Monitoring and assessing the impact of vaccination and other childhood interventions for both boys and girls

Executive summary

The DANIDA-sponsored INDEPTH-vaccine network introduced standardised data collection on childhood interventions within health and demographic surveillance systems (HDSS) and trained 5 PhD students and 1 post-doc at 6 HDSS sites in Africa and Asia. The study showed that real-life observations may contradict our current assumptions, opening for new strategies to improve child health. For example, live vaccines are associated with much stronger beneficial effects than can be explained by the prevention of the vaccine-targeted infections. On the other hand, the non-live vaccines examined so far are associated with negative effects for girls resulting in higher female than male mortality. There are numerous implications of this contrast in survival impact. Live vaccines should be given earlier and to all to obtain the maximum benefit. All sites experienced major declines in under-five mortality in the last 15-20 years. Campaigns with OPV and MV may have been major drivers of this decline. Hence, we need to examine these campaigns in future studies and whether other vaccines can be used to reproduce similar beneficial NSEs once OPV (2020) and MV are withdrawn or down-scaled. There was no sex-difference in coverage of vaccines, but the effect differed by sex. Future studies should explore whether co-administration with a live vaccine may reduce the negative effects of non-live vaccines for girls. A stronger emphasis on examining and using the non-specific immune training effects of vaccines could lead to major improvements in child survival.

Introduction

The many vertical health programmes led by WHO, UNICEF, GAVI and other international organisations are undertaken with little attempt to assess their real-life impact on health. Child health programmes in low-income countries are justified by their assumed impact on child survival. The impact assessment is based on measurements of performance indicators like vaccination coverage and assumptions about intervention efficacy. These assumptions are based only on studies of the target condition; for example, a vaccine is evaluated for its protection against the targeted disease. However, an increasing number of studies have found immune stimulatory properties of vaccines and they may therefore have other non-targeted health outcomes.

To assess these real-life effects of child interventions, individual-based data on health intervention uptake and health outcomes are necessary. The INDEPTH-vaccine network sponsored by DANIDA created/strengthened the platform to assess real-life effect at six Health and Demographic Surveillance System (HDSS) sites in the INDEPTH Network (www.indepth-network.org). Through the DANIDA-sponsored vaccine network, data collection on childhood interventions at six INDEPTH sites was supported and PhD-students/post-docs have been trained to evaluate the real-life effect of interventions on child survival and whether interventions affected girls and boys differently.

Background

Many health interventions (vaccines) in low-income countries have been introduced based on their assumed effects on survival by preventing a specific infection, but they have not been tested in randomised trials measuring the overall effect on childhood survival. That might have been appropriate if vaccines had only the intended effect against a specific disease. However, observational studies and randomised controlled trials (RCTs) in several African and Asian countries have now shown that interventions have so-called non-specific effects (NSEs) by reducing or enhancing susceptibility to unrelated infections. In other words, vaccines and micronutrients reprograms the immune system in ways which may reduce child mortality much more than expected but in some cases may also increase susceptibility to unrelated infections and thereby increase mortality. NSEs are frequently sex-differential. Furthermore, interventions interact producing stronger beneficial or negative effects; for example, vitamin A given with diphtheria-tetanus-pertussis (DTP) may increase mortality for girls. There is now strong evidence from immunology that such epidemiological observations are plausible because interventions with vaccines and micronutrients can induce epigenetic changes which reprogram the immune system.

Hence, making evaluations based merely on the assumed effects is not appropriate. Since trials did not measure the impact on survival when the interventions were introduced, we do not know the full effect of these interventions on child survival and our assessment of impact and cost-effectiveness of interventions is faulty. Once an intervention is recommended by WHO it is considered unethical to test the effect in an RCT. Hence, there is a need to develop new methods to assess the real-life effects. We have used the routine data collection systems from Health and Demographic Surveillance Systems (HDSS) within the INDEPTH Network to document the uptake of childhood interventions and to assess whether these interventions are associated only with the expected specific effects. On the other hand, if similar unexpected associations are found at different INDEPTH sites, NSEs are likely to be important; for example, measles vaccine (MV) has been found to have unexpected beneficial effects at many different sites.

The present project therefore had an emphasis on standardising the collection of routine data on interventions. The specific preventive effects of interventions are usually assumed to be similar for girls and boys. However, the immune stimulatory effects of interventions have often been different for girls and boys and the DANIDA-sponsored vaccine network has therefore had a special focus on documenting whether effects were similar for girls and boys.

Results

The project developed common standards for routine data collection on childhood interventions (www.indepth-network.org). Many WHO-sponsored studies have introduced survival bias in the analysis of mortality, and the present project therefore had a particular focus on preventing "survival bias" by documenting when the information was collected and by not assuming that children for whom no information was collected were "unvaccinated".

Seven individuals from six INDEPTH sites were enrolled in post-doc (N=1) or PhD (N=6) programs. The PhD programmes were delayed because national universities had difficulties in finding relevant supervisors or kept changing the PhD admission criteria and curriculum. So far, two have

defended their PhD theses; two PhD theses have been submitted; one PhD thesis is being finalised; and one candidate has interrupted his PhD due to ill health.

During the course of this project, there has been an increasing interest in the NSEs of interventions, in particular vaccines and vitamin A supplementation. WHO's Strategic Advisory Group of Experts on Immunization (SAGE) reviewed the potential NSEs of BCG, MV and diphtheria-tetanus-pertussis vaccine (DTP) and concluded that the NSEs warrant further studies.

The project has documented major reductions in under-five mortality (see Figure) in recent years; for example, Bandim and Navrongo have reached the Millennium Development Goal 4 (MDG4) of reducing mortality by 2/3 between 1990 and 2015. Since improvement in health services and general wealth cannot always explain these trends, these results for under-five mortality should generate a new research agenda of what have been the driving mechanism in the decline.

Using routine data from all 6 sites we analysed what are the determinants of not being a fully immunized child (FIC) by 12 months of age, a key concept for GAVI. Vaccination data collected from 109,473 12-23 months old children was used to analyse the trend over time, determinants of being FIC and the consequence for subsequent child mortality of being FIC. There was an upward trend over time in the proportion of FIC children at all centres except one; the coverage in 2013 ranged between 71% and 88%. No centre found differences in the proportion of being FIC among females and males. The predominant cause of not being FIC was lack of MV, explaining from 75% to 100% of not being FIC at the six centres. Controlling for background factors, lack of MV was associated with 28% (14-45%) higher mortality in the following years. No centre reported measles epidemics, supporting that the main effect of MV is non-specific. Hence, to improve FIC coverage and child survival a stronger emphasis should be given to ensure that all children are measles vaccinated on time.

Though there was little difference in vaccination coverage for girls and boys, we found marked sex-differential association for mortality and different vaccines. DTP and Penta vaccine were associated with increased female-male mortality rate ratio (F/M MRR). On the other hand, MV was associated with lower F/M MRR. These data support an emerging pattern where live vaccines are associated with lower female mortality but inactivated vaccines like DTP, Penta, HBV, IPV and RTS,S are associated with increased female mortality. This pattern was very pronounced in the Bangladesh study, which had data from before the introduction of the routine vaccination programme (EPI). There has been a complete inversion of the female-male MRR in the age groups where DTP and MV, respectively, were the predominant vaccines.

We are also examined the implications of the many variations in actual vaccination practice. For example, administering DTP and BCG simultaneously reduces the negative effect of DTP. Receiving DTP with or after MV, i.e. out-of-sequence vaccinations, increases mortality markedly compared with having MV as the most recent vaccination. It is therefore important that vaccination programmes function well. For example, 25 years ago 86% of MV and DTP vaccinations were out-of-sequence in Navrongo, Ghana. Today this is less than 1%. This change in implementing the vaccination programme has reduced mortality after one year of age with 30% and has therefore contributed importantly to reaching the MDG4.

The general vaccination campaigns with OPV and MV have had major beneficial effects for child survival and may be an important part of why under-five mortality has declined so much (Figure).

Conclusions

HDSSs have the capacity to assess the real-life effect of routine childhood interventions, documenting both expected specific effects and unexpected non-specific immune-stimulatory effects. The project has contributed to several new observations regarding the importance of NSEs. Live vaccines are associated with much stronger reductions in child mortality than can be explained by the prevention of the vaccine-targeted infections. On the other hand, non-live vaccines like DTP and Penta are associated with increased mortality even though the vaccine prevents the vaccine-targeted infection(s). The sequence or combination of vaccinations may therefore have major consequences for child survival. The eradication campaigns against polio and measles infections have had a much stronger impact in reducing mortality than normally assumed.

Implications

The emphasis on the non-specific effects of vaccines is still highly controversial since it contradicts numerous assumptions underlying current childhood vaccination programmes. However, the situation may be changing since WHO has recently reviewed the non-specific effects of BCG, DTP and measles vaccines and recommended further research. Furthermore, other groups are starting to confirm our observations of fundamental differences in NSEs of live and inactivated vaccines (Bardenheier, CID 2017). There are numerous implications of this difference. First, it could be disastrous to remove a live vaccine after eradication of the targeted disease. For example, it may have very negative effects for child survival to remove OPV in 2020 as decided by WHO. Second, live vaccines like OPV and MV may reduce the negative effects of DTP and further research should therefore examine whether other live vaccines like BCG or rotavirus vaccine can substitute the effect of OPV when this vaccine is withdrawn in 2020. Third, live vaccines should be given earlier and have a higher coverage to obtain the maximum benefit for child survival. Fourth, in the pre-vaccination era girls did not have higher mortality than boys in Africa; it should therefore be of major concern that all studies of inactivated vaccines suggest that these vaccines are associated with higher female than male mortality.

Recommendations

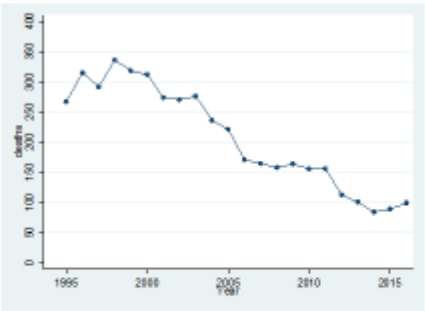
The DANIDA-sponsored vaccine network has shown the importance of having real-life observations which may contradict our normal assumptions and therefore lead to new strategies for improving child health. The INDEPTH Network of HDSSs have the capacity to conduct such studies and should be used to assess the real-life effects of current and new childhood interventions.

Much more research is needed to assess the non-specific effects of vaccines and their underlying mechanisms in order to improve child survival in low-income countries and health care costs in high-income countries. For example, it is ”unnatural” that inactivated vaccines are associated with increased female mortality. It is illogical that Global Health uses the coverage of DTP, an inactivated vaccine associated with higher female mortality, to monitor the performance of the

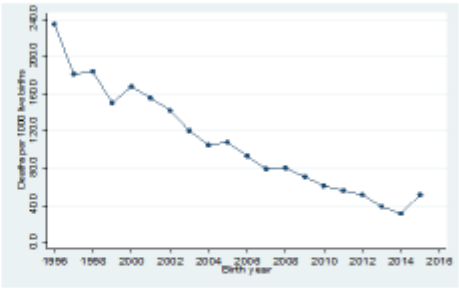
routine vaccination programme. We need to explore how negative effects can be prevented, e.g. by co-administering a live vaccine with the inactivated vaccine.

Campaigns with OPV and MV may have been major drivers of the marked improvement in under-five child survival in the last 20 years. Hence, we need to examine these campaigns in future studies and whether other vaccines can be used to reproduce similar beneficial NSEs once OPV and MV are withdrawn or down-scaled.

Under-five mortality 1995-2015



Guiné-Bissau: Interior



Ghana: Navrongo