaigns and could a third dose of rotavirus vaccine (where only two doses are given) or an additional BCG vaccination with DTP3 reduce the need for co-administration of OPV with DTP?

If these associations of OPV and non-specific reduction in child mortality rates are truly related, phasing out of OPV and replacing it with IPV may have large-scale negative implications. If true, such changes may in fact stop the progress towards MDG4 in poorer countries such as Guinea-Bissau. We trust that SAGE will do due diligence, and review this in the necessary detail.

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Appendix: OPV campaigns may change the results of RCTs

As seen in Table S1, in RCTs testing the effects of early live vaccines on child survival, the effect of the live vaccine was stronger before an OPV campaign occurred. Hence, campaign-OPV neutralised the difference between the randomisation groups.

Table S1. RCTs of early virus vaccination: effect of OPV campaigns on overall estimate

Vaccine	Design; Age group	Mortality reduction before OPV campaigns #	Overall mortality reduction
Measles vaccine (9,10)	Additional MV at 4½ months; mortality 4-36 months per-protocol analysis;	47% (13-68%)	30% (6-48%)
OPV-at-birth (11)	RCT of OPV0 vs no OPV0; infant mortality	32% (0-57%)	17% (-13-39%)
BCG-II (12,13)	BCG at birth to LBW children; infant mortality	20% (-6-40%)	17% (-8-37%)
BCG-III (13)	BCG at birth to LBW children; neonatal mortality	34% (0-56%)	30% (-4-53%)

Notes: # follow-up was censored when the children became eligible for campaign OPV.

Similarly, studies examining the effect of different vaccination statuses have shown that OPV campaigns reduce the difference between groups. In Navrongo, Ghana, we examined whether out-of-sequence vaccinations - i.e. DTP administered with MV or DTP after MV - was associated with higher mortality than following the recommended sequence of MV-after-DTP3. With 12 months of follow-up, the overall result was 1.42 (1.06-1.90)-fold higher mortality for children having received DTP/Penta out-of-sequence. The negative effect was much stronger before the campaigns (Table S2) (14). In other words, campaigns (mostly OPV) reduced the mortality rate and thereby the relative difference between the groups being compared.

Table S2. Mortality rates and hazard ratios for different vaccine groups before and after campaigns. Children aged 12-23 moths (14)

Vaccination status	Mortality rate per 1000 pyrs		Adjusted HR
Out-of-sequence vaccinations	DTP>=MV	MV-after-DTP3	
Before campaigns	86 (8/94)	27 (25/930)	2.58 (1.14-5.84)
After campaigns	25 (54/2,131)	14 (391/27,080)	1.37 (1.02-1.85)

A similar result was obtained in an analysis of the effect of not being measles-vaccinated versus being measles-vaccinated among children aged 9-23 months (Table S3) (15). With 12 months of follow-up, the overall effect was 1.38 (1.15-1.66)-fold higher mortality for children who were initially measles-unvaccinated compared with measles-vaccinated children. Again, the negative effect was stronger before campaigns and campaigns reduced the mortality rate and the relative difference between the groups being compared.

Table S3. Mortality rates and hazard ratios for different vaccine groups before and after campaigns. Children aged 9-23 months (15)

Vaccination status	Mortality rate per 1000 pyrs		Adjusted HR
Vaccination status at enrolment	No MV	MV-after-DTP3	
Before campaigns	52 (86/1653)	19 (144/7719)	1.63 (1.23-2.17)
After campaigns	33 (104/3174)	17 (376/21892)	1.23 (0.97-1.54)

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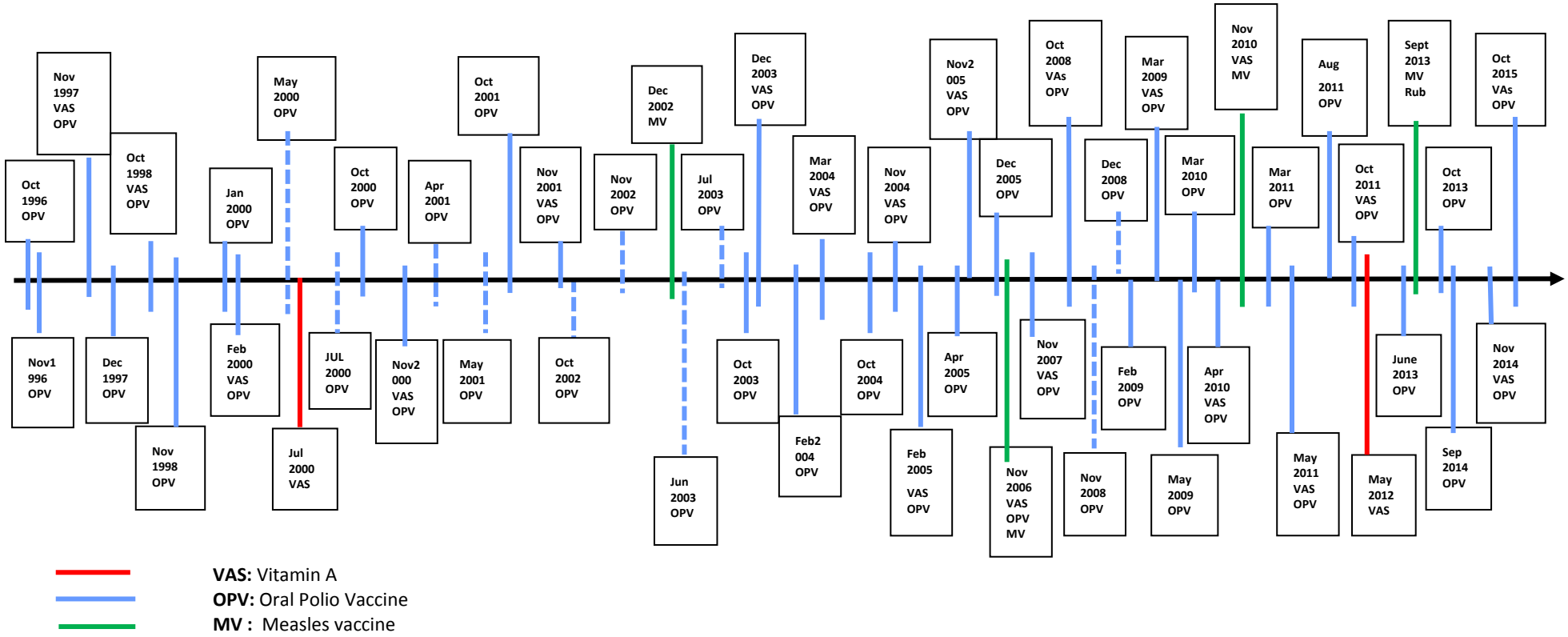

Figure 1: National immunization campaigns in Ghana: 1996-2015

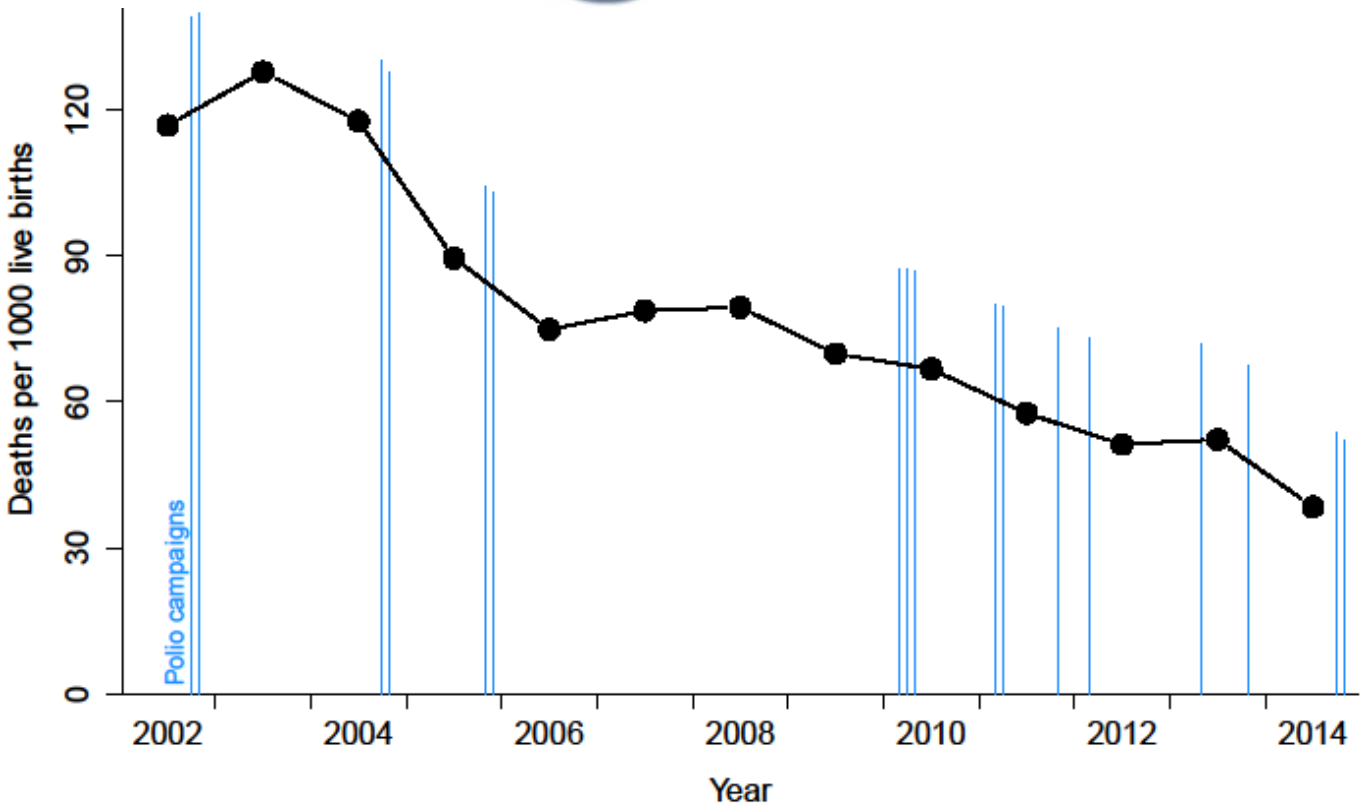

Figure 2: Under-3-mortality in urban Guinea-Bissau, 2002-2014

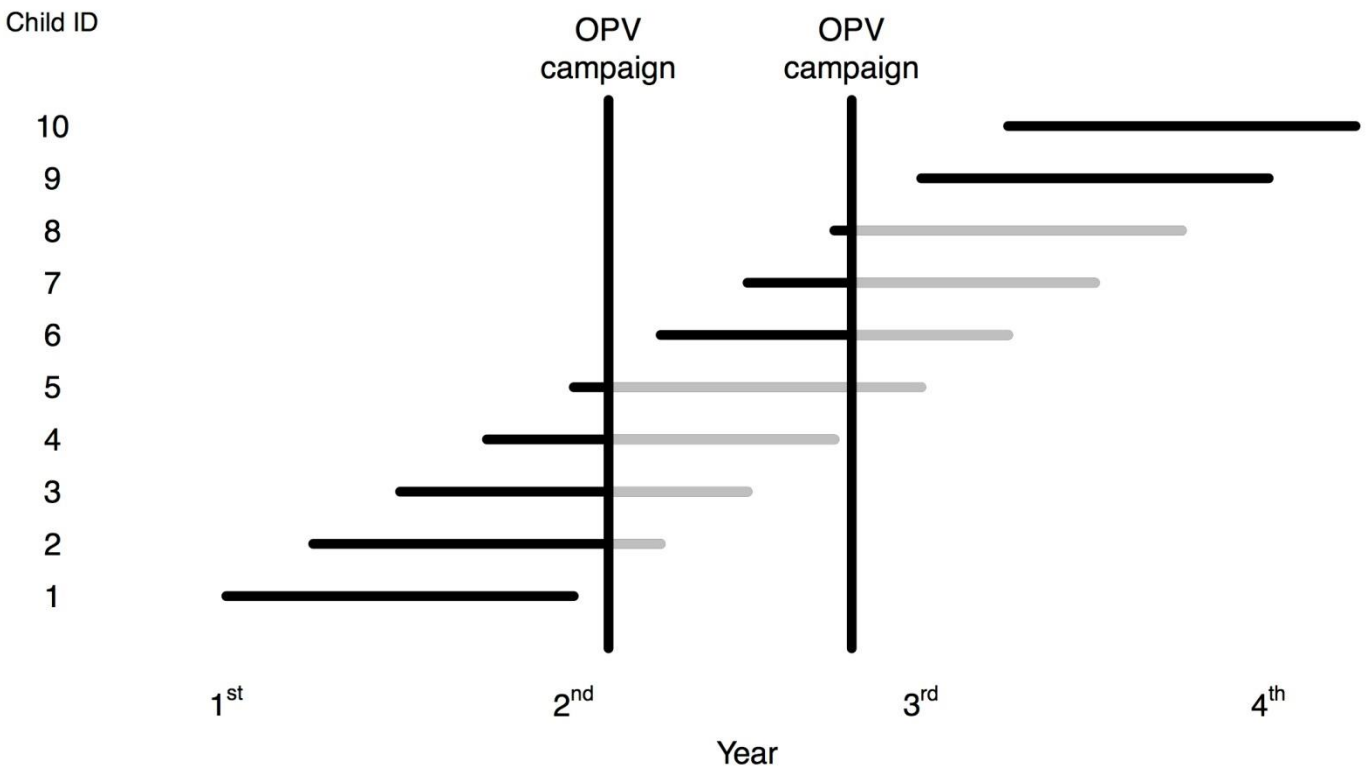

Figure 3. A hypothetically presentation of individuals in a trial: Follow-up time before OPV campaign in black; follow-up time after OPV campaign in grey

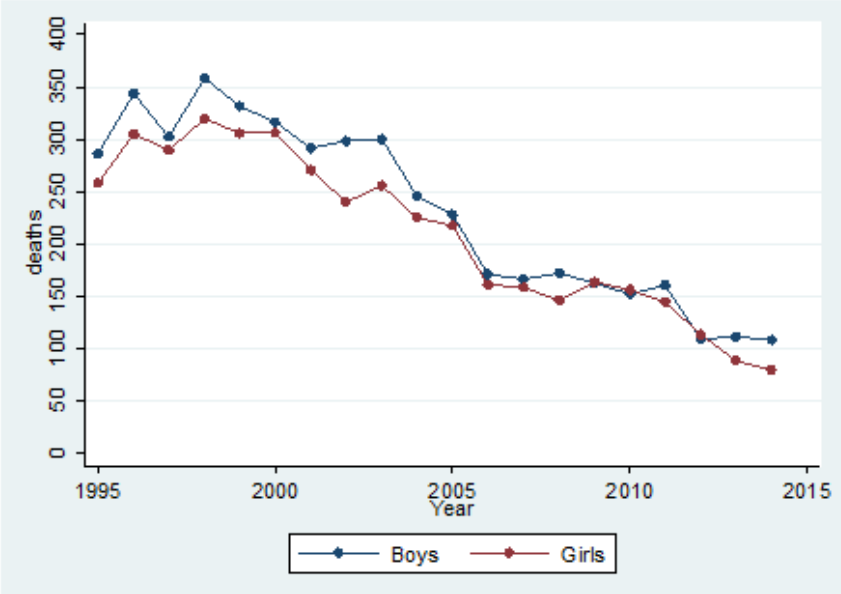

Figure 4. Under-five mortality in rural Guinea-Bissau, 1995-2014

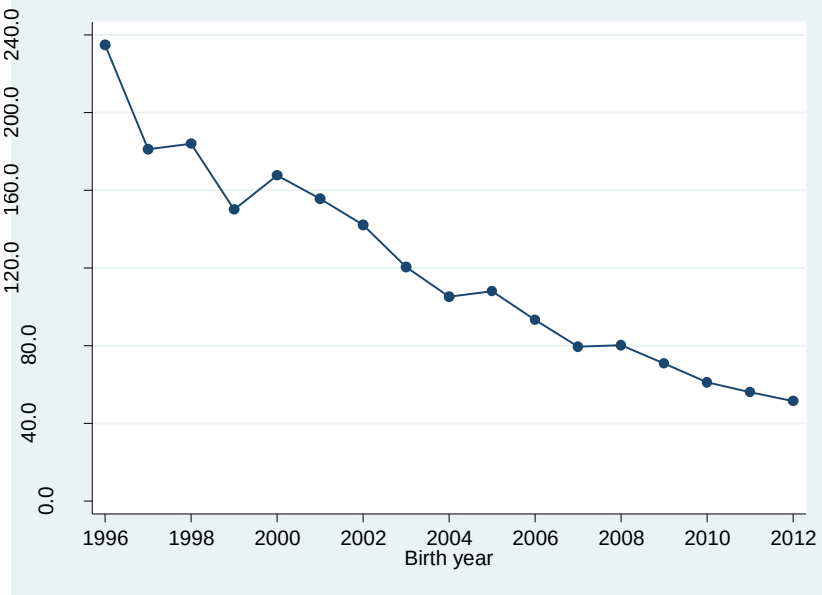

Figure 5. Under-5 mortality in Navrongo, Ghana, 1996-2012