Testing the hypothesis that neonatal vitamin A supplementation has a negative health effect in females once they receive DTP (not administered with BCG):

Proposed statistical analysis in the neonatal vitamin A trials

By Christine Stabell Benn, Copenhagen, November 2014

Hypothesis

My group has put forward the hypothesis that neonatal vitamin A supplementation (NVAS) compared with placebo has negative effects for females once they start receiving DTP (not administered with BCG) and as long as they have DTP as their most recent vaccine.

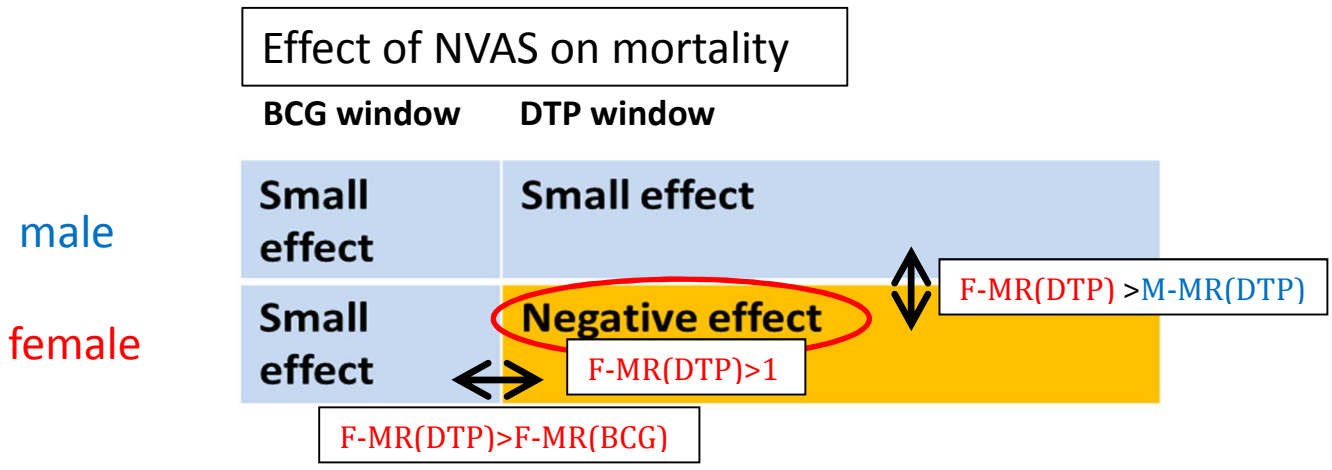
The hypothesis is based on consistent observations within the three Guinea-Bissau NVAS trials of NVAS versus placebo being associated with lower mortality among males, but significantly higher mortality among females, in the DTP window **(Figures 1-4)**. These observations were done in a context where:

a) most children follow the WHO recommended vaccine schedule and receive first BCG (at birth), then DTP at age 6-8 weeks, and then measles vaccine (MV), recommended at age 9 months;
b) no mothers received vitamin A supplementation (VAS);
c) the children had not received additional VAS during follow-up/were censored at the time of additional VAS;
d) the HIV prevalence was low;

The testing of the hypothesis should respect these external/environmental conditions.

I consider the hypothesis supported if the NVAS/placebo mortality rate ratio (MR) in females is above 1 in the DTP-window (F-MR (DTP)>1).

It would also support the hypothesis if the female NVAS/placebo MR is higher than the male NVAS/placebo MR in the DTP-window (F-MR(DTP) >M-MR(DTP)) or the female NVAS/placebo MR in the DTP-window is higher than the female NVAS/placebo MR in the BCG-window (F-MR(DTP)>F-MR(BCG))[1]. See figure below.



[1] In most NVAS trials there is probably too little follow-up time with MV as the most recent vaccine to compare NVAS effects in the DTP window and the MV window, but my prediction would be that F-MR(DTP)>F-MR(MV)

Ways to test the hypothesis – theoretical considerations

It should be possible to test our hypothesis in some of the other NVAS trials using one of the following analytical approaches, depending on the availability of vaccination data:

A) Vaccination status analysis. This applies to **studies which have collected individual vaccination data**. Depending on how vaccination data were collected, the analysis can be done either as a **vaccine status analysis with actual vaccine dates** or as a **landmark vaccination status analysis**.

B) Age-specific NVAS/placebo analysis. This applies to **studies which have *not* collected individual vaccination data**, but were conducted in a population where vaccination coverage is high and the recommended schedule has been followed.

The two approaches have been described in more detail below. An example where both approaches have been used is given in **Table 1**.

A) Vaccine status analysis: Ideally, to test the hypothesis, the trial should have collected ***individual vaccination status data*** from participants, and the NVAS and placebo mortality rates should be compared from the time point a DTP vaccine is received (often with OPV, but not together with BCG) and until another type of vaccine (typically MV) is given, or the child reaches the recommended age of MV (the latter being an "administrative censoring" to avoid prolonging follow-up selectively for children who are not vaccinated on time).
Similarly, the NVAS/placebo MR for BCG should be calculated from the time point of BCG vaccine is received and until whichever comes first: another type of vaccine (typically DTP) is given, or the child reaches the recommended age of DTP (administrative censoring).

There are several aspects which should be kept in mind:

1) The effect of receiving first BCG and then DTP on overall mortality is different from receiving BCG and DTP simultaneously (**Figure 5**). Hence, the studies should have collected dates of vaccination so that they are able to discriminate between "BCG and then DTP" (WHO recommended schedule) and "BCG plus DTP" (alternative schedule). In many settings like in urban Guinea-Bissau, most children follow the WHO schedule, but in Asia and in rural settings there is a lot of variation. See **Figure 6**, based on an Indian study.
   To test our hypothesis, the only children who should be counted as DTP-vaccinated are the children from Groups II, IV and VII (**Figure 6**). It would be ideal also to include children from Group V till they receive the next vaccine, but that will often not be possible unless vaccination data are collected with very short intervals. The children who should participate as BCG-vaccinated are children in Group I, censored at the time point a new vaccine is given, or latest at the scheduled age of DTP (administrative censoring).
2) To avoid survival bias, vaccination information should only be used if the very same information would have been obtained if the child had died (Jensen et al, TMIH 2007, Farrington et al, TMIH 2009). Vaccination data is often collected with large intervals and it is often not possible to obtain information from dead children. In that case a **landmark vaccination status analysis** should be conducted. This means that a child

should only be counted as vaccinated from the date the information was obtained. For instance, if it is noted at age 3 months that a child was DTP vaccinated at age 2 months, then the child should only be considered DTP vaccinated from age 3 months.
If the intervals between the data collection are very small or there is fully updated information on the vaccination status of children who died, then the risk of bias is limited and a **vaccine status analysis with actual vaccine dates** can be performed.
In both the **landmark vaccination status analysis** and the **vaccine status analysis with actual vaccine dates**, children who are travelling or away should not be included as it was not possible to check their vaccination status.

B) ***Age-specific NVAS/placebo analysis:*** In ***studies which have not collected individual level data on vaccination status*** it might be possible to test the hypothesis indirectly if it is known that the vaccination coverage is high and the recommended schedule has been followed. In such situations it might be possible to examine the NVAS/placebo MR by sex in the age groups where DTP and BCG are likely to be the most recent vaccinations. From 5-8 months of age it is reasonable to assume that all children are DTP vaccinated (Aaby et al, Vaccine 2006). If it can be documented that most children are DTP vaccinated within a wider age-span, then that can be applied; for instance we used 3-8 months in a highly vaccinated population (Benn et al, Vaccine 2009, **Table 1 below**). The BCG analysis should be limited to the age before recommended DTP vaccination, hence typically from 0-6 weeks of age.

For both A) and B) types of analyses, the following points should be applied:

1) Maternal VAS seems to have independent effects on child mortality (**Table 2**). To test our hypothesis, children whose mothers received VAS should be excluded or analysed separately.
2) NVAS may interact with VAS during follow-up (Fisker et al, PLoS ONE 2011 and BMJ Open 2013). Hence, to test our hypothesis, children eligible for a VAS campaign or for VAS at a certain age at a health centre, should be censored at the age when they become eligible (administrative censoring)[2].
3) Children born of HIV positive mothers have very high mortality, in particularly males. VAS and HIV may interact. To test our hypothesis, children whose mothers are known HIV positive should be excluded or analysed separately. If there is no information on HIV status the analysis should be restricted to low HIV prevalence settings.

It is possible that if NVAS affects health before the age of DTP-vaccination then it may affect the proportion of children getting DTP vaccinated in the NVAS and placebo groups. This can be assessed a) by comparing the distribution of background factors in the NVAS and placebo groups at the time of registered DTP vaccination, and b) by testing if the time to registered DTP vaccination differs between the NVAS and placebo groups. It should be noted that the selection bias would have to take place in a narrow time window between randomisation and around 6 weeks of age. We have found no indication that this was the case in our data.

[2] Other health interventions during follow-up should also be taken into account.

Suggested data analysis within the different NVAS trials

The actual data analysis would depend on vaccine data available in each of the NVAS trials. Below follows suggestions for analysis for each of the NVAS trials; they are also summarised in **Table 3** and a separate table has been made for each of the relevant trials.

Nepal 1995: No vaccination data collected. Vaccination coverage was low. Vitamin A was given late in the neonatal period. **Not feasible.**

Indonesia 1996: No vaccination data collected. As far as I have understood, normal-birth-weight children received BCG at birth, but low-birth-weight children did not. If vaccination coverage was high and most children were vaccinated according to the recommended schedule, it could be possible to conduct an **age-specific NVAS/placebo analysis** (see definition above). However, as there is only one death after 4 months of age in the trial, the possibilities of studying NVAS/placebo effects in the DTP window will be very limited unless it is very safe to assume that all children had received DTP by for instance 2 months of age – and that is probably unlikely that sufficient evidence is available. **Not feasible unless the authors have other information.**

India 2003: This trial collected vaccination data every 14 days. An analysis of vaccine effects by NVAS status has been made (Moulton et al, TMIH 2005). Unfortunately, it is not possible to deduce NVAS/placebo estimates in the DTP and BCG windows from the publication because the analysis censored the first week post-NVAS/placebo-supplementation and there was no discrimination between "BCG and then DTP" and "BCG plus DTP".

As far as I understand the trial, the analysis testing our hypothesis could be done as a **vaccine status analysis with actual vaccine dates (Table 4)**. NVAS-placebo mortality rates could be calculated for males and females who had DTP alone as their most recent vaccine, until a new vaccine type was given or to the end of follow-up at 6 months of age (before the recommended age of MV). Similarly NVAS-placebo mortality rates could be calculated for males and females who had BCG alone as their most recent vaccination, until a new vaccine type was given or the scheduled age of DTP vaccine (administrative censoring). Additional VAS during follow-up should not be an issue since the children were only followed to 6 months. To my knowledge the HIV prevalence was low.

***Zimbabwe 2005/2006*:** Presumably no vaccination data was collected. Jean Humphrey once told me that vaccination coverage was high and most children received first BCG, then DTP, like in Guinea-Bissau. Hence, if no vaccination data was collected, but vaccination coverage was high and most children were vaccinated according to the recommended schedule, it should be possible to conduct an **age-specific NVAS/placebo analysis (Table 5)**. The maternal VAS group and the maternal HIV cohort should be excluded or analysed separately.

Bangladesh 2008: Vaccination data was only obtained as "Yes/No" at home visits at age 3 months and at end of follow-up at age 24 weeks. Hence, it is impossible to distinguish between "BCG and then DTP" and "BCG plus DTP". Thus, an analysis up to 6 months of age is **probably not feasible**. **Potentially**, if follow-up data to 9 months of age can be added, one could do a **landmark vaccination status analysis (Table 6)**, studying the effect of NVAS among males and females who had DTP2 or DTP3 registered by 6 months of age (and thus presumably received the last DTP without BCG and were unlikely to receive anything but DTP

from 6 to 9 months) on survival up to 9 months of age (the scheduled age of MV). Children whose mothers received VAS or beta-carotene should be excluded or analysed separately. I do not know if additional VAS was given between 6 and 9 months of age. To my knowledge the HIV prevalence was low.

***New Ghana trial 2014*:** The trial collected vaccination status data every month. The probability of obtaining vaccine status data from dead children was low. To address our hypothesis I propose to make a **landmark vaccination status analysis (Table 7)**, letting children change vaccination status at the date when the new vaccination status is obtained. Hence, children enter the analysis if their card is seen at a given visit. They are stratified by vaccination status at the visit in the groups I, II, III etc. (**Figure 6**). This is repeated at subsequent visits. Note that a child can change status at each visit.

Children whose mothers received VAS should be excluded or analysed separately. Depending on the frequency of VAS during follow-up, administrative censoring for VAS should be considered from age 6 months. The HIV prevalence is so low that this could be disregarded.

***New Tanzania trial 2014*:** The trial collected vaccination status data every 3 months, i.e. at 3, 6, 9, and 12 months of age. The probability of obtaining vaccine status data from dead children was low. To address our hypothesis I propose to make a **landmark vaccination status analysis (Table 8)**, comparing mortality from 1st to 2nd visit (i.e. from around 3 months of age to 6 months of age) and from 2nd to 3rd visit (approx. 6-9 months of age)**.**

Children enter each of the analysis if their card is seen at the visit initiating the follow-up period. They are stratified by vaccination status at the visit initiating the follow-up period in the groups I, II, III etc. (**Figure 6** and **Table 8**). Note that it is not necessarily the same children who participate in the two analyses, since it depends on the vaccination card being seen.

Since there is quite a long interval between the data collection rounds, the validity of the analysis depends on the vaccination intensity with new vaccine types between the rounds. Therefore it would be useful to make a table for surviving children like the one illustrated in **Table 9**.

Children whose mothers received VAS should be excluded or analysed separately. Depending on the frequency of VAS during follow-up, administrative censoring for VAS should be considered from age 6 months (it is not recommended for children below 6 months of age, so it should not interfere with the 1st analysis). The HIV prevalence is so low that this could be disregarded.

New India trial 2014: Mothers often do not keep their vaccination card, so information was to a large extent maternal recall. If a mother said she thought a child had received a given vaccine, she was often asked to verify the information, and the information was then only noted at the next visit. It is not possible to see at which visit a given vaccination date has been noted. Hence, if a child was vaccinated at 2 months of age, the interviewer came by at 3 months of age and asked the mother to verify the information and then only saw her again at 9 months of age, the verified vaccination date at 2 months of age would be noted, but it would not be possible to see that it was only noted at age 9 months rather than at age 3 months. So there could be very big delays between vaccination and obtained information and no way to

assess that since dates of obtaining information were not collected. The vaccination coverage was rather low. **Probably not feasible.**

Overall conclusion

It should be feasible to test the hypothesis in at least the India 2003 trial, the Ghana trial, the Tanzania trial and possibly the Bangladeshi trial (table 3). Analysis by age group can be considered in the Zimbabwean trial (table 3).

The way to proceed would be for all the relevant trials to prepare curves as those suggested in Figure 7, and prepare the tables suggested for their trial. This could potentially be done during an analysis workshop in Copenhagen.

The idea would be to produce a common paper presenting the hypothesis and how it has been addressed in all existing NVAS trials which could provide data to address it. Based on the homogeneity of the results we can decide whether it will be most meaningful to present trial specific analyses or whether they can be combined in a final meta-analysis.

Do not hesitate to get back to me if there are comments, suggestions or questions.

Kind regards,

Christine

Figures 1-3. Cumulative mortality curves for male (blue curves) and female (red curves) NVAS and placebo recipients after registration of DTP vaccine, censored at which came first: the date of registration of a measles vaccine or age 9 months (age 12 months in low-birth-weight children due to low vaccination coverage).

Figure 1. Normal birth weight trial 2002-2004 (Benn et al, BMJ 2008 and Benn et al, Vaccine 2009)

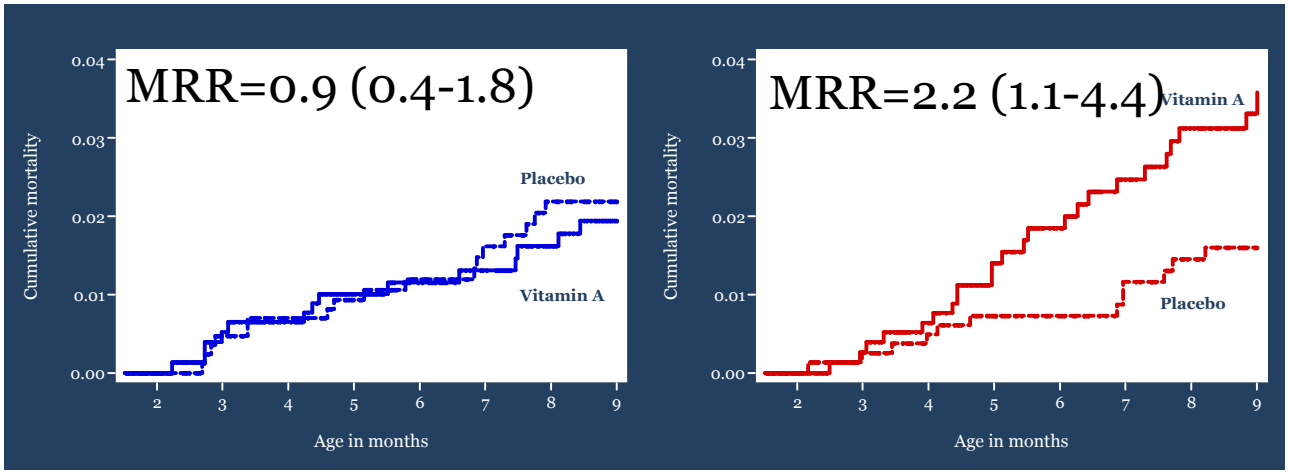


Figure 2. Low birth weight trial 2004-2007 (Benn et al, BMJ 2010)

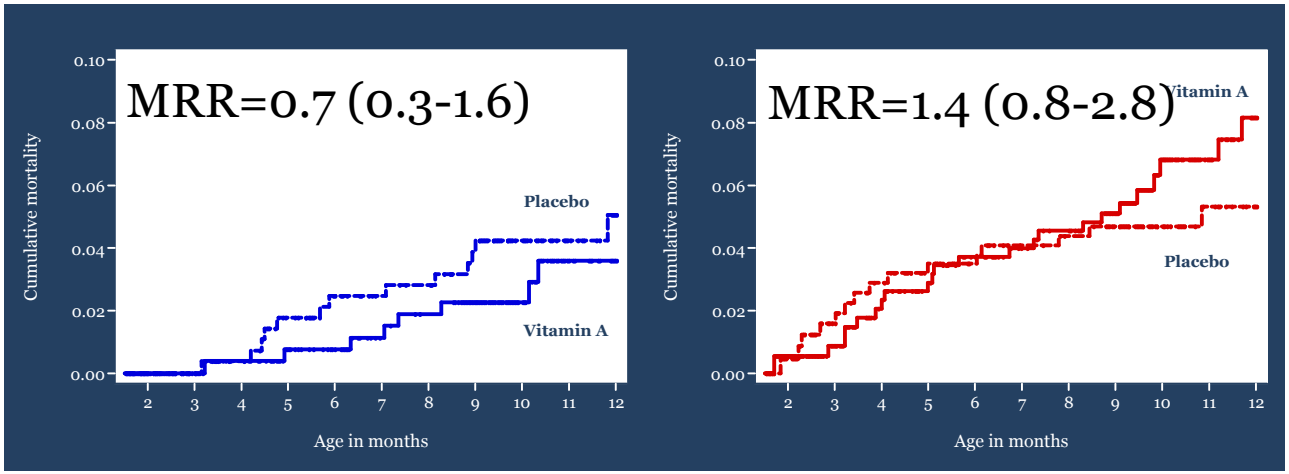


Figure 3. Normal birth weight trial 2004-2008 (J Nutr, 2014)

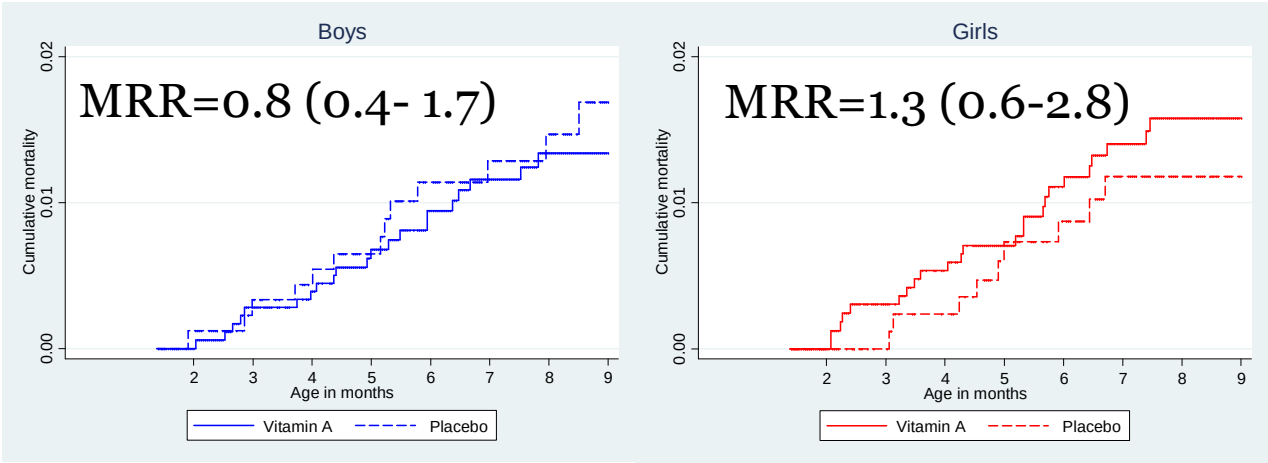


Figure 4. Combined analysis of the three trials in Figures 1-3

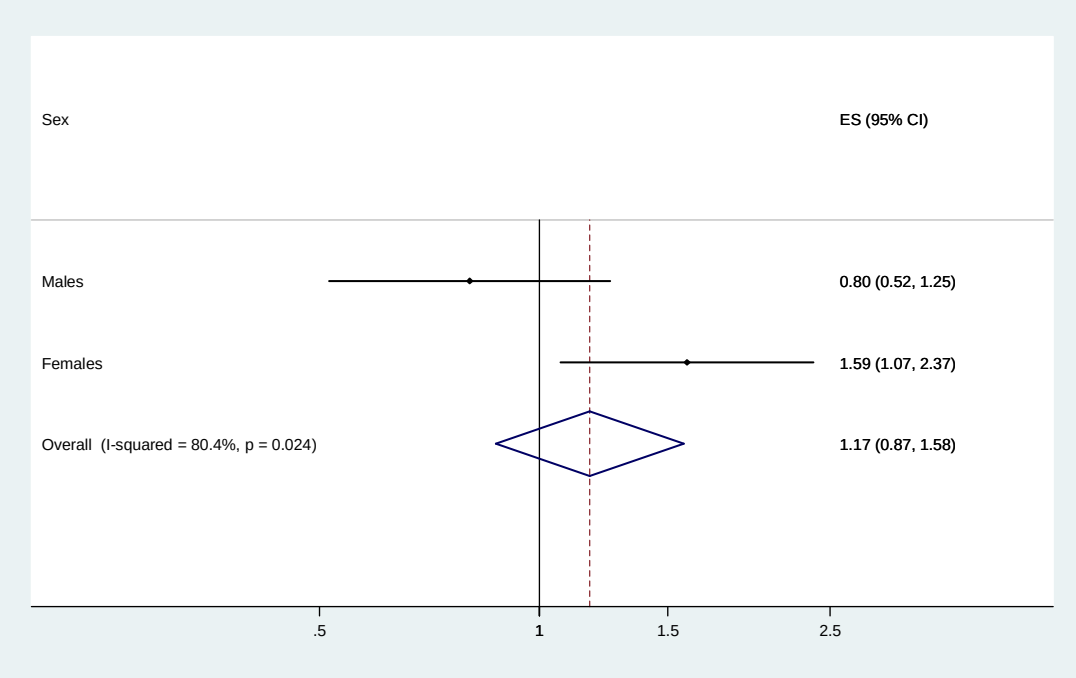
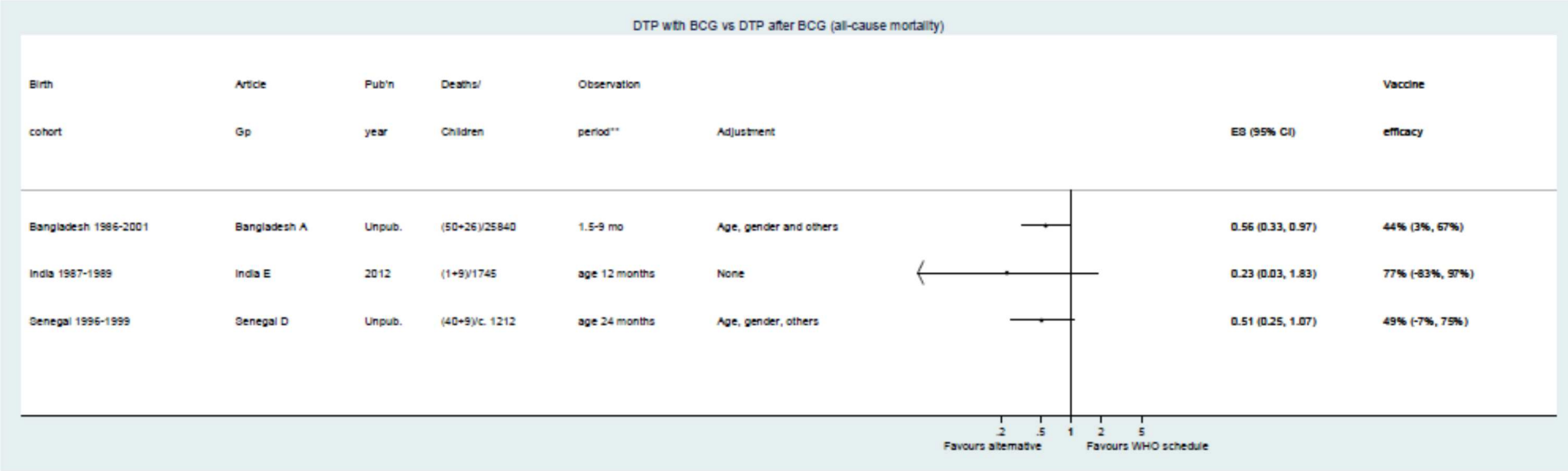


Figure 5. The effect BCG and then DTP differs from the effect of BCG plus DTP. From WHO review
(http://www.who.int/immunization/sage/meetings/2014/april/3_NSE_Epidemiology_review_Report_to_SAGE_14_Mar_FINAL.pdf?ua=1)

Figure 13. Sequence of DTP and BCG and all-cause mortality: simultaneous administration of DTP and BCG compared with BCG before DTP.



ES = effect size (hazard ratio, rate ratio or risk ratio)
Deaths/Children = (Deaths simultaneous + Deaths WHO recommended)/Total children or Total deaths/Total children
All studies are cohort studies.

Figure 6. Real-life variations in the sequence and combination of vaccines. From Hirve et al, Vaccine 2012

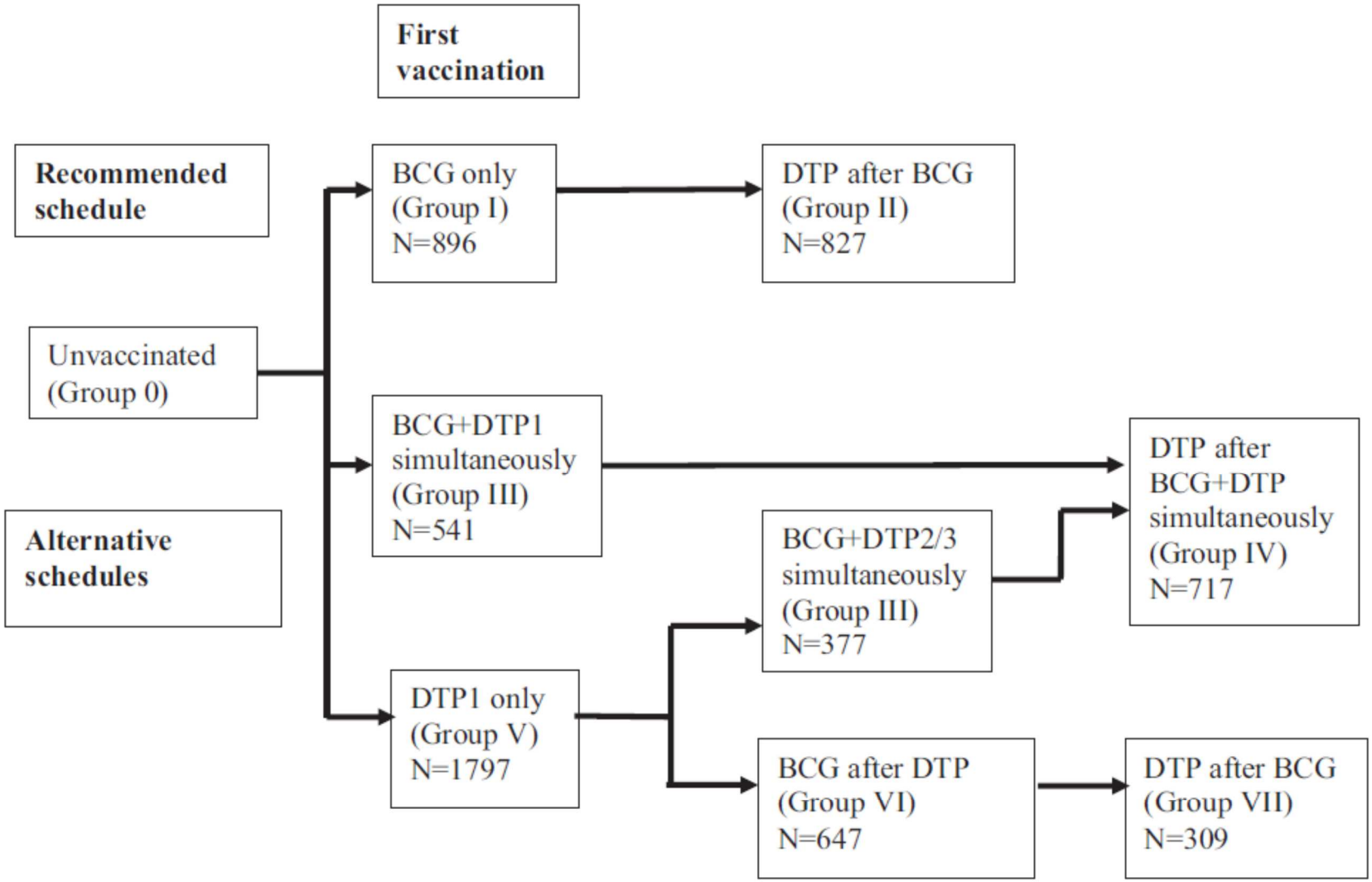
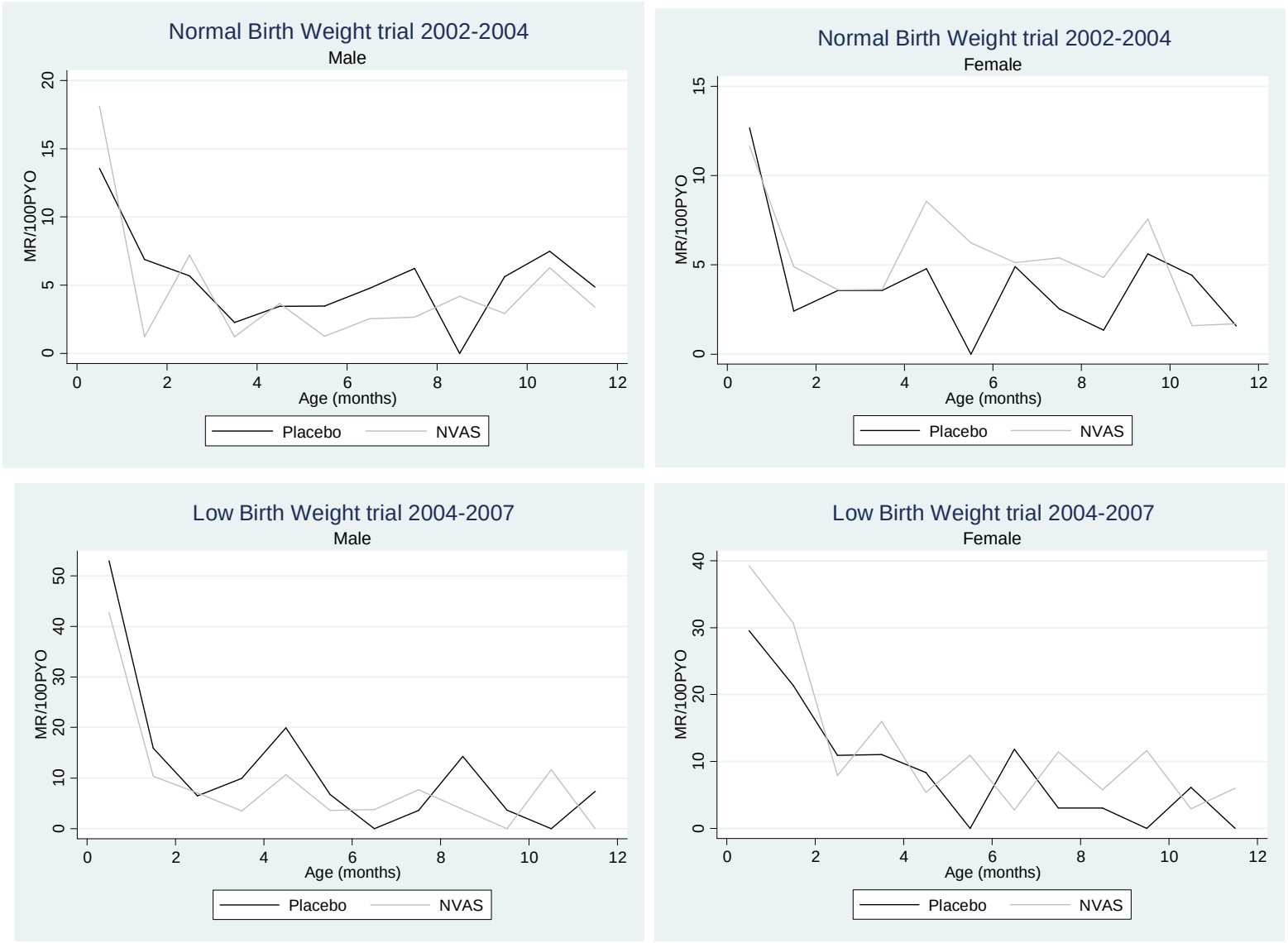
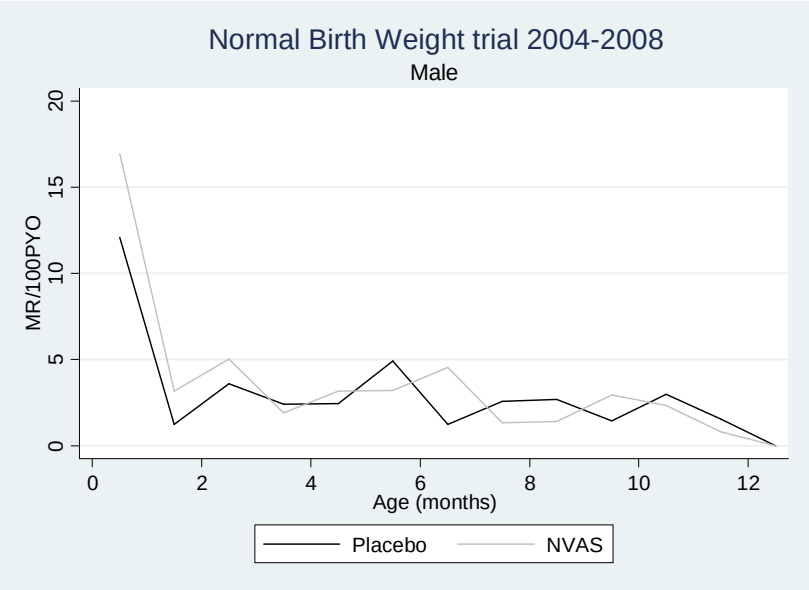


Fig. 1. Common sequences of vaccinations.

Figure 7. Mortality rates for males and females in each of the three NVAS trials from Guinea-Bissau




Normal Birth Weight trial 2004-2008
Male
MR/100PYO
0
5
10
15
20
0
2
4
6
8
10
12
Age (months)
Placebo
NVAS

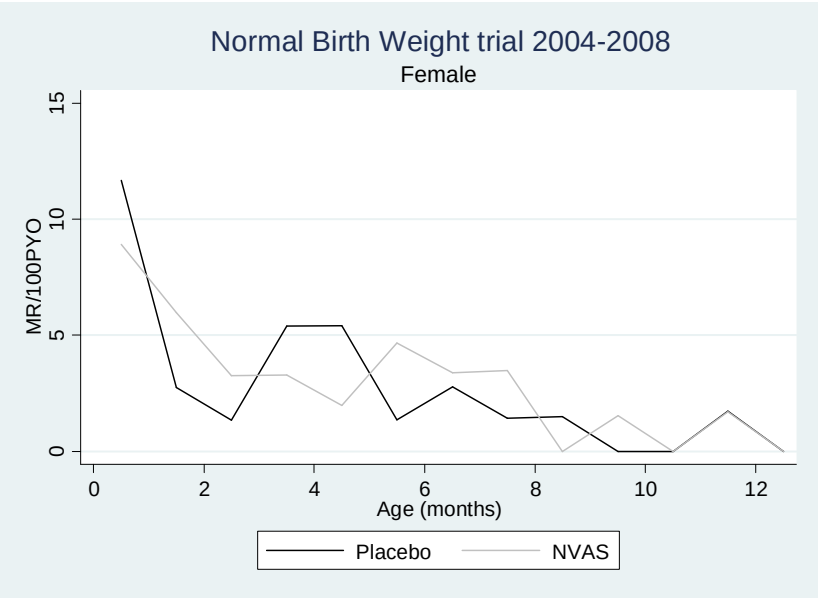

Normal Birth Weight trial 2004-2008
Female
MR/100PYO
0
5
10
15
0
2
4
6
8
10
12
Age (months)
Placebo
NVAS

Table 1. Examples of *Age-specific NVAS/placebo analysis* and *Vaccine status analysis.* Having BCG as most recent vaccine is defined by the period from receipt of BCG (provided by the researchers) to 6 weeks of age. Having DTP as most recent vaccine is defined in two ways: by age group (3-8 months of age, defined after investigation of vaccination timeliness and coverage in the study population) and by means of actual vaccination status (starting from the date *the information about the DTP vaccination was obtained* (landmark vaccination status analysis) (Benn et al, Vaccine 2009).

Table 1
Mortality rate ratios (MRR) according to vaccination status.

	Overall			Boys			Girls			Equal VAS effects, boys vs. girls
	VAS	Placebo	MRR	VAS	Placebo	MRR	VAS	Placebo	MRR	
	Deaths/Pyrs			Deaths/Pyrs			Deaths/Pyrs			
BCG most recent vaccine	21/194	25/200	0.86 (0.48–1.54)	13/98	15/102	0.89 (0.43–1.88)	8/95	10/97	0.82 (0.32–2.08)	$p = 0.89$
DTP most recent vaccine (age group)	33/757	28/819	1.28 (0.77–2.11)	10/387	15/416	0.72 (0.32–1.60)	23/370	13/403	1.93 (0.98–3.81)	$p = 0.07$
Equal VAS effects in DTP (age group) vs. BCG			$p = 0.31$			$p = 0.70$			$p = 0.15$	
DTP most recent vaccine (vaccination status)	38/849	29/925	1.43 (0.88–2.32)	14/432	17/469	0.90 (0.44–1.82)	24/417	12/455	2.19 (1.09–4.38)	$p = 0.08$
Equal VAS effects in DTP (vaccination status) vs. BCG			$p = 0.19$			$p = 0.98$			$p = 0.10$	

Table 2. (From Benn et al, Lancet 2011, based on the Zimbabwe trial data). Mother VAS- child placebo-group (Ap) has borderline significantly higher mortality than Mother placebo-child placebo-group (Pp)

	9208 children of HIV-uninfected mothers (170 deaths)*[4]	4495 children of HIV-infected mothers (865 deaths)*[5]	14 110 children†‡[5]
Mother VAS, child VAS (Aa)	1·28 (0·83–1·98)	1·08 (0·88–1·31)	1·06 (0·89–1·26)
Mother VAS, child placebo (Ap)	1·27 (0·82–1·97)	1·24 (1·02–1·50)	1·18 (0·99–1·40)
Mother placebo, child VAS (Pa)	1·18 (0·76–1·83)§	1·21 (0·99–1·46)§	1·16 (0·98–1·38)
Mother placebo, child placebo (Pp)	Reference	Reference	Reference

*Unadjusted results. †Adjusted results. ‡Total included 407 children whose mothers had HIV indeterminate results or seroconverted during follow-up. §In a combined analysis of the unadjusted results from this randomised clinical trial, the mortality hazard ratio comparing Pa vs Pp was 1·21 (95% CI 1·01–1·44).

Table: Mortality hazard ratios (95% CI) for different vitamin A supplementation strategies compared with placebo for children according to maternal HIV status, Zimbabwe

Table 3. Overview of NVAS trials, vaccine data available and suggested analysis

Study	Vaccine data	Other important issues	Suggested analysis	Possible to address the following aspects
Nepal	No	Vitamin A given quite late	**Not feasible**	
Indonesia	No	Probably no maternal VAS or VAS during follow-up, and low HIV prevalence	Presumably no vaccination dates and very few deaths after the first months of life. **Not feasible unless the authors have other information.**	
India	Yes, every 14 day	Probably no maternal VAS or VAS during follow-up, and low HIV prevalence	**Vaccine status analysis using actual vaccine dates**, stratified by "BCG alone", "BCG and then DTP", BCG+DTP", and potentially other variations (**Table 4)**	F-MR (DTP)>1 F-MR(DTP) >M-MR(DTP) F-MR(DTP)>F-MR(BCG)
Zimbabwe	No	HIV positive cohort excluded or separately. Maternal VAS cohort excluded/separately. VAS during follow-up?	If high vaccination coverage and most children follow normal schedule of "BCG and then DTP" then **age-specific NVAS/placebo analysis* (Table 5)**	F-MR (DTP)>1 F-MR(DTP) >M-MR(DTP) F-MR(DTP)>F-MR(BCG)
Bangladesh	At age 3 months and 24 weeks, but only "Yes/No", no dates.	No vaccination dates collected. Maternal VAS/beta-carotene cohort excluded/separately. Probably no VAS during follow-up, and low HIV prevalence	**Not feasible.** Potentially, if follow-up data to 9 months can be added: **Landmark vaccine status analysis** assessing the impact of NVAS in males and females with DTP2/3 at 6 months of age; censoring at VAS campaigns after 6 months. **(Table 6)**	F-MR (DTP)>1 F-MR(DTP) >M-MR(DTP)
Ghana	Monthly – noted whether card was seen or not	Maternal VAS excluded or separately. VAS during follow-up censor? Low HIV prevalence	**Landmark vaccine status analysis** – vaccination status at each monthly assessment; follow-up for one month until next assessment **(Table 7)**	F-MR (DTP)>1 F-MR(DTP) >M-MR(DTP) F-MR(DTP)>F-MR(BCG)
Tanzania	At ages 3,6,9 and 12 months	Maternal VAS excluded or separately. VAS during follow-up censor? Low HIV prevalence	**Landmark vaccine status analysis (Table 8) -** vaccination status at 3 months, follow-up to 6 /9 months. Validity depends on vaccination intensity between 3 and 9 months of age.#	F-MR (DTP)>1 F-MR(DTP) >M-MR(DTP)
India	At ages 3,6,9 and 12 months - mostly recall	No maternal VAS VAS during follow-up? Low HIV prevalence	**Not feasible** since no dates of obtaining the information was noted and there could be big delays between vaccination and obtained information.	

*If the vaccination coverage is high and most children receive vaccines according to schedule, one can calculate F-MR and M-MR in a) the BCG window (birth to official age of first DTP); b) the DTP window from age of first DTP to age of MV; and possibly c) the MV window from age of MV to end of follow-up (or age of booster DTP if provided).

#The chances of children becoming vaccinated with a different vaccine type during follow-up can be assessed by studying the children who survived to end of follow-up. If a high proportion of children receive a different vaccine type during follow-up, the analysis should not be done (See also **Table 9**).

Table 4. Suggested table for assessing interactions between NVAS and vaccination status in the India 2003 trial.

	All			Males			Females			P for equal effect of NVAS in males and females
Most recent vaccine at home visit	NVAS	Placebo	Hazard ratio	NVAS	Placebo	Hazard ratio	NVAS	Placebo	Hazard ratio	
No vaccine information obtained	Deaths/pyrs [N]	Deaths/pyrs [N]								
No vaccines (Group 0)	Deaths/pyrs [N]	Deaths/pyrs [N]								
BCG only* ***(Group I)***	etc									P
One or more DTP after BCG (Group II)										P
BCG+DTP together (Group III)										
One or more DTP after BCG+DTP (Group IV)										P
DTP alone (Group V)										P
BCG after DTP (Group VI)										
One or more DTP after-BCG-after-DTP (Group VII)										P
P for equal effect in **DTP** versus ***BCG*** vaccinated			P			P			P	

*Administrative censoring by 6 weeks of age, the scheduled age of DTP.
The group numbers refers to Figure 6. Note that follow-up can start at the date the vaccine was given. Note that a child can change group.
DTP-vaccinated children are children in Groups II, IV, V and VII. ***BCG***–vaccinated children are children in Group I (and theoretically Group VI, but such children should all be 6 weeks or older and hence not eligible for the BCG group).

Table 5. Suggested table for assessing interactions between NVAS and vaccination status in the Zimbabwean trial. This trial had follow-up to at least a year and high mortality throughout the trial, so it should be possible to look also at the MV window as suggested.

	All			Males			Females			P for equal effect of NVAS in males and females
	NVAS	Placebo	Hazard ratio	NVAS	Placebo	Hazard ratio	NVAS	Placebo	Hazard ratio	
BCG window from 0-6 weeks of age	Deaths/pyrs [N]	Deaths/pyrs [N]		Etc						P
DTP window from ?-8 months of age	Deaths/pyrs [N]	Deaths/pyrs [N]		Etc						P
P for equal effect in DTP versus BCG windows			P			P			P	

Table 6. Suggested table for assessing interactions between NVAS and vaccination status in the Bangladeshi trial – should be made from the 6-month-visit to 9 months of age (or the age of MV).

	All			Males			Females			P for equal effect of NVAS in males and females
Most recent vaccine at home visit	NVAS	Placebo	Hazard ratio	NVAS	Placebo	Hazard ratio	NVAS	Placebo	Hazard ratio	
No vaccine information obtained	Deaths/pyrs [N]	Deaths/pyrs [N]								
No vaccines (Group 0)	Deaths/pyrs [N]	Deaths/pyrs [N]								
DTP 2/3	Deaths/pyrs [N]	Deaths/pyrs [N]								

Table 7. Suggested table for assessing interactions between NVAS and vaccination status in the Ghana trial.

	All			Males			Females			P for equal effect of NVAS in males and females
Most recent vaccine at home visit	NVAS	Placebo	Hazard ratio	NVAS	Placebo	Hazard ratio	NVAS	Placebo	Hazard ratio	
No vaccine information obtained	Deaths/pyrs [N]	Deaths/pyrs [N]								
No vaccines (Group 0)	Deaths/pyrs [N]	Deaths/pyrs [N]								
BCG only* ***(Group I)***	etc									P
One or more DTP after BCG (Group II)										P
BCG+DTP together (Group III)										
One or more DTP after BCG+DTP (Group IV)										P
DTP alone (Group V)										P
BCG after DTP (Group VI)										
One or more DTP after-BCG-after-DTP (Group VII)										P
P for equal effect in **DTP** versus ***BCG*** vaccinated			P			P			P	

*Administrative censoring by 6 weeks of age, the scheduled age of DTP.

The group numbers refers to Figure 6. Note that follow-up start at the date the information on the vaccine was registered. Note that a child can change group. **DTP**-vaccinated children are children in Groups II, IV, V and VII. ***BCG*** –vaccinated children are children in Group I (and theoretically Group VI, but such children should all be 6 weeks or older and hence not eligible for the BCG group).

Table 8. Suggested table for assessing interactions between NVAS and vaccination status in the Tanzania trial – should be made a) from the 3-month-visit to the 6-month-visit and b) from the 6-month-visit to 9 months of age (or the age of measles vaccination).

	All			Males			Females			P for equal effect of NVAS in males and females
Most recent vaccine at home visit	NVAS	Placebo	Hazard ratio	NVAS	Placebo	Hazard ratio	NVAS	Placebo	Hazard ratio	
No vaccine information obtained	Deaths/pyrs [N]	Deaths/pyrs [N]								P
No vaccines (Group 0)	Deaths/pyrs [N]	Deaths/pyrs [N]								P
One or more DTP after BCG (Group II)	etc									etc
BCG+DTP together (Group III)										
One or more DTP after BCG+DTP (Group IV)										
DTP alone (Group V)										
BCG after DTP (Group VI)										
One or more DTP after-BCG-after-DTP (Group VII)										

The group numbers refers to Figure 6. Note that follow-up start at the date of the home visit, when the information on the vaccine was registered. Note that a child can change group. **DTP**-vaccinated children are children in Groups II, IV, V and VII.

Table 9. Example of table describing vaccination intensity among children who survived to next follow-up (from Benn et al, Am J Clin Nutr 2009)

APPENDIX A

Proportion of children receiving vaccination between enrollment and 4 mo, between enrollment and 12 mo, and between enrollment and 24 mo among children with a health card and children without a health card at enrollment[1]

Health card status and vaccination status at enrollment	Vaccinated between enrollment and 4 mo later[2]		Vaccinated between enrollment and 12 mo later[2]		Vaccinated between enrollment and 24 mo later[3,4]
	Received ≥1 DTP during follow-up	Received MV during follow-up	Received ≥1 DTP during follow-up	Received MV during follow-up	Received ≥1 DTP during follow-up
	% (n/total n)	*% (n/total n)*	*% (n/total n)*	*% (n/total n)*	*% (n/total n)*
No health card at enrollment					
Presumably unvaccinated	7 (297/4027)	7 (274/4027)	11 (434/4027)	12 (473/4027)	11 (383/3564)
Had health card at enrollment					
No MV at enrollment					
BCG (no DTP or MV)	38 (30/80)	29 (23/80)	55 (44/80)	56 (45/80)	56 (39/70)
DTP1-2 (no MV)	49 (392/799)[a]	39 (308/799)	71 (566/799)[b]	66 (529/799)	74 (529/717)[c]
DTP3-4 (no MV)	6 (14/230)[a]	49 (113/230)	9 (20/230)[b]	61 (141/230)	9 (17/200)[c]
Had health card at enrollment					
MV at enrollment					
DTP0-2	37 (419/1147)[d]		51 (585/1147)[e]		51 (515/1010)[f]
DTP3-4	4 (91/2036)[d]		6 (124/2036)[e]		6 (103/1774)[f]

[1] BCG, bacille Calmette-Guérin; MV, measles vaccine; DTP, diphtheria-tetanus-pertussis vaccine; DTP1-2, 1–2 doses of DTP; DTP3-4, 3–4 doses of DTP; DTP0-2, had not yet received 3 doses of DTP. Values with the same superscript letters had a significantly different incidence of DTP vaccination, $P < 0.00001$.

[2] All children whose vaccination status was assessed in the first and the fourth round.

[3] All children whose vaccination status was assessed in the first and the seventh round.

[4] Data on measles vaccination from the seventh round are missing. Hence, it was not possible to measure the incidence of measles vaccination in the last year of the study.