Supplementary table 1. Female-male mortality ratios in community studies from the pre-vaccination era in West Africa (Observation III)

Study (ref)	Period	Age group	Mortality rate (deaths/person-years)		Female-male mortality ratio
			Girls	Boys	
Age of BCG and DTP					
Bissau, Urban (28)	1978-81	1-8 mo	21.0%(30/142.6)	18.3%(29/158.5)	1.15 (0.7-1.9)
Bissau, Rural (28)	1979-83	1-8 mo	7.7%(32/416.0)	9.8%(42/427.1)	0.78 (0.5-1.2)
Senegal, Bandafassi (13)	1981-86	1-8 mo	11.2%(65/581.8)	10.6(61/574.8)	1.05 (0.76-1.46)
Senegal, Niakhar (88)	1963-67	0-11 mo	193/1000	206/1000	0.94
Senegal, P-Koto (89)	1963-67	0-11 mo	112/1000	128/1000	0.88
Age of measles vaccination					
Bissau, Urban (28)	1978-81	9-17 mo	11.5%(21/182.6)	14.0%(27/193.4)	0.82 (0.5-1.5)
Bissau, Rural (28)	1979-83	9-17 mo	12.2%(49/400.2)	12.0%(46/383.3)	1.02 (0.7-1.5)
Senegal, Bandafassi (13)	1981-86	9-59 mo	7.6%(171/2250.9)	7.3%(174/2387.1)	1.04 (0.85-1.28)
Senegal, Niakhar (88)	1963-67	12-23 mo	198/1000	210/1000	0.94
Senegal, Niakhar (17)	1985-86	9-23 mo	7.3%(62/847.5)	7.2%(62/866.3)	1.02 (0.72-1.45)
Senegal, P-Koto (89)	1963-67	12-23 mo	140/1000	112/1000	1.25

Supplementary table 2: Mortality ratios for different routine vaccinations within the same study (Observation I)

Study (ref)	Length of follow-up in study	Mortality rates per 1000 person-years or case fatalities (%) and mortality ratios (MR) for different vaccine groups			Significance testing, p-value	
		BCG	DTP	Measles (MV)	BCG versus DTP	DTP versus MV
Guinea-Bissau: (1)	Mortality during 6 months	BCG 3.8% (125/3301) NoBCG 4.9% (97/1973) MR 0.55 (0.36-0.85)	DTP 4.8% (62/1295) NoDTP 4.0% (72/1822) MR 1.84 (1.10-3.10)	MV 1.8% (19/1036) NoMV 4.0% (94/2378) MR 0.48 (0.27-0.87)	0.005	0.001
Benin (18)	Case control study 3 years of age	MR 0.68 (0.38-1.23)	MR 2.20 (0.93-5.22)	MR 0.55 (0.28-1.07)	0.027	0.013
Guinea-Bissau: DTP-introduction (42)	6 months	BCG 62/10/161.9) [1] NoBCG 95 (80/846) [1] MR 0.63 (0.30-1.33)	DTP 113 (47/415.7) No DTP 51 (20/388.6) MR 1.92 (1.04-3.52)	**	0.038	NA
Guinea-Bissau: Hospital case fatality (27)	End of hospitalisation	*	DTP 16.1% (28/174) noDTP 9.1% (1/11) MR 2.32 (0.53-40.0)	MV 7.0%(18/259) NoMV 13.7% (19/139) 0.51 (0.27-0.98)		0.188
Guinea-Bissau (26)	Case fatality during 3 months of war	BCG 2.4% (9/375) [1] NoBCG 9.4% (3/32) [1] MR 0.11 (0.02-0.69) [1]	DTP 4.2% (19/455) NoDTP 2.6% (2/78) MR 1.58 (0.36-7.02)	MV 2.6% (25/958) NoMV 5.5% (12/220) MR 0.44 (0.20-1.00)	0.024	0.138
Malawi (53) @	1 week to 8 mo for BCG and DTP 9-17 mo for MV	BCG 157 (17/108.0) NoBCG 389 (13/33.4) MR 0.45 (0.16-1.23)	DTP1 188 (20/106.6) NoDTP1 157 (17/108.0) MR 3.19 (0.80-12.8)	MV 35 (11/314.0) NoMV 69 (12/174..2) MR 0.42 (0.16-1.14)	0.021	0.019
Guinea-Bissau: LBW cohort (64,65)#	Neonatal for BCG 2-6 mo for DTP	BCG 358 (27/75.4) NoBCG 646 (48/74.3) MR 0.55 (0.35-0.89)	DTP 100 (20/200.7) NoDTP 49 (5/102.3) MR 4.33 (1.58-11.9)#	**	<0.001	

Notes: The control group for BCG would usually be unvaccinated children except in the randomised trial of BCG to LBW children (64) where the controls had received OPV according to current recommendations; the control group for DTP would be BCG-vaccinated and a few unvaccinated children except in the study of introduction of DTP (42) in which virtually none of the children had received BCG; the control group for MV would mainly be DTP vaccinated children. The first study from Bissau (1) and from Benin (18) estimated effects in a model with all vaccinations, whereas the remaining studies have estimated the effect of the "most recent vaccination". NA = not applicable

1. Data not reported in the published paper

* Unvaccinated children did not have a vaccination card and therefore the status as BCG-unvaccinated could not be documented by a vaccination card as for the other vaccines;

**The studies were limited to children under 6 or 9 months of age who had not received measles vaccine.

@ The rates are for all children but the MRs are only for children present in the community and for whom the information on vaccinations would be most accurate.

Estimate for BCG is from a randomised comparison of BCG at birth versus BCG later as currently recommended for LBW children (65). The estimate for DTP is adjusted for mid-upper-arm-circumference; the estimate is only from the BCG at birth arm of the trial since most children in the control arm of the study received DTP before or simultaneously with BCG (64)

Supplementary table 3. Female-male (F/M) mortality rates and mortality ratios for DTP-vaccinated children (Observation III)

Study (ref)	Vaccine	Mortality rate per 1000 person-years (deaths/person-years) or case fatality % (deaths/cases)		F/M for DTP	F/M Unvaccinated
DTP as most recent vaccine		Female	Male		
Guinea-Bissau: Female-male twin pairs (28)	DTP1-3	22 died first	3 died first	7.33 (2.20-38.3)	NA
Guinea-Bissau: DTP-introduction (42)[1]	DTP1-3	126 (27/215.0) [1]	100 (20/200.4) [1]	1.29 (0.72-2.31)	0.86 (0.35-2.08)
Gambia (31)	DTP1-3	67 (32/475.0)	40 (20/498.3)	1.68 (0.96-2.93)	NA
Guinea-Bissau: Hospital case fatality (27)	DTP1-3	17.8% (35/197)	10.9% (29/264)	1.63 (1.03-2.59)	No vaccination card*
Guinea-Bissau: Case fatality during 3 months of war (26)	DTP1-3	6.1% (14/228)	2.2% (5/227)	3.08 (1.11-8.56)	0.92 (0.06-15.1)
Malawi (53)	DTP1	218 (11/50.4)	176 (9/51.1)	All 1.24 (0.51-2.99) Present: 1.36 (0.52-3.58) ¤	0.55 (0.16-1.87)
Bangladesh (54)	DTP1-3 @	22.5% (16/71)	7.8% (10/129)	2.91 (1.39-6.06)	NA
Guinea-Bissau: Vitamin A at birth trial (52)$	DTP1-3 &	41 (36/872)	34 (31/901)	1.20 (0.74-1.94)	NA (all children received BCG at enrolment)
Guinea-Bissau: LBW cohort (64,65)#	DTP1-2	115 (13/113.3)	80 (7/87.4)	1.44 (0.57-3.61)	NA

Note: Include only studies of DTP provided before measles vaccination. Most DTP-vaccinated had received BCG prior to DTP except in the study of introduction of DTP (42) in which virtually none of the children had received BCG. NA = not applicable

1. Data not reported in the published paper

* Children who brought no vaccination card to the hospital could be unvaccinated but could also have forgotten or lost the card.

¤ The rates are for all children but the MRs are only for children present in the community and for whom the information on vaccinations would be most accurate.

@ Mortality between DTP1 and 6 months after DTP3. The F/M mortality ratio was 4.17 (1.39-13) for children receiving DTP1-3 with Vitamin A and 2.08 (0.76-5.73) for children receiving DTP1-3 with placebo.

& The F/M mortality ratio was 1.78 (0.92-3.42) after DTP for children who had received VAS with BCG at birth and 0.73 (0.35-1.52) after DTP for children who had received placebo together with BCG at birth.

Estimate for BCG is from a randomised comparison of BCG at birth versus BCG later as currently recommended for LBW children (65). The estimate for DTP is adjusted for mid-upper-arm-circumference; the estimate is only from the BCG at birth arm of the trial since most children in the control arm of the study received DTP before or simultaneously with BCG (64)

$ The study (52) is partially overlapping with the trial of early measles vaccination (3) and the result from this trial has therefore not been presented separately (MRR=1.30 (0.74-2.30))

Supplementary table 4. Female-male (F/M) mortality ratios (MR) for DTP, BCG and MV vaccinated children (Observation III)

Study (ref)	Female vs male mortality rates or case fatalities after DTP	F/M MR for DTP	Female vs male mortality rates or case fatalities after BCG	F/M MR for BCG	DTP versus BCG	Female vs male mortality rates or case fatalities after MV	F/M MR for measles vaccine	DTP versus MV
Guinea-Bissau: Female-male twin pairs (28)	22 F vs 3 M died first	7.33 (2.20-38.3)	3 F vs 12 M died first	0.25 (0.05-0.93)	P<0.001	2 F vs 5 M died first	0.40 (0.04-2.44)	P=0.001
Gambia (31)	F: 67 (32/475.0) M: 40 (20/498.3)	1.68 (0.96-2.93)	NA	NA	NA	F: 38 (26/689.2) M: 55 (40/722.3)	0.70 (0.43-1.15)	P=0.02
Guinea-Bissau: Hospital case fatality (27)	F: 17.8%(35/197) M: 10.9%(29/264)	1.63 (1.03-2.59)	F: 12.1% (4/33) M: 22.5% (11/49)	0.54 (0.16-1.43)	P=0.07	F: 6.2% (14/225) M: 12.7% (29/249)	0.54 (0.28-0.97)	P=0.003
Guinea-Bissau: Case fatality during 3 months of war (26)	F: 6.1% (14/228) M: 2.2% (5/227)	3.08 (1.11-8.56)	F: 1.9% (1/35) M: 2.3% (1.43)	0.92 (0.06-15.1)	p=0.44	F: 2.1% (10/472) M:3.1% (15/486)	0.63 (0.28-1.40)	P=0.01
Malawi (53) ¤	F: 218 (11/50.4) M: 176 (9/51.1)	All 1.24(0.51-2.99) Present: 1.36 (0.52-3.58)¤	F: 134 (7/52.2) M: 180 (10/55.7)	All 0.80 (0.30-2.10) Present: 0.58 (0.11-3.19)¤	P=0.40	F: 13 (2/151.1) M: 47 (7/149.8)	All 0.28 (0.06-1.37) Present: 0 (0-0.67)¤	P=0.002
Guinea-Bissau: Vitamin A at birth trial (52)&	F: 41 (36/872) M: 34 (31/901)	1.20 (0.74-1.94)	F: 94 (18/192) M: 140 (28/200)	0.66 (0.37-1.20)	p=0.12	NA	NA	NA
Guinea-Bissau: LBW cohort (64,65)#	F: 115 (13/113.3) M: 80 (7/87.4)	1.44 (0.57-3.61)	F: 1.7% (11/667) M: 3.3% (16/493)	0.51 (0.24-1.08)	P=0.087	NA	NA	NA

Notes: Most DTP-vaccinated had received BCG prior to DTP except in the study of introduction of DTP (42) in which virtually none of the children had received BCG. In the original study (1) suggesting a negative impact of DTP we did not report sex-specific estimates; we subsequently reported that the effect of BCG was 0.45 (0.23-0.86) and 0.63 (0.38-1.04) whereas the effect of DTP compared with no DTP was 2.31 (1.16-4.59) for girls and 1.45 (0.81-2.59) for boys. The divergent estimates were significant for girls (p=0.009) but not for boys suggesting a relative worse effect of DTP for girls than for boys (1).

NA = not applicable/not available;

¤ The rates are for all children but the MRs are only for children present in the community and for whom the information on vaccinations would be most accurate.

& Among children who had received VAS with BCG at birth, the F/M mortality ratios were 0.64 (0.26-1.54) after BCG and 1.78 (0.92-3.42) after DTP; for children who had received placebo together with BCG at birth the F/M mortality ratios were 0.69 (0.31-1.54) after BCG and 0.73 (0.35-1.52) after DTP

Estimate for BCG is the case fatality for neonatal mortality among LBW children receiving BCG in randomised trial comparing BCG at birth versus BCG later as currently recommended for LBW children (65). The estimate for DTP is adjusted for mid-upper-arm-circumference; the estimate is only from the BCG at birth arm of the trial since most children in the control arm of the study received DTP before or simultaneously with BCG (64)

Supplementary table 5. Mortality or morbidity patterns among DTP-vaccinated and measles vaccinated children of similar age (Observation III)

Study outcome and age group compared (ref)		Female and male mortality/incidence rates or case fatalities and female/male mortality ratios (F/M MR/IR)		Ratio for MV/DTP for girls
		DTP most recent vaccine	Measles vaccine (MV) most recent vaccine	
Deaths in female-male twin pairs (28)	9 to 17 months	7 F vs 0 M died first	1 F vs 5 M died first	P=0.009, test of homogeneity
Hospital case fatality (27)	6 to 8 months	F: 14.7% (16/109) M: 10.1% (15/149) F/M MR 1.46(0.75-2.82)	F: 3.7% (1/27) M: 15.4% (2/13) F/M MR 0.24 (0.02-2.42)	0.25 (0.03-1.82)
Guinea-Bissau: Case fatality during 3 months of war (26)	6 to 20 months	F: 7.1% (7/99) M: 4.4% (4/92) F/M MR 1.81(0.53-6.17)	F: 2.1% (10/472) M: 3.1% (15/486) F/M MR 0.63 (0.28-1.40)	0.30 (0.12-0.77)
Early MV trial (3)	4.5 to 9 months	F: 35 (27/765.5) M: 27 (21/775.2) F/M MR 1.30 (0.74-2.30)	F: 16 (6/376.0) M: 26 (10/390.0) F/M MR 0.62 (0.23-1.71)	0.46 (0.19-1.11) No neonatal VA: 0.30 (0.07-1.31)
Incidence of cryptosporidium (55)	6 to 11 months	F: 1391 (9/6.5) M: 417 (3/7.2) F/M IR 4.14 (1.09-15.6)	F: 292 (3/10.3) M: 334 (4/12.0) F/M IR 0.94 (0.21-4.25)	0.20 (0.05-0.89)

Note: The age groups are the ones used in the original presentation of the data

Supplementary table 6. Mortality after enrolment in measles vaccination trials according to DTP status at enrolment (Observation V)

Study (ref) Observation interval		Girls			Boys			All
		Missing doses of DTP (DTP0-2)	Fully vaccinated for DTP (DTP3)	MRR (DTP0-2/DTP3)	Missing doses of DTP (DTP0-2)	Fully vaccinated for DTP (DTP3)	MRR (DTP0-2/DTP3)	MRR (DTP0-2/ DTP3)
Guinea-Bissau-A (51)	4-9 mo	6.0% (3/50.2)	0% (0/0.5)	ND	8.7% (6/68.9)	0% (0/1.3)	ND	ND
Guinea-Bissau-B (51)	4-9 mo	17.8% (10/56.2)	0% (0/0.9)	ND	7.4% (4/53.7)	0% (0/0.6)	ND	ND
Guinea-Bissau-C (51)	6-9 mo	7.5%(29/387.8)	3.8%(14/368.3)	1.97 (1.04-3.72)	6.4%(25/390.3)	6.0%(21/348.6)	1.06 (0.60-1.90)	1.42 (0.93-2.17)
Guinea-Bissau-D (78)	9-36 mo	6.1% (8/131,1)	1.7% (6/352.9)	3.55 (1,23-10.3)	3.2% (5/156.3)	3.3% (11/333.3)	0.97 (0.34-2.80)	1.83 (0.89-3.76)
Sudan (22)	5-36 mo	6.0% (8/133.1)	2.8%(1/35.9)	2.16 (0.27-17.3)	1.4%(2/145.4)	1.9%(1/51.9)	0.71 (0.06-7.87)	1.58 (0.35-7.19)
Kinshasa, Congo (22)	3½-9½ mo	10.0% (3/30.0)	2.8%(3/106.2)	3.54 (0.71-17.5)	10.6%(3/28.4)	5.1%(6/116.7)	2.05 (0.51-8.21)	2.54 (0.91-7.15)
Total				2.36 (1.43-3.89)#			1.11 (0.69-1.77)#	1.60 (1.14-2.24)

Notes: Trials in Guinea-Bissau: A= Medium EZ-trial (51); B=Medium and high-titre EZ-trial (51); C=2-dose MV trial (51); D=trial of MV with vitamin A (78); ND=Not defined. #The test of homogeneity for the estimates for boys and girls was p=0.031.

Supplementary table 7. Mortality rates (deaths/person-years) in different age groups dominated by specific vaccines (Observation VI)

Study (ref)	All children or vaccine groups	Age groups compared	DTP age group	MV age group	MRR (MV/DTP)
Girls					
Gambia (31)	All children¤	5-8 mo vs 9-17 mo	6.7% (32/475.4)	4.3%(45/1040.0)	0.64 (0.41-1.01)*
Malawi (53)	DTP1 vs MV&	3-8 mo vs 9-17 mo	21.1% (9/43)	1.4% (2/143)	0.07 (0.01-0.31)
Guinea-Bissau: War (26)	DTP vs. MV&	1-5 mo vs. 6-17 mo	5.4% (7/129)@	2.1% (10/472)@	0.39 (0.15-1.03)*
Boys					
Gambia (31)	All children¤	5-8 mo vs. 9-17 mo	4.0% (20/498.3)	5.9% (65/1094.9)	1.48 (0.90-2.44)*
Malawi (53)	DTP1 vs MV&	3-8 mo vs. 9-17 mo	14.6% (6/41)	6.1% (9/148)	0.41 (0.15-1.17)
Guinea-Bissau: War (26)	DTP vs. MV&	1-5 mo vs. 6-17 mo	0.7% (1/135)@	3.1% (15/486)@	4.17 (0.55-31.5)*

Note: ¤ Mortality rate for all children in the indicated age group; & Mortality rate for children known to have received the vaccine which predominates in the relevant age group; @ Fatality ratios during the war; *A comparison of the change for boys and girls, respectively, is significant ($p<0.05$) in a homogeneity test.

Appendix: ***Analysis of incomplete vaccination data***

In the analysis of vaccination data, the completeness of the data and the mode of analysis as well as the study designs and associated biases have been critically important (113,114). The way data on vaccinations is collected in low-income countries has implications for the analysis. Data on vaccinations will most often be incomplete. In longitudinal studies, information on vaccination status has typically been collected at home visits with a certain interval between visits, for example, 1, 3, 6 or even 12 months. It is unlikely that information is obtained for all children and some vaccinations administered between visits will not be known. A few projects have provided all vaccinations for a certain period or collected information from the health centres (18, 44, 46, 48, 53) but few have successfully collected information from all children, including those who travelled or died (31). The one exception would be a recent study from Cebu, The Philippines, which collected post-mortem vaccination information from 99% of the children who died (58). As many mothers in Africa will throw away the vaccination card or move from the area if a child dies, information on vaccinations is likely to be better for children who survive.

Few studies excluded the children with "no information", instead these children were usually assumed to be unvaccinated controls (60,61). Hence, controls will include absent children who may be absent because they are sick or travelling, and this group may therefore be a high-risk group with a particularly high mortality (Table 1). For example, in one study from Malawi, the estimated impact of DTP1 on mortality changed from 0.99 to 3.19 when the comparison was restricted to unvaccinated children present in the community (53). Furthermore, such controls are likely to include children who would not have been included in a randomised clinical trial (RCT) due to chronic disease or malformation.

Retrospective updating and landmark approaches. Methodological issues because of incomplete vaccination data are discussed in detail elsewhere (60-63,113,114). In brief, when incomplete data are analysed with *retrospective updating* of vaccination status as a *time-varying* covariate, *survival bias* is introduced because information is better for surviving children. Some dead vaccinated children will be misclassified as unvaccinated giving a high mortality rate in the unvaccinated group. This will exaggerate the estimated survival benefit of vaccinations (60). For these reasons (60), we did not include studies with retrospective updating in the present examination of mortality levels after DTP (Table 1); these studies are reviewed elsewhere (61).

To avoid survival bias, vaccination dates should only be taken into consideration from the date they were registered. The status as "not vaccinated" should be based on assessment; "no information" should *not* be interpreted as "not vaccinated". These restrictions lead to a *landmark approach* (60) in which vaccination status is a *fixed covariate for the period of follow-up.* In other words, mortality is analysed from the date of data collection until the next time vaccination data are collected, disregarding vaccinations given during follow-up. The landmark approach is not affected by survival bias, though *misclassification of vaccination status* due to new vaccinations during follow-up may be important as discussed below.

Most recent vaccination. The relevance of data analysed with the landmark approach depends on how many children might have received other vaccinations during follow-up; the unvaccinated group may receive the vaccine being examined and the vaccinated group may receive a subsequent vaccination during follow-up. If the unvaccinated and vaccinated groups receive only the examined vaccine, say further doses of DTP, the estimates of the effect of DTP vaccine on mortality will be conservative, i.e. biased towards 1.0 (1, 60). However, if alternative vaccines are also given, the resulting bias is unpredictable depending on the effect of the additional vaccines on mortality. We therefore emphasised periods in which additional

vaccinations are unlikely. Hence, we are ideally analysing the effect of a specific vaccine in the restricted period in which it is the "*most recent vaccination".*

Study design issues

We have mostly used two lines of enquiries to examine the possible non-specific effects of DTP. These approaches are associated with very different biases.

Comparison of sequential vaccinations. We compared DTP-vaccinated versus DTP-unvaccinated children, i.e. totally unvaccinated or BCG-only vaccinated children. This comparison is inherently biased since vaccination statuses which are scheduled to be sequential are compared at the same age in a survival analysis. The selective factors which determine which children are vaccinated first are therefore critically important for what is being compared. It has been suggested several times that the weakest children are vaccinated first, because they got vaccinated when consulting at a health centre (18,45,48). The estimated effect of the most recent vaccination might therefore be negative. However, there is no well documented case of weak children being vaccinated first. Instead, most studies, including those from Guinea-Bissau, have found that vaccinated children have better nutritional status and that children with better nutritional status are vaccinated first (1,19,53,64). Furthermore, all studies suggest that vaccination coverage is associated with better maternal education (1,44,49,58), which is associated with better survival. Hence, all the current evidence suggests that low-risk children are vaccinated first, and the weak or "frail" children get delayed vaccination or no vaccination (63). This bias, which we call *frailty bias*, would leave the weak children to die in the unvaccinated or current-vaccination group, while moving the follow-up time for the low-risk children to the group of the next vaccination (58,59). The longer the comparison is extended the more the previous-vaccination group will consist of frail children, and the more biased the comparison will be (59). In situations with high vaccination coverage, comparison of BCG-vaccinated versus unvaccinated, DTP versus BCG, or MV versus DTP, can only be conducted over a short age range (44,59). Frailty bias would tend to bias the estimates of the effect of all vaccines on mortality towards zero, i.e. better than the true effect.

Comparison of sequential vaccinations in a survival analysis would therefore inherently tend to provide a beneficial survival estimate for the most recent vaccinations even in the absence of any impact on survival. Such comparisons are therefore only informative when they provide an unexpected negative estimate for a specific vaccine, or contrasting estimates for different vaccines (1,64). Contrasting effects of different vaccines are an indication of non-specific effects unless it can be shown that different forms of selection or frailty bias are important for different vaccines. The available evidence suggests that these determinants are the same for different vaccines.

In comparisons of sequential vaccinations, the healthy newly-vaccinated children are compared with the weak not-yet vaccinated children at a specific age. Such frailty bias is not controlled by adjusting for common determinants of mortality level (maternal education, socio-economic status). Frailty bias is only fully controlled in randomised studies (82). Since randomised studies are not currently acceptable, we might seek *"natural experiments"* with limited self-selection for vaccination, for example, when vaccines were missing during a certain period (43), vaccines were only available in a certain period (37), or vaccines were stopped due to a war (21, 26). In such situations, vaccinated and unvaccinated children may be compared as they would in a randomised trial without the unvaccinated children being inherently more frail. However, such "natural experiments" with DTP are rare (42, 43).

Comparison of female and male mortality rates. In the pre-vaccination era, post-neonatal child mortality was similar for boys and girls in Africa (Figure 2). All data from Africa also suggest

that girls and boys are treated equally with respect to vaccination and the age of vaccination, and that the coverage is the same for boys and girls. In these circumstances, a deviation of the female-male mortality rate ratio (MRR) from 1.0 for children who have received a specific vaccine as the most recent vaccination would suggest that this vaccine is associated with sex-differential non-specific effects. We therefore conducted several studies examining the female-male MRR. It should be noted that a comparison of female-male mortality rates is not affected by the same survival, selection and frailty biases as comparison of sequential vaccinations. As long as biases are the same for boys and girls, and are proportional to the mortality level, they would not affect the estimated MRR for girls compared with boys. The more likely methodological problem in analyses of the female-male MRR of DTP vaccinated children is that the children could have received the subsequent MV during follow-up. If that were the case, it would lead to a conservative estimate because MV is associated with lower female mortality (11) and would dilute the effect of DTP. To prevent such misclassification, we have tried to restrict follow-up to age groups (less than 9 months) or situations (hospital admissions, war) in which it is unlikely that MV would have been provided during follow-up - in these situations we can be fairly sure that DTP has remained the "most recent vaccination".