Research Paper

Revaccination with Live Attenuated Vaccines Confer Additional Beneficial Nonspecific Effects on Overall Survival: A Review

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ABSTRACT

Background: Live vaccines against measles (MV), tuberculosis (BCG), polio (OPV) and smallpox reduce mortality more than explained by target-disease prevention. The beneficial nonspecific effects (NSEs) of MV are strongest when MV is given in presence of maternal antibodies. We therefore hypothesised that revaccination in presence of prior immunity enhances beneficial NSEs.
Methods: Literature search for studies of revaccination and mortality.
Findings: In two randomised trials (RCTs), two doses versus one dose of MV reduced all-cause mortality by 63% (95% CI: 23–83%) from 9 to 18 months of age. In a quasi-experimental study two doses before and after 9 months compared with one dose of MV after 9 months of age reduced mortality by 59% (25–81%). BCG-revaccination significantly enhanced BCG's effect against overall child mortality in two RCTs. In a natural experiment study of OPV campaigns over a 13-year-period in Guinea-Bissau, each additional dose of OPV was associated with a 13% (4–21%) reduction in mortality rate. The beneficial NSEs of smallpox vaccination for survival increased significantly with the number of smallpox vaccination scars.
Interpretation: Revaccination with live vaccines led to substantial reductions in overall mortality. These findings challenge current understanding of vaccines and may explain the beneficial effects of campaigns with live vaccines.

1. Introduction

Live attenuated vaccines including measles vaccine (MV), BCG, oral polio vaccine (OPV) and smallpox vaccine have beneficial effects on survival beyond protection against the targeted infections (Aaby et al., 1995; Kristensen et al., 2000; Aaby et al., 2010; Aaby et al., 2011; Biering-Sørensen et al., 2012; Lund et al., 2015; Sørup et al., 2014). Hence, these vaccines induce some form of nonspecific immunity. For example, two doses of MV at 4.5 and 9 months reduced all-cause mortality between 4.5 and 36 months by 30% (95% CI: 6–48%) compared with a single dose at 9 months (Aaby et al., 2010). WHO recently reviewed the evidence for nonspecific effects (NSEs) of BCG, MV and diphtheria-tetanus-pertussis (DTP) vaccine and concluded that BCG and MV were associated with beneficial effects in the range of halving mortality (Higgins et al., 2014; Strategic Advisory Group of Experts on Immunization, 2014).

Measles vaccination in presence of maternal antibodies is associated with lower antibody responses. However, the beneficial NSEs of early MV were particularly strong if the initial MV was administered in the presence of maternal measles antibody (Aaby et al., 2010; Benn et al., 1997; Aaby et al., 2014). We speculated that NSEs are induced more strongly with pre-existing immunity (Aaby et al., 2014). If this is the case, then one would expect to see strong beneficial NSEs of live attenuated vaccines when given to children who have specific immunity from a previous vaccination or even in children who already had the target disease.

We therefore reviewed available evidence to test the hypothesis that revaccination with live vaccines is associated with additional strong beneficial NSEs. If confirmed, it would contradict the disease-specific understanding, as most live vaccines confer good specific protection after a single dose, and very limited additional survival benefit might be expected after a second dose.

2. Methods

We searched PubMed and Medline for papers on revaccination with BCG, MV, OPV and smallpox vaccine and mortality/death. The literature

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searches are explained in Supplementary Figs. 1–4. WHO recently organised a major review of the potential nonspecific effects of BCG vaccination and MV on child survival (Higgins et al., 2014; Strategic Advisory Group of Experts on Immunization, 2014). Since this review was also taken into consideration, it is unlikely that there would be additional studies on BCG and MV that we have not found. It will be seen (Supplementary Figs. 3–4) that there were few studies on revaccination with OPV or smallpox vaccine.

Papers in English, French, German, Spanish, Portuguese and Scandinavian languages were screened by two authors (CSB, PA) on the basis of their abstract and potentially relevant papers were read. The studies were classified as RCTs, natural experiments or observational studies (Supplementary Figures). In the extraction of data, we compared the age-adjusted mortality rate of individuals, who had received two vaccinations, with those who had received only one vaccination. The RCTs had different designs as described in the result section. If several RCTs had similar design, we combined their estimates with the meta-command in Stata. For OPV and smallpox vaccination more than two doses had been given and it was possible to estimate a linear trend for additional doses of these vaccines.

Interventions may interact; thus to determine the effect of revaccination with a live vaccine we tried to eliminate the effect of other interventions. For example, many studies have suggested that DTP has negative effects on child survival when given after a live vaccine (Roth et al., 2010; Aaby et al., in press; Benn and Aaby, 2012). We recently reviewed the available data and found, in studies with registration of vaccination status and prospective follow-up, that DTP given as the most recent vaccination was associated with two-fold higher mortality than not being DTP-vaccinated (Aaby et al., in press). We therefore censored children who were likely to receive DTP in the studies of revaccination with BCG or MV. In one RCT (Aaby et al., 2010), many children had previously received neonatal vitamin A supplementation (NVAS) and NVAS neutralised the beneficial effect of MV (Benn et al., 2014). NVAS is unlikely to become official WHO policy as it has shown a negative effect on survival in African studies (Benn et al., 2015) and we have restricted the analysis to those who did not receive NVAS. Restrictions have been explained in footnotes to the tables.

Since natural measles infection is easy to diagnose and is assumed to provide life-long immunity, a child with known measles infection can be seen as a child who has been "immunized" against measles. Nonetheless such children have sometimes received a measles vaccine afterwards. This provided an opportunity to test whether measles vaccination of children who were known to have had natural measles infection was associated with additional nonspecific benefits (literature search presented in Supplementary Fig. 5).

3. Results

3.1. Measles Vaccine

We were able to identify two RCTs, a quasi-experimental study, and a natural experiment with relevant data (Supplementary Fig. 1).

In Guinea-Bissau, two RCTs compared two doses of MV (at 4–6 months and 9 months of age) with the WHO-recommended single dose of MV at 9 month (Aaby et al., 2010; Benn et al., 1997). In both RCTs randomisation took place at the initial enrolment at 4–6 months of age. This design allowed us to compare mortality for two versus one dose of MV after 9 months of age when the children had received standard MV. The children were followed to 18 months of age since booster doses of DTP at 18 months were common during the conduct of both RCTs. In a combined analysis, two doses of MV were associated with a 63% (22-83%) mortality reduction between 9 and 18 months of age (Table 1).

In the early 1980s, MV was administered in campaigns in Guinea-Bissau once or twice a year; children who received their first MV before 9 months received a second MV at the next visit (Aaby et al., 1993). Hence, receiving one or two doses of MV was a natural experiment determined by age at the time of the first campaign. We adjusted for region, sex, measles infection and season at risk in the analysis. Comparing the mortality of children from the time they received either a second or a first MV after 9 months of age, those who received the second dose had 59% (25–81%) lower mortality between 9 and 59 months of age (Table 1) (Aaby et al., 1993).

After a MV campaign in rural Guinea-Bissau, we followed children aged 1–4 years from the first visit after the MV campaign in which their vaccination status was determined, to 12 months after the campaign, and compared their survival with children who had their vaccination card examined in the similar period in the two previous years. The children who had received both routine MV and campaign MV had 50% (12–72%) lower mortality than the children who received only routine MV in the previous two years.

3.2. Additional Analyses: Measles Vaccination After Natural Measles Infection

If revaccination in the presence of pre-existing vaccine-induced antibodies enhances the nonspecific effects, one might surmise that measles vaccination of children with a history of measles infection could have beneficial effects. A search for such studies provided two relevant studies (Supplementary Fig. 5).

Table 1
The mortality rate ratio (MRR) comparing two doses of MV with one dose of MV.

Country and period	Age interval	Comparison (vaccines)	Administration of DTP	Deaths/person-years (pyrs) [N]	MRR two MV vs one MV
RCTs of two doses of MV					
Guinea-Bissau 1992–1994 (Benn et al., 1997)	9–18 months	2 MV vs 1 MV	DTP not given with MV; only children with DTP3 before 9-months	0/72.1 pyrs [113] vs 2/70.3 pyrs [107]	0 (0–3.95)[a]
Guinea-Bissau 2003–2009 (Aaby et al., 2010)	9–18 months	2 MV vs 1 MV	DTP not given with MV; all had DTP3 one month before enrolment	8/713.9 pyrs [1014] vs 39/1370.5 pyrs [1946]	0.39 (0.18–0.83)[b]
Combined MRR					0.37 (0.17–0.78)
Natural experiment					
Guinea-Bissau 1980–1982 (Aaby et al., 1993)	9–60 months	2 MV vs 1 MV	DTP not given in Guinea-Bissau in this period	Not reported in paper	0.41 (0.19–0.75)
General MV campaign					
Guinea-Bissau, 2006–2007 (Fisker et al., 2015)	1–4 years, follow-up for 12 months	Had received routine MV and campaign MV vs only routine MV	Effect analysed for those who had received DTP3 before follow-up	16/1372 pyrs [2067] vs 60/2445 pyrs [3074]	0.50 (0.28–0.88)[c]

[a] The study was restricted to children who had received DTP3 before 9 months. If all children were included the MRR was 0.33 (0.03–3.14).
[b] Study restricted to children who had not received NVAS. If all children were included in the analysis the MRR was 0.61 (0.37–1.01).
[c] Adjusted for age, maternal age, maternal education and stratified by village cluster.

When MV was first introduced in half of the Matlab study area in Bangladesh, 8134 measles-immunized children were matched by age to 8134 unimmunized children from the control areas (Aaby et al., 2003). In 136 matched pairs both children had had measles infection previously. Among these pairs six unimmunized children died and none of the immunized (p < 0.05). In an unpaired, adjusted analysis 13 of 924 children, who had measles and were given MV later, died; 27 of 891 children, who had measles but did not subsequently get MV, died. Thus, among children who had measles, those who were later given MV had a 55% (10–77%) reduction in overall mortality compared with children who were not given MV (Aaby et al., 2003).

In a study of antibody responses to MV among 6–13 months old Haitian children (Holt et al., 1990), participating children were tested before vaccination for measles antibodies; 71 had pre-vaccination levels which indicated prior infection according to the authors. During 2½ years of follow-up none of the 71 vaccinated children with pre-vaccination antibodies died, whereas mortality was 7% (70/1056) for the community controls (children in the same birth cohort who had not received MV), resulting in a RR of 0 (0–0.77). The study is compatible with MV also having a beneficial effect among previously infected children, though it did not have a control group of children who had measles antibodies from previous infection and were not measles vaccinated.

3.3. BCG

Two studies of BCG revaccination contained information on child survival (Roth et al., 2010; Sergent et al., 1954) (Supplementary Fig. 2).

A large trial was conducted in Alger 1935–1947 including more than 40,000 children who were allocated to BCG or nothing at birth based on the civil registration system (Sergent et al., 1954) (Table 2). Three oral doses of BCG were provided with intervals of 2 days shortly after birth; the children were revaccinated at 1, 3, 7 and 11 years of age. The study provided no information on specific protection against tuberculosis (TB) or the proportion of deaths due to TB. The reduction in overall mortality was only 3% (−2 to 7%) in infancy (Table 2). The initial doses provided at home by community nurses were often delayed. The mortality analysis was intention-to-treat and deaths which occurred before the children could have been BCG-vaccinated were included in the analysis. After the first revaccination, overall child mortality was reduced by 17% (11–22%) in the BCG group. After the second revaccination at 3 years, the reduction in mortality was 47% (38-55%) between 3 and 4 years of age, a significant increase in effect (interaction tests, p < 0.001). The change from 17% to 47% is particularly striking because the estimates are based on a per-protocol analysis of those who did and did not get BCG. Since the initial random allocation remained the same and the number of follow-up visits by study nurses was the same for the BCG-vaccinated and BCG-unvaccinated children, and since TB is unlikely to have caused many deaths in this young age group, the results indicate that BCG revaccination may have conferred strong additional beneficial NSEs.

More recently we conducted a BCG revaccination trial in Guinea-Bissau. In Bissau nearly all children receive BCG very early in life. Children were randomised to BCG revaccination (intra-dermally) or no vaccination at 19 months of age (Roth et al., 2010). When children had received DTP booster before enrolment and therefore did not get booster DTP after enrolment, BCG revaccination versus no BCG revaccination at 19 months of age was associated with a 64% (1–87%) reduction in mortality between 19 months and 60 months of age.

3.4. Oral Polio Vaccine (OPV)

OPV is recommended at birth and an additional three doses with DTP vaccine at 6, 10 and 14 weeks of age. Hence, OPV revaccination is normally given with DTP. Since DTP may be associated with negative effects on mortality (Aaby et al., in press), it becomes difficult to evaluate whether revaccination with routine OPV has an independent beneficial effect.

One community study of OPV campaigns permitted us to evaluate the effect of revaccination with OPV-only (Supplementary Fig. 3). From 2002 to 2014 we examined how national OPV campaigns in Guinea-Bissau affected the mortality rate within seven RCTs (unpublished data, authors). OPV campaigns – but not other campaigns - reduced the mortality rate significantly when controlled for age, season and time trends. Since the children were to receive campaign-OPV several times we assessed the effect of repeated doses assuming that all children received all doses of campaign-OPV; each additional dose of OPV was associated with an additional 13% (4–21%) reduction in mortality.

We also examined whether OPV revaccination in Denmark reduced hospital admissions. In Denmark, in addition to three doses of inactivated polio vaccine (IPV) in infancy, three doses of OPV (OPV1–3) were administered without other simultaneous vaccinations at 2, 3 and 4 years of age until 2001. Children who had previously received DTP-containing vaccines followed by OPV-1 around 2 years of age had reduced hospital admission rate during the third year of life compared with children who had DTP-containing vaccine as their most recent vaccination. There were further significant reductions in admissions when the children received OPV-2 and OPV-3 at 3 and 4 years of age (Sørup et al., 2015).

3.5. Smallpox Vaccine

Two cohort studies from urban and rural areas of Guinea-Bissau have examined the correlation between the number of smallpox vaccination scars and subsequent mortality (Aaby et al., 2006; Jensen et al., 2006) (Supplementary Fig. 4). As seen in Table 3, having a smallpox vaccination scar was associated with significantly lower mortality. This survival benefit occurred 20–25 years after smallpox was eradicated and vaccinations were stopped. In the urban study, there was a significant trend for larger reduction in mortality with increasing number of smallpox vaccination scars (Aaby et al., 2006). Though not statistically significant, the trend was similar in the smaller rural study (Jensen et al., 2006).

4. Discussion

4.1. Main Observations

Revaccination with MV, BCG, OPV and smallpox was associated with strong reductions in overall mortality compared with having received one dose only. The effect is not explained by specific disease-protection: The vaccine efficacy of MV is so high that very few children would die of

Table 2
Trial with alternate allocation to BCG or no BCG at birth, at 1 year and at 3 years of age. Alger, 1935–1952 (Sergent et al., 1954).

Age	Mortality risk (deaths/person-years)[a]		Mortality rate ratio (BCG/no BCG)
	Randomised to BCG-vaccination	Randomised to no BCG vaccination	
1st year of life (before and after enrolment)	20.4% (4121/20167)	21.0% (4008/19092)	0.97 (0.93–1.02)
2nd-3rd year (after first revaccination of BCG group)	5.9% (1721/29310)	7.1% (1919/27233)	0.83 (0.78–0.89)
4th–5th year (after second revaccination of BCG group)	1.0% (243/25444)	1.8% (414/23034)	0.53 (0.45–0.62)

[a] The paper indicated the number of children under observation at the beginning of each year. It has been assumed that all were followed for 365 days.

Table 3
Number of smallpox vaccination scars and subsequent mortality.

Study (reference)	Comparison (deaths/persons)	Adjusted mortality rate ratio (MRR, 95% CI)	MRR (95% CI) by number of scars	Testing trend by number of scars
Bissau city (Aaby et al., 2006), Guinea-Bissau (1998–2002), N = 1893 aged 25+ years	Vaccinia scar (75/1187) vs no scar (60/500)	0.60 (0.41–0.87) F: 0.51 (0.30–0.84) M: 0.72 (0.42–1.24)	1 scar: 0.65 (0.40–0.91) 2 scars: 0.54 (0.29–0.97) 3+ scars: 0.44 (0.13–1.46)	Trend for decreasing MRR with number of scars: MRR = 0.73 (95% 0.56–0.95)
Rural area (Jensen et al., 2006), Guinea-Bissau (2003–2006), N = 367	Vaccinia scar (29/251) vs no scar (9/35)	0.22 (0.08–0.61) F: 0.19 (0.06–0.57) M:0.40 (0.04–3.74)	1 scar: 0.24 (0.09–0.68) 2+ scars: 0.14 (0.03–0.56)	

measles after one dose of MV. The effect of BCG revaccination is too large to be explained by better prevention of TB. Guinea-Bissau has had no polio infection for the last 15 years so the beneficial effects of OPV revaccination are clearly nonspecific. Likewise, the reduced mortality after repeated smallpox vaccination is entirely nonspecific since smallpox has been eradicated. The observation that revaccination is associated with strong mortality reductions challenges the current understanding of vaccines as mediators of specific protection only.

4.2. Strength and Weaknesses

The literature is sparse and most studies stem from our group. Almost all studies, however, were conducted prior to the formulation of our hypothesis, and it is noteworthy that we were able to re-visit existing studies and consistently find support; there was no data which contradicted the hypothesis. The data for MV, BCG and OPV was mainly from RCTs or natural experiments so it seems unlikely that selection bias and inherent differences between those who received two doses or one dose can explain differences in mortality reduction. Since the children were randomised at the time of the first vaccination, they may no longer have been perfectly balanced at the time of the second vaccination from which we compared the effect of having received two doses of MV vaccine versus only one dose. Since the intention-to-treat and the per-protocol analyses gave similar results (Aaby et al., 2010) it is unlikely that such imbalances have had a major impact on the estimates.

The studies of smallpox vaccinations were not randomised. In Guinea-Bissau, smallpox vaccines were provided in campaigns, and it seems unlikely that the potential determinants for being present at several vaccinia campaigns in childhood could explain the observed large differences in mortality risk. A smallpox scar is only a marker of smallpox vaccination but smallpox vaccine was a very effective vaccine, with long lasting immunity which caused a characteristic scar in almost all vaccinated individuals; we have previously found good correlation between records of smallpox vaccination and presence of a detectable scar (Aaby et al., 2006). Though it is surprising that smallpox vaccination should have an effect so many years after smallpox was eradicated, we have found that it had strong beneficial NSEs also in Denmark (Reickmann et al., 2016). (The Danish data only had information on the primary vaccination before school entry and is therefore not included in the present analysis of revaccinations).

4.3. Interpretation

WHO recently reviewed the evidence and recommended further research into NSEs (Higgins et al., 2014; Strategic Advisory Group of Experts on Immunization, 2014). Emerging immunological studies have shown that beneficial NSEs of vaccines can be due both to T-cell cross-reactions and training of the innate immune system (Kleinnijenhuis et al., 2012; Benn et al., 2013). For example, BCG induces epigenetic modulations that reprogram monocytes to a stronger

response to unrelated antigens (Kleinnijenhuis et al., 2012). In hospital studies from both Guinea-Bissau and Denmark, MV and OPV have provided the strongest nonspecific protection against lower respiratory infections (Sørup et al., 2014; Sørup et al., 2015; Veirum et al., 2005; Martins et al., 2014).

Revaccination has mainly been studied in relation to whether it boosts the antibody response. The idea of examining NSEs after revaccination with live vaccines came from several observations: First, we had seen that giving early MV versus later MV was associated with reduced overall mortality (Aaby et al., 2015). Second, we observed that the beneficial effect of an early measles immunization was strongest in children who had maternal antibodies at the time of first vaccination (Aaby et al., 2014). The latter finding led us to speculate that the formation of antibody-antigen complexes led to a particularly beneficial immune response (Aaby et al., 2014). The natural deduction was then that vaccination in the presence of the child's own vaccine-induced or illness-induced antibody would be beneficial.

We were able to verify that revaccination led to a strong beneficial nonspecific effect on overall survival, even though revaccinations should have a very limited impact on overall mortality. These initial observations, derived deductions and verifications, add up to one unifying hypothesis: vaccination with a live vaccine in the presence of pre-existing immunity enhances the beneficial NSEs of the live vaccine. This hypothesis is supported by data from four different live vaccines and has thereby produced a previously unrecognized pattern which has the potential to explain contradictions, resolve enigmas and raise questions which were never asked before (Kuhn, 1962).

For example, the literature regarding the decline towards the Millennium Development Goal 4 (MDG4) to reduce child mortality with 2/3 between 1990 and 2015, does not consider an effect of general vaccination campaigns, but ascribes the decline to improvement in health services (Amouzou et al., 2012). After a civil war, numerous military coups, political instability and donor fatigue there is nothing to suggest that health services have improved dramatically in Guinea-Bissau in the 2000s. Nonetheless the country experienced a large decline in mortality in the 2000s and actually reached the MDG4. The repeated national OPV and MV campaigns conducted since 1999 may have had major effects in terms of reducing general mortality (Fisker et al., 2015; unpublished data; authors).

The dramatic beneficial effect of revaccination with live vaccines should be seen in the context that some non-live vaccines, including DTP, may be associated with increased mortality, particularly for girls (Aaby et al., in press; Benn and Aaby, 2012). Hence, a better understanding and control of both beneficial and deleterious NSEs could lead to major improvements in health.

4.4. Immunological Mechanisms

The most likely explanation for the observed beneficial NSEs of revaccination with live vaccines is that the immunising antigen forms complexes with pre-existing antibody and these determine a

particularly beneficial nonspecific immune response providing protection against a range of infectious diseases. Infants given early MV in the presence of maternal antibody had a marked survival advantage that only became apparent after a booster dose of MV was given at 9 months of age (Aaby et al., 2014). Animal studies have shown that a previous viral infection may lower viral replication of a subsequent heterologous viral infections due to stimulation of T-cell cross reactivity (Selin et al., 2006). We suggest such T-cell reactivity is stimulated by antigen-antibody complexes following a booster dose of MV or OPV, which subsequently attenuates or protects against a range of viral infections. A human study has shown that BCG vaccination induces strong antibody responses and these were further enhanced after a revaccination with BCG 6 months later (De Valière et al., 2005). Pre-existing antibodies enhanced the internalization of BCG by neutrophils and monocytes (De Valière et al., 2005). In mice, pre-opsonization of BCG with anti-BCG-IgG potentiated phagocytosis by macrophages and led to increased NO production (Silva et al., 2013). Intriguingly, BCG has been shown to induce NOD2-dependent epigenetic modifications of monocytes which lead to increased innate immune responses, so-called "trained innate immunity" (Kleinnijenhuis et al., 2012). This effect, though still partially present after a year (Kleinnijenhuis et al., 2014), may wane over time. Thus, the beneficial effect of BCG revaccination may represent increased internalization of BCG into monocytes, increased NOD2 activation and NO production, mediating even stronger epigenetic effects leading to increased trained innate immunity. Interestingly the effects of BCG immunotherapy against bladder cancer are stronger and more beneficial in patients who had received BCG vaccination prior to treatment initiation (Biot et al., 2012).

The exact immunological mechanisms underlying this phenomenon obviously need to be explored. However, the consistency of the epidemiological findings indicates that such mechanisms do exist. We need to identify them.

4.5. Implications

The hypothesis that vaccination with a live vaccine in the presence of existing immunity is associated with major beneficial effects has major implications for our understanding of vaccines and the way they may modulate the immune system and induce NSEs. We have provided a few examples of immediate deductions and how they were tested. But there are many other deductions which need to be examined: First, it may be beneficial to provide live vaccines earlier when maternal antibody is more likely to be present. For MV (Aaby et al., 2015), OPV (Lund et al., 2015) and BCG (Storgaard et al., 2015) we have already found that earlier vaccination confer stronger beneficial NSEs. Second, it might be beneficial to vaccinate women of fertile age with live vaccines to increase the amount of maternal antibody they transfer. Third, it might be beneficial to give a live vaccine together with antibody against the target disease. This could be tested by adding a small amount of measles immunoglobulin to MV given at 9 months of age; the hypothesis being that children who received immunoglobulin with MV had improved health compared with children who received MV alone (Aaby et al., 2010; Aaby et al., 2014). Fourth, it may be beneficial to provide second doses of BCG and MV. Since GAVI is currently promoting a second measles-containing vaccine in the second year of life, this supposition could be tested in a RCT.

The hypothesis has major implications for immunization programmes. If true it implies that much could be gained by restructuring immunization schedules to benefit from revaccinations.

Worryingly, several expected changes are likely to reduce the frequency of revaccinations. With decreasing incidence of measles infection, the national measles vaccination campaigns, which have been frequent since the 2000s, may be scaled down or stopped. Furthermore, OPV campaigns will soon be stopped and OPV will be replaced with inactivated polio vaccine (IPV). Both changes may result in increased child mortality (Aaby et al., 2007), so it is urgent to test the potential nonspecific benefits of revaccination with these vaccines before they are discontinued.

5. Conclusion

Revaccination with live vaccines enhances the beneficial NSEs for morbidity and mortality. This observation challenges the single-disease-prevention paradigm underlying the current programmes by showing much larger reductions in mortality than can be explained by protection of those who did not respond after the first vaccination. The hypothesis has generated testable deductions which if verified could lead to major changes in our understanding of vaccines and in the organisation of vaccination programmes.

Contributions

CSB and PA developed the hypothesis (Aaby et al., 2014) and all authors further developed the idea and reviewed the literature.

Conflict of Interest

Nothing to declare.

Ethical Approval

All the more recent studies had ethical approval from the Danish Central Ethical Committee and the Guinean Ministry of Health's Research Coordination Committee.

Role of the Funding Source

The funding agencies had no role in the study design, data collection, data analysis, data interpretation, or the writing of the paper.

Data Sharing

Data available upon request.

Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.ebiom.2016.07.016.

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