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Research Paper

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

Christine S. Benn [a,b,c], Ane B. Fisker [a,b], Hilton C. Whittle [d], Peter Aaby [a,b,*]

[a] Bandim Health Project, Indepth Network, Apartado 861, Bissau, Guinea-Bissau
[b] Research Centre for Vitamins and Vaccines (CVIVA), Bandim Health Project, Statens Serum Institut, Artillerivej 5, 2300 Copenhagen S, Denmark
[c] OPEN, Odense Patient data Explorative Network, Odense University Hospital/Institute of Clinical Research, University of Southern Denmark, Denmark
[d] The London School of Hygiene and Tropical Medicine, Keppel Street, London, UK

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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

* Corresponding author at: Bandim Health Project, Indepth Network, Apartado 861, Bissau, Guinea-Bissau.
E-mail address: p.aaby@bandim.org (P. Aaby).

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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.