Policy brief

Community studies to improve primary health care in Guinea-Bissau - Research capacity-building in Guinea-Bissau: ENRECA III

Executive summary

The project has trained the key group of 12 MScs and 7 PhDs in health science in Guinea-Bissau. All PhDs continue to play key roles in the Guinean health care system or to conduct research in Guinea-Bissau. The Bandim Health Project has focused on measuring the real life effects of the interventions which are used in low-income countries to reduce child mortality and reach MDG4. Unfortunately these interventions have usually been based on assumptions not supported by evidence. The underlying model that a vaccine prevents only the targeted disease and doses nothing else has been contradicted numerous times. The immune system is a learning system which affects general susceptible and may lead to strongly beneficial non-specific effects reducing mortality far more than expected but may also be misdirected and increase mortality. WHO is beginning to recognise that a new paradigm is justified. There is a need that donors support more real life research to test the effects of our interventions and their interactions. This could ultimately lead to much lower mortality in low-income countries but also to huge cost savings in both low and high-income countries.

Introduction

This research training project for Guinea-Bissau was based on the previous experiences of the Bandim Health Project (BHP) which has conducted population-based research in Guinea-Bissau since 1978. The key lesson from previous research has been that most of our health interventions in low-income countries, particularly those to improve child survival, have been based on assumptions about effectiveness rather than on studies of the real life effect of the intervention on overall morbidity and mortality. To conduct such real life assessment it is necessary to follow a total population through a health and demographic surveillance system (HDSS) documenting the major life events. In the present ENRECA project we therefore used the BHP's HDSS to define a series of master and PhD training projects related to vaccinations, malaria treatment, cholera treatment, HIV and TB control, and maternal mortality.

Background

BHP's development is based on the experience in the early 1980s that that there was no basis for the belief which was common at the time that malnutrition explained why infections like measles which were non-fatal in the high-income countries were associated with high mortality in low-income countries. Measles was the major killer in low-income countries and the measles case fatality in Guinea-Bissau was 21% for children under five years of age. We were able to show that there was absolutely no link between nutritional status and risk of dying of measles – and even more surprising no one else had such data. The common belief at the time was plausible but based on no data and had become so much part of the culture of the medical profession that no one thought about testing it. Instead we were able to show that the real determinant of measles mortality was the intensity of exposure; the children dying were those who were exposed as secondary cases at home presumably because they got a huge dose of infection. We subsequently showed that this pattern applies to all major childhood infections like whooping cough, chickenpox, RSV and polio. The reason mortality was particularly high in Guinea-Bissau was that they had extensive polygamy, large extended families, and multi-family houses. As a consequence there were a large number of small children at risk of being exposed at home when an older sibling came home with an infection.

At the time the interest in vaccinations was limited because it was believed that vaccines would only save the "weak" children from dying from one specific infection; if saved from dying from measles they would probably die of something else and vaccination programmes could therefore not be expected to have a large effect on overall child survival. When we introduced measles vaccination in the BHP study area mortality declined nearly 3-fold from one year to the next (see Figure 1). Once again: the belief that measles vaccine had limited effect on child survival was based on no data.

Hence, some of the key interventions to reduce child mortality were based only on assumptions and had no support in the limited amount of data available. To counteract this situation we had to get beyond the situation where donors are merely measuring the coverage for different interventions and then calculate impact based on assumptions about effectiveness. It was necessary to follow a community (total population) to measure the total impact and to be able to see when the current policies and assumptions are contradicted.

Over the years BHP has grown to follow an urban population of around 100,000 and a similar rural population is followed in the interior through a national cluster sample of villages which are visited every 6 months. We have had the intention of testing the real life effects of the major interventions used in Guinea-Bissau and many other low-income countries. Using this demographic basis we have been able to construct a number of Guinean master and PhD studies as well as being the basis for strengthening the Danish resource basis in international health through a number of PhD projects.

Results

Including the previous phases of the ENRECA project we have trained 12 MSc and 7 PhDs. These are the only people with an advanced research training degree in Guinea-Bissau. They have become the backbone of the Guinean health research community. Since 2009 Guinea-Bissau has built a national institute of health (INASA) and the directors have come from the group of ENRECA students. Other ENRECA PhDs work as chief advisors to the TB program, the WHO sponsored vaccination programme, director of the national laboratory and as director of the school for training health staff and some are pursuing a career conducting full-time research. Though the ENRECA PhDs have gone abroad for training courses and to write their PhD they have done all their data collection in Guinea-Bissau linked Guinean health issues. None of the PhDs have left their country after completing their degree at the University of Copenhagen. Two of the PhDs are now actively involved in training young Guineans for research and they have developed their own network of international contact to facilitate this training, often through Portuguese universities now that they no longer receive support from DANIDA.

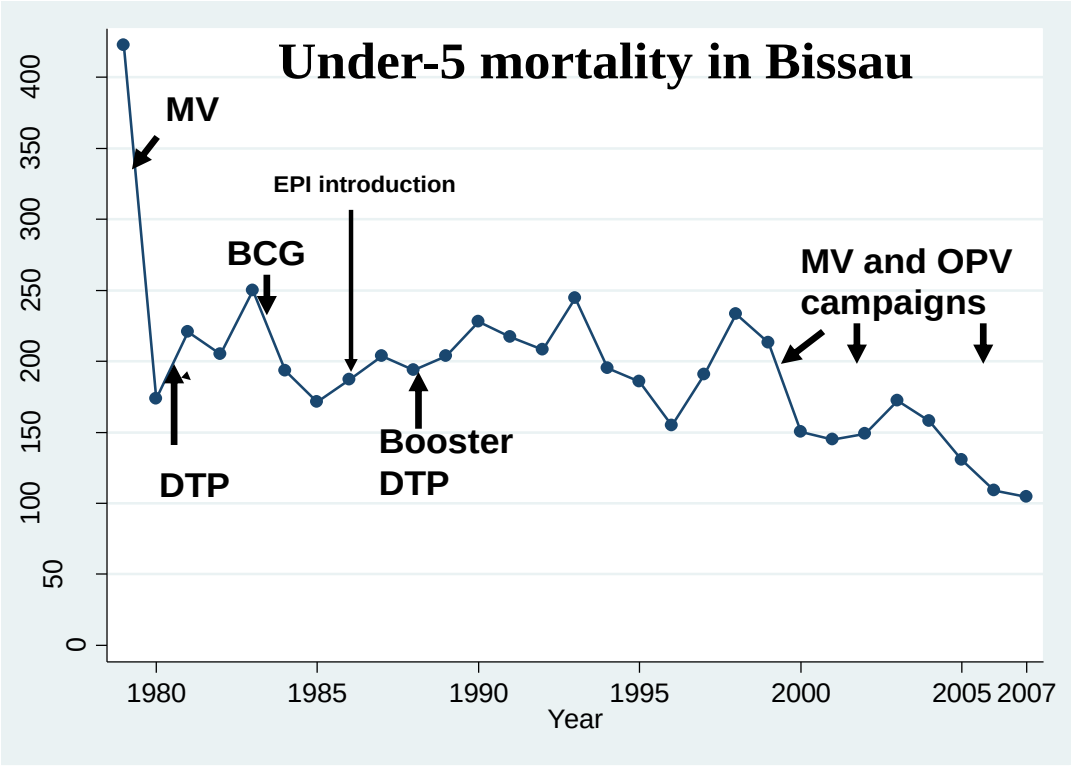

Figure 1: Under-five mortality curve for the Bandim urban area. The graph shows the decline in mortality since the campaigns with MV and OPV started in 1998. MV=measles vaccine; DTP=diphtheria-tetanus-pertussis OPV=oral polio vaccine EPI=national vaccination program

Research wise the strongest part of the BHP program in Guinea-Bissau has been the focus on measuring the real life effects of common health interventions. The key issues involved can be illustrated with Figure 1 which depicts under-5 mortality in urban Bissau since the start of the project. If internationally supported health interventions reflected cumulative knowledge of what worked or did not work in term of reducing child mortality one would have expected to see child mortality decline gradually over the years. Instead what we have seen is some periods with long-term increases in child mortality and then sudden drops in mortality level; for example, when the national immunization program (EPI) was introduced with UNICEF support in 1986 mortality increased over the next 10 years. This should not be possible – but it is because global health is built on a single-disease-single-intervention paradigm. If one vaccine prevents a specific disease it is assumed that overall mortality is reduced proportional to the share of this disease as a cause of deaths. So when EPI introduced booster DTP in the mid-1980s mortality should have declined corresponding to the role of whooping cough as a cause of deaths. Instead mortality increased.

The reason is that the basic model for global health that there is one intervention for one disease is wrong. The immune system is a learning system so when we stimulate immunity with a BCG or measles vaccine (MV) the system may learn something which is useful also in term of protecting the child against totally related infections. It will be seen in Figure 1 that when MV and BCG were first introduced mortality declined far more than should have been expected from prevention of measles and TB. In other words the vaccines had beneficial **non-specific effects (NSE)**. From what we have learnt so far all the *live* vaccines including measles, BCG, OPV and smallpox vaccination have this capacity. However, a learning system can also be misdirected and unfortunately the *inactivated* vaccines like DTP seem to have this effect. They prevent the targeted disease but increase susceptibility to unrelated infections. Therefore the net-effect on survival can be negative as can be seen in several places in Figure 1 even though the vaccine prevents the targeted infection. It has been common to present only results for "children" in analyses of health interventions.

However, girls and boys have different immune systems and it has turned out that the NSEs of vaccines often differ by sex. Hence a rational intervention programme should also test the effects separately for girls and boys.

Another key problem is that different interventions interact in the immune system and therefore we can get totally unexpected results; for example, WHO recommends vitamin A supplementation (VAS) to be given with vaccines. This recommendation was never tested before being introduced. We have conducted the only randomised trial of giving VAS with vaccines; VAS compared with placebo was associated with two-fold higher mortality for boys but a halving of mortality for girls.

Since such observations question the key assumptions of many WHO intervention programs, there has been a general trend to negate these results as coming just from one group, from one country and being based on observational studies with inbuilt confounding. Hence, WHO has tried to make the problem go away with methodological arguments. However, these arguments are not true. We have repeatedly found the same trends in other low-income countries. In the last decade we have also with help from ENRECA III been able to test many of the interventions in randomised trials and have found major unexpected effects. The situation may be changing since the Strategic Advisory Group of Experts on Immunization (SAGE) has recently reviewed the potential NSEs of BCG, DTP and MV. It concluded that BCG and MV may have beneficial NSEs and they warrant further studies.

Conclusions

The story of the NSEs of vaccines illustrates how much science is influenced by paradigms and how difficult it is to change the paradigm. The paradigm that "one vaccine protects against one disease and does nothing else" has been contradicted numerous times (Figure 1) and should have been removed a long time ago. The science community has tried to dismiss the issue with methodological arguments rather than by testing the alternative hypotheses and the one-vaccine-one-disease paradigm is still the underlying model for nearly all programs in international health.

A change in paradigm to focus on the immune training effects of vaccines has huge potential in terms of reducing child mortality in low-income countries and in reducing health care cost in both low and high-income countries. We have subsequently taken the experience from West Africa back to Denmark and shown that vaccines have major NSEs also in Denmark, e.g. measles vaccine reducing hospital admissions from unrelated infections with 14%. Hence a change in the age of measles vaccination or vaccination coverage could potential save a lot of money. Another interesting implication of the NSEs paradigm is that if a vaccine with beneficial NSEs is removed after eradication this could cause more harm than the good done by eradicating the disease. It will be seen in Figure 1 that in the last 15 years where the global health community has tried to eradicate polio and measles infection with numerous general vaccination campaigns there has been a major decline in mortality. From the single-disease perspective these campaigns should have no effect on survival since the incidence of polio and measles is already very low. However, we have shown in randomised trials that both OPV and MV do reduce mortality in major ways (around 30%). Hence, if we stop the campaigns once polio and measles have been eradicated mortality may actually increase again.

Implications

International donors and nations should do far to test the assumptions on which the common health care programs are built. This would require supporting a system of HDSSs which could monitor the

real life effects of both old and new health interventions and changes in policy. This is particularly important now where the industry is getting up to speed with the introduction of new vaccines. It is not enough to assume that we know what the effect is and then not check whether we were right. There is need for demographic surveillance systems to help monitor the real life effects but also to let us be contradicted if our assumptions were wrong or new interactions arise because new interventions have been introduced. When smallpox was eradicated 35 years ago and the vaccine was stopped, no one examined whether removing the vaccine was a good idea. We have subsequently found in both Guinea-Bissau and Denmark that smallpox vaccination reduced morbidity and mortality non-specifically. So there has probably been no benefit from stopping smallpox vaccinations. The upcoming eradication of polio and measles infections will raise these issues again.

Donors and health politicians should make sure they know that we are on the right track because we have tested the assumptions on which the interventions are based.

Further reading:

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