



Editorial

The non-specific effects of vaccines and other childhood interventions: the contribution of INDEPTH Health and Demographic Surveillance Systems

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Accepted 3 April 2014

Abstract

Most childhood interventions (vaccines, micronutrients) in low-income countries are justified by their assumed effect on child survival. However, usually the interventions have only been studied with respect to their disease/deficiency-specific effects and not for their overall effects on morbidity and mortality. In many situations, the population-based effects have been very different from the anticipated effects; for example, the measles-preventive high-titre measles vaccine was associated with 2-fold increased female mortality; BCG reduces neonatal mortality although children do not die of tuberculosis in the neonatal period; vitamin A may be associated with increased or reduced child mortality in different situations; effects of interventions may differ for boys and girls. The reasons for these and other contrasts between expectations and observations are likely to be that the immune system learns more than specific prevention from an intervention; such training may enhance or reduce susceptibility to unrelated infections. INDEPTH member centres have been in an ideal position to document such additional non-specific effects of interventions because they follow the total population long term. It is proposed that more INDEPTH

member centres extend their routine data collection platform to better measure the use and effects of childhood interventions. In a longer perspective, INDEPTH may come to play a stronger role in defining health research issues of relevance to low-income countries.

Key words: BCG, childhood interventions, DTP, INDEPTH Network, measles vaccine, non-specific effects of vaccines

Key Messages

- Interventions with vaccines and vitamin A have non-specific effects on child survival, i.e. effects not explained by prevention of specific diseases or deficiency.
- Live vaccines have beneficial effects which are more important than the specific prevention. Inactivated vaccines may have negative effects particularly for girls.
- Non-specific effects often differ for girls and boys.
- INDEPTH centres are in an ideal position to monitor non-specific effects of common childhood interventions.

Introduction

Immunization has been advocated as the most successful public health intervention to improve child survival. Each year, immunization averts an estimated 2–3 million deaths from diphtheria, tetanus, pertussis (whooping cough) and measles. However, there is now strong evidence that vaccines have substantial non-specific (heterologous) effects in children in high-mortality regions, i.e. by changing mortality from infections unrelated to the vaccine-targeted infections.^{1–5} As a consequence, the World Health Organization's (WHO's) Strategic Advisory Group of Experts (SAGE) on Immunization has recently initiated a review of the non-specific effects (NSEs) of BCG, diphtheria-tetanus-pertussis (DTP) and measles (MV) vaccines.

The NSEs have a large potential to improve child health and survival and may eventually lead to major evidence-based changes in vaccination and vitamin A supplementation (VAS) policies. Most research on NSEs has had to be observational rather than experimental because it is not considered ethical to perform randomized trials (RCTs) of interventions already recommended by WHO.^{1,2} Observational studies are usually considered insufficient to prove unequivocally that vaccines have NSEs.^{1,2,6,7} However, the NSEs were initially detected in RCTs of high-titre measles vaccine (HTMV) conducted at the Bandim and Niakhar INDEPTH member centres.^{8–10} The present paper reviews briefly the evidence for NSEs of vaccines and other childhood interventions as well as the role of the INDEPTH network in determining the consistency of observation on the NSEs. Furthermore, RCTs of measles vaccine (MV),³

BCG^{4,5} and inactivated vaccines have been conducted under special circumstances in some INDEPTH centres.

The Bandim Health Project (BHP) group and a few other INDEPTH member centres have tested the hypothesis that vaccines may have non-specific effects (NSE) as shown in Table 1.

High-titre measles vaccine (HTMV)

HTMV was tested in RCTs in the late 1980s, comparing HTMV at 4–5 months of age with standard MV at 9 months of age. The HTMV was protective against measles infection and was recommended by WHO in 1989 for general use in low-income countries with a high incidence of measles infection.^{8–10} A meta-analysis of studies from Bissau, Gambia and Senegal showed that this vaccine was associated with 33% increased mortality rate between 4 and 60 months of age.¹¹ The excess mortality was among girls, whereas the new vaccine compared with the traditional MV had no differential effect on survival for boys. These results were subsequently confirmed in RCTs from Sudan and Haiti, and WHO withdrew the 1989 recommendation for HTMV in 1992.¹⁰ These RCTs showed:

- first, that a fully protective vaccine can have negative NSE
- second, that these effects can be sex-differential and
- third, that NSE can have major effects on child mortality patterns; had the vaccine not been withdrawn, a 33% excess mortality rate between ages 4 and

Table 1. Observations on non-specific effects of childhood interventions tested at INDEPTH member centres

Observations	Supported by studies from INDEPTH member centres ^a	Estimated size of effect
Negative effect of high-titre measles vaccine (HTMV)	Bandim, ⁸ Niakhar ^{9–11}	Meta-analysis: ¹¹ HTHV increased the mortality rate by 33% compared with controls
MV has beneficial non-specific effects not explained by prevention of measles infection	Bandim, ^{1,3} Bandafassi, ¹³ Niakhar, ¹⁴ Farafenni, ¹⁵ Navrongo ¹⁶ , Matlab ¹⁷ , Ballabgard, ¹⁸ Vadu ¹⁹	Observational studies and RCTs: ^{3,20} standard MV compared with unvaccinated controls reduces the mortality rate by 30–50% as long as DTP is not given with or after MV
MV has a better effect for girls than for boys	Bandim, ^{21,22} Niakhar, ¹⁴ Bandafassi, ¹³ Farafenni, ¹⁵ Navrongo (unpublished)	Among MV-vaccinated children, girls have 30–40% lower mortality rate than boys as long as DTP is not given after MV ^{16,17,30}
BCG has beneficial non-specific effects not explained by prevention of tuberculosis	Bandim, ^{4,5,23} Vadu ¹⁹	RCTs: ^{4,5} BCG-at-birth compared with delayed BCG reduces the neonatal mortality rate by 40%
OPV	Bandim ²⁴	OPV campaign associated with lower mortality rate among the youngest children ²⁴
Vaccinia	Bandim ^{25–28}	Observational studies: ^{25,26} having a smallpox vaccination scar associated with 40% lower mortality rate than not having a scar
DTP has negative non-specific effects, particularly for girls ^b	Bandim, ^{2,21,22,29} Niakhar, Farafenni, ¹⁵ Navrongo, ³⁰ Vadu, ¹⁹ Ballabgard ³¹	Observational studies: ² DTP-vaccinated girls compared with DTP-unvaccinated girls have at least 50% higher mortality rate until a different vaccine is received
DTP administered with MV or after MV is associated with higher mortality than MV administered alone	Bandim, ² Niakhar, Navrongo (unpublished), Vadu, ¹⁹ Matlab ³²	Observational studies and RCTs: ^{2,10} DTP and other inactivated vaccines after MV compared with MV alone as most recent vaccine is associated with 50–100% higher mortality rate among girls but made little difference to boys
BCG administered with DTP reduces the negative effects of DTP	Bandim, ^{33,34} Niakhar, ³³ Vadu, ¹⁹ Matlab (unpublished)	Observational studies: ^{19,31,34} first, girls have 30–40% lower mortality rate than boys when BCG is administered with DTP1; and second, the mortality rate before 9 months of age (i.e. before MV) is lower if the vaccination schedule started with BCG + DTP1 rather than with the WHO-recommended schedule of BCG and then DTP1
Vitamin A supplementation (VAS) interacts with vaccines	Bandim, ^{35–37} Navrongo ³⁸	Observational studies and RCTs: VAS may enhance the beneficial effects of vaccines but also amplify the negative effects of some vaccines

^aThese centres are located in Guinea-Bissau (Bandim), Senegal (Niakhar, Bandafassi), The Gambia (Farafenni), Ghana (Navrongo), India (Ballabgard, Vadu) and Bangladesh (Matlab).

^bStudies from Niakhar⁴⁰ and Matlab³² found beneficial effect of DTP. However, these studies did not take into consideration that nearly all children had received BCG and DTP simultaneously even though the official WHO recommendation is to give BCG first, at birth, and then DTP later. The effect of combined BCG and DTP is quite different in reducing female mortality. When this is taken into consideration, the data from Niakhar and Matlab (unpublished) no longer contradict the principle that DTP alone is associated with increased female mortality.

60 months would at the time have meant at least an additional half-million female deaths annually, in Africa alone.

Live vaccines: measles vaccine

The main effect of MV on child survival may be NSE; in other words, the NSE of MV may be considerably more important for child survival than the specific prevention of

acute measles infection. These beneficial effects have been found both in observation studies and in RCTs.^{1,3,17,20} In a RCT comparing early MV vs DTP3, MV was associated with a marked reduction in the risk of hospital admission for respiratory infection.⁴¹ The beneficial effect of MV is much stronger for girls than for boys. The beneficial effect for MV-children compared with measles-unvaccinated children is particularly strong when measles is given before 12 months of age. In the four studies reporting data for children

both below and above 12 months of age, the reduction in mortality before 12 months was 74% (51–86%) but only 29% (8–46%) after 12 months of age.^{12,42–44}

Why should earlier vaccination be better than later vaccination? In Guinea-Bissau, early MV in the presence of maternal measles antibodies had a much stronger beneficial effect on child survival than when MV was provided in the presence of no maternal antibodies.⁴⁵ These observations clearly contrast with the current MV policy, which is based on the idea that the production of measles-specific antibodies (seroconversion) is best when maternal antibodies have disappeared; and it is therefore recommended to delay MV to after 12 months of age, when measles infection has come under control. To the extent MV has beneficial NSEs, delaying MV will increase child mortality.

Furthermore, MMR (measles-mumps-rubella) used in high-income countries may have similar beneficial effects. In a study of 475 000 Danish children, MMR was associated with a significant lower risk {14% [95% confidence interval (CI): 12–16%]} of hospital admission compared with children who still had DTaP-IPV-Hib3 as their most recent vaccination. If the inactivated DTaP-IPV-Hib3 was given after MMR, the risk of admission increased by 62% (29–105%).⁴⁶ Also in Denmark, the protective effect against hospital admission was strongest for respiratory infections.

Live vaccines: BCG, OPV, vaccinia and others

Several observational studies suggest that BCG has beneficial NSEs.^{29,47} It has been possible to test the effect of BCG in a RCT in low-birth-weight (LBW) children because they often do not receive BCG-at-birth; in two RCTs in Guinea-Bissau, children randomized to BCG-at-birth had a marked reduction in the neonatal mortality rate.^{4,5} Furthermore, reanalysis of BCG trials from the

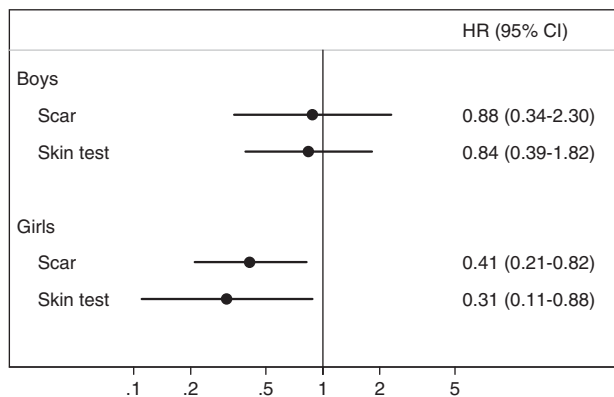


Figure 1. Hazard ratios (HR) for BCG scar-positive vs scar-negative individuals and for tuberculin-skin-test (TST)-positive vs TST-negative individuals among BCG-vaccinated children in urban Guinea-Bissau, 2000–02.²³

USA and the UK in the 1940–50s, in which prevention of TB was the main outcome, showed that BCG vaccination was associated with a 25% reduction in non-TB and non-accident deaths.⁴⁸ Among the children vaccinated with BCG, those having a scar or a positive TST test have much lower mortality than those who have not responded (see [Figure 1](#)).

Oral polio vaccine (OPV) is difficult to study because it is WHO policy to give OPV with DTP. However, it seems that OPV may have beneficial NSE.^{24,49} When OPV was introduced in the 1960s in Chile, a virologist noted that OPV enhanced the interferon-gamma response and reduced the risk of other entero-pathogens and diarrhoeal deaths.⁴⁹ If OPV has beneficial NSEs, this has important consequences because most global health researchers want to stop OPV and replace it with inactivated polio vaccine (IPV). The only reason this has not happened yet is that IPV is much more expensive than OPV.

Inactivated vaccines: DTP, HBV and IPV

There is only one study of what happened when DTP was introduced in low-income countries 2–3 decades ago.⁴⁷ As seen in [Figure 2](#), the mortality rate was 2-fold higher for DTP-vaccinated compared with DTP-unvaccinated

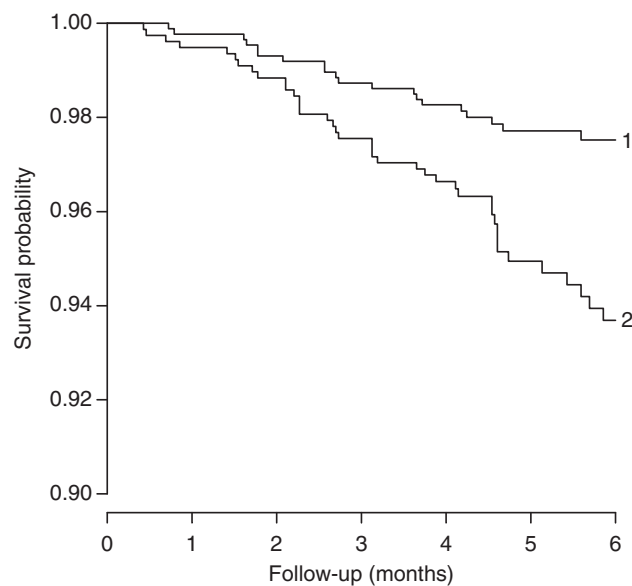


Figure 2. Kaplan–Meier survival curves for unvaccinated children and recipients of DTP in rural areas of Guinea-Bissau, 1984–87.⁴⁷ Note: the graph shows mortality during 6 months of follow-up for DTP-vaccinated (trace 2) and DTP-unvaccinated (trace 1) children aged 2–8 months at the initial visit to their villages. Unvaccinated children received no DTP because they were travelling on day of vaccination, were too sick to get vaccinated and had lower nutritional status than DTP vaccinated children, or were visited on days when the team for logistic reasons had no vaccines. The adjusted mortality rate ratio for DTP-vaccinated (trace 2) vs DTP-unvaccinated (trace 1) children was 1.92 (1.04–3.52).

children when DTP was introduced in rural areas of Guinea-Bissau in the 1980s. The DTP-unvaccinated children were travelling or were too sick to get vaccinated. Hence, if anything, the DTP-unvaccinated children should have had a higher mortality rate than the healthier DTP-vaccinated children.⁴⁷ There is consistent evidence that DTP given after MV is associated with increased female mortality. Five RCTs in the 1980s had a cross-over design in which the children were randomized at 4–5 months of age to receive early MV or a control vaccine (inactivated).¹¹ At 9–10 months of age, the children were crossed over: the control group received the standard MV and the early MV group received the control vaccine (DTP, IPV or meningococcal vaccine). Hence, these trials compared inactivated vaccine (after MV) vs MV as most recent vaccination from 9 months to 3–5 years of age. The overall effect was a 38% (95% CI: 5–83%) higher mortality rate not related to prevention of measles infection since all children had been vaccinated against measles infection; the negative effect was found only among girls who had 89% (27–180%) higher mortality when they had received inactivated vaccine after MV.

Vitamin A supplementation (VAS)

VAS is assumed to be associated with a 25% reduction in child mortality due to the prevention of vitamin A deficiency.⁵⁰ However, VAS appears to be particularly good when given with live vaccines like BCG and MV but potentially having negative effects when given with inactivated vaccines like DTP. RCTs of neonatal VAS have found a significant negative effect of 41% increased mortality rate after VAS for girls whereas the effect tended to be beneficial among boys.^{35,36} The negative effect for girls only started when the children received DTP at around 6 weeks of age.³⁷

These trials have showed that effects can be sex-differential and that VAS can affect the mortality pattern long after the initial supplementation. Hence, VAS primes the immune system in more general ways, which were not taken into consideration when the WHO policy to provide vitamin A with vaccines was formulated. In a recent RCT testing of the effect of providing VAS with vaccines, there was no overall benefit of VAS but results were significantly different for boys (harmful) vs girls (beneficial). Recently, the *Lancet* published a cluster-randomized trial of bi-annual VAS campaigns to 1 million children in India; the study found only a 4% (–3–11%) effect of VAS.⁵¹ Given these results, there should be a clear interest in further examining for which sex and with which vaccines VAS may have a beneficial effect.

Sex-differential effects

In global health there are virtually no studies of boys and girls, everything is ‘children’. However, as indicated above, once we ask the question there are very often marked sex-differential effects. Live vaccines like MV, vaccinia and probably also BCG tend to be more beneficial for females than for males, whereas inactivated vaccines like DTP, IPV and HBV have a negative effect which is also stronger for girls.^{2,15,52,53} Strong sex-differential effects have been found for vitamin A and also for other micronutrients.⁵⁵ This may not be inherent to the micronutrients but more a question of the micronutrients amplifying the NSE of the vaccines.

By only looking at ‘children’ we may find no effect, whereas it is in reality a beneficial effect for one sex and a negative effect for the other sex. A focus on sex differences could also suggest that in some situations the optimal solution for both sexes might be that they are treated differently according to their genetic constitution.

Interactions

A recurrent theme in these studies has been that interventions may interact. Changing the sequence of vaccinations may change the effect completely—as when early HTMV was associated with increased female mortality because the children got inactivated vaccines after HTMV. Giving a live and inactivated vaccine at the same time can also change the effects completely. Adding VAS or micronutrients can amplify the effect of the intervention. Something that was once a good intervention may no longer be so if new interventions are added. There are likely to be many other interactions with immune-enhancing interventions or conditions which have not been explored. For example, we have very often found that effects differed between the dry and the rainy season.⁴¹

Therefore, it seems important to test the possible interactions with the most likely other interventions. INDEPTH is in a unique position to do so and to explore the interactions, because they follow the whole population and could document all the interventions.

Potential biological mechanisms

The perceived lack of biological plausibility has been a major obstacle in recognizing and further investigating non-specific effects. Hence, it is important to consider immunological mechanisms that may mediate such effects. Novel insights in understanding both the adaptive immune system and innate immunity has provided arguments that exposure to a pathogen leads not only to specific immunological memory (represented by memory T- and B-cells),

Box 1 The focus on NSEs of interventions has provided several lessons for future research and policy making, as follows.

- The NSEs are usually more important for overall morbidity/mortality than the targeted effects.^{1–5}
- Though we always plan for beneficial effects in health, we may actually produce the opposite.^{2,8–10,24,47,49}
- Effects are often sex-differential, emphasising that male and female immune systems differ and the results of their training from interventions may therefore differ.
- Since different interventions train the same immune system, the interventions may interact in unpredictable ways as when vitamin A supplementation (VAS) increases female mortality.^{35,37,38} As a consequence, something which was shown to be effective when first introduced, e.g. VAS when tested in the 1980s, may later lose its effect due to interactions with other interventions.

but also to T-cell mediated cross-reactivity, as well as training of the innate immune system.⁵⁵

T-cell mediated cross-reactivity—‘heterologous immunity’

Each individual has a unique lifelong history of infections and vaccinations, and each exposure leaves an imprint on the immune system that can affect future innate and adaptive immune responses to new pathogens.⁵⁶ This concept of ‘heterologous immunity’ could explain the observation that vaccines may have non-specific effects, because the vaccines encode antigens that cross-react with other pathogens. In some scenarios, beneficial heterologous immunity can provide partial protective immunity and be the difference between life and death. In other scenarios, detrimental heterologous immunity can lead to severe immunopathology. Hence, T-cell mediated heterologous immunity provides a plausible biological mechanism by which vaccines may affect the immune response to a subsequent unrelated infection and also explains how, in certain situations, a vaccine could have detrimental effects on the outcome of secondary infections.

Training of the innate immune system

Activation of cross-reactive T-cell responses, as seen in heterologous immunity, might explain some of the non-specific effects of vaccination. However, there is also evidence suggesting that the altered resistance to subsequent infections after vaccination or infection with an unrelated pathogen cannot be attributed to adaptive immune responses alone, and that innate immune responses result in a heightened state of activation. Vaccination of volunteers with BCG showed that in addition to induction of specific T-cell responses, non-specific innate immune responses to unrelated pathogens were also increased for at least 3 months after the vaccination.⁵⁷ This ‘trained immunity’

was associated in humans with epigenetic reprogramming of monocytes at the level of H3K4 trimethylation. Hence, these data suggest a picture in which the innate immune system is characterized by adaptive features, and can be trained to provide a partial protection against infection independent of the classical T- and B-cell adaptive immunity.

These immunological mechanisms do support the biological plausibility by demonstrating that the encounter with one pathogen may alter the immune response to subsequent completely unrelated pathogen challenges, and this may result in improved outcomes, but also at times be detrimental. So far this has been demonstrated most convincingly for BCG.

Conclusion

Observational studies have been consistent in showing NSEs in spite of many different study designs being used, and several key observations have been confirmed in RCTs.^{3–5,8,9,35,36} The epidemiological data indicate that vaccines have non-specific effects which may be just as important, or even more important, for childhood survival than their specific effects (Box 1). Existing studies suggest a general pattern, namely that the live vaccines (BCG, measles vaccine, OPV and vaccinia) are associated with beneficial non-specific effects, leading to reduced all-cause mortality, whereas the inactivated, alum-adjuvanted DTP vaccine is associated with increased susceptibility to other unrelated infections, particularly in females.²

The INDEPTH Network has already played a key role in testing the NSE hypotheses. This role is likely to be even more important in the future. So far there are no studies of the possible NSEs of the many new vaccines, including rotavirus vaccine, PCV, yellow fever, conjugated meningococcal vaccine, or malaria vaccine. Only one study²⁴ has examined the possible NSEs of vaccination campaigns with OPV or MV. Studies at INDEPTH member centres

may help to explain how the immunological profile can change so quickly between different vaccines, why live vaccines have beneficial effects and inactivated vaccines have negative effects, and why the reactions of boys and girls differ. Furthermore, if the NSEs are accepted by the global health community, there will be a need to conduct many new trials to guide global policies. For example, multi-centre community trials of OPV and MV vaccination campaigns should clarify whether these trials have played a role in the major reductions in child mortality which have occurred during the last 10–15 years. Trials to assure that BCG is delivered at birth and not much later (by 4 weeks of age), as is current practice in many African countries, could help reduce neonatal mortality; trials may examine whether co-administration of BCG and DTP reduces the negative effect of DTP as suggested by all the observational studies; trials of not giving DTP with or after MV, even though the child may be missing some doses of DTP, could help establish the principle that live-vaccine-last is the best general vaccination schedule; and trials should also test the hypotheses that vaccination in the presence of maternal antibodies and boosting with live vaccines enhances the beneficial NSEs.

Funding

The INDEPTH vaccine network was supported by the Danish Council for Development Research, the European Union FP7 support for OPTIMUNISE (grant: Health-F3-2011-261375) and the Danish National Research Foundation (DNRF108). P.A. holds a research professorship grant from the Novo Nordisk Foundation. INDEPTH funded the workshop which formed the basis of this paper. O.S. and J.B.O.E. are funded by core support grants from Sida, Wellcome Trust, William & Flora Hewlett Foundation.

Conflict of interest: Osman Sankoh is the Executive Director of the INDEPTH Network; Jacques BO Emina is the Science Programme Manager of the INDEPTH Network.

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Commentary: Potential implications of non-specific effects of childhood vaccines

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International Journal of Epidemiology, 2014, 653–654
doi: 10.1093/ije/dyu109



The World Health Organization states that: ‘A vaccine is a biological preparation that improves immunity to a particular disease. A vaccine typically contains an agent that resembles a disease-causing microorganism, and is often made from weakened or killed forms of the microbe, its toxins or one of its surface proteins. The agent stimulates the body’s immune system to recognize the agent as foreign, destroy it, and ‘remember’ it, so that the immune system can more easily recognize and destroy any of these microorganisms that it later encounters’.¹ This statement is in conformity with the usual scientific and lay perceptions that vaccines have only specific disease-protective effects. However, historically it has been suspected that *Vaccinia*² and BCG vaccination³ confer protection against non-targeted infectious diseases. Emerging evidence suggests that vaccines can positively or negatively affect the resistance to other infectious diseases—the so-called non-specific effects of vaccines or non-specific immunomodulation by vaccines. The bulk of this evidence has been generated from Guinea-Bissau by researchers led by Peter Aaby. The current status of global evidence has been summarized by them in this issue of *IJE*⁴ and elsewhere.⁵ On this basis, they also suggest a new definition of vaccines: ‘A vaccine is a biological preparation that improves immunity to a particular disease and at the same time, may alter the general level of resistance towards unrelated pathogens in the recipient’.⁵

If this perception is indeed true, it may have important public health implications especially in relation to child survival in high-mortality settings. The relevant findings are: (i) BCG and measles vaccinations reduce mortality from non-targeted infectious diseases till the child receives an inactivated vaccine; (ii) whole cell DTP vaccine increases mortality from infections other than diphtheria, tetanus and pertussis until a live vaccine is given; the effect is stronger in females than in males; and (iii) live and killed vaccines may interact to produce good or bad non-specific effects when given simultan-

ously or when the sequence is changed, and the effect may be modified by Vitamin A.⁶ There may well be potential implications for high-income countries, if the following observations are confirmed: (i) in Danish children, rates of hospital admission for any infection were lower in children most recently vaccinated with live MMR vs those most recently receiving inactivated DTaP-IPV-Hib;⁷ and (ii) BCG vaccination had a small protective effect against development of asthma.⁸

This accumulated evidence has not influenced global immunization policy, because of epidemiological and biological plausibility concerns. A major criticism is that a substantial proportion of the evidence emanates from poor West African populations, with high child mortality risks reflecting their infectious disease burden, which evidence cannot be generalized to other settings with a different profile of target diseases. However, recently corroborative evidence has also emerged from other African and South Asian high-mortality settings; investigators from the Guinea-Bissau team were co-authors in some of these publications.⁴ Second, the bulk of the evidence is observational in nature (case-control and cohort studies), which is prone to residual confounding and other biases including selection, survival, attrition and missing data. Simultaneous administration of live oral polio vaccine (OPV) would have almost completely confounded the observations related to whole-cell DTP vaccine. The GRADE rating⁹ of this evidence is unlikely to be above low quality. The few supporting randomized and quasi-randomized trials (none in relation to DTP) are undoubtedly of better quality but are restricted to some regions only. Finally, incomplete understanding of biological mechanisms is a valid but not an indispensable concern. Exciting work has begun to unravel the possible biological mechanisms^{5,10,11} which could be related to cross-reactivity of the adaptive immune system with unrelated pathogens, and to training of the innate immune system through genetic reprogramming.