

Expecting the un-expected in child health

Research Policy Brief

Executive summary

This policy brief summarizes important new issues that have arisen from research, at the Bandim Health Project in West Africa, aiming at evaluating mother and child interventions in a long term perspective through continuous community household surveys. Many current health interventions in developing countries were introduced without a clear scientific support. Some childhood vaccines have positive while others have negative effects on child survival. None of the vaccines currently used in low-income countries were introduced after studies showing that the vaccine reduced overall mortality. These effects are furthermore completely dependent on sex and timing of the individual vaccines. Vitamin-A supplementation has diverging effects on mortality according to age, sex and vaccinations. It has become clear that health interventions should be better evaluated and monitored and there is an acute need for randomised trials to determine which immunizations schemes offer the best long term protection and whether girls should follow a different scheme from boys.

The Bandim Health Project

A Danish child health research site in Guinea-Bissau, West Africa, started in 1978. A central feature of the work in Guinea-Bissau has been the attempt to follow long-term consequences of various infections, health conditions and interventions through a routine demographic and health data collection system. However, many health problems take years to detect, to understand, or to find a solution. One of the key advantages of longitudinal studies is that it is possible to pursue the inconsistencies and contradictions letting one project follow another and maybe eventually find a solution. Good mapping, numbering of houses, census and regular checking of the whereabouts of the individuals are necessary to make long-term follow-up possible in a country with no civil registration.

Key points



1
Un-expected beneficial and adverse effects of vaccines



2
Un-expected cross-reaction between vitamin-A and vaccines



3
Boys and girls react differently to vaccines and may require separate immunization schemes



4
Health interventions should be evaluated for overall effect in community settings before introduction



5
Health interventions should be continuously monitored for adverse effects and interactions with other interventions



6
Independent longitudinal community surveys provide such information

Improving health?

It is becoming increasingly recognised that vaccines may induce non-specific immunomodulation having an effect on unrelated morbidity and mortality patterns. The development of current vaccination policies in both high and low-income countries has been based on documenting disease-specific immunity, disease-specific protection or both. However, the type of vaccine, the sequence or combinations of vaccines, and interaction with other concurrent factors which affect the immune system, e.g. other vaccines, season and vitamin A, may all lead to important **non-specific effects** on morbidity and mortality. These non-specific effects may be more important for overall health than the disease-specific protection. Importantly the non-specific effects often differ for boys and girls, a beneficial effect may apply only to one sex or effects may be beneficial for one sex and negative for the other sex.

Safe and efficient vaccines

To secure safe and efficient vaccines for infants and toddlers, it is necessary to control the nonspecific immune stimulatory effects of current vaccination policies. Modification of current vaccination schedules could have major beneficial effects on child survival in low-income countries. Allowing for the possibility that the optimal policy might differ for boys and girls could potentially lead to major improvement in child health. We therefore intend to test modifications in current immunisation schedules, using these trials to understand the immunological basis for the non-specific and sex differential effects. At the same time these trials are likely to lead to results which can be translated into clinical practice.

What has been found?

Sex-differential and non-specific effects of infant immunisations

Vaccines are the most cost-efficient interventions for reducing child mortality. The impact is assumed to be due to disease-specific protection. However, many observational studies and a few randomised clinical trials (RCT) suggest that these interventions in addition have beneficial or harmful *non-specific effects*, i.e. effects beyond the targeted prevention. In the early 1990s, research conducted by our group led to the withdrawal of high-titre measles vaccine (HTMV). The WHO had recommended this vaccine for low-income countries. Surprisingly HTMV administered at 4-5 months of age was associated with 2-fold higher mortality for girls whereas it might have had a slight beneficial effect for boys. HTMV was fully protective against measles infection; hence, the increase in mortality was a non-specific effect. The WHO withdrew the vaccine in 1992. Following this observation, we have examined the effect of the common childhood vaccinations. So far this research has suggested: Live vaccines including BCG, standard measles vaccine (MV), oral polio vaccine (OPV), and smallpox vaccine have beneficial non-specific effects. The effects are particularly good for girls. For example, in nearly all studies measles-vaccinated girls have lower mortality than measles-vaccinated boys. In contrast, inactivated vaccines including diphtheria-tetanus-pertussis (DTP), hepatitis B vaccine (HBV), and inactivated polio vaccine (IPV) are associated with little overall benefit and may even have a harmful non-specific effect for girls. For example, in all studies DTP-vaccinated girls have higher mortality than DTP-vaccinated boys. It seems counter-intuitive that live standard MV is associated with a beneficial effect in girls whereas live HTMV was associated with increased female mortality. However, we later discovered that excess female mortality was not due to HTMV *per se*. HTMV had been given at 4-5 months of age and most children got DTP after HTMV. The excess female mortality was only found among children who received DTP after HTMV, thus emphasising the consistent effects of live and inactivated vaccines. Hence, HTMV may have been withdrawn for the wrong reason, it still being a very good vaccine against measles infection.

BCG and vaccinia - small scar, large effect

Live vaccines, including BCG and measles vaccine, are associated with marked reductions in childhood mortality, which are not due to the prevention of measles or tuberculosis. The beneficial non-targeted effects have been strongest for girls. A BCG scar or a positive tuberculin reaction is associated with lower mortality among children. The current BCG vaccine has been in use for more than 80 years and seems to have a profound beneficial impact on child health leading to decreased child morbidity and mortality unrelated to protection against TB. In a study from rural Guinea-Bissau, BCG vaccination as opposed to no BCG vaccination was associated with a 45% reduction in infant mortality. In three prospective studies from Bissau there was an association between BCG scar and better infant survival. In two studies, a positive tuberculin reaction showed the same association (See figure). Nothing similar was found for responders to diphtheria-tetanus-pertussis (DTP) vaccine, and the effect could not be explained by protection against tuberculosis. BCG vaccination may induce non-specific immune-stimulation protecting against other infections than TB.

Vaccinia vaccination is associated with a strong immune stimulation and could have important non-targeted effects in an environment with high morbidity and mortality. In two studies from urban and rural Guinea-Bissau we have shown that vaccinia scar is associated with better survival particularly for women. We have pursued these observations in studies of specific morbidity in both Denmark and Guinea-Bissau. In a community study in Guinea-Bissau we found that having a vaccinia scar was associated with a lower prevalence of HIV-1 infection. In Copenhagen having a documented smallpox vaccination in the school health cards was associated with less asthma.

Gender and immune system

Gender aspects are the very essence of the proposal. Routinely, the same interventions and same treatment are used for boys and girls. Though everybody knows that male and female is different, there is virtually no study which has examined whether boys and girls reacted in the same way to health interventions in low-income countries. It has - fortunately - become politically correct to emphasise equality between boys and girls. However, if boys and girls have fundamental differences in their immune system, the same treatment might lead to strong differential effects. Ten years ago the high-titre measles vaccine was withdrawn because of two-fold increased female mortality among the recipient of this vaccine. It had no special effect among boys, if anything slightly lower mortality. Subsequently several other studies found standard measles vaccine to be much better for girls. Other routine vaccinations have sex-differential effects as well. In the pre-vaccination era in West Africa, there were no marked sex differences in child mortality in the age group in which vaccines are administered. Hence, our immunisation policies may have introduced sex difference where there were none. For example, two studies from Bissau and The Gambia, indicate that the female mortality rate is increased over the mortality of boys in the age group in which DTP is likely to have been the last vaccination (3-8 months), whereas female mortality is markedly reduced in the age group in which measles vaccine predominates (9-18 months of age).

Vaccines with vitamin A - an immunomodulatory interaction?

Vitamins, such as vitamin A and D are known to have immunomodulatory functions. Not only in *in vitro* studies but also in animal models, both 1,25-Dihydroxyvitamin D(3), but also retinoic acid have been shown to modulate dendritic cell and T cell function. More importantly, vitamin A supplementation (VAS) has been associated with a 23-30% reduction in mortality in randomised trials in low-income countries. For logistic reasons WHO recommends VAS at vaccination contacts after 6 months of age. VAS influences the specific immune response to vaccines. We have proposed the hypothesis that VAS also amplifies the non-specific effects of vaccines. Hence, VAS acts as an immunomodulator and may amplify the beneficial as well as the non-beneficial non-specific effects. The negative effect of VAS for girls only start around 2-3 months of age, the age group in which DTP is normally the main vaccination. Analysis of our data suggests that girls who received VAS at birth had two-fold higher mortality than placebo recipients once they received DTP while boys had no difference compared to placebo. Hence, the initial dose of VAS interact negatively in girls with a vaccine only given 2-3 months later. This perspective is being supported by several other studies showing that DTP and VAS may also interact negatively with respect to the incidence of measles, diarrhoea morbidity, growth, and blood VAS levels.

Health interventions - fashion or science?

The Bandim Health project has provided a basis for observing how health interventions are introduced as well as how they perform in a community setting interacting with other interventions. Health interventions are driven by donors with a need for short term results. One year primary health care is prioritised with free medicine, next year it is malaria prevention that is popular and then it is control of diarrhoeal diseases with oral rehydration that is important or a cholera epidemic calls for desperate health measures, then it is polio eradication campaigns because the vaccines were donated, vitamin-A in campaigns, then everybody needs impregnated bed nets, two drug malaria treatment last year and now HIV treatment. The health care sector is forced to focus on the current priorities of the donor organisations, while there is no national incentive to try and monitor efficacy and long-term consequences of these radical yearly changes. As a result we see a falling coverage of measles vaccination because health workers get the idea that this activity is no longer an important health activity or because the donors monitor DTP immunization instead of measles vaccination. In today's Western medicine it is impossible to introduce a pink child plaster without a placebo controlled double blind studies, but in Africa it is possible to turn entire health care systems upside down without the least bit of evidence or scientific background. Child vaccines produced and tested under the past reality of European and American epidemics were introduced, without further testing in DC, with completely different patterns of disease transmission and morbidity burden including high incidences of diarrhoea and malaria. Only now after 20-25 years of use the first studies on long term effects of child immunizations in DC have demonstrated that some of the vaccines in the best case scenario are useless and in the worst case scenario are detrimental to health.

What are the conclusions?

The type of vaccine, the combination or sequence of vaccinations as well as the concurrent administration of other immunomodulators, such as VAS, may be important for the impact on overall health. It is clear that the effects are often different for boys and girls and boys and girls might therefore benefit from different treatments.

The immunological and genetic basis for sex-differential non-specific effects should be explored through human immunological and animal studies to determine which immune reactions are associated with beneficial and harmful non-specific effect in male and female individuals.

To the extent non-targeted effects are true there are numerous possibilities for improving the vaccination programme and child survival in low-income countries. Our observations are obviously problematic to health authorities. WHO has decided that there is no negative effect of DTP and no interaction with gender but has yet to publish any result in support of this conclusion. Hence, the immediate problems are to establish the consistency of these findings, to examine the possible immunological basis and to convince health professionals that there might be a problem.

Independent longitudinal community surveys provide an excellent opportunity to test new and existing health interventions in a controlled community environment before they are introduced. In this way interactions with other interventions can be observed and the long term and overall effect on mortality can be measured.