Projecto de Saúde
BANDIM

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To SAGE and GACVS

Professor A. Cravioto, Chair of SAGE
Professor Robert Pless, Chair of GACVS
Dr. Robert Breimann, Chair IVIR-AC
Dr. Kate O'Brien, Director IVB, WHO

The sequence of measles and DTP-containing vaccines has important consequences for overall child mortality

SUMMARY

From the perspective of disease-specific prevention, it may matter little whether a child receives diphtheria-tetanus-pertussis (DTP)-containing vaccine before or after measles vaccine (MV). However, from the perspective of potential non-specific effects (NSEs) of vaccines the sequence of vaccinations may be important. Available data indicate that **DTP administered after MV is associated with higher child mortality** than having MV-only as the most recent vaccine, the effect being particularly negative for females. **Likewise, DTP co-administered with MV is associated with higher child mortality** than having MV-only as the most recent vaccine, the effect being slightly worse for males. Thus, **it could improve child survival considerably if WHO recommends that DTP-containing vaccines not be administered with MV or after MV.** From this perspective, **it would make sense that the coverage of MV-after-DTP3 rather than the simple MV coverage became the main program indicator for MV**.

INTRODUCTION

Currently, three doses of DTP-containing vaccines are recommended at 6, 10 and 14 weeks, followed by MV at 9 months of age. In Sub-Saharan Africa and Asia, many children may come late for vaccination. According to the recommendations, children missing one or more doses of DTP may receive those with or after MV. It may not be optimal in terms of child survival. Below we review the evidence originating from all available data: for the high- and medium-titre MV, which have been in use previously, and the currently used standard-titre MV.

RESULTS

High-titre measles vaccine (HTMV) and Medium-titre MV (MTMV)

The first signal that the sequence and combination of vaccines is very important came in the HTMV/MTVT trials (1). MT/HTMV was tested in the 1980s and was found to be fully protective against measles infection even in the presence of maternal antibodies; HTMV was recommended globally by WHO in 1989 (2). Long-term follow up of RCTs in Guinea-Bissau, Senegal, Sudan and Haiti found that the HTMV given at 4-5 months of age was associated with 2-fold higher mortality for females, but made little difference for the survival of males (1,3,4). The pattern was consistent in four countries with very different health conditions. HTMV was therefore rescinded in 1992 (5).

We subsequently showed that excess female mortality was linked to receiving non-live vaccines, DTP or inactivated polio vaccine (IPV), after MV (1,3). In the RCTs (Supplementary (S)Table 1), the children had been enrolled at 4-5 months of age and randomised to an early HT/MTMV or a control vaccine (IPV, pneumococcal vaccine, placebo). At 9-10 months, there was a switch over, where the early MV group received a non-live vaccine and the control group received a standard-titre MV. **Hence, it was possible from 9 months of age to compare the intervention group receiving non-live vaccine after HT/MTMV versus the control group receiving standard MV after early non-live control vaccine. The mortality rate ratio (MRR) was 1.38 (1.05-1.83**)(STable 1) (3). The effect was similar in the two MTMV RCTs (MRR=1.43 (0.83-2.47)) and the five HTMV RCTs (MRR=1.37 (0.99-1.89)). This deleterious negative effect was seen only for girls (MRR=1.89 (1.27-2.80)) (STable 1). There were also community studies showing that excess female mortality was limited to situations where the children had received non-live vaccine after HTMV whereas there was no excess female mortality when non-live vaccine had not been given after HTMV (1,3,4).

Hence, the interpretation that fits all the data and can be shown to be both necessary and sufficient cause of the increased female mortality associated with MT/HTMV is: **receiving non-live vaccines after MTMV/HTMV was associated with increased mortality for females.**

In 1992, it was only HTMV, which was withdrawn. However, MTMV had a similar effect (STable 1) and the effect was similar when DTP was given after standard MV (see below).

Standard-titre MV

Inspired by the above results for HTMV and MTMV, we examined what happens when DTP is given after standard MV. As seen in Figure 1 (STable 2), **receiving DTP-containing vaccine after MV compared with MV-only as most recent vaccine is associated with a MRR of 1.92 (1.49-2.46).** The tendency was essentially the same in the nine studies examining DTP and the two studies using DTP-containing Pentavalent vaccine. In the eight studies, which had reported estimates for both sexes, **the MRR was 2.31 (1.59-3.36) for females and 1.24 (0.84-1.83) for males** (p=0.024, test of homogeneity). The same increased female mortality (MRR=2.36 (1.43-3.89)) was found in six studies following children, who missed doses of DTP when receiving MV and were likely to receive DTP afterwards whereas this difference did not matter for boys, the MRR being 1.11 (0.69-1.77) (p=0.031, test of homogeneity) (STable 3) (6).

Co-administration of vaccines

We have also looked at whether co-administration of DTP and MV had an effect on survival. As seen in Figure 2 (STable 4), **DTP+MV compared with MV-only as most recent vaccine was associated with 2-fold higher child mortality** in the 15 studies available. The negative effect was slightly worse in males than in females (STable 4).

DISCUSSION

The SAGE review of the NSEs estimated that DTP after MV was associated with a MRR of 2.16 (1.25-3.74) (3 studies) and DTP+MV was associated with a MRR of 2.29 (1.55-3.37)(5 studies) (7). These results are essentially similar to the present review, only there are many more studies now, 11 and 15, respectively.

The SAGE reviewers mentioned that the studies were observational and that there was a high risk of bias. However, **bias is unlikely to explain the results.** As documented here, the studies showed similar effects in RCTs (STable 1) and observational studies (STable 2). The pattern of increased female mortality for DTP after MV was further supported by the six studies of those children missing doses of DTP at the time of MV (STable 3). If the excess mortality in the observational studies were due to worse off children being vaccinated later, then the negative effects would most likely occur for both males and females. However, across both RCTs and observational studies the higher mortality for DTP after MV was only for girls (STables 1, 2 and 3). On the other hand, had it been a general bias only related to girls, then girls receiving DTP+MV should also have had stronger negative effects; they did not (STable 4).

Given the present evidence, **it is far more plausible that different sequences of vaccinations program the immune system in different ways, with consequences for child survival that differ for females and males.**

One of the important implications of these observations is that **child mortality may have declined because the EPI vaccine programme became better in delivering the doses of DTP before MV** rather than out-of-sequence vaccinations with DTP after MV or together with MV. For example, at the health and demographic surveillance system site in Ghana, Navrongo, out-of-sequence vaccinations with DTP and MV happened for 86% of the children around 1990 when registration started (8); today out-of-sequence vaccinations are <1%. Using data from Navrongo, the reduction in out-of-sequence vaccinations is estimated to have reduced child mortality by at least 26% (9).

We have only presented the mortality data, but morbidity and hospital admission data show a similar pattern in Guinea-Bissau and in Denmark (10,11), US (12), and Holland (13-15).

CONCLUSION

Triangulation of all the available data shows that providing DTP-containing vaccines with or after MV may be harmful. Hence, SAGE and GACVS should strongly encourage that vaccines are given timely and in the recommended sequence, so that MV is given after the third dose of DTP-containing vaccine. This may have a considerable impact on child survival as documented by the Navrongo data. Current MV program performance indicators emphasize merely coverage of MV by 12 months of age. **It would make sense that MV-after-DTP3 coverage rather than the simple *MV* coverage became the main program indicator for MV.**

PERSPECTIVES

DTP and Penta (DTP-containing) have similar effects. There are reasons to think that other non-live vaccines may have similar effects since they are also surprisingly associated with increased female mortality. Since the global health community is planning to introduce several non-live vaccines (booster DTP, RTSS, meningococcal vaccine) as part of the 2nd year of life platform for vaccinations, **it would seem to be very important to clarify whether the other non-live vaccine also have negative effects when administered with MV or after MV.**

We look forward to your reply.

Best wishes,

Peter Aaby Ane B. Fisker Sanne M. Thysen Christine S. Benn

All from Bandim Health Project, Guinea-Bissau and Denmark

Figure 1. Meta-analysis of the effect DTP-after-MV compared with MV-after-DTP (data in STable 2)

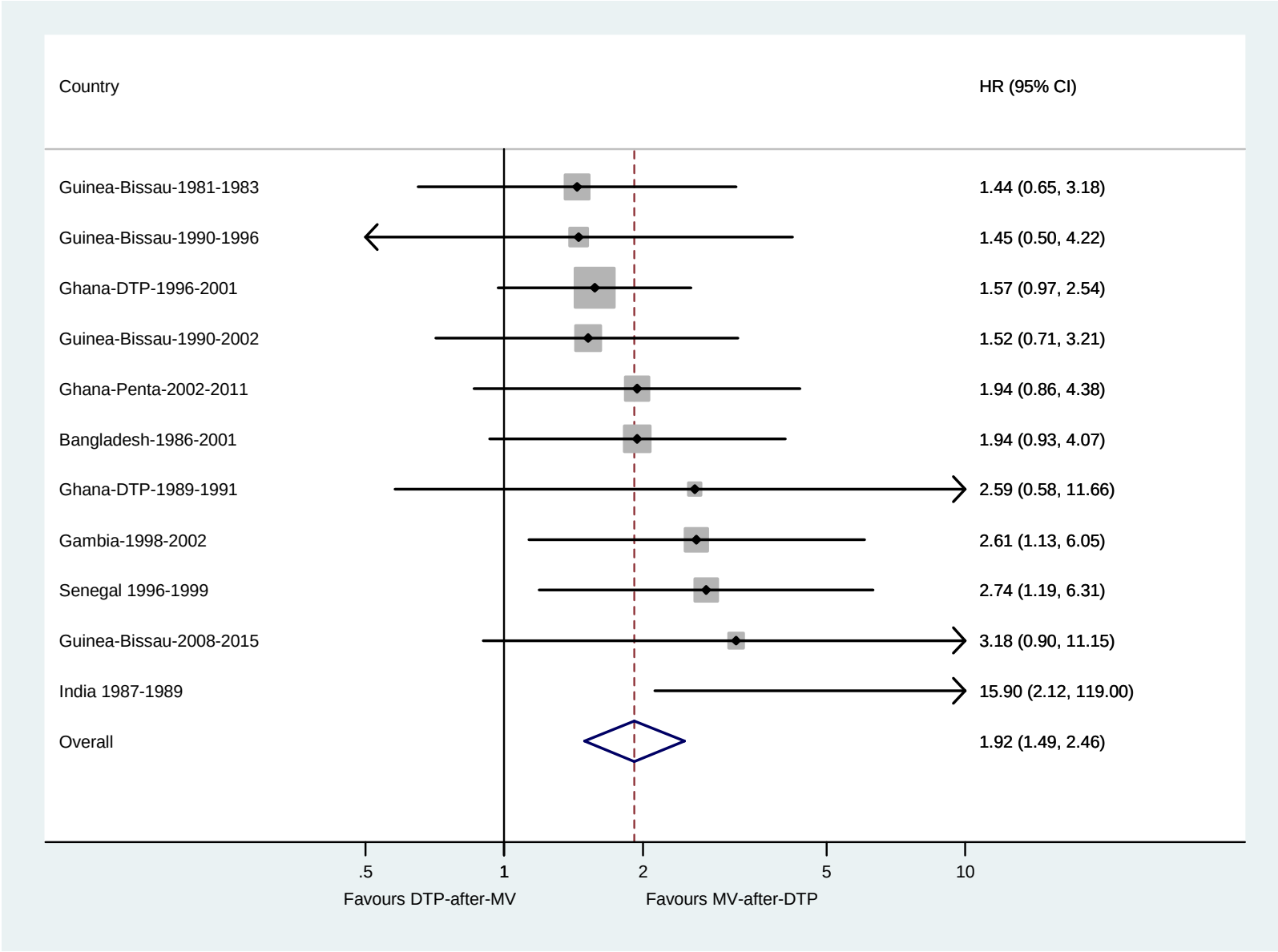
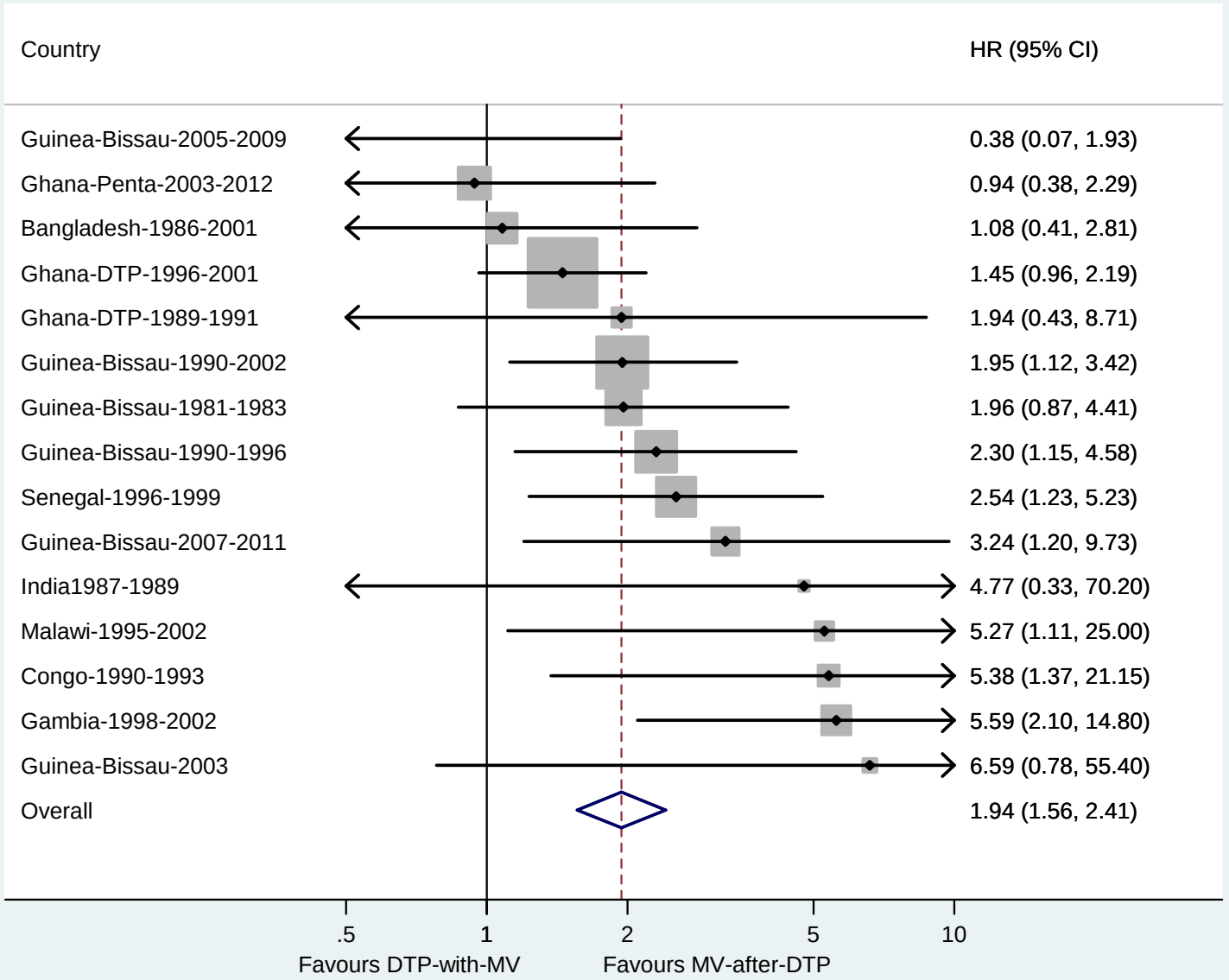


Figure 2. Meta-analysis of the effect DTP-with-MV compared with MV-after-DTP (data in STable 4)



Supplementary material

STable 1. Randomised controlled trials of MT/HT measles vaccine versus non-live vaccine given to African boys and girls at 9-10 months of age.

Study (ref)	Age followed	Vaccines[a]	Inactivated vaccine after early MTMV/HTMV	MV after non-live vaccine	Mortality rate ratio (95% CI) Non-live vs. MV as most recent vaccine	Mortality rate ratio (95% CI) Non-live vs. MV as most recent vaccine	Mortality rate ratio (95% CI) Non-live vs. MV as most recent vaccine
			Number of children: died / person-years (deaths per 100 person-years)		All	Females	Males
Bissau MTMV EZ1 (16)	10-60 mo	MV vs IPV	23/644.1 (3.6%)	17/632.3 (2.7%)	1.32 (0.71-2.47)	0.81 (0.30-2.18)	1.84 (0.79-4.30)
Bissau MTMV EZ2 (1)	10-48 mo	MV vs IPV	9/134.0 (6.7%)	5/134.3 (3.7%)	1.82 (0.61-5.43)	1.87 (0.38-7.48)	1.64 (0.27-9.81)
Bissau HTMV EZ2 (1)	10-48 mo	MV vs IPV	11/158.5 (6.9%)	9/161.8 (5.6%)	1.24 (0.51-2.99)	3.17 (1.01-9.98)	0.0
Gambia HTMV (1)	10-36 mo	MV vs IPV	3/137.2 (2.2%)	0/134.7 (0%)	NA	NA	NA
Senegal (HTMV EZ and SW) (17)	10-60 mo	MV+DTP+IPV+YF vs DTP+IPV+YF	54/1354.8 (4.0%)	23/844.0 (2.7%)	1.45 (0.89-2.37)	2.32 (1.12-4.81)	0.85 (0.43-1.72)
Senegal cohort 17-24 (only HTMV EZ) (17)	10-60 mo	MV+DTP+IPV+YF vs DTP+IPV+YF	22/540.4 (4.1%)	20/530.1 (3.8%)	1.07 (0.59-1.97)	1.75 (0.69-4.44)	0.72 (0.32-1.64)
Sudan HTMV (4)	10-36 mo	MV vs N	12/641.8 (1.9%)	7/606.8 (1.2%)	1.60 (0.63-4.07)	2.32 (0.70-7.72)	1.31 (0.29-5.85)
All trials					1.38 (1.05-1.83)	1.89 (1.27-2.80)	0.98 (0.66-1.46)

Notes: Trials of early measles vaccination (MV) before 9 months of age: In these trials the early MV group received HTMV or MTMV around 4-6 months and then DTP/inactivated polio vaccine (IPV)/Meningococcal vaccine around 9-10 months of age whereas the control children received the non-live vaccine at 4-6 months of age and then standard MV at 9-10 months of age. We have compared mortality from 9-10 months onwards when one group received non-live vaccine after MT/HTMV whereas the other group received MV after non-live vaccine. The analysis here is per-protocol (PP) in the sense that it only includes children who had received both the first vaccine before 9 months and the second vaccine after 9 months.

[a]Vaccines: DTP = diphtheria-tetanus-pertussis, MV = measles vaccine, N = Neisseria meningitis polysaccharide, IPV = inactivated polio, YF = yellow fever

STable 2. Observational studies of DTP/Penta after MV compared with MV-only as most recent vaccination.

			Most recent vaccine				
Country/study (ref)	**No. of children**	**Study design**	**DTP/Penta after MV**	**MV alone**	**MRR(DTP>MV vs MV alone)**	**Females**	**Males**
DTP			Mortality rate (deaths/person-years pyrs)				
*Senegal, 1996-99 (18)	4133	Routine vaccination – 9-24 mo; follow-up to 24 mo	8.8% (9/102.4)	3.9% (13/335.6)	2.74 (1.19-6.31)#	2.40 (0.57-10.03)	2.05 (0.71-5.92)
*India; 1987-89; Vaccine 2012 (19)	876	Routine vaccinations before 12 mo – follow-up to 5 years	1.2% (2/173)	0.1%(2/2710)	15.9 (2.12-119)#	NA	NA
*Bissau, 1990-2002 (20)	689	Hospital case fatality 6-17 mo; only 1 MV; follow-up at hospital	12% (7/58 N)	8% (43/540 N)	1.52 (0.71-3.21)&	2.22 (0.81-6.09)	1.06 (0.34-3.32)
Gambia; 1998-2002 (21)	Vaccinations status of 41 dead children aged 9-17 mo	22%(9/41) of dead measles vaccinated children aged 9-17 mo had received DTP>=MV compared with 6% (163/2539) in community surveys	NA	NA	2.61 (1.13-6.05)#	3.34 (1.15-9.74)	NA
Guinea-Bissau, 1990-1996 (22)	2083	Rural area, 1990-1996, children aged 9-17 mo; follow-up to 18 mo	4.3% (6/116)	3.3% (16/491)	1.45 (0.50-4.22)#	1.38 (0.25-7.52)	1.48 (0.37-5.88)
Navrongo, Ghana, 1989-1991 (9)	667	Routine surveillance; children aged 6-35 mo; 12 mo follow-up; adjusted age, weight-for-age, zone, ownership radio	2.4% (12/497)	1.3% (2/157)	2.59 (0.58-11.7)#	NA	NA
Navrongo, Ghana 1996-2001 (9) For sex: 1996-2012 (9)	32,021	Routine surveillance; children aged 12-23 mo; 12 mo follow; adjusted age, wealth index, maternal education, sex, year	3.4% (22/650)	2.0% (179/8843)	1.57 (0.97-2.54)#	1.88 (1.08-3.27)	1.35 (0.73-2.50)
Guinea-Bissau, 1981-1983 (23)	1491	Urban surveillance; age 9-36 mo; follow-up to 36 mo	2.9% (16/554.1)	2.2% (10/448.0)	1.44 (0.65-3.18)#	2.53 (0.67-9.55)	0.97 (0.35-2.69)

Bangladesh, 1986-2001 (24)	36,650	Rural surveillance; aged 9-24 mo; follow-up to 24 mo	1.3% (22/1754.8)	0.8% (16/2035.6)	1.94 (0.93-4.07)#	3.67 (1.40-9.60)	0.56 (0.15-2.12)
PENTA							
Guinea-Bissau, 2008-2015 (25)	5560	Rural surveillance; aged 9-18 mo; MV children but missing Penta; received Penta or not at visit; 6 mo follow-up	6.2%(4/65)	2.0%(5/245)	3.18 (0.90-11.15)&	5.10 (1.02-25.4)	1.51 (0.20-11.2)
Navrongo, Ghana 2002-2011 (9)	32,021	Routine surveillance; children aged 12-23 mo; 12 mo follow-up; adjusted age, wealth index, maternal education, sex, year	2.6% (6/235)	1.2% (237/19167)	1.94 (0.86-4.38)#	NA	NA
Meta estimate					**1.92 (1.49-2.46))**	**2.40 (1.69-3.42)**	**1.24(0.84-1.83)**
DTP					**1.87 (1.43-2.45)**		
Penta					**2.24 (1.13-4.45)**		
Estimates for both sexes						**2.31 (1.59-3.36)**	**1.24 (0.84-1.83)**

Notes: * Study was included in the SAGE-review (Higgins BMJ 2016); # Estimate or numbers are in the paper; & calculated by the person responsible for the data set.

STable 3. Mortality after enrolment in measles vaccination trials according to DTP status at enrolment.

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 (26)	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 (26)	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 (26)	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 (27)	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 (4)	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 (4)	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; B=Medium and high-titre EZ-trial; C=2-dose MV trial; D=trial of MV with vitamin A; ND=Not defined.
#The test of homogeneity for the estimates for boys and girls was p=0.031.

STable 4. Co-administration of MV and DTP vaccines compared with MV-only as most recent vaccine on overall mortality.

Country/study	No. of children	Study design	DTP and MV combined	MV alone	MRR(DTP+MV vs MV alone)	Adjustment	MRR(DTP+MV vs MV alone) Females	MRR(DTP+MV vs MV alone) Males
			Mortality rate (deaths/person-years)					
Congo; 1990-1993 (4)	485	EZ-trial at 6 mo with follow-up to 36 mo	5.4% (3/55.2)	1.0% (11/1113.8)	5.38 (1.37-21.15)#	Age, sex maternal schooling, typo of MV, and health centre of recruitment.	4.27 (0.50-36.5)	6.40 (1.29-31.7)
*Malawi; 1995-2002 (28)	514	Routine vaccination; mortality follow-up until 18 mo	2/22 (N)	9/492 (N)	5.27 (1.11-25.0)#	Age and factors which changed MRR by more than 10%	No female death	>5.27 (1.11-25.0)
*Bissau, 1990-2002 (20)	705	Hospital case fatality 6-17 mo; hospital follow-up	16% (14/90 N)	8% (43/540 N)	1.95 (1.12-3.42)&		1.95 (0.76-4.95)	1.93 (0.96-3.88)
Gambia; 1998-2002 (21)	41 dead children aged 9-17 mo	22% (9/41) of dead measles vaccinated children aged 9-17 mo had received DTP3 >=MV compared with 6% (163/2539) in community surveys	NA	NA	5.59 (2.10-14.8)#		No female death	11.61 (4.33-31.2)#
*India; 1987-1989 (19)	912	Routine vaccinations before 12 mo; follow-up to 5 years	0.4% (1/228)	0.1%(2/2710)	4.77 (0.33-70.2) #		NA	NA
*Senegal, 1996-1999 (18)	4133	Routine vaccination – 9-24 mo; follow-up to 24 mo	8.1% (21/260.6)	3.9% (13/335.6)	2.54 (1.23-5.24)#		2.03 (0.65-6.41)	2.00 (0.84-4.78)
*Guinea-Bissau; 2007-2011 (29)	2331	Control group receiving placebo (not VAS) with vaccines; follow-up for 6 mo. During the period with Penta, the MV vaccinated children received YF	4.4% (14/318)	1.1% (8/760)	All: 3.24 (1.20-8.73)# DTP: 1.56 (0.39-6.29)# Penta: 7.73 (1.79-33.4)#	Age, rural-urban, season of vaccination, ethnicity, morbidity at enrolment, maternal education, stunting, able to sign in writing.	3.71 (1.14-12.0)	2.46 (0.51-11.9)
Guinea-Bissau; 2007-2011		Received VAS with vaccines; follow-up for 6 mo. During the period with Penta, the MV vaccinated children received YF	2.6% (8/303)	1.4% (10/723)	All 1.27 (0.46-3.48)& DTP: 1.83(0.42-7.91) Penta: 0.91 (0.20-4.26)	Age, urban-rural, season of vaccination, ethnic group, morbidity at enrolment, maternal schooling and able to sign, stunting	1.67 (0.32-8.71)	1.06 (0.31-3.60)
Guinea-Bissau; 2003 (30)	2014	Children aged 6-17 mo during NID; received VAS; follow-up	5/88 (N)	0/116 (N)	Not defined; p=0.014 MH#		>6.44 (0.60-69.0)	>6.69 (0.71-62.8)

		to 18 mo			Assuming 1 death in MV only group >6.59 (0.78-55.41)&			
Guinea-Bissau, 1990-1996 (22)	2083	Rural area, 1990-1996, children aged 9-17 mo; follow-up to 18 mo	6.4% (29/455)	3.3% (16/491)	2.30 (1.15-4.58)#		2.50 (0.88-7.12)	2.08 (0.83-5.46)
Navrongo, Ghana 1989-1991 (9)	628	Routine surveillance; children aged 6-35 mo; 12 mo follow-up; adjusted age, weight-for-age, zone, ownership of radio	2.6% (12/455)	1.3% (2/157)	1.94 (0.43-8.71)#		NA	NA
Navrongo, Ghana 1996-2001 (9)	32,021	Routine surveillance; children aged 12-23 mo; 12 mo follow-up; adjusted age, wealth index, maternal education, sex, year; DTP	2.8% (27/980)	2.0% (179/8843)	1.45 (0.96-2.19)#		1.19 (0.68-2.08)	1.40 (0.85-2.31)
Navrongo, Ghana 2002-2011 (9)	32,021	Routine surveillance; children aged 12-23 mo; 12 mo follow-up; adjusted age, wealth index, maternal education, sex, year; PENTA	1.9% (7/359)	1.2% (237/19167)	0.94 (0.38-2.29)#			
Guinea-Bissau, 1981-1983 (23)	1491	Urban surveillance; age 9-36 mo; follow-up to 36 mo	4.7% (14/295.6)	2.2% (10/448.0)	1.96 (0.87-4.41)#		3.18 (0.82-12.3)	1.44 (0.50-4.10)
Bangladesh, 1986-2001 (24)	36,650	Rural surveillance; aged 9-24 mo; follow-up to 24 mo;	0.6% (9/1603.0)	0.8 (16/2035.6)	1.08 (0.41-2.81)#		0.73 (0.15-3.45)	1.29 (0.40-4.18)
Guinea-Bissau, 2005-2009 (31)	568	RCT of MV+DTP+OPV vs MV+OPV; 12 mo follow-up	0.7% (2/287 N)	1.9% (5/271 N)	0.38 (0.07-1.93)&		0.31 (0.03-2.96)	0.51 (0.05-5.57)
Meta-estimate FE[&]					**1.94 (1.54-2.41)**		**1.73 (1.23-2.44)**	**2.04 (1.55-2.68)**
RE[&]					**2.08 (1.54-2.80)**			**2.25 (1.49-3.40)**

Notes: * Study was included in the SAGE-review (Higgins BMJ 2016); & FE= fixed effect estimate, RE=random effect estimate # Estimate or numbers are in the paper; & calculated by the person responsible for the data set.

LITERATURE SEARCH

We searched the literature after November 2012, which is the period after the SAGE Review (Higgins et al, BMJ 2016) with the following terms:

("Measles Vaccine"[Mesh] *OR* "measles vaccination" *OR* ”measles vaccine” *OR* ”measles vaccines” *OR* "measles immunisation" *OR* "measles immunization")

AND

(("Diphtheria-Tetanus-Pertussis Vaccine"[Mesh] OR "DTP Vaccine"[Mesh] OR "Diphtheria-Tetanus-Pertussis vaccination" OR ”Diphtheria-Tetanus-Pertussis vaccine” OR ”Diphtheria-Tetanus-Pertussis vaccines” OR "Diphtheria-Tetanus-Pertussis immunisation" OR "Diphtheria-Tetanus-Pertussis immunization" OR "DTP vaccination" OR ”DTP vaccine” OR ”DTP vaccines” OR "DTP immunisation" OR "DTP immunization")

OR

("DtwP-HepB-Hib vaccine"[Mesh] OR "Pentavalent vaccination" OR ”Pentavalent vaccine” OR ”Pentavalent vaccines” OR "Pentavalent immunisation" OR "DtwP-HepB-Hib vaccination" OR ”DtwP-HepB-Hib vaccine” OR ”DtwP-HepB-Hib vaccines” OR "DtwP-HepB-Hib immunisation" OR "Penta vaccination" OR ”Penta vaccine” OR ”Penta vaccines” OR "Penta immunisation"))

Furthermore, unpublished studies known to the authors were include in the meta-analyses.

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