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Aaby, Peter; Benn, Christine Stabell

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Peter Aaby[1,2], Christine S Benn [2,3]

1) Bandim Health Project, Indepth Network, Apartado 861, Bissau, Guinea-Bissau

2) Research Centre for Vitamins and Vaccines (CVIVA), Bandim Health Project, Statens Serum Institut, Artillerivej 5, 2300 Copenhagen S, Denmark

3) OPEN, Institute of Clinical Research, University of Southern Denmark/Odense University Hospital

Corresponding author: Peter Aaby, Email: p.aaby@bandim.org

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Abstract

Several live vaccines may have beneficial non-specific effects (NSEs) reducing mortality more than can be explained by the prevention of the target infection, a phenomenon which has been linked to innate immune training. Most randomised controlled trials (RCTs) of oral polio vaccine (OPV) and measles vaccine (MV) have shown a large reduction in mortality that must have been at least partly nonspecific because it was much larger than the reduction explained by prevention of the target disease. Hence, stopping a live vaccine after disease-eradication could have negative health effects if the potential beneficial NSEs are not considered. We reviewed one eradicated disease, smallpox, and two infections likely to be eradicated in coming decades, polio and measles. No study was made of unintended effects of stopping smallpox vaccination when it happened in 1980. We have subsequently documented in both Guinea-Bissau and Denmark that smallpox-vaccinated individuals continued to have a survival advantage long after smallpox had been eradicated. The few studies which have examined the effect of OPV on survival all suggest strong beneficial NSEs; in RCTs, OPV compared with inactivated polio vaccine (IPV) has been associated with non-specific reductions in morbidity. RCTs, natural experiments and observational studies have found strong beneficial NSEs for MV. Hence, the imminent eradication of polio and the planned stop of OPV in 2024 and the subsequent eradication of measles infection and the possible stop to live MV could have negative effects for child survival. Before live vaccines are phased out, potential unintended effects of stopping these vaccines should be thoroughly studied.

Introduction: Ending infection and stopping vaccination

The last case of naturally transmitted smallpox infection was seen in Somalia in 1977 and the infection was declared eradicated in 1980[1]. Polio infection is close to extinction[2], possibly in 2020, and measles infection will be next in line. Live smallpox vaccine was stopped globally in 1980, three years after eradication. Trivalent oral polio vaccine (OPV) was stopped globally in April 2016[2] and live bivalent or monovalent OPV will be stopped in 2024, and replaced by inactivated polio vaccine (IPV). These eradicable diseases have all been controlled by live vaccines.

Stopping a live attenuated vaccine or replacing it with a non-live version after eradication is a logical step if the vaccine has adverse effects, is potentially problematic to immune compromised individuals, and otherwise only protects against an extinct infection. However, if the underlying assumptions about a one-to-one link between one vaccine and one disease are incorrect, and the live vaccine protects against more than the targeted infection, there may be unexpected consequences if vaccination with a live vaccine is stopped.

Live vaccines have beneficial non-specific effects enhancing survival

When BCG, OPV, diphtheria-tetanus-pertussis (DTP) and measles vaccine (MV) were introduced in the global vaccination programme in the 1970s, the overall effect on survival was not examined in randomised controlled trials (RCTs)[3,4]. It was considered sufficient to show that the vaccine produced specific immune responses or clinical protection against the targeted infection[3].

The non-testing of live vaccines was unfortunate[3]. Subsequent studies in Africa and Asia have shown that a much larger reduction in overall mortality could have been obtained by vaccinating against measles before 9 months of age, but after the third dose of DTP, possibly in a two-dose schedule[3,5]. For example, during a civil war in Guinea-Bissau children randomised to measles vaccine at 6 months of age had 70% (13-92%) lower mortality than control children receiving inactivated polio vaccine (IPV)[6]. This effect on overall mortality was not due to better prevention against measles infection[5,6]; early MV protected against other infections.

From these studies has grown the evidence that live vaccines may increase protection against unrelated infections; in addition to their disease-specific protective effects, vaccines have so-called heterologous or non-specific effects (NSEs)[7]. In many of the RCTs of live vaccines with mortality as the outcome, the reduction in mortality related to the NSEs is greater than the reduction related to the specific protection against the targeted infections (Table 1). The NSEs have primarily been examined with respect to the impact on mortality in low-income countries, but there is now evidence that NSEs also affect morbidity of children in high-income countries; for instance, a recent US study found that having a live vaccine rather than a non-live vaccine as the most recent vaccination reduced the risk of hospital admission for non-targeted infections by 50%[11].

Immunology has supported that NSEs are plausible by showing that live vaccines not only induce highly specific immune responses, but also reprogram the innate immune system epigenetically so that it responds more vigorously to unrelated pathogens[7]; for example, in an RCT, being previously randomised to BCG reduced the viral load in humans challenged with yellow fever vaccine[12].

WHO's Strategic Advisory Group of Experts on Immunization (SAGE) recently sponsored a review of the evidence for NSEs of BCG, DTP and MV on mortality of children under 5 years of age[13]. In the published review, the live vaccines BCG and MV were associated with almost a halving of mortality[14]. The effect of BCG was not likely to be attributable to fewer deaths from tuberculosis. Similarly, the studies removing or censoring measles deaths suggested that "*these effects, if real, were not fully explained by deaths due to measles*" [14]. The scientists who conducted the review of NSEs for SAGE, recommended further research into the NSEs[14]

There are contrasting paradigms for the understanding of vaccines, and they have very different implications for the perception of eradication. In the current paradigm, a vaccine protects only against a specific disease and can be stopped once the infection is eradicated; for example, no study was made of the health consequences for overall mortality of stopping smallpox vaccination. On the other hand, the paradigm of NSEs raises an intriguing possibility: removal of a live vaccine after eradication could lead to increased mortality due to the loss of the beneficial immune training from the live vaccine. Hence, the overall effect of eradication might be harmful, with more children dying from the lack of beneficial NSEs than were saved from dying of the eradicated infection. When this enigma first presented itself to us in the 1990s, we started community studies of smallpox vaccination (vaccinia) - nearly 20 years after vaccinations had stopped[15-17].

Stopping smallpox and BCG vaccines

To investigate whether smallpox vaccination carried health benefits long after eradication, we examined adults in urban and rural Guinea-Bissau for smallpox scars. Results were far beyond expectation[16,17]. In the urban study, having a smallpox scar versus no scar was over the next 4 years associated with a 40% (95%CI: 13-59%) reduction in mortality for adults over 25 years of age[16]. In the rural study, the reduction in mortality was 78% (39-92%)[17]. The survival benefit associated with smallpox vaccination increased significantly with the number of vaccination scars[16]. Socio-economic confounding did not explain these effects.

To investigate the effects of stopping BCG and smallpox vaccination in Denmark, we studied the vaccination status recorded in the school health cards of children in Copenhagen. We focussed on 47,622 children born 1965-1976, the cohort which experienced the concurrent phase-out of smallpox and BCG vaccines[18]. By linkage to national registers, adjusting for social class, year of birth and sex, having received both smallpox and BCG vaccines was associated with 46% (19-64%) lower mortality rate from natural causes of death between school entry and 45 years of age, whereas there was no protection against accidents, suicides and murders. In another study, combining data from Guinea-Bissau and Denmark, having received smallpox and/or BCG was

associated with a 34% (4-54%) lower risk of HIV-1 infection[19]. Hence, smallpox vaccine had beneficial NSEs, which were sustained for decades after eradication, in both low-income and high-income settings. No study has reported no beneficial NSEs after smallpox vaccination.

Stopping smallpox vaccination is therefore likely to have had negative overall effects for survival. The same could happen with the eradication of polio and measles infections.

Predicting the future: What will happen when OPV is stopped?

What will happen when OPV is stopped globally? The rare cases of vaccine-associated paralytic polio (VAPP) will disappear and it will be unnecessary to pursue surveillance for circulating vaccine-derived poliovirus[20,21]. However, if OPV had beneficial NSEs, overall morbidity and mortality may increase.

OPV is now phased out in high-income settings and replaced by inactivated polio vaccine (IPV). This may not have had beneficial health effects. A Finish RCT of OPV versus IPV found that OPV was associated with 24% (6-41%) reduced risk of otitis media[22]. Using national register data from Denmark, where OPV was used until 2001, being OPV-vaccinated was associated with 27% (13-39%) lower risk of hospital admission with lower respiratory infections than not having received OPV[23].

SAGE did not include OPV in the review of NSEs of vaccines on child survival. As for other vaccines, the overall effect on survival of the introduction of OPV had not been studied in RCTs. However, there are observational studies from Latin America suggesting that OPV was associated with a reduction in diarrhoea deaths[24,25]. Furthermore, in addition to the few studies of OPV in high-income countries, several lines of research described in the following suggest that OPV have major beneficial NSEs in low-income countries.

First, in an RCT, receiving OPV with BCG at birth versus BCG-only was associated with a 17% (-13-39%) reduction in infant mortality; the reduction was 42% (10-62%) if OPV was provided within the first 2 days of life[8]. There were numerous OPV campaigns during the conduct of this RCT. In the period before the children received campaign-OPV, being randomised to OPV was associated with 32% (0-57%) reduction in infant mortality (Table 1). In this analysis, randomisation to OPV at birth reduced infant mortality with 12.6 deaths/1000 person-years.

Second, OPV is administered in three doses with DTP in the routine vaccination programme (EPI) and few researchers have attempted to estimate the separate effects of these vaccines. However, when DTP and OPV were first introduced there were periods with no OPV, and mortality was significantly higher when the children had received DTP-only than when children had received DTP+OPV[4,26]. There were also periods with no DTP, and mortality was much lower for children who received OPV-only compared with children who had received DTP+OPV[27]. Hence, OPV

appears to have reduced the negative effects of DTP. In other words, removal of OPV may lead to higher mortality among DTP-vaccinated children.

Third, there have been numerous OPV-campaigns to eradicate polio infection in the last 20-25 years. During the first OPV-campaign in Guinea-Bissau in 1998, the children who received OPV had significantly lower mortality. More recent OPV-campaigns have had very high coverage, usually over 90%, and we therefore analysed OPV-campaigns as natural experiments, assuming they affected all children under 5 years of age in the community[28-30]. These studies have shown that campaign-OPV is associated with reductions of 10-25% in the general mortality rates[28-30]. The more doses of campaign-OPV a child received, the better the effect on survival. Similar effects of OPV campaigns have been found in Guinea-Bissau[28-30], Ghana[31], Burkina Faso[32] and Bangladesh[33]. In the largest study of OPV campaigns in Guinea-Bissau, the number needed to treat (NNT) to save one child up to 3 years of age was only 47 neonates[30]. In several studies OPV campaigns have been associated with lower mortality rate and reduced mortality rate ratio (MRR) between different vaccination status groups, e.g. DTP-after-MV versus MV-only as most recent vaccine[31,33,34]. In other words, OPV lowers the mortality rate for all children. The effect of this is to minimize the difference between groups defined by other exposures which may otherwise have a differential effect on child survival; for example, in the RCT of OPV at birth the MRR for OPV versus no OPV was 32% but after the OPV campaigns there were no difference[8]. With the consistent effect of campaign-OPV, it is likely that campaign-OPV has played an important role in the major decline in child mortality, which has occurred in most low-income countries during the last two decades[28-33]. No study has reported no reduction in the mortality rate after OPV campaigns.

These studies were conducted in the context of no circulating polio virus. Hence, the observed beneficial effects are by definition non-specific. Taken together the data suggest that OPV have had beneficial NSEs, and removing OPV from EPI and stopping OPV campaigns may therefore affect child survival negatively. In the endgame for polio, it is planned to replace OPV with IPV in the EPI. There are few studies of the general health effect of IPV. In a recent RCT testing OPV versus IPV in Bangladesh, IPV was associated with increased risk of bacterial diarrhoea[35]. We used IPV as a comparator vaccine in several RCTs in Guinea-Bissau; IPV was associated with 52% (2-128%) higher female than male mortality[36]. Hence, we predict that removal of OPV will lead to higher child mortality in low-income countries.

Predicting the future: What will happen when measles infection is eradicated?

Once polio infection and OPV are gone, measles infection and MV will be next in line for an endgame. The SAGE-sponsored review used evidence from 18 observational studies and four RCTs and concluded that MV appeared to be associated with major beneficial NSEs on child survival[14]. In high-income settings, measles vaccine in the form of measles-mumps-rubella vaccine (MMR)

has been associated with reductions in hospital admissions, particularly for respiratory infections[11,37].

Though most studies from low-income countries are observational, there are also RCTs and natural experiments, which have found major survival benefits from MV. In 1998, the civil war in Bissau interrupted an RCT testing an additional dose of MV at 6 months of age with IPV as the comparator vaccine. All children were to receive MV at 9 months of age, but due to the war, this did not happen. For the three months' duration of the war period, having received MV was associated with 70% (13-92%) lower mortality than having received IPV, an effect which was not explained by prevention of measles infection[6]. In a subsequent RCT in peacetime, two doses of MV at 4.5 and 9 months were associated with 30% (6-48%) lower mortality between 4.5 and 36 months of age than receiving the currently recommended dose of MV at 9 months of age (Table 1); only 4% was explained by specific prevention of measles infection[5]. Most studies have shown that OPV and MV have beneficial NSEs, but other interventions may interact and neutralise the NSEs of these vaccines (Table 1); for example, the beneficial NSEs of early MV may be reduced or removed by neonatal vitamin A supplementation[5], numerous OPV campaigns[8,34] and DTP administered after MV[10].

As for campaign-OPV, campaign-MV is associated with marked reductions in the mortality rate and the effect is particularly strong when the children have already been primed with MV prior to the campaign[31,38,39]. As far as we know, no study has reported no reduction in the mortality rate after MV campaigns.

The endgame against measles infection has entailed many additional measles vaccination activities in low-income countries, including regular MV-campaigns every 3 years and the introduction of a second dose of MV in the second year of life. Once measles infection is eradicated, MV may be stopped entirely, replaced by an inactivated vaccine, or MV campaign activities will be scaled down significantly.

When OPV is gone and MV stopped or scaled down, much fewer live vaccines will be left in the routine immunization programme: BCG at birth, rotavirus vaccine at 6-14 weeks, and yellow fever vaccine at 9 months of age in some countries. The non-live vaccines will increasingly dominate. This may have a negative effect for female survival. The six non-live vaccines we have examined (DTP, Penta, IPV, Hepatitis B vaccine, RTS,S malaria vaccine, H1N1 influenza vaccine) were all associated with higher female than male mortality[29,36,40].

Conclusion

Global health is justifying interventions by their effects on overall child health. However, these effects are rarely measured but rather estimated from modelling of the specific effects; this is likely to be detrimental if we stop using live vaccines that have strongly beneficial NSEs.

Stopping smallpox vaccine may have had rather modest effects on overall mortality because the vaccine was not given in all countries and often not to the youngest children for whom the gains from beneficial NSEs would be the strongest. The situation is different for OPV and MV, which are administered in repeated doses to all infants in low and middle-income countries. Thus, stopping live OPV and live MV could roll back the decline in child mortality that we have witnessed in recent decades.

Most observational studies and RCTs of live vaccines (Table 1) suggest that the reduction in mortality is so large that it should be cost-effective to continue to use these live vaccines. Even though a few children may have adverse effects, the live vaccines may save far more children. The number of studies on OPV and MV is limited. Hence, it is high time that these effects be studied before it is too late and the vaccines, like OPV, can no longer be used. We need RCTs of the effects of live vaccines on overall mortality and morbidity.

Provided research continues to support that live vaccines have beneficial NSEs, we need to reconsider their use. These vaccines should not only be seen as important tools to provide specific disease protection. In addition, they should be examined as immune enhancers. One consequence would be to continue to use live vaccines like OPV and MV even after the target infections were eradicated – not for their infection-specific effects, but for their immune-training effects. As there may be other reasons not to continue with OPV, another possibility is to study whether other vaccines can provide similar beneficial effects, e.g. whether the live rotavirus vaccine has similar beneficial NSEs as OPV, or whether more frequent campaigns with MV can replace the beneficial effects of OPV-campaigns. Several studies suggest that BCG co-administered with DTP reduces mortality[41] and revaccination with BCG have beneficial NSEs[42]. Hence, additional doses of BCG could also contribute to lower child mortality.

We need this knowledge to plan future immunization schedules but also to know the extent of the beneficial effects, and the damage which has to be mitigated if the live vaccines with beneficial NSEs are stopped. In other words, we need to reconsider the current paradigm for vaccines with its focus on eradicating specific diseases and stopping the corresponding vaccine, and take a more holistic approach, if we want to make important contributions to child survival globally.

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Key messages:

- Many studies have shown that live vaccines have beneficial non-specific effects on child survival, protecting not only against the targeted infection but also against unrelated infections.
- Hence, eradicating an infection and then stopping the corresponding live vaccine could have overall negative effects by depriving the children of the beneficial immune training.
- We examined the evidence for such possible negative effects of eradication in relation to smallpox infection (eradicated in 1980), polio infection (soon to be eradicated), and measles infection (next in line as a target for eradication).
- The studies on the live vaccines against smallpox, polio and measles infections are consistent in showing that these vaccines have beneficial effects well beyond specific-disease prevention. Consequently, eradication of infections, controlled by live vaccines, could have overall negative effects.

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Table 1. Randomized controlled trials (RCTs) of live vaccines: Mortality reductions due to specific effects and NSEs of vaccine

Vaccine	Design; Age group	Reduction in mortality: Specific disease protection	Reduction in mortality: Non-specific effects
OPV-at-birth[8]	RCT, censoring for OPV-campaigns; Infant mortality	0%	32% (95% CI: 0 to 57%)
Measles vaccine[5]	RCT; per-protocol analysis; MV at 4.5+9 months vs 9 month; Mortality 4.5-36 months	4%	26% (95% CI: 0 to 45%)
Measles vaccine[9]	RCT; per-protocol analysis; MV at 4.5+9 months vs 9 month; Mortality 4.5-36 months	0%	-5% (95% CI: -32 to 33%)

Note: The table does not include the RCTs of the live medium-titre and high-titre measles vaccines, which were associated with increased female mortality because the children received DTP or IPV after MV[10]. Excluding children who received DTP with MV or DTP or IPV after MV, live medium-titre and high-titre measles vaccines were also associated with a strong beneficial effect on child survival[10].

Contributors*:* PA and CSB have worked in Guinea-Bissau for more than 25 years to understand the real-life effects of our childhood interventions. This has led to the realisation that live vaccines have beneficial immune-training effects, which go well beyond merely protecting against a specific infection. From this pursuit has come the enigmatic question: Though we all believe that it would be good to eradicate more infections, could it actually have negative overall effects to eradicate an infection and stop the live vaccine? The first draft was written by PA and CSB; both authors contributed to the final version of the paper. PA will act as guarantor of the article.

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