RESEARCH CENTER FOR VITAMINS & VACCINES

The Strategic Advisory Group of Expert of Immunization (SAGE)
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WHO, Geneva

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Dear SAGE,

SAGE recently reviewed the potential non-specific effects (NSEs) on mortality of BCG, diphtheria-tetanus-pertussis (DTP) and measles vaccine and concluded that NSEs warrant further study.

SAGE did not review potential NSEs of oral polio vaccine (OPV). The purpose of this letter is to suggest that SAGE reviews these effects before OPV is phased out.

OPV has been used in campaigns, at birth (OPV0) with or without BCG, and as a routine vaccination with DTP. Below we summarise the evidence for potential NSEs for each of these applications.

OPV campaigns

We have previously reported a beneficial effect in the first OPV campaigns in Guinea-Bissau in 1998 after comparing mortality among children who participated in the campaign and received OPV, and non-participants who did not receive OPV (1).

In a much larger study we have now analysed the effect of the 15 OPV campaigns which have been implemented in Guinea-Bissau (as in other low-income countries) during the last 15 years (2). In contrast to the first campaign in 1998 these campaigns have had very high coverage (>95%) so comparisons of participants and non-participants is not possible. Instead, we examined whether the mortality rate changed from before to after campaigns within each of seven randomised clinical trials (RCTs) conducted in urban Bissau between 2002 and 2014. There are prospectively defined entry criteria for inclusion in the RCTs and the participants are closely monitored, so studies of RCT cohorts can be especially informative. Using the data from all seven RCTs it was possible to adjust for age, possible seasonal effects and changes in mortality over time.

We found that campaign OPV was associated with a 19% (95% CI=5-32%) reduction in the age-adjusted mortality rate. No beneficial effect was found for the other campaigns with vitamin A supplementation (VAS) [4% (-20-35%) increase] and MV [24% (-26-109%) increase]; a H1N1 campaign was associated with a significant increase in the mortality rate [86% (2-242%)].

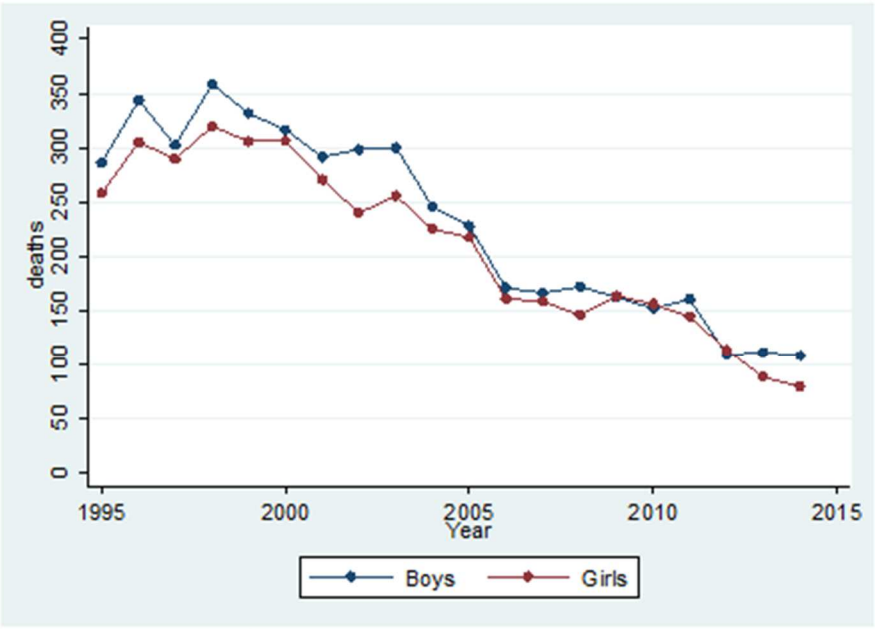
Each additional OPV campaign reduced mortality by 13% (4-21%). The observation that repeated OPV conferred additional benefits is consistent with data from the other live vaccines. Repeated doses with either BCG or MV have also been shown to have additional beneficial effects (3-5).

Especially for MV such additional effects are clearly non-specific since the first dose is usually protective against measles.

The results are consistent with the trend seen in under-five mortality in Guinea-Bissau. The figure below illustrates the annual under-five mortality in rural Guinea-Bissau (unpublished data).

Between 1999-2006 OPV and/or MV campaigns were implemented annually (except 2003), and mortality declined markedly. Then there were no OPV campaigns until 2010, and during this period mortality remained stable. From 2010 and onwards several annual OPV campaigns were conducted which again coincided with a decline in mortality. Cases of polio infection have not been detected in Guinea-Bissau for the last 15 years. Thus, all current evidence supports that OPV campaigns have been a major driver in reducing all-cause child mortality via mechanisms not directly associated with reduction of poliovirus infection, i.e. with beneficial NSEs. To our knowledge other groups have not studied the effect of OPV campaigns on overall mortality. However, given the data we outline above, such investigation would appear warranted.

Figure. Under-five mortality in rural Guinea-Bissau



Under-five mortality in rural Guinea-Bissau

OPV-at-birth

We have recently conducted the first randomised trial (RCT) of OPV-at-birth (OPV0) with mortality as the main outcome (6). In the analysis censoring for the general OPV campaigns, allocation to OPV0+BCG versus only BCG was associated with a 32% (0-57%) reduction in infant mortality.

In another small RCT among low-birth-weight (LBW) 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% (-54-79%) reduction in infant mortality; the trial had limited power because it was stopped due to a cluster of deaths among males who had received NVAS (7).

We previously published an observational study of a 'natural experiment' arising from a situation where OPV0 was not administered in Guinea-Bissau for 6 months due to vaccine shortage. Comparing periods where OPV0 had been given and not given, routine OPV0 appeared to have a negative effect for boys (8). However, we did not find the same thing in a subsequent similar study when OPV0 was again missing (9). Furthermore, we tested this in the RCT presented above and the effect of OPV0 was significantly beneficial for boys (6). Thus, the negative effect in the first observational study (8) was presumably due to chance or an interaction with the many campaigns conducted during the study period (2).

Again, to our knowledge other groups have not studied the impact of OPV0 on overall mortality.

Routine OPV administered with DTP

There has been very little research on the effect of routine OPV on mortality, presumably because prevention of poliovirus infection is not believed to have any large effect on child mortality levels, and furthermore it is difficult to separate the effects of OPV given simultaneously with DTP. Hence, to some extend we rely on circumstantial evidence and natural experiments.

DTP was first introduced by our team in 20 villages in the interior of Guinea-Bissau in 1984-1987. OPV was not used the first year and the mortality rate ratio (MRR) for DTP versus unvaccinated was 5.00 (0.63-39.7). In the period from 1985-1987, when DTP and OPV were nearly always administered together, the MRR was 1.90 (0.91-3.97). Hence, simultaneous administration may have reduced the negative non-specific effect of DTP.

We have also reported a natural experiment in which DTP was missing for several months in Guinea-Bissau in 2001. Because we monitored the vaccination status of hospitalised children we could compare children who had received only OPV and those who had received the recommended combination of DTP and OPV. OPV-only children had a 3-fold lower case fatality (any cause) at the hospital than the DTP+OPV vaccinated children (RR=3.45 (1.30-9.09))(11).

Few studies of the effect of vaccines on child survival have analysed the effect of DTP and OPV separately. We have found three studies in which some children did not get both vaccines at the same time (Table). Since the unvaccinated group in these studies may be subject to many forms of bias (selection, frailty, and survival bias) we have not used the absolute estimates compared with unvaccinated children as an indication of the effect of OPV; instead we have evaluated the relative effect of DTP and OPV within the same model as they have a common reference in the unvaccinated group. The results suggest that DTP is worse than OPV for child survival, or OPV is better than DTP, or both (Table). For example, when DTP and OPV was introduced in Guinea-Bissau in our urban study area in 1981-1983, children who had OPV-only as their most recent

vaccination had significantly better survival than children who had DTP-only or DTP+OPV as their most recent vaccination (14).

Table. Mortality rate ratios (MRR) for DTP and OPV vaccinated children within the same study.

Study	Mortality rate ratio (95% CI) for vaccinated children compared with unvaccinated children in the same study		The MRR for DTP-vaccinated compared with OPV-vaccinated children
	DTP	OPV	
Haiti (12)#	1.27 (0.68-2.39)	0.24 (0.12-0.45)	5.29 (2.13-13.17)
India (13)#	0.85 (0.53-1.4)	0.76 (0.54-1.1)	1.12 (0.61-2.04)
Bissau (14)##	Mortality rate: 16.3 (13 deaths/68.6 per-years)	Mortality rate: 0 (0/50.4 person-years)	P=0.002 (log-rank test)

Note: #The studies compared the effect of DTP and OPV with unvaccinated children within the same population. We have calculated the MRR for DTP-vaccinated compared with OPV-vaccinated. ## The estimate is children who had DTP-only or OPV-only as their most recent vaccination between 3 and 11 months of age.

Additional research on OPV and IPV

We tested the hypothesis that OPV might have beneficial NSEs using Danish register data. In Denmark, OPV was given at 2, 3 and 4 years of age until 2001 in addition to the inactivated polio vaccine (IPV) given with DTP and Hib in infancy (15). Controlling for a large number of potentially confounding factors, the Danish data showed that children receiving OPV as most recent vaccination compared with children who had received DTaP-IPV-Hib as their most recent vaccination had a 15% (5-23%) reduction in the risk of hospital admission between 24 and 36 months of age. The effect was similar to the effect we have previously reported for Measles-Mumps-Rubella vaccine (MMR) (16). Both OPV and MMR had the strongest protective effect against admission for lower respiratory infections.

In Finland, children who received OPV in a trial had fewer episodes of otitis media at age 6-18 months than control children who received IPV (17).

Two older studies from Latin America have suggested that the introduction of OPV was associated with a non-specific reduction in diarrhoea-related, polio-unrelated mortality (18,19).

A PubMed search does not suggest that anyone outside our group has examined the possible impact of IPV on child survival. We used IPV as a comparator vaccine in four RCTs of early measles vaccine before 9 months of age. In these studies the female-male MRR among children randomised to IPV was 1.52 (1.02-2.28) and this difference disappeared once they got measles vaccine (20).

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 (21). Hence, IPV may be associated with negative NSEs for females as we have also documented for other inactivated vaccines (DTP, HBV and H1N1) (2,22,23).

Conclusions

The data summarised here and presented in the attached papers suggest that OPV has beneficial effects beyond prevention of poliovirus infection, i.e. non-specific effects (NSEs). These NSEs were apparent when OPV was administered during nation-wide campaigns, when administered at birth, and as a routine vaccination with DTP. IPV does not have positive NSEs, and may have negative NSEs for females.

We recognise that the limited number of RCTs available and several observational studies alone may not suffice to guide policy decisions. We propose that several RCTs be conducted to examine the potential beneficial NSEs of OPV, before OPV has been 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. Third, before IPV is used to replace OPV, trials should compare the effect on all-cause mortality of the old OPV schedule with an IPV-based schedule.

If these associations of OPV and non-specific reduction in child mortality rates are truly related, phasing out of OPV or 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 thus trust that SAGE will do due diligence, and review this in the necessary detail.

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