# Guide: field studies to monitor and assess the impact of vaccinations and other childhood interventions on morbidity and mortality

## Objective

This guide is intended to help health and demographic surveillance system (HDSS) centres develop a platform for monitoring real life effects of current child health programmes with the aim of assessing the overall effect of the interventions on mortality and morbidity, including the specific and non-specific and sex-differential effects of interventions and their potential interactions.

## Introduction

This document presents a number of considerations related to how to collect and analyse data which can be used to assess the effect of childhood interventions on morbidity and mortality. The key concepts include the non-specific effects of interventions, pregnancy registration, completeness of data and survival bias.

We also present descriptions of six systems for collecting data on childhood interventions. The examples (Ex) come from five HDSS centres:

1. Nouna, Burkina Faso (mainly rural)
2. Navrongo, Ghana (mainly rural)
3. Bandim Health Project (BHP), Guinea-Bissau - urban
4. Bandim Health Project (BHP), Guinea-Bissau - rural
5. Nairobi, Kenya, (urban)
6. Chakaria, Bangladesh, (rural)

## Non-specific effects of interventions

An important background to the present guide is that interventions may have ***non-specific effects***. Most interventions, for example measles vaccine, were introduced because they were ***assumed*** to have beneficial ***specific*** effects on child mortality by preventing measles deaths but the effect was never evaluated in controlled trials (1). If effects were evaluated it was usually only the specific effect; for example, the effect of MV on measles infection but not on overall mortality. An increasing number of epidemiological observational studies and randomised trials show that interventions may have much larger effects than the specific one (2). These effects are related to stimulation of the immune system, for example, by reprogramming cells of the innate immune system (3) or generating cross-reacting T-cells. The non-specific effects can be beneficial and reduce mortality much more than expected (2), but they may also enhance susceptibility to unrelated infections leading to higher mortality (2,4).

Since the non-specific effects "occur" in the immune system, the effects of one intervention may be modified by other interventions. For example, vitamin A supplementation (VAS) seems to have a beneficial effect when administered together with live MV but a negative effect when given with inactivated DTP vaccine (5,6). One implication of this is that even when an intervention has been evaluated for its overall effect on mortality in one setting, if it is used with other interventions the effect may be totally different from the one originally estimated. For example, VAS was originally

evaluated in trials comparing VAS with placebo and these trials suggested that VAS reduced mortality by approximately 25%. Subsequently WHO recommended that VAS be given with vaccines because the immunisation programme has been the best functioning intervention programme. The effect of VAS with vaccines was never evaluated. We have subsequently shown that VAS had a negative effect for girls when they were likely to receive DTP during follow-up (6,7).

Girls and boys have different immune systems and the interaction between interventions may be different between the sexes, as shown by the example of VAS and DTP vaccination (4,6). There are many other results showing that interventions have different effects in boys and girls (7). It is therefore essential that effects are always assessed separately for boys and girls. It is current practice to report effects of interventions for "children", possibly for different age groups, but virtually never by sex. However, effects may be opposite for boys and girls. Hence, "no effect" of an intervention may cover a positive effect for one sex but a negative effect for the other sex. For example, in randomised controlled trials (RCT) neonatal VAS increased infant mortality for girls by 41% but reduced male mortality with around 20% producing a combined "no effect" of a small increase in overall mortality (7). It is therefore stressed that effects should be assessed separately for boys and girls.

Since the current global health system is based on assessment of *specific* effects, HDSS systems have a particular opportunity to contribute to global health by assessing the non-specific effects. Most research is based on observing only the outcomes that were pre-specified, which will nearly always be specific effects. Because HDSS systems follow everybody for certain defined outcomes like mortality, they have a unique possibility of observing very important unexpected results. Hence, HDSSs are the natural place for observing the non-specific effects, the interactions between interventions, and the possible sex-differential effects.

The ultimate goal of research on the non-specific effects of interventions is to detect patterns which are sufficiently consistent in observational studies to warrant being tested in randomised trials (if possible) before possibly leading to changes in public health practice. For example, we have repeatedly observed beneficial non-specific effects of BCG and measles vaccines. Subsequently, we have been able to test the effect in randomised trials and essentially found the same effect as suggested by the observational studies (1,2). The use of high-titre measles (HTMV) is an example where HDSS sites in Guinea-Bissau and Senegal made the very surprising observation that the new measles vaccine was associated with increased female mortality and WHO eventually had to remove the vaccine in 1992 (1,2).

These considerations imply that we should try to collect routine data on all health interventions and campaigns in infancy and childhood to fully understand the impact of current interventions.

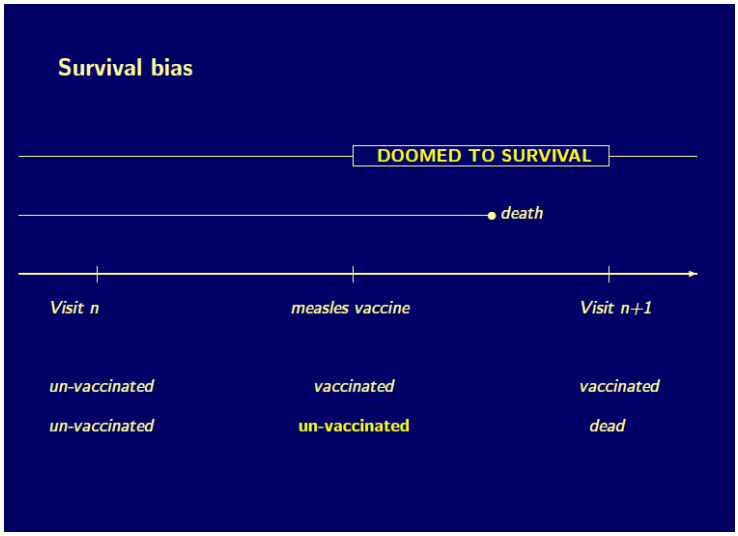
## Pregnancy registration and health outcomes

The present guide focuses on two main types of health outcomes, mortality and morbidity. It is assumed that mortality is registered routinely for all children through the HDSS. The description of data collection on deaths and causes of death (verbal autopsies) is not further discussed. However, it should be emphasised that HDSS may underestimate perinatal and early infant mortality if the starting point is not ***pregnancy registration***. In some HDSSs, all new children delivered by women who are registered in the census are considered to be members of the HDSS population ***from birth***. This mode of registration may lead to severe bias because a child who survived is much more likely

to be registered than a child who died before the next round of demographic data collection. In many cultures, a woman will not voluntarily report that she has lost a newborn child since the last visit of the demographic team. However, if the pregnancy was registered and the woman is asked what happened to the pregnancy registered at the last visit she will answer truthfully if the child has died. If the HDSS system is not based on pregnancy registration it may underestimate neonatal mortality and this may lead to erroneous evaluations of interventions implemented early in life, e.g. BCG or neonatal vitamin A supplementation (VAS). Hence, it is advisable to base the evaluation of interventions at birth on children registered during pregnancy. If children are registered after birth they should only be counted from the day they were registered and not from birth. Pregnancy registration is therefore a key feature of the examples presented.

## Completeness of data and survival bias

It is essential to evaluate how complete a data set is for the exposures and outcomes analysed. Unfortunately HDSS data have often been analysed as if they were complete even though this was clearly untrue; for example, if a child has no information about vaccinations it may be assumed that the child was unvaccinated (8). This will have dramatic consequences for the estimates produced (8,9). It is a key consideration that analyses of HDSS data should be careful not to introduce ***survival bias*** in the analysis of the impact of health interventions (4,8,9). The problem is illustrated in Figure 1 with an example of the analysis of survival after vaccinations.




At visit ***n*** both children were unvaccinated. At round n+1 – say 4 months later - one child had died and the other was registered to have received measles vaccine 2 months ago. It has been common to assume that the child who died and for whom no information on reception of the vaccine was available was "unvaccinated" (8). If such data is used to analyse the effect of measles vaccination on survival the result will be an unnatural strong beneficial effect. The reason is that if the child had received MV and died we would not have received the information because it is very difficult retrospectively to collect information about children who have already died. In other words we will only get the information about measles vaccination from children who survived – i.e. "Doomed to survival". If such immortal time or survival bias enters into the analysis, the results will always be to the benefit of the intervention, giving a falsely positive assessment (9). As discussed elsewhere such analyses have been common (8) and they can exaggerate positive effects but it can also turn a negative effect of an intervention into an estimated beneficial effect (9). It is therefore a key

consideration in these monitoring systems that data should be collected and analysed without introducing survival bias.

There are important implications:

- **If data are not complete:**
    - Health effect can only be estimated prospectively from the time the status of the children was known. In terms of Figure 1, both children will be unvaccinated between n and n+1. The surviving child is only known to be measles vaccinated from n+1 onwards.
    - It is essential that the monitoring system knows precisely when the information about vaccinations or other interventions was collected (see Examples).
- **If the data are complete:**
    - The data set could be complete within some subgroups (for example, because the research team delivered all the vaccines, or the vaccination cards were seen for all children, or the cards were seen for all children after they died - see below). Then the data could be analysed as a complete data set and the children could be considered at risk from the date of vaccination rather than from the date the information was collected.

## *Key features of the data collection system on childhood intervention:*

### *1. Overall purpose of the data collection*

It is essential to define the outcomes and exposures being monitored. In the examples provided here the main outcomes and exposures are:

*Outcomes:*

- Mortality
- Morbidity (consultations, hospitalisations)
- Growth (mid-upper arm-circumference (MUAC))

*Exposures:*

- Vaccinations
- Micronutrient supplementation
- Malaria control (bed net use, IPTi)
- Breastfeeding
- De-worming
- Others (socio-economic conditions, hygienic conditions, health insurance status, nutritional intervention programs)

### 2. *The monitoring system and the general HDSS*.

- ***Integration into the HDSS.*** Though special teams can collect data about childhood interventions, it is preferable for the long-term maintenance of such monitoring systems that they are built into the general HDSS routines. This has been done in Nouna, Navrongo, Nairobi and Chakaria (Ex 1, 2, 5,6). In Bandim, there has not always been resources for following all the census routines and the data collection has therefore been done by teams focusing on children and childhood interventions (Ex 3 and 4).
- ***The interval between rounds of data collection***. If the monitoring system is integrated into the HDSS it will have the interval between rounds of the HDSS. This interval is usually 6, 4 or 3 months corresponding to 2, 3 or 4 annual visits (see Examples). Most interventions takes place in infancy, and the longer there is between visits, the less likely we are to detect the intervention before the event occurred. Hence, shorter intervals like three months are better. To pick-up the relevant information in an even better way a system might be established (a) where the information is collected from the institutions providing the interventions (health centres, clinics) or to (b) visit the high risk groups – infants or children under 6 months of age – every month. Both these solutions have been attempted in Guinea-Bissau (see Ex 3 and 4).
- ***Age group followed***. Most child deaths occur before 3 years of age, and most interventions focus on children under 12 or 24 months, so in the routine data collection system we have focused on children under three years of age - but where resources permit all children less than five years of age have been followed (Ex 4). Hence, the information on interventions should be collected for the age group under 3 or 5 years of age.

- ***Data from vaccination cards***. Information on childhood interventions is usually collected from vaccinations cards and we tend to assume that the information is correct. It is important to recognise that there may well be errors and omissions on vaccination cards. Campaigns information is usually not noted on the card and it is therefore necessary to collect the data on campaigns through recall (see below).
  With an increasing number of interventions nurses may well forget to write the information for all interventions. For example in Navrongo the children should have 5 interventions at the same time: Penta2, OPV2, Rotavirus2, PCV2, and IPTi1. They forget. Hence, FW need to be trained to understand which interventions should have been administered; for example there is no information for PCV2 but the child has Penta2, OPV2, Rotavirus2, and IPTi1 on the card. The FW should then ask the mother whether the child received the intervention (PCV2) (=the nurse forgot) or the health centre was out of stock for that vaccine. If a child has OPV1 but no Penta1 the mother should also be asked whether the child received the vaccine in the thigh. It is necessary to develop a notation to indicate that the vaccine/intervention was administered on the date expected according to information from the mother (even though it was not noted on the card). To collect such information the FWs need to be able to do more than just copy from the vaccination card. They must fully understand the expected vaccination programme and how the vaccinations/drugs are presumed to be delivered, for example that PCV is given as an injection in the right thigh (may be different in different countries).
  These considerations on completeness of data also hold for vitamin A supplementation (VAS) information collected from the vaccination card. In area where it is policy to deliver VAS every 6 months, the FW should be able to detect that the child has been weighed at the health centre both at 12 and 13 months of age but has received no 12-month VAS. In that case the mother should be asked whether the child also received some drops in the mouth (=VAS).
- The ***vaccination card/health card*** used as an ***ID card***. When a child is first registered, information will be collected from the vaccination card. The ID of the child should be written on the card. If the child has no vaccination card, he or she should be provided with a vaccination card to facilitate future collection of data.
- ***Health centre identification numbers.*** Where health centres/clinics maintain registration books for vaccination and consultation with an individual identification number, for example 67/2012, it is essential that the HDSS field workers (FW) collect this number. This has so far not been implemented in HDSSs but is attempted in Nouna and Navrongo (see Ex 1 and 2). If this number can be obtained, it will be possible to use health centre registers to verify information on inconsistent dates and collect information on missing vaccinations. It will for example be possible to make case-control studies of the vaccination status of children who died. Using the health card as an ID may also facilitate the identification of HDSS children coming for consultations or hospitalisations at a health care institution.

## *3. Home-based and service-provider-based data collection.*

- ***Home-based.*** The main data collection on interventions, outcomes and background factors will be at the regular home visits. Even when institution-based data collection is attempted, it is important to maintain home-based collection as well. For example, it may be possible to get information on vaccinations from health centres (see Ex 3), but there is likely to be a growing private sector or alternative health centres where these

interventions can also be delivered which we would not know about unless the home-based system is maintained. For example, in Bissau city where information on vaccinations is collected at the three local health centres, 15% of the DTP/Pentavalent vaccinations are not given locally and are only picked-up through the regular home visits.

- ***Service-provider-based.*** If the information on interventions can be obtained through the service providers, this will greatly increase the quality of the data and it will be easier to analyse the effect of interventions on health outcomes. In urban Bissau an attempt has been made to collect information about all vaccinations directly from the health centres and the campaign teams during vaccination campaigns (see Ex 3).
- ***Hospital-based data collection.*** As a special case, BHP (Ex 3) has collected information on vaccinations and campaigns at admission to hospital (paediatric ward). This has only been possible because most children bring their vaccination cards to the hospital. In a setting with a high case fatality at the hospital, this provides a good way to assess the relative importance of different interventions. The system can not be used to assess the total risk of dying because neither the population nor the number of children vaccinated will be known. However, among children who were sufficiently sick to get hospitalised, it may provide an assessment of the relative importance of different interventions. This system has been used several times to compare the non-specific effects of different vaccines for boys and girls, and the effect of different sequences of vaccination for hospitalisation or mortality (10-13).

## *4. Outcomes*

- ***Mortality and cause-specific mortality.*** If possible overall mortality should be the main outcome in analyses of the overall effect of childhood interventions. In all HDSSs identification of death and possible cause of death (using verbal autopsy) is standard procedure. Please note also the issues discussed below under hospitalisations and consultations about getting correct information on the date of the event. This will be very important for the evaluation of early-life interventions. In many HDSS systems the timing of death is imprecise; for example, many deaths have the date "15" because only the month could be ascertained by the FW. Some HDSS have village key informants (VKI) who records pregnancies, births, and deaths (see Ex 1-2). This may improve the dates considerably if the VKI are properly supervised.
- ***Hospitalisations and consultations***. Child mortality is fortunately declining, so we also need to emphasise other important and easily identifiable health outcomes like hospitalisations and health centre consultations. Identification of hospitalisations during a certain period has been built into all the data collection systems presented here (see examples) typically by asking in each data collection round whether the child has been hospitalised since the last visit (and a questionnaire with more specific information can be completed). In relation to measuring an effect of specific interventions, it is essential that the information on timing is good enough to determine that hospitalisation occurred ***after*** some specific intervention. Maternal recollection of dates may not always be very accurate. Sometimes the hospitalisation/consultation has been noted in the child health book/vaccination card or dated prescriptions can be found in the cards and these can be used to date the event. However, such information is rarely complete. If possible, attempts should also be made to verify the information in inscription/consultation books at the health institution. If the health institution has a numbering system for the children,

it is therefore important that this has been picked-up by the HDSS FW (see above). Alternatively, collaboration between the HDSS and the health care system could lead to health centres/hospitals using the ID placed on the health card by the HDSS. This is being tested by the BHP in the rural areas of Guinea-Bissau (see Ex 4). In a somewhat more costly version, the BHP HDSS (Ex 3) has FWs stationed at the hospital and health centres who register all consultations and hospitalisation and assure proper identification of the children.

- ***Growth.*** Growth is a potential outcome in analyses of the effects of interventions, but it is also a very important confounder because mothers may be less likely to bring sick/malnourished children to receive interventions like vaccines (frailty bias). For example, children with poor nutritional status are unlikely to get vaccinated (14,15). The simplest measure of growth is mid-upper arm-circumference (MUAC) which can be measured by one person using an insertion tape. Weight or length measurements require more equipment and are more complicated to do for just one person. Hence, MUAC is best suited for a demographic surveillance round, and MUAC is measured at each visit in all the registration systems. WHO has developed age/sex specific z-scores for MUAC but these can not be used for children under three months of age. Crude MUAC is as good a predictor of subsequent mortality risk as MUAC-z-score (16). Controlling for MUAC in survival analyses may have major effects on the estimated impact of an intervention (14,15); for example in one analysis of early DTP, the negative effect of DTP for girls increased from 3-fold to 6-fold higher mortality when the analysis was adjusted for MUAC (15).

## *5. Interventions (exposures)*

- ***Interventions***. So far, the intervention monitored have been child vaccination, vitamin A supplementation (VAS), provision of other micronutrients, de-worming drugs, promotion of exclusive breastfeeding, intermittent preventive treatment in infancy (IPTi), and bed net impregnation. Feeding programmes, intermittent preventive treatment in childhood (IPTc), antenatal control and maternal vaccinations could probably also have been analysed. Some of these interventions are scheduled to be taken at a specific age at a health facility, whereas others are mainly delivered in campaigns or through some form of out-reach service. This difference is essential for how data can be collected.
- ***Age-Scheduled interventions***.
  - Vaccine data should be collected from the health card of the children during home visits. It is essential to note whether and when the health card was seen since the child can only change status for prospective follow-up from that date. Care should be taken to distinguish between the children for whom there is no information (who could have been vaccinated) and the truly unvaccinated children. Information should therefore be recorded about whether the card was seen, the child had no card but had been vaccinated, the child had no card and had not been vaccinated, the card was lost, or the card was not available for inspection (see ***Examples*** for coding). For children with no card, a history of vaccinations should be collected. For unvaccinated children, information should be collected on why the child had not been vaccinated. These interviews may reveal groups at high risk of not getting vaccinated (e.g. children with

malformations, children with AIDS) and also at high risk of dying. If possible, such children are better excluded from the analysis.

- Micronutrients and intermittent preventive treatment may also be administered according to a schedule; for example, VAS is often given in health clinics every six months from 6 months of age. If it is written on the health card, this information should also be recorded. However, it is necessary to assess whether other interventions are recorded as meticulously as vaccinations. If not, it will be necessary to ask whether the child has received the 6-month VAS dose or IPTi with Penta2 and Penta3.
- Where possible, information should be collected from the vaccination card of dead children in conjunction with the verbal autopsy procedure. This has in some instances provided very interesting information on vaccination status (17) and the data can potentially be used as a basis for case control studies. Practices differ, but in many places the health card is thrown away when the child dies and it will therefore not be possible to get information from all children who died. In the rare case that *post-mortem* information is available for all children, it would be possible to analyse the data from the data of vaccination rather than the date the health card was seen.

- ***Campaigns*.** An increasing number of interventions are being delivered as campaigns - in other words not at a specific age but when it is logistically feasible (depending on funding, etc). Information on campaigns provided by the health services (e.g. vitamin A supplementation, bed-net impregnation, measles vaccine) is often not noted on the health card. This makes it difficult to collect the data. Campaigns are either fixed-post where the health workers set up an out-reach post at a key community point and the mother has to bring the child, or (b) house-to-house where the health workers will attempt to visit all households in the area (18).
  - ***Collection of information during the campaign***. The best information will be obtained if field workers can follow all the health workers to record who received the intervention and who did not. This has been accomplished several times in urban Bissau (18-21) but may be too logistically demanding in most places because a large number of field workers and transport is necessary. If logistically possible, field workers will record all interventions given during a campaign and note them on the vaccination card. If the campaign is implemented as a fixed-table campaign to which the mother brings the child, a field worker could record all interventions at the post. When campaign interventions are administered through mobile teams visiting all households, all teams should be accompanied by a field worker. When a campaign has finished, it will be necessary to conduct a swap-up survey to ask the mothers of all children who were not recorded to receive the intervention whether the child received the intervention elsewhere. Having received the intervention or not having received the intervention must only be counted from the date the information was obtained in the swap-up survey.
  - **Collection of information after the campaign**. If it has not been possible to collect information during the campaign, questions should be asked in the following home visit regarding whether the child received the intervention(s). It is essential that the field worker knows the campaigns and can refer specifically to the different campaigns (for example whether it was polio vaccine given in the

mouth, or measles vaccine injected in the shoulder). If this is not done the results will not be reliable. It is not enough to ask whether the child took part in a campaign. There may have been several campaigns since the last round. The field worker has to refer specifically to each campaign and ask whether the child received it. Examples of list of campaigns in a study area are given in Ex 2 and 4). Unless these rules are followed, complete information will not be obtained for any specific campaign, but only that some children received some vaccines and some children received micronutrients. Hence the monitoring system has to have a variable for each specific campaign so that the completeness of the data can be assessed.

## 6. Background information

- ***Socio-economic conditions,*** cultural variation and health status may be important determinants of the uptake of interventions, and therefore important confounders to control in the assessment of health impact. As mentioned in the examples, we have tried to collect some background information on possessions as a basis for evaluating socio-economic position.
- It is assumed that background factors like maternal age, maternal education and ethic group will be available from the HDSS.

## 7. Postscript

We would appreciate to receive comments and additional experiences from researchers collecting similar information about childhood interventions.

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