CVIVA RESEARCH CENTER FOR VITAMINS & VACCINES

Bissau, 7 April 2016

Dear

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**THE SAGE REVIEW OF DIPHTHERIA-TETANUS-PERTUSSIS (DTP) VACCINE: FOLLOW-UP ON THE POTENTIAL DELETERIOUS NON-SPECIFIC AND SEX-DIFFERENTIAL EFFECTS OF DTP**

***Executive Summary:*** The 2014 SAGE-commissioned review of the non-specific effects of vaccines concluded that the mortality results for DTP were inconsistent and that there were no sex-differential effects of DTP. Nothing has happened since. We worry that the above conclusions have created the illusion that this is not a pertinent problem. We believe that there is ample evidence that action needs to be taken now. First, we have just completed the analyses of the introduction of DTP in Guinea-Bissau in 1981-1983. DTP-vaccinated children had 5 times higher mortality than controls. Furthermore, we attach the first study examining whether pentavalent vaccine (DTP+Hib+HBV) has similar sex-differential effects as DTP; the female-male mortality rate ratio (MRR) among children with pentavalent vaccine as their most recent vaccine was 1.73 (1.11-2.70), supporting that pentavalent vaccine possesses the same negative non-specific effects for females as DTP. Second, in spite of many previous papers concluding that studies with frailty and survival bias cannot be used to assess the effect of a vaccine, the SAGE review included studies with major frailty and survival bias. If these studies are excluded, DTP is associated with at least two-fold higher mortality, and DTP-vaccinated females had a MRR of 1.50 (1.21-1.85) compared with DTP-vaccinated males in the 16 available studies. Thus, even before the new studies, DTP was associated with significantly higher overall and female mortality if the correct methods were applied, and including the new studies mentioned above make the conclusions even stronger. Third, it should be noted that both the overall estimates and within-study estimates show that the overall mortality effect of DTP is highly significantly different from the effect of BCG and MV. Thus, there is a real danger-signal and vaccinology urgently needs to prove that DTP-containing vaccines are safe (also for females).

**Attached papers:**

I. Mogensen SW*, Andersen A*, Rodrigues A, Benn CS, Aaby P. The introduction of diphtheria-tetanus-pertussis and oral polio vaccine among infants in an urban African community: A natural experiment (under review)
II. Fisker AB, Biering-Sørensen S, Lund N, Djana Q, Rodrigues A, Martins CL, Benn CS. Contrasting female-male mortality ratios after routine vaccinations with pentavalent vaccine versus measles and yellow fever vaccine in urban Bissau (submitted)
III. Aaby P, Ravn H, Benn CS. The WHO review of the possible non-specific effects of diphtheria-tetanus-pertussis vaccine (under review)
IV. Aaby P, Ravn H, Fisker AB, Rodrigues A, Benn CB. Is DTP associated with increased female mortality? Testing the specific hypotheses of the non-specific effects of vaccines (under review)

**INTRODUCTION**

In 2008, GACVS declared that it would keep a watch on the evidence of non-specific effects of vaccines, including a potential deleterious effect of DTP (1).

In 2013-2014, SAGE sponsored a review of the potential non-specific effects (NSEs) of BCG, DTP and measles vaccine (MV). The studies on BCG and MV suggested beneficial NSEs, but the review found that most studies (7/10) suggested a deleterious effect of DTP. However, since two studies had a beneficial effect of DTP, the reviewers concluded that studies were inconsistent (2). Furthermore it was concluded that there was no convincing evidence for a sex-differential effects of DTP (2,3). The matter was transferred to IVIR-AC to plan further studies to examine the NSEs of vaccines. Nothing has happened yet. Apparently, though the indication of possible harm from a vaccine ought to create a response, the issue is not given very high priority. We worry that the conclusion that the DTP studies were inconsistent has created the illusion that this is not a pertinent problem.

Here, we argue that A) two additional studies conducted after the completion of the review further substantiate that DTP has deleterious and sex-differential effects on all-cause mortality, even in the context of no herd immunity; B) the reason for inconsistent results was that the review included studies using a flawed methodology; and C) furthermore, it should be cause for action that the overall mortality effect of DTP was highly significantly different from the effect of BCG and MV, both overall and within individual studies.

## A. New results on DTP/pentavalent vaccine

### DTP (Paper I):

We have recently evaluated what happened when we first introduced DTP and OPV to infants in Bissau, Guinea-Bissau, in 1981 as described in the attached paper (I). Children were called for nutritional examinations every three months and they were then offered vaccinations at the same time. At the time, DTP and OPV were given to children from 3 months of age. The children were only called for examinations and vaccinations every three months. Hence, due to the variation in date at birth some children were vaccinated shortly after 3 months of age whereas other were nearly 6 months old when they received DTP. This experiment is illustrated in Figure 1.

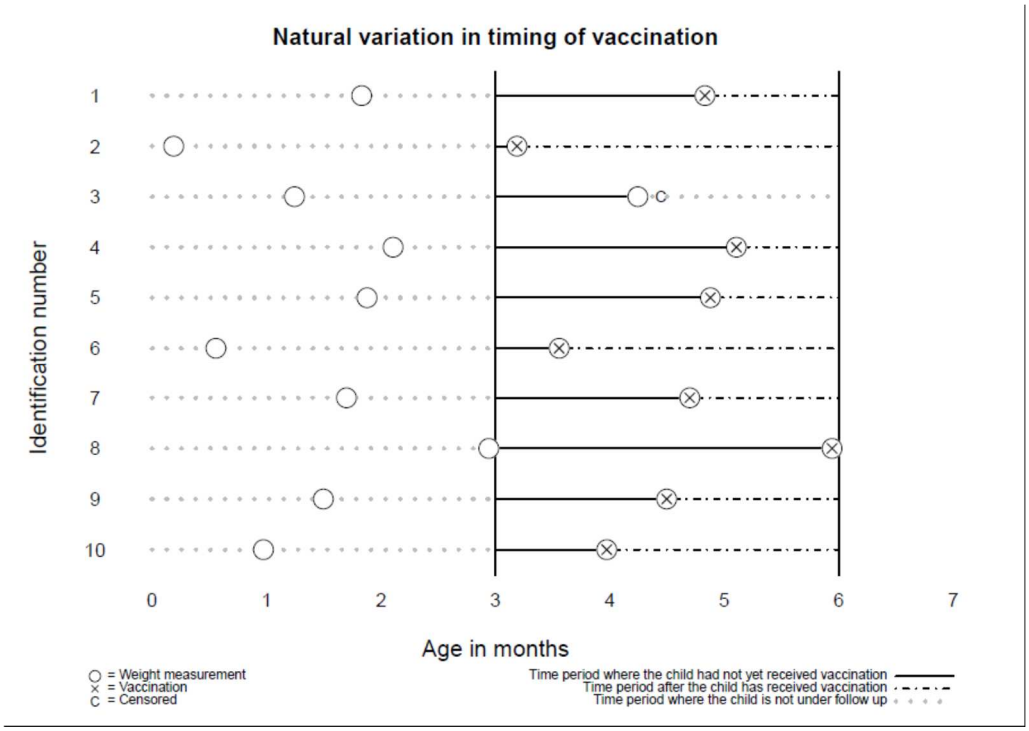


**Figure 1. Natural experiment study design**

Note: Children were weighed every third month. After 3 months of age they received DTP and OPV on weighing days if they were healthy. Children who were not vaccinated at a weighing session after 3 months of age were censored in the survival analysis comparing DTP-vaccinated and unvaccinated children.

In this natural experiment we compared mortality between 3 and 6 months of age according to vaccination status. Adjusting for age, the children who had received DTP (+/-OPV) had a hazard ratio (HR) of 5.00 (1.53-16.3) compared with being unvaccinated (Table 1). This may be the closest we will get to a study where unvaccinated children are a group not selected by frailty bias.

**Table 1. Mortality rates and hazard ratios (HR) for DTP-vaccinated and DTP-unvaccinated children aged 3-5 months, Guinea-Bissau, 1981-1984**

| Age group<br>3-5 months | Mortality rate /100 person-years (deaths/person-years) | HR (95% CI) for DTP vs unvaccinated |
|---|---|---|
| Unvaccinated (N=652) | 4.5 (5/111.4) | 1 (Ref) |
| DTP (+/-OPV) (N=462) | 17.4 (11/63.1) | 5.00 (1.53-16.3) |
| DTP only (N=101) | 35.2 (5/14.2) | 10.0 (2.61-38.6) |
| DTP+OPV (N=361) | 12.3 (6/48.9) | 3.52 (0.96-12.9) |

In 1981, we also administered DTP to older children aged 12-35 months; DTP was associated with a two-fold increase in mortality (draft, to be submitted later).

**Pentavalent vaccine (Paper II):**

So far, there has been no published study of the potential sex-differential effect of the DTP-containing pentavalent vaccine (penta, DTP+Hib+HBV) which is now used in most low-income countries. When penta was introduced in Bissau we monitored the routine vaccinations at the local health centres and followed the children to next vaccination or for 6 months. It will be seen in Figure 2 that there was a clear sex-differential pattern. The female/male mortality rate ratio was 1.73 (1.11-2.70) following penta and 0.38 (0.12-1.19) after MV (p=0.02 for same effect) (II).

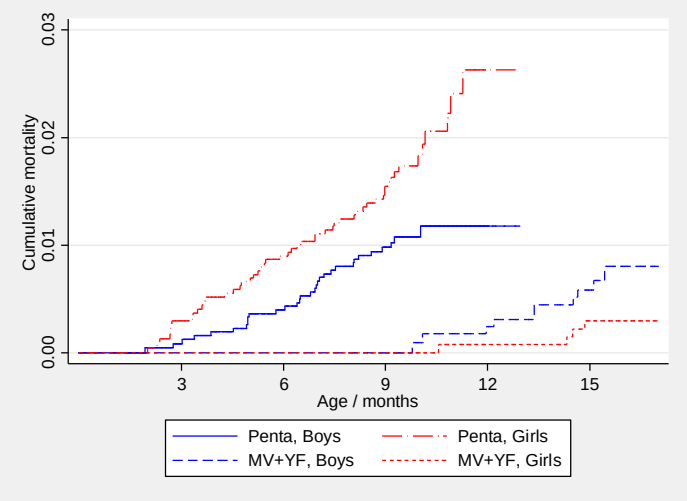


**Figure 2. Cumulative mortality for penta and measles vaccinated girls and boy (II)**

Thus, substituting DTP with penta will not remove the DTP problem.

## B. Critique of the SAGE review (Paper III)

Below we review several of the methodological problems, which have been used to disregard/dismiss a negative effect of DTP (2-5):

- The DTP studies are only observational
- The DTP studies have been conducted in a context of herd immunity
- Since DTP is usually administered with OPV it Is not possible to determine the independent effect of DTP
- All studies have high or very high risk of bias

- ***Only observational studies***

Since it is the general understanding that RCTs delaying DTP are unethical (5), the evidence base consists of natural experiments and controlled observational studies. This should be an argument for conducting RCTs, but as long as such trials are deemed unethical we have to rely on observational studies.

- ***Herd immunity and DTP***

The SAGE Working Group indicated that DTP could not really be evaluated appropriately in situations with herd immunity, since this would misrepresent the value of DTP, as the beneficial protective effect against the target diseases would be invisible (6). However, the best community study of the mortality impact of pertussis was conducted in the 1970s in Kenya in the initiation phase of the vaccination programme; the case fatality was assessed to be 1.3% for all ages, and pertussis was 6% of the infant deaths (7). Given the rather limited contribution of pertussis deaths to overall infant mortality, it seems unlikely that the presence or absence of herd-immunity would lead to serious underestimation of the survival benefits of DTP vaccination.

Furthermore, now two studies from the introduction of DTP in urban and rural Bissau (I, 8) also address this issue. There was no vaccine-induced herd immunity at the time. Hence, there is no justification for thinking that DTP had a strong beneficial effect when there was a lot of pertussis and no herd immunity.

- ***DTP and OPV***

It has been suggested that DTP could not be evaluated because it was always given together with OPV (2,3,6). In the studies of the introduction of DTP in urban and rural Guinea-Bissau there were periods where OPV was not available (I). As seen in Table 2 the negative effect of DTP was much stronger in the periods where there was no OPV. Hence, co-administering OPV has probably reduced the negative NSEs of DTP.

**Table 2. Hazard ratios (HR) for DTP-vaccinated and DTP-unvaccinated children in periods with an without co-administration of OPV**

| Study of introduction of DTP | Hazard ratio (HR) (95% CI) for DTP vaccinated versus DTP-unvaccinated children | |
|---|---|---|
| | DTP-only | DTP+OPV |
| Urban Bissau, 1981-1984 (I) | 10.0 (2.61-38.6) | 3.52 (0.96-12.9) |
| Rural Guinea-Bissau, 1984-1987 (8) | 5.00 (0.63-39.7) | 1.90 (0.91-3.97) |
| Meta estimates | 8.14 (2.63-15.2)# | 2.21 (1.16-4.19)# |

Note: # Interaction test, p=0.049

In the study of the introduction of DTP and OPV in urban Guinea-Bissau, it was possible to estimate the relative impact of DTP-only and OPV-only because there were many children who were vaccinated in periods where vaccines were not available and hence received only DTP or only OPV. As seen in table 3, DTP-only was associated with much higher mortality than OPV-only.

**Table 3. Hazard ratios (HR) for DTP-only and OPV-only vaccinated children**

| Study of introduction of DTP, urban Bissau, 1981-1984 | Mortality rate (deaths/person-years) | | HR (95% CI) for DTP-only versus OPV-only |
|---|---|---|---|
| | DTP-only | OPV-only | |
| Infants aged 3-11 months (I) | 35.2 (5/14.2) | 1.8 (1/57.0) | 10.40 (1.37-78.6) |
| Children aged 12-35 months (draft) | 3.1 (3/96.7) | 1.1 (1/87.6) | 3.47 (0.36-33.57) |
| Meta-estimate | | | 6.39 (1.41-28.94) |

We have found two other studies – both conducted by researcher from John Hopkins University – which estimated the separate effects of OPV and DTP, by comparing children who have received OPV (with or without DTP) to unvaccinated children and DTP (with or without OPV) to unvaccinated children (Table 4). Both studies suggest a worse effect for DTP than OPV. It should be possible to look for other such studies to assess the relative effect of OPV and DTP. How strong the difference will be obviously depends on how many got DTP+OPV and how many got only one of them.

**Table 4. Mortality rate ratios (MRR) for DTP and OPV vaccinated children within the same study.**

| Study | Mortality rate ratio (95% CI) for vaccinated children compared with unvaccinated children in the same study | | The MRR for DTP-vaccinated compared with OPV-vaccinated children |
|---|---|---|---|
| | DTP | OPV | |
| **Haiti (9)** | 1.27 (0.68-2.39) | 0.24 (0.12-0.45) | 5.29 (2.13-13.17) |
| **India (10)** | 0.85 (0.53-1.4) | 0.76 (0.54-1.1) | 1.12 (0.61-2.04) |

**Note:** These studies compared the effect of DTP and OPV with unvaccinated children within the same population. The estimates are not estimates of DTP and OPV given separately but of any DTP or OPV given. Hence, the estimates may depend strongly on how many got the vaccines simultaneously and how many got them separately. We have calculated the MRR for DTP-vaccinated compared with OPV-vaccinated.

- ***High risk of bias (III)***

The main methodological emphasis in the SAGE review was the assessment of potential risk of bias. However, the review did not assess the direction or magnitude of bias, nor whether the hypothetical biases actually had the presumed effect (11).

All available DTP-studies, except one, suggest that the healthiest children are vaccinated first (III); such bias would normally lead to DTP-vaccinated children having lower mortality than DTP-unvaccinated children.

The only proposed biases working in the opposite direction have been firstly, that starting follow-up after vaccination (as would happen with data from demographic surveillance systems) could mean that frail children had already died in the unvaccinated group leading to higher measured mortality in the DTP group; secondly, censoring for MV during follow-up could mean that the healthiest DTP-children were measles vaccinated first and the frail were left to die in the DTP group. In response, it has been shown specifically in one study that delay in starting follow-up had no impact on the estimate (13) and several studies have started follow-up at the time of DTP vaccination (I,II, 8,17) and found similar strong negative effects so there is no evidence that this bias is important. Similarly the studies which have tested whether censoring for MV matters have found no effect (19,24,25) and many studies have not censored for MV and still found a strong negative effect (I, 8,15,23,26) so there is no evidence that this bias is important. Thus, all available evidence, as summarized in paper III, suggests that these invoked biases working in the direction of an overestimation of harm from DTP are not relevant.

With the lack of assessment of the direction in bias and the lack of demonstration of the effect of bias on the estimate, the distinction between 'high risk of bias' or 'very high risk of bias' is not

helpful in assessing the quality and relevance of the DTP-studies included in the SAGE-review. In situations where biases will lead to conservative but still negative estimates it is methodologically incorrect and neither wise nor sage to use the mere existence of 'bias' to suggest that there is no real problem.

**Our consideration of bias in vaccination studies (Paper III)**

The most important biases in vaccination studies are survival bias and frailty bias leading to an unnaturally high mortality rate in the unvaccinated group. If the mortality rate among unvaccinated is unnatural then the estimated benefit of vaccination will be unnaturally high.

The different ways bias may lead to unnaturally high mortality in the unvaccinated group have been described in paper III. For example, when there is imperfect data about vaccinations many children will end up in the "unvaccinated" group not because they are known to be unvaccinated but because there is no other information available (III). An important reason for there being no other information is that the child has already died. As a consequence vaccinated children who are misclassified as "unvaccinated" (because there is no other information) will end up in the unvaccinated group and mortality in the unvaccinated group becomes very high.

As a "bias index" we have therefore examined the HR between unvaccinated and vaccinated (any vaccine) children in the DTP studies included in the SAGE review (Figure 3). It can be seen clearly that when the bias index is very high, the estimates for DTP-vaccinated versus DTP-unvaccinated tend to be particularly beneficial.

In all the studies in the SAGE review *with documentation of vaccination status – also for unvaccinated children* – the bias index was below 1.8. The reasons that some studies had a very high bias index were that bias was introduced by: a) assuming that children for whom no information was available were unvaccinated, b) updating vaccination status for vaccinated children who survived but not for children who died and had no vaccination card available, c) giving fully vaccinated children (which you can only become after 9 months of age) follow-up time from birth, and d) not vaccinating sick children. All studies with survival and frailty bias had a bias index above 2.0.

An illustration of the importance of survival bias stems from our initial DTP study (26,27). In this study we used the "landmark approach" and only included prospective follow-up; the bias index was 1.35 (0.97-1.89) and the estimate for DTP vaccinated versus DTP-unvaccinated was 1.84 (1.10-3.10) (26). However, if we updated information on vaccinations retrospectively in the same data set, thereby introduced survival bias and a higher mortality rate in the unvaccinated group as done in many of the WHO-sponsored studies, the bias index became 2.96 (2.15-4.08) and now DTP had a major beneficial effect on child survival (MRR=0.62 (0.41-0.92)) (27). There is no cut-off value for when the bias index is unnaturally high but this example (27) and the data presented in Figure 2 suggest that when the bias index is above 2 there is reason to be sceptical.

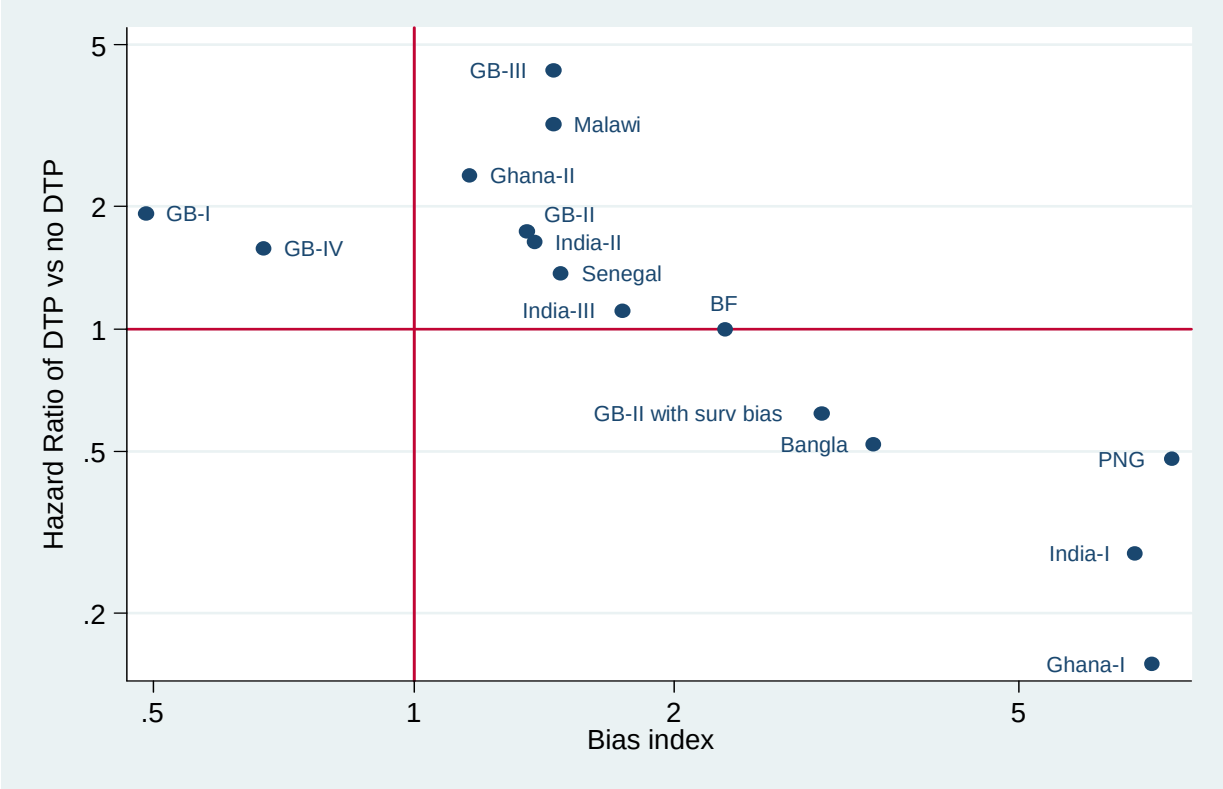


**Figure 3. Scatter plot of the mortality hazard ratio (HR) for DTP-vaccinated versus DTP-unvaccinated and for the bias index (mortality HR for unvaccinated versus vaccinated (any vaccine) children)** Note: The GB-II study is represented with the originally published results (26) and with results when survival bias was introduced in the analysis (27). Abbreviations and references: GB-III=Guinea-Bissau-III (13); GB-II=Guinea-Bissau-II (26); GB-I=Guinea-Bissau-I (8); GB-II with surv bias=Guinea-Bissau-II with survival bias (25); GB-IV=Guinea-Bissau-IV (23); BF=Burkina Faso (28); Bangla=Bangladesh (19,24); PNG=Papua New Guinea (12); Senegal (22); India-II (15); India-I (20); India-III (18); Ghana-II (29); Ghana-I (21); Malawi (17)

Thus, the studies with survival bias should not be used to estimate the effect of DTP compared with no DTP-vaccination. Unfortunately, however, that is what the SAGE review did. The studies which the reviewers claimed had beneficial effects had major survival bias (12,19, 24). These were the studies which permitted the reviewers to say that results were inconsistent. However, the only thing which was inconsistent was the methodology.

In the studies with registration of vaccination status and prospective follow-up, DTP was associated with 2- fold higher mortality (Figure 4). Even though the studies had prospective follow-up there may still have been selection biases in who were vaccinated and not vaccinated. Since the healthiest children are vaccinated first, it is likely that the estimate in Figure 4 is conservative. That is also supported by the new study presented above where DTP had an even stronger negative effect.

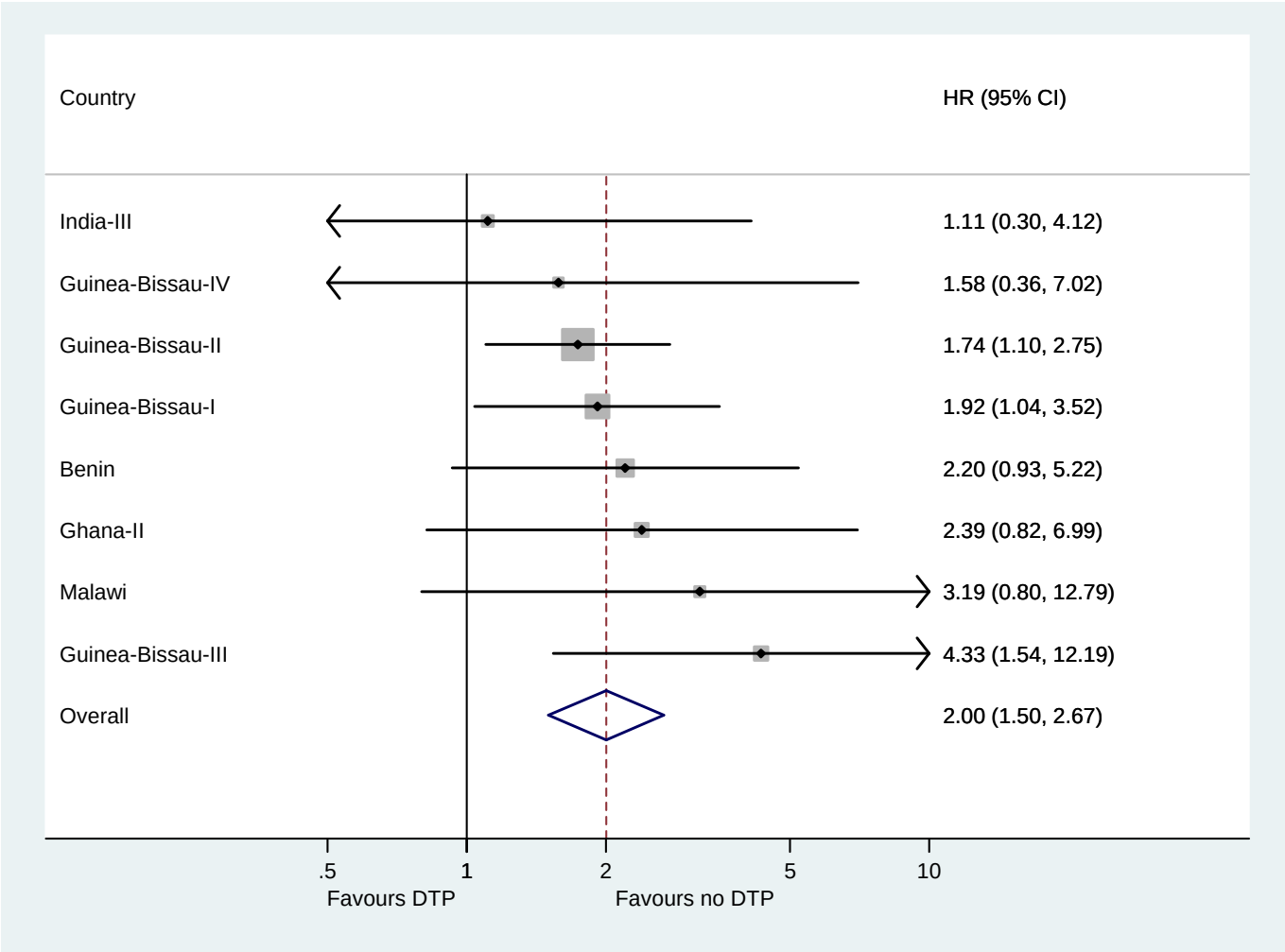


**Figure 4. The mortality rate ratio for DTP-vaccinated versus DTP-unvaccinated children in studies with no survival bias (III)**

**Sex-differential effects of DTP (Paper IV).** The SAGE review summarized that 'one study reported a large differential effect in girls, but overall there was not convincing evidence of a differential between girls and boys' (2). This is an unwarranted conclusion.

We have previously hypothesised that DTP is associated with increased female mortality both in relation to DTP-unvaccinated females and DTP-vaccinated boys (30). However, instead of testing the hypothesis the way we had formulated it, the SAGE review tested the potential sex-differential effects by examining whether the HR for DTP-vaccinated versus DTP-unvaccinated children differed significantly for girls and boys in each study. This does not fit available data.

First, the SAGE way of testing requires information also on unvaccinated children but many studies did not report information on the mortality rate among unvaccinated girls and boys; hence, many studies were not used in the assessment of potential sex-differential effects of DTP.

Second, an age-adjusted comparison of DTP-vaccinated versus DTP-unvaccinated for girls and boys, respectively, will tend to be a comparison in which the unvaccinated children will be a small subgroup not yet DTP-vaccinated because they were frail. When the SAGE reviewers made this unnatural comparison the SAGE review included all studies in Figure 3 – even if they had major survival bias. The reason for doing this remains obscure. Since these studies have "unnaturally" high mortality in the unvaccinated groups there will be a lot of misclassification of deaths in the 'unvaccinated' group. Many estimates will therefore be false (nonsense) and they should clearly not be used to assess whether DTP has a differential effect for girls and boys.

When the analysis is done the way we had outlined 10 years ago the result is clear. DTP is associated with 50% higher mortality for girls than for boys (Figure 5).

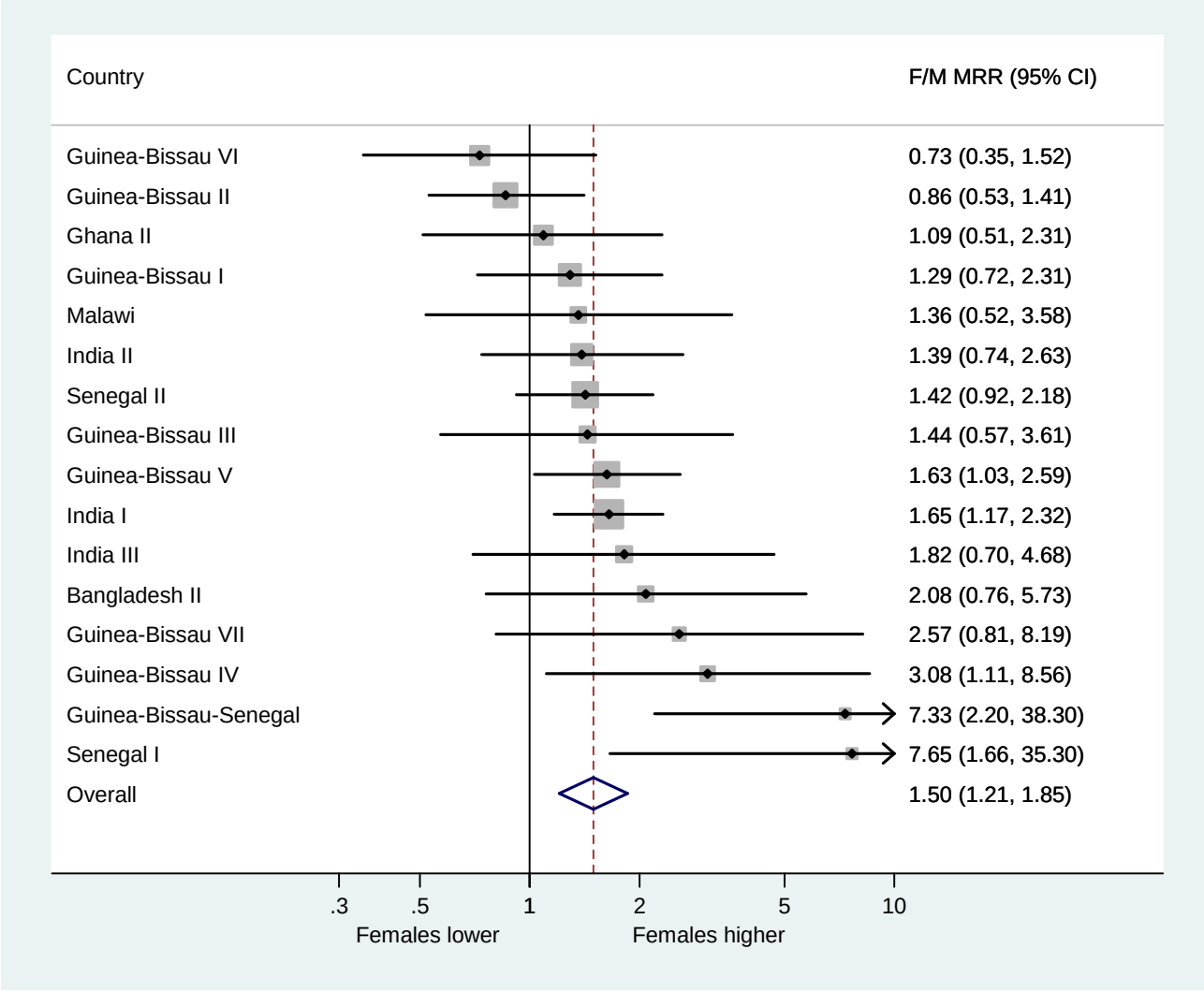


**Figure 5. Female-male mortality rate ratios among DTP-vaccinated children (IV)**

## C) Differential effect of DTP, MV and BCG (2)

The SAGE review failed to acknowledge the contrast between the beneficial effects of BCG and MV and the tendency for a negative effect of DTP vaccine illustrated in Figure 6.

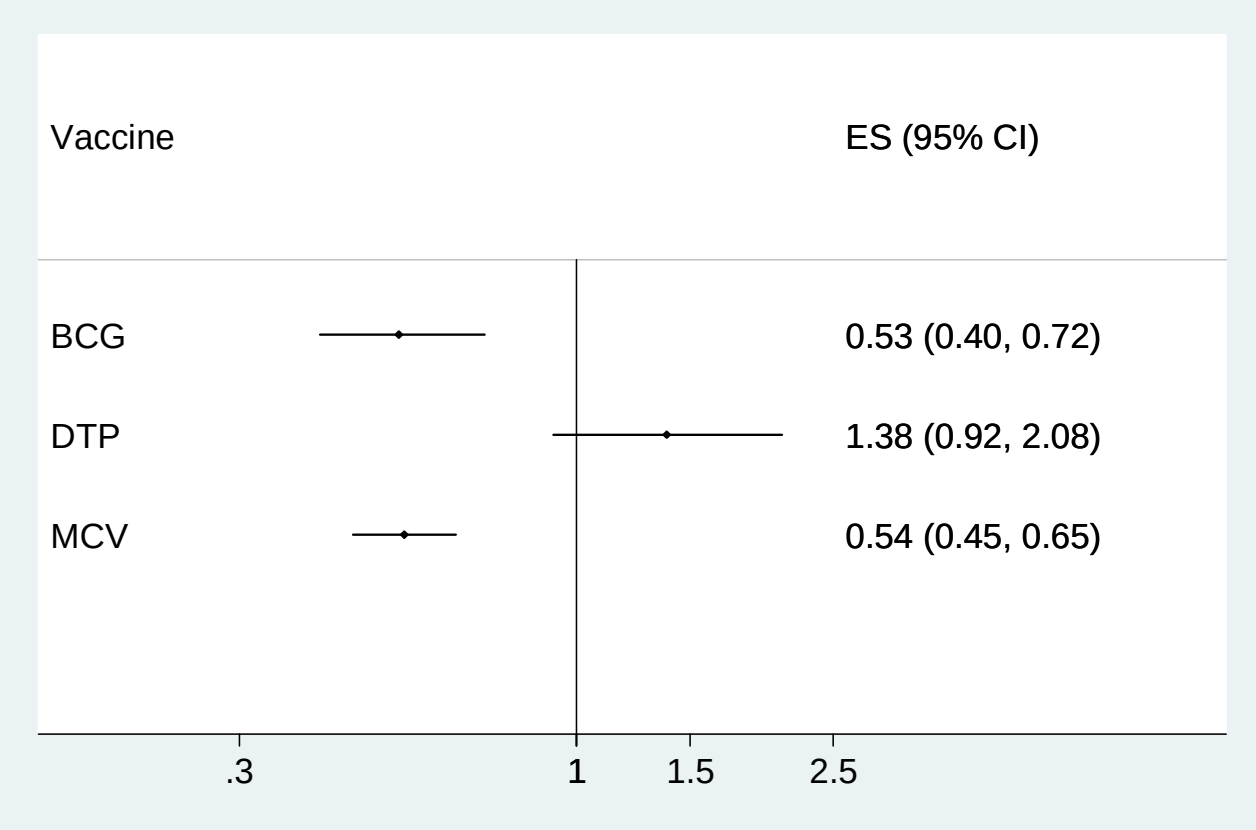


**Figure 6: Meta-analysis estimates of effects on mortality of BCG, DTP and MV**
P for the same effect of all vaccines<0.001; P for same effect of BCG and MV=0.92;
P for same effect of BCG and DTP<0.001; P for same effect of DTP and MV<0.001.

The differential effects of the different vaccines are also seen in individual studies which have assessed the effect of several vaccines within the same study population. As seen in Figure 7 all studies which had estimates for both BCG and DTP within the same cohort found that BCG had a better effect on child survival than DTP. In 8 of the 9 studies there were significantly different effects of BCG and DTP. Five of the 6 studies with estimates for both DTP and MV found lower mortality after MV than after DTP; in 3 studies there were significantly different effects of DTP and MV.

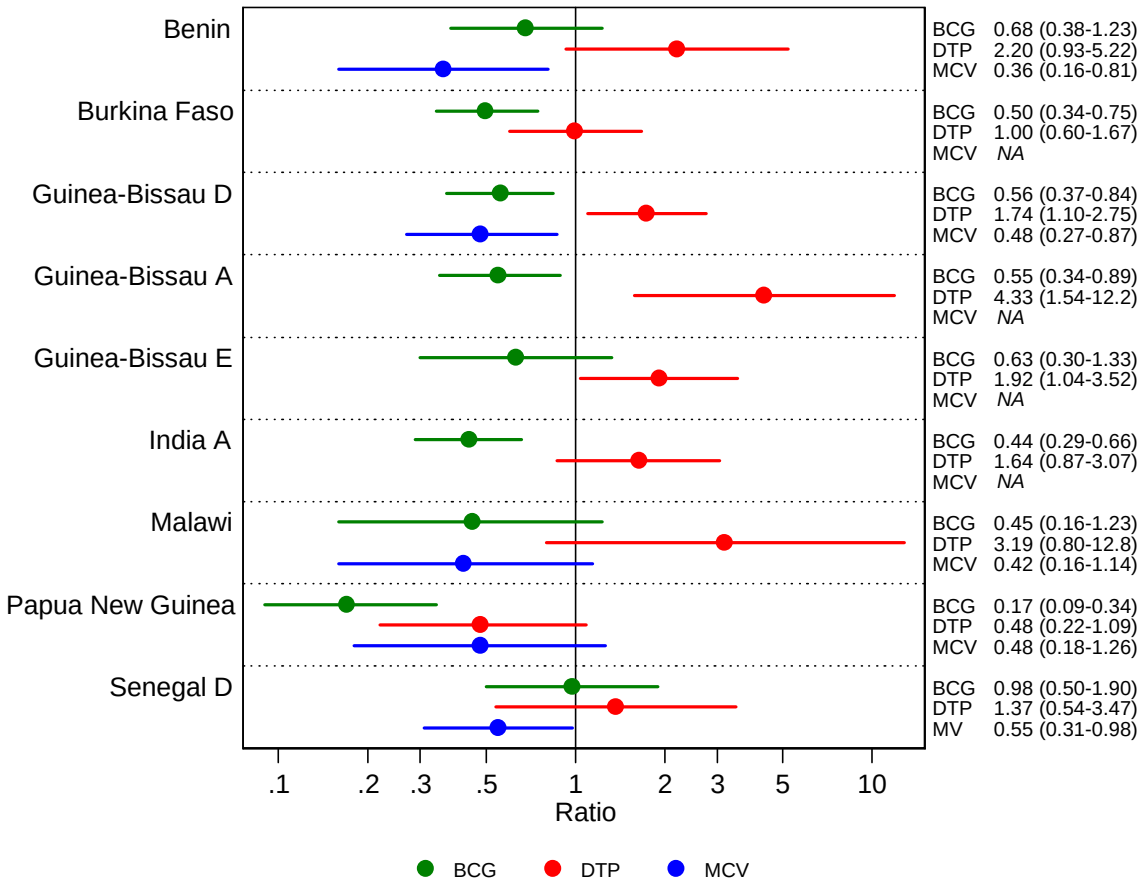


**Figure 7: Vaccine effects in studies which have assessed the effect of two or more vaccines in the same study**

Notes: Studies classified as "very high risk of bias" for all estimates have been excluded. However, the same pattern of differential effects for the three vaccines applies to the study at very high risk of bias.

It is hard to imagine one single bias, which could cause reduced mortality after BCG and MV but an increased mortality after DTP. This is a danger-signal about a potential negative effect of DTP. It is supported by the out-of-schedule observations that BCG+DTP is better (22,24) than DTP alone and that DTP with or after MV is worse than MV alone (2,22).

**Conclusion: There is a serious danger signal with respect to DTP-containing vaccines**

Though the SAGE review is clearly much better than the previous review in this area (31), the reviewers have included a number of studies with inappropriate bias. This is unfortunate since it was pointed out 10 years ago, in connection with the GACVS review of the NSEs of DTP, that studies with survival bias should be excluded (30,32,33). The inclusion of these studies has created an illusion of inconsistency. Furthermore, the methodology to study sex-differences has excluded a number of studies and blurred the sex-differences.

In addition, new data has become available, all supporting negative and sex-differential non-specific effects of DTP-containing vaccines. This consistent accumulation of data showing a negative effect of a vaccine cannot by any means be explained by chance findings. The contrasting effects of BCG and MV on one hand and DTP on the other hand are also an important observation, which cannot be explained by any kind of bias.

We hope SAGE and GACVS will reemphasise that studies of the NSEs are warranted. Since all studies of DTP with prospective follow-up suggest a danger-signal, it is particularly urgent that more studies are conducted of DTP-containing vaccines. If the safety of DTP cannot be documented, the vaccine community should find ways of minimising the effects of DTP in situations where DTP is associated with deleterious effects.

Yours sincerely

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## References


1. Meeting of Global Advisory Committee on Vaccine Safety, 18-19 June 2008. Week Epid Rec 2008;83:287-292
2. Higgins JPT, Soares-Weiser K, Reingold A. Systematic review of the non-specific effects of BCG, DTP and measles containing vaccines. http://www.who.int/entity/immunization/sage/meetings/2014/april/3_NSE_Epidemiology_review_Report_to_SAGE_14_Mar_FINAL.pdf?ua=1 – accessed April 7, 2016
3. Strategic Advisory Group of Experts on Immunization. Week Epidemiol Rec 2014;89: 233-235
4. Report on the Advisory Committee Meeting Immunization and Vaccines Related Implementation research (IVIR). WHO_IVB-15.01_eng.pdf
5. Global Advisory Committee on Vaccine Safety. Weekly Epidemiological Record 2004; 79:269-72;
6. SAGE non-specific effects of vaccines Working Group. Evidence based recommendations on non-specific effects of BCG, DTP-containing and measles-containing vaccines on mortality in children under 5 years of age. Background paper for SAGE discussions. Geneva 2014
7. Mahieu JM, Muller AS, Voorhoeve AM, Dikken H. Pertussis in a rural area of Kenya: epidemiology and a preliminary report of a vaccine trial. Bull WHO 1978:56:773-80
8. Aaby P, Jensen H, Gomes J, Fernandes M, Lisse IM. The introduction of diphtheria-tetanus-pertussis vaccine and child mortality in rural Guinea-Bissau: an observational study. Int J Epidemiol 2004,33:374-80
9. Moulton L, Holt E, Coberly J, Ruff A, Halsey N. Report on the Haiti Cohort I data set. Power Point presentation for WHO meeting on the effect of vaccines. Geneva 2002
10. Moulton LH, Rahmathullah L, Halsey NA, Thulasiraj RD, Katz J, Tielsch JM. Evaluation of non-specific effects of infant immunizations on early infant mortality in a southern Indian population. Trop Med Int Health 2005;10:947-55
11. Aaby P, Ravn H, Benn CS. The WHO review of the possible non-specific effects of diphtheria-tetanus-pertussis vaccine (submitted)
12. Lehmann D, Vail J, Firth MJ, de Klerk NH, Alpers MP. Benefits of routine immunisations on childhood survival in Tari, Southern Highlands Province, Papua New Guinea. Int J Epidemiol 2004, 10.1093/ije/dyh262
13. Aaby P, Ravn H, Roth A, Rodrigues A, Lisse IM, Diness BR, Lausch KR, Lund N, Biering-Sørensen S, Whittle H, Benn CS. Early diphtheria-tetanus-pertussis vaccination associated with higher female mortality and no difference in male mortality in a cohort of low birthweight children: an observational study within a randomised trial. Arch Dis Child 2012: doi:10.1136/archdischild-2011-300646
14. Velema JP, Alihonou EJ, Gandaho T, Hounye FH. Childhood mortality among users and non- users of primary health care in a rural West African community. Int J EpidemioI 1991;20:474- 479
15. Moulton LH, Rahmathullah L, Halsey NA, Thulasiraj RD, Katz J, Tielsch JM. Evaluation of non-specific effects of infant immunizations on early infant mortality in a southern Indian population. Trop Med Int Health 2005;10:947-55
16. Chan GJ, Moulton LH, Becker S, Muñoz A, Black RE. Non-specific effects of diphtheria-tetanus-pertussis vaccination on child mortality in Cebu, The Philippines. Int J Epidemiol 2007; 36:1022-9
17. Aaby P, Vessari H, Nielsen J, Maleta K, Benn CS, Jensen H, Ashorn P. Sex differential effects of routine immunizations and childhood survival in rural Malawi. Pediatr Inf Dis J 2006;25:721-727
18. Hirve S, Bavdekar A, Juvekar S, Benn CS, Nielsen J, Aaby P. Non-specific and sex-differential effects of vaccinations on child survival in rural western India. Vaccine 2012;30:7300-7308

19. Breiman RF, Streatfield PK, Phelan M, Shifa N, Rashi M, Yunus M. Effect of infant immunization on childhood mortality in rural Bangladesh: analysis of health and demographic surveillance data. Lancet 2004; 364:2204-11
20. Krishnan A, Srivastava R, Dwivedi P, Ng N, Byass P, Pandav CS. Non-specific sex-differential effect of DTP vaccination may partially explain the excess girl child mortality in Ballabgarh, India. Trop Med Int Hlth 2013;18:1329-37
21. Bawah AA, Phillips JF, Adjuik M, Vaughan-Smith M, Macleod B, Binka FN. The impact of immunization on the association between poverty and child survival: Evidence from Kassena-Nankana district of northern Ghana. Scand J Pub Hlth 2010;38:951-03
22. Aaby P, Nielsen J, Benn CS, Trape JF. Sex-differential and non-targeted effects of routine vaccinations in a rural area with low vaccination coverage: Observational study from Senegal. Trans Roy Soc Trop Med Hyg 2015;109:77-85
23. Aaby P, Jensen H, Garly ML, Balé C, Martins C, Lisse I. Routine vaccinations and child survival in war situation with high mortality: effect of gender. Vaccine 2002;21:15-20
24. Aaby P, Ravn H, Andersen A. Combined BCG and DTP vaccinations may reduce infant mortality more than the WHO-schedule of BCG first and then DTP. A re-analysis of demographic surveillance data from rural Bangladesh. Draft manuscript provided to the SAGE review committee.
25. Aaby P, Jensen H. Routine vaccination and child survival in Guinea-Bissau. Authors' reply to Commentary. BMJ 2001;322:360
26. Kristensen I, Aaby P, Jensen H. Routine vaccinations and child survival: follow up study in Guinea-Bissau, West Africa. BMJ 2000;321:1435-8
27. Jensen H, Benn CS, Aaby P. DTP in low-income countries: improved child survival or survival bias? BMJ 2005;330:845-6
28. Vaugelade J, Pinchinat S, Guielle G, Elguero E, Simondon F. Lower mortality in vaccinated children: follow up study in Burkina Faso. BMJ 2004;329:1309-11
29. Welega P, Nielsen J, Adjuik M, Debpuur C, Ross DA, Ravn H, Benn CS, Aaby P. Non-specific effects of diphtheria-tetanus-pertussis and measles vaccinations? An analysis of surveillance data from Navrongo, Ghana. Trop Med Int Health 2012;17:1492-505
30. Fine PEM, Smith PG. `Non-specific effects of vaccines´ - an important analytical insight, and a call for a workshop. TMIH 2007;12:1-4
31. www.who.int/entity/vaccine_safety/topics/dtp/taskforce_report.pdf.
32. Aaby P, Benn CS, Nielsen J, Lisse IM, Rodrigues A, Jensen H. DTP vaccination and child survival in observational studies with incomplete vaccination data. Trop Med Int Hlth 2007;12:15-24
33. Jensen H, Benn CS, Lisse IM, Rodrigues A, Andersen PK, Aaby P. Survival bias in observational studies of the impact of routine vaccinations on childhood survival. Trop Med Int Hlth 2007;12:5-14