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1 Risk-of-bias assessments for randomized and quasi-randomized trials of BCG

Canada 1933-1945

Result selected ¹	Sample	Allocation or randomization	Blinding and co-interventions	Ascertainment of mortality	Data & analysis
Canada #8912 Risk ratio (unadjusted) = 0.94 (0.67, 1.32) Computed from counts in Table IV (first row, less than 1 year)	Quasi-randomized trial of BCG vs no BCG. All Indian infants born in the Qu'Appelle Indian Health Unit between October 1933 and December 1945. 309 vaccinated and 310 unvaccinated children. 306 and 303 respectively were included in the analyses. <u>Selected for inclusion in review:</u> All	<u>Allocation:</u> "Families of comparable status in respect of housing, sanitation and certain other economic and social factors likely to affect the health of children were paired, and one member of each such pair was allotted at random to one of two groups, designated 'Group A' and 'Group B'. All children born into the families of Group A were vaccinated in one year, while all children born into families of Group B in the same year were taken as controls. In the following year this situation would be reversed and so on throughout the duration of the study." Allocation appears to be random in principle, but unlikely to be adequately concealed. No information on similarity of groups.	<u>Blinding of participants:</u> None. <u>Blinding of vaccine administrators:</u> None. <u>Co-interventions and departures from allocated intervention:</u> No information.	Assessed at 12-month visit. <u>Blinding of outcome assessors:</u> Probably not, but objective outcome.	<u>Missing data:</u> Outcome data reasonably complete. <u>Analysis:</u> Unadjusted comparison of numbers of deaths.

Unclear risk of bias due to confounding (allocation may be unconcealed and no information about similarity of groups)
Moderate risk of performance bias due to departures from intended interventions (participants knew vaccination status)
Low risk of detection bias in measurement of outcomes
Low risk of attrition bias due to missing outcome data.
Unclear risk of bias in selection of the reported result
Overall: Moderate risk of bias (participants knew vaccination status)

¹ Throughout this annex, this column includes the name of the article group (e.g. Canada; Guinea-Bissau A), followed by the ID number of the paper containing the result (e.g. #8912, #61), followed by information about the result.

Guinea-Bissau 2002-2008 (early phase of trial)

<i>Result selected</i>	<i>Sample</i>	<i>Allocation or randomization</i>	<i>Blinding and co-interventions</i>	<i>Ascertainment of mortality</i>	<i>Data & analysis</i>
Guinea-Bissau A #61 MRR (unadjusted) = 0.28 (0.06, 1.37) Table 1 (4 weeks)	Randomized trial of early BCG vs delayed BCG (only time before delayed BCG considered in this review). 105 low birth weight children from 2 health centres randomized Nov 2002 to Nov 2004. <u>Selected for inclusion in review:</u> All	<u>Allocation:</u> Cites #166 for randomization methods (see #166).	(see #166) <u>Blinding of participants:</u> None <u>Blinding of vaccine administrators:</u> None	No details. <u>Blinding of outcome assessors:</u> Probably not, but objective outcome.	<u>Missing data:</u> Outcome data reasonably complete. <u>Analysis:</u> Cox proportional hazards model.

Low risk of bias due to confounding

Low risk of performance bias due to departures from intended interventions

Low risk of detection bias in measurement of outcomes

Low risk of attrition bias due to missing outcome data.

Unclear risk of bias in selection of the reported result

Overall: Low risk of bias

Guinea-Bissau 2002-2008 (main phase of trial)

<i>Result selected</i>	<i>Sample</i>	<i>Allocation or randomization</i>	<i>Blinding and co-interventions</i>	<i>Ascertainment of mortality</i>	<i>Data & analysis</i>
Guinea-Bissau A #166 MRR (adjusted) = 0.55 (0.34, 0.89) Table 3 total at 4 weeks	Randomized trial of early BCG vs delayed BCG (only time before delayed BCG considered in this review). 2343 low birth weight children from 3 health centres. 607 randomized November 2004 to May 2005, and 1736 randomized May 2005 to January 2008. In the second of these periods, trial extended to factorial design with addition of vitamin vs placebo comparison. <u>Selected for inclusion in review:</u> All	<u>Allocation:</u> "Block randomization procedures have been described in detail elsewhere [ref to #339]. Twins were allocated the same treatment to prevent potential confusion regarding who had been vaccinated." #339 refers to the factorial period of the trial only: "Once consent was provided, the mother drew an envelope from a bag. Each bag was prepared by the study supervisor and contained 48 envelopes; each envelope contained a lot name. Within each bag were 12 envelopes with lots marked "BCG 6," 12 marked "BCG 7," 12 marked "no BCG 6," and 12 marked "no BCG 7." The numbers "6" and "7" indicated from which of two numbered bottles, "6" or "7," the child should receive treatment (that is, either 25000 IU vitamin A or placebo)." "The envelopes were closed and non-transparent, making it impossible to identify the allocation before the envelopes were opened." "There were few differences in anthropometric measurements, gestational age, or background factors between children who received BCG and controls. The BCG group had more twins and tended to have more mothers who had died before enrollment"	<u>Blinding of participants:</u> "No placebo for BCG was given."; "a control vaccine may have a nonspecific impact on mortality. Furthermore, if we had used a placebo, control mothers might have believed that the child had received BCG and might therefore not have sought BCG vaccination. We therefore preferred not to use a placebo". <u>Blinding of vaccine administrators:</u> None. <u>Co-interventions and departures from allocated intervention:</u> No information <u>Comment:</u> 11% of children in the control group received BCG during follow-up.	When a death was identified a standard verbal autopsy was conducted by a clinician about 3 months after the death. <u>Blinding of outcome assessors:</u> Probably not, but objective outcome.	<u>Missing data:</u> "Of the 2343 children enrolled in the trial between November 2004 and March 2008, 23 were excluded (Figure 1). The remaining 2320 children were included in the main analysis" <u>Analysis:</u> Cox proportional hazards model with age as underlying time.

Low risk of bias due to confounding

Low risk of performance bias due to departures from intended interventions

Low risk of detection bias in measurement of outcomes

Low risk of attrition bias due to missing outcome data.

Unclear risk of bias in selection of the reported result

Overall: Low risk of bias

USA c.1935

Result selected	Sample	Allocation or randomization	Blinding and co-interventions	Ascertainment of mortality	Data & analysis
USA A #8747 MRR (unadjusted) = 0.91 (0.41, 1.99) Computed from rates in Table 9, aged 0-4 years	Randomized trial of BCG vs no BCG. 3008 children attending the Indian Service schools, followed-up for up to a possible 11 years (interrupted by WWII). <u>Selected for inclusion in review:</u> 846 age under 5	<u>Allocation:</u> “a record was prepared for each person who failed to react to tuberculin PPD. All of these records for each school an adjacent area were then sorted b sex and year of birth. An alternate division of the records was then made within each sex and age group. Approximately one-half received the BCG vaccine while the remaining number served as controls. In a small number of instances, the person selected was absent from school and one of those listed for the control group was substituted and the absentee then served as a control.”	<u>Blinding of participants:</u> Probably not. “At the same time that the vaccine was given, the control group received an intracutaneous injection of 0.1 cc physiological saline.” However children receiving BCG would develop a reaction. <u>Blinding of vaccine administrators:</u> No information. <u>Co-interventions and departures from allocated intervention:</u> No information. “Neither vaccinated nor controls were isolated before or after vaccination, nor was their mode of living modified.”	No details. <u>Blinding of outcome assessors:</u> Probably not, but objective outcome.	<u>Missing data:</u> Virtually all children followed for 6 years. There were variations after this due to World War II; attempts made to collect data up to 11 years later but numbers are much lower for later years. <u>Analysis:</u> Unadjusted comparison of counts of deaths.

Moderate risk of bias due to confounding (absentees allocated to the control arm)

Moderate risk of performance bias due to departures from intended interventions (any blinding unlikely to be maintained; no information on co-interventions)

Low risk of detection bias in measurement of outcomes

Low risk of attrition bias due to missing outcome data.

Unclear risk of bias in selection of the reported result

Overall: Moderate risk of bias (lack of randomization, blinding and no information on co-intervention)

Result selected	Sample	Allocation or randomization	Blinding and co-interventions	Ascertainment of mortality	Data & analysis
USA B #9244 Risk ratio (unadjusted) = 0.42 (0.13, 1.35) Computed from counts in Table 14A	Randomized trial of BCG vs no BCG. 451 children of expectant mothers with tuberculosis or where tuberculosis was present in the immediate household. Followed up to 13 years. 231 vaccinated and 220 controls. BCG was given at different times depending on subgroup. Babies were placed in state approved foster homes until approximately 6-8 weeks old, this varied based on the above factors. <u>Selected for inclusion in review:</u> All	<u>Allocation:</u> "In each subgroup... the children were randomly drawn and alternately assigned to vaccinated or control groups. Thus, the randomized drawing was independent of the process of classifying into subgroups. The formation of the subgroup before alternation reduces the size of population required to ensure unbiased vaccinated and control groups. This alternation was done on a master chart in the main office by a physician who did not do the field work." No significant differences found between vaccine and control groups with the exception of birth weight when split into 13 weight intervals. When regrouped into 3 groups, no significant difference found.	<u>Blinding of participants:</u> "In the novaccinated, the same procedure was followed except that saline was used instead of the vaccine (placebo). However children receiving BCG would develop a reaction." <u>Blinding of vaccine administrators:</u> No information. <u>Co-interventions and departures from allocated intervention:</u> BCG was administered at different times depending on whether child was removed at birth / later and the level of TB risk. It ranged from birth to 3 months old. "There were no appreciable differences in the vaccinated and control groups in any of the above categories" [home visits, roentgenograms, examinations by physicians]	Visited weekly while in foster home. Every 6 months they returned to the clinic. <u>Blinding of outcome assessors:</u> Probably not, but objective outcome.	<u>Missing data:</u> Results table imply deaths known for all participants. However, "some 23 per cent were not followed for the specified time in both groups... There were no significant differences in the total of vaccinated and control subjects lost from the study. However, there were significant differences between the groups in regard to reason for loss. This was due to an excess of vaccinated lost because of delinquency or moving and an excess of controls lost for "other" reasons". It is not clear whether these are counted in the denominator when presenting mortality data. <u>Analysis:</u> Unadjusted comparison of counts of deaths.

Moderate risk of bias due to confounding (alternation with no allocation concealment)

Low risk of performance bias due to departures from intended interventions

Low risk of detection bias in measurement of outcomes

Moderate risk of attrition bias due to missing outcome data (unclear whether outcomes known for 23% lost to follow up were).

Unclear risk of bias in selection of the reported result

Overall: Moderate risk of bias (no allocation concealment and uncertainty around missing data)

2 Risk-of-bias assessments for non-randomized studies of BCG

Bangladesh 1986-2001

Result selected	Sample	Confounders measured (*adjusted for)	Comparability of groups	Ascertainment of vaccine status	Co-interventions	Ascertainment of mortality	Data & analysis
Bangladesh A #797 Hazard ratio (adjusted) = 0.2 (0.07, 0.54) Table 6 (0-60 days)	Observational comparison. Based on 39,625 children born between Jan 1 1986 and Jan 1 2000. 1731 excluded because they died (1600) or migrated (131) before 42 days (vaccines start at 6 weeks). Analysis of 37,894 children for BCG Selected for inclusion in review: 9704 children who received BCG aged 0-60 days	<u>SES</u> : Maternal education, asset score <u>Child's health</u> : Distance from hospital, MUAC (not used, too much missing data) <u>Other</u> : Birth order, religion, maternal age <u>Age</u> : Yes* <u>Gender</u> : Yes	<u>Vaccines more likely among</u> : older mothers, higher education, not first born, higher asset score (least poor), non Muslims, closer to hospital <u>Mortality more likely among</u> : older mothers, lower education, first born (DTP)/third born (MV), lowest asset score.	<u>Frequency</u> : every 2 weeks until Jan 1998, once a month since then <u>Method</u> : Monthly immunization days, community worker vaccinates children on this day and records them in record keeping book. <u>Vaccinated</u> : Children given vaccine during immunization day <u>Unvaccinated</u> : No explicit definition given. Children with no vaccine recorded in book/did not attend vaccination day. <u>Dead children</u> : status based on vaccines received up to 30 days before death. <u>Approach</u> : Information updated on day vaccine given	<u>DTP/OPV</u> : High probability of co-administration (55% of BCG given simultaneously with DTP1, 10.1% with DTP2 and 5.5% with DTP3). High probability of differential DTP co-intervention (follow-up 60 months) <u>MV</u> : High probability of differential MV co-intervention (follow-up 60 months) <u>Other</u> : No information about any other co-interventions.	All deaths included except those due to trauma or accidents	Cox proportional hazards model "with time varying covariates with DTP grouped by age at time of BCG vaccination." Reference group not vaccinated with BCG. No confounders included in the model. Reanalysed using 30 day lag period & got consistent results (data not shown). Not clear but looks like mortality is up to 60 months, not adjusted for MV, unclear about DTP

Moderate risk of bias in selection of participants into the study

High risk of bias due to confounding (no adjustment for child's health or SES / unadjusted comparison of two groups)

Moderate risk of bias in measurement of vaccination

Very high risk of bias due to departures from intended interventions (High probability of differential co-intervention of DTP and MV)

Low risk of bias in measurement of outcomes

Moderate risk of bias due to missing outcome data

Moderate risk of bias in selection of the reported result

Overall: Very high risk of bias (co-intervention with DTP, MV)

Result selected	Sample	Confounders measured (*adjusted for)	Comparability of groups	Ascertainment of vaccine status	Co-interventions	Ascertainment of mortality	Data & analysis
Benin #9372 Odds ratio (adjusted) = 0.68 (0.38, 1.23) Table 2	Case-control study. Cases: All children who died between January 1986 and October 1987 and before the age of 3 years. Controls: selected from register of all children in the area, matched for age, sex and village of residence. "Some 74 cases and 230 controls were available for analysis" with 1-4 matched controls per case. "Children who were born and died within the interval of about 3 months between surveys were rarely reported. 2 infants who were known to have died within one month of birth were excluded. All other children had at least attained 4 months of age." <u>Selected for inclusion in review:</u> 143 children who were unvaccinated and 151 children who were vaccinated.	<u>SES:</u> socioeconomic score* (no details how this is calculated) <u>Child's health:</u> Weight for age* <u>Other:</u> NR <u>Age:</u> NR <u>Gender:</u> NR	<u>Vaccines more likely among:</u> no information <u>Mortality more likely among:</u> lower socioeconomic status	Frequency: None Method: Preventive child care cards, kept at the communal health centre. Vaccinated: Children with a vaccine recorded by vaccination team during visits to the village. Unvaccinated: Children with no recorded vaccine. Vaccination card could not be found for 10 children (1 case, 9 controls).	<u>DTP:</u> No information. High probability of differential co-intervention (follow-up 4-35 months) <u>MV:</u> No information. High probability of differential co-intervention (follow-up 4-35 months) <u>Other:</u> No information about any other co-interventions.	When a child under 3 died the interviewer recorded the symptoms parents mentioned. A medical doctor subsequently visited the household to establish a probable cause of death.	Analysis by conditional logistic regression.

High risk of bias in selection of participants into the study (deaths in first month excluded)

High risk of bias due to confounding (despite matching, some key confounders were not addressed)

Moderate risk of bias in measurement of vaccination

High risk of bias due to departures from intended interventions (High probability of differential co-intervention of DTP and MV)

Low risk of bias in measurement of outcomes

Moderate risk of bias due to missing outcome data

Moderate risk of bias in selection of the reported result

Overall: High risk of bias (confounding and subsequent vaccinations)

Burkina Faso 1985-1993

Result selected	Sample	Confounders measured (*adjusted for)	Comparability of groups	Ascertainment of vaccine status	Co-interventions	Ascertainment of mortality	Data & analysis
Burkina-Faso #799 Risk ratio (adjusted) = 0.5 (0.34, 0.75) Table 3 adj results BCG vs unvaccinated, first visit*	Observational comparison. During 1985 and 1996 9412 births were registered. 204 stillbirths and 123 infants with no recorded month of birth were excluded leaving 9085 infants. Selected for inclusion in review: Children who survived until first visit (up to 7 months of age).	<u>SES:</u> Area* <u>Child's health:</u> Child's health service use, diarrhoea*, fever, cough and malnutrition during first year <u>Other:</u> Age of mother, age of father, number of wives, mode of delivery, dispensary in village*, family health service use*, birth season*, birth period <u>Age:</u> Yes* <u>Gender:</u> Yes	<u>Vaccines more likely among:</u> boys, children in Yako, older mothers, modern delivery mode, dispensary in village, frequent health service use (child & family), having diarrhoea, fever, cough & malnutrition, being born Mar-Oct, being born after 1988 in Pissila and 1989 in Yako. <u>Mortality more likely among:</u> boys, Pissila, younger mothers, more wives, modern delivery, no dispensary, frequent child's health service use, rare family health service use, having diarrhoea, fever, cough & malnutrition, born Nov-Feb, birth in 1986-88 in Pissila and 1987-89 in Yako.	<u>Frequency:</u> Every 6 months although in 1993-5 the average interval was 12 months <u>Method:</u> Vaccination cards <u>Vaccinated:</u> Vaccination recorded on vaccination card. <u>Unvaccinated:</u> Children with no vaccine recorded or whose card weren't seen <u>Dead children:</u> When child died, belongings were discarded including vaccination cards <u>Approach:</u> Landmark, based on vaccination status at first visit only.	<u>DTP:</u> "Most of the vaccinated children received either BCG followed by DTP or the vaccines simultaneously"; no information on proportions. High probability of differential DTP co-intervention (follow-up 6 months from first visit (which was in the first 6 months of life)). <u>MV:</u> High probability of differential MV co-intervention (follow-up 6 months from first visit (which was in the first 6 months of life)). <u>Other:</u> No information about any other co-interventions.	Collected during 6 monthly-annual visits	Cox proportional hazards model. Follow-up began at first visit (before 7 months). Censoring at 2 nd visit, 6 months after 1 st visit, out-migration or death.

Very high risk of bias in selection of participants into the study (first visit took place up to 7 months old, so early effects of BCG on mortality not considered)

High risk of bias due to confounding (likely confounding, including by SES)

High risk of bias in measurement of vaccination (children assumed unvaccinated when card not seen)

High risk of bias due to departures from intended interventions (likely co-interventions including DTP and MV)

Low risk of bias in measurement of outcomes

Moderate risk of bias due to missing outcome data

Moderate risk of bias in selection of the reported result

Overall: Very high risk of bias (start of follow-up for children up to 7 months old)

Result selected	Sample	Confounders measured (*adjusted for)	Comparability of groups	Ascertainment of vaccine status	Co-interventions	Ascertainment of mortality	Data & analysis
Ghana C #9464 Hazard ratio (adjusted) = 0.18 (0.17, 0.2) Table II	Observational comparison. 17,967 children born between 1 st January 1998 and 31 st December 2004. <u>Selected for inclusion in review:</u> All	<u>SES:</u> Mother's education*, poverty status* <u>Child's health:</u> NR <u>Other:</u> <u>Age:</u> Yes* <u>Gender:</u> No	<u>Vaccines more likely among:</u> no information <u>Mortality more likely among:</u> lower education, higher poverty	<u>Frequency:</u> Annual collection of vaccination status <u>Method:</u> Annual survey <u>Vaccinated:</u> Unclear <u>Unvaccinated:</u> Unclear <u>Dead children:</u> No information <u>Approach:</u> Unclear <u>Comment:</u> "Annual updates of immunization status and educational attainment and indicators of socioeconomic status are linked to the demographic register."; "Models for the analysis presented here are based on the status of each child at the time of last observation with respect to the WHO definition."	<u>DTP:</u> High probability of differential DTP co-intervention (follow-up to 5 years) <u>MV:</u> High probability of differential MV co-intervention (follow-up to 5 years) <u>Other:</u> No information	All-cause mortality, quarterly visits	Time conditional HR. No description of any censoring.

Low risk of bias in selection of participants into the study

High risk of bias due to confounding (no adjustment for SES or child's health)

Insufficient information risk of bias in measurement of vaccination (high risk of bias or possibly very high risk of bias: cannot tell how vaccination status was defined; retrospective approach may have been used)

Very high risk of bias due to departures from intended interventions (high degree of co-intervention with DTP and MV)

Low risk of bias in measurement of outcomes

Moderate risk of bias due to missing outcome data

Moderate risk of bias in selection of the reported result

Overall: Very high risk of bias (high degree of co-intervention with other vaccines; unable to judge methods for determining vaccination status from publication)

Guinea-Bissau 1984-1985

Result selected	Sample	Confounders measured (*adjusted for)	Comparability of groups	Ascertainment of vaccine status	Co-interventions	Ascertainment of mortality	Data & analysis
Guinea-Bissau E #851 Risk ratio (adjusted) = 0.63 (0.3, 1.33) Text of paper (p. 377)	Observational comparison, 1984-1987. 1657 infants examined between 2 and 8 months of age. May be children who were never registered as they were not reported during pregnancy and they died or moved before they had the chance to be seen at one of the mobile bi-annually visits. Children followed-up until next visit or 6 months later if next visit was later than that (children presumably aged up to 14 months). BCG coverage increased from 1% and 7% in 1984 and 1985 respectively, to 26% and 29% in 1986 and 1987 respectively. No indication what age BCG recommended. <u>Selected for inclusion in review:</u> All	<u>SES:</u> Region* <u>Child's health:</u> Weight for age <u>Other:</u> Season*, period*, DTP*(very few children received BCG before DTP) <u>Age:</u> Yes* <u>Gender:</u> Yes*	<u>Vaccines more likely among:</u> no information <u>Mortality more likely among:</u> no information	<u>Frequency:</u> 6 monthly <u>Method:</u> BHP records/vaccination cards <u>Vaccinated:</u> BHP provided vaccine/saw vaccination card <u>Unvaccinated:</u> Those who didn't attend initial examinations, children travelling or absent and children examined but too sick to be vaccinated <u>Dead children:</u> No information <u>Approach:</u> Landmark	<u>DTP:</u> High probability of differential co-intervention with DTP <u>MV:</u> Low probability of differential co-intervention (up to 18% received MV during 6 months of follow-up) <u>Other:</u> OPV was given with DTP. No information about any of the other co-interventions.	Mortality recorded at 6 monthly visits. If a child did not attend examinations assistants visited the compound to inquire whether the child was travelling, had moved, or died. Cause of death was reviewed and children who died as the result of an accident were censored.	Cox proportional hazards model. Censoring at earliest of 6 months of follow-up, death, migration or new examination.

High risk of bias in selection of participants into the study (appears that follow-up could begin after DTP vaccination)

High risk of bias due to confounding (no adjustment for child's health, potential adjustment for post BCG variable (DTP))

High risk of bias in measurement of vaccination (unvaccinated group may include vaccinated children, and bias towards null from landmark approach)

High risk of bias due to departures from intended interventions (high rate of subsequent DTP vaccination)

Low risk of bias in measurement of outcomes

Moderate risk of bias due to missing outcome data

Moderate risk of bias in selection of the reported result

Overall: High risk of bias (no adjustment for child's health; selection bias; potential misclassification of vaccination status; co-intervention with DTP)

Guinea-Bissau 1989-1999 (I)

Result selected	Sample	Confounders measured (*adjusted for)	Comparability of groups	Ascertainment of vaccine status	Co-interventions	Ascertainment of mortality	Data & analysis
Guinea-Bissau I #839 Risk ratio (adjusted) = 0.05 (0.01, 0.46) Table 2 vaccinated 1st week vs unvaccinated at 6 months	Observational comparison. 22,657 children were born in the area between 1989 and 1999. Birth weight for registered for 8481 children born at the hospital. Of these, vaccination status was determined for 7138 children (1343 missing). Only those registered as low birth weight (LBW) were included in the final analyses (N=845). <u>Selected for inclusion in review:</u> 695 LBW children included in the analysis censoring at 6 months	<u>SES:</u> Maternal schooling*, area* <u>Child's health:</u> birth weight* <u>Other:</u> Mother's age, year of birth*, mother's ethnicity*, civil status, season, day of birth* <u>Age:</u> Yes* <u>Gender:</u> Yes*	<u>Vaccines more likely among:</u> no information <u>Mortality more likely among:</u> no information	<u>Frequency:</u> 3 monthly <u>Method:</u> Registering vaccine at local health centre or vaccination card <u>Vaccinated:</u> Card seen with vaccine recorded <u>Unvaccinated:</u> Children with no recorded vaccine, no information on children missing cards. <u>Dead children:</u> No information <u>Approach:</u> Landmark	<u>DTP:</u> High probability of differential co-intervention with DTP (Followed-up to 6 months) <u>MV:</u> Low probability of differential co-intervention with DTP (Followed-up to 6 months) <u>Other:</u> Nothing reported for any of the co-interventions	Likely 3 monthly visit	Cox proportional hazards model. All survival analyses started from age at first examination or 8 days of age, whichever came latest. Children were censored at moving or 6 months of age, whichever came first. Also did separate analyses censoring at the start of the war.

Moderate risk of bias in selection of participants into the study

High risk of bias due to confounding (likely residual confounding despite adjustment)

High risk of bias in measurement of vaccination (likely that unvaccinated group included assumed unvaccinated children)

High risk of bias due to departures from intended interventions (high degree of co-intervention with DTP)

Low risk of bias in measurement of outcomes

Moderate risk of bias due to missing outcome data

Moderate risk of bias in selection of the reported result

Overall: High risk of bias (co-intervention with DTP; likely residual confounding)

Result selected	Sample	Confounders measured (*adjusted for)	Comparability of groups	Ascertainment of vaccine status	Co-interventions	Ascertainment of mortality	Data & analysis
Guinea-Bissau D Risk ratio (adjusted) = 0.56 (0.37, 0.84) #9466 Text of paper	Observational comparison. 10,298 children born alive of which 686 died, 90 moved and 770 were too young before the first visit. 8752 were alive at first visit and their survival ascertained at the second visit. 8104 were under 7 months at first visit. <u>Selected for inclusion in review:</u> 5274 children aged under 0-6 months at first visit and who either had a vaccination card examined or had no card. Children followed-up until next visit or 6 months later if next visit was later than that (children aged up to 12 months). Results may refer to 4418 children.	<u>SES:</u> cluster*, maternal education, latrine <u>Child's health:</u> maternal tetanus, MUAC, well, birth at home <u>Other:</u> Length of follow-up*, season, period, maternal age, birth order, ethnicity, previous dead children, DTP* <u>Age:</u> Yes* <u>Gender:</u> Yes	<u>Vaccines more likely among:</u> children who had more contact with health system, mothers who received tetanus during pregnancy and who gave birth outside the home. They also had larger MUAC, younger mothers, had fewer children, have a latrine and not belong to Balanta or Pepel ethnicity. <u>Mortality more likely among:</u> no information	<u>Frequency:</u> Not updated <u>Method:</u> vaccination card <u>Vaccinated:</u> children whose card was seen <u>Unvaccinated:</u> children who had no date or were declared not to have received the vaccine <u>Dead children:</u> No information <u>Approach:</u> Landmark (date vaccination assessed)	<u>DTP:</u> High probability of differential co-intervention with DTP (By 6 months 19 (1%) unvaccinated children had received at least one dose of DTP, 1298 (53%) vaccinated children had received at least one dose of DTP. Followed-up to maximum of 12 months). <u>MV:</u> Moderate probability of differential co-intervention with MV (children followed up until to maximum of 12 months, and 791 children received MV between 7 and 11 months). <u>Other:</u> No information provided for any other co-interventions.	Information on mortality was obtained at subsequent visits (meaning children had to be visited twice to be included in the study).	Cox proportional hazards model. "There was no loss to follow-up because it was always possible to get information on all children from relatives living in the same compound". Analysis repeated excluding children considered unvaccinated because they had no card.

High risk of bias in selection of participants into the study (follow-up begins after BCG vaccinations for some children)

High risk of bias due to confounding (no adjustment for SES and child's health, potential adjustment for post BCG variable (DTP))

High risk of bias in measurement of vaccination (Assumed no card meant unvaccinated)

High risk of bias due to departures from intended interventions (high degree of co-intervention with DTP and moderate risk of co-intervention with MV)

Low risk of bias in measurement of outcomes

Moderate risk of bias due to missing outcome data

Moderate risk of bias in selection of the reported result

Overall: High risk of bias (late start of follow-up; likely confounding; co-intervention with DTP; vaccination ascertainment)

Result selected	Sample	Confounders measured (*adjusted for)	Comparability of groups	Ascertainment of vaccine status	Co-interventions	Ascertainment of mortality	Data & analysis
India E #8996 MRR (unadjusted) = 0.6 (0.18, 1.97) Computed based on Table 4 (Groups 1 vs 0)	Observational comparison. Live births between December 1987 and November 1989 in 45 contiguous villages. Analysis files from a previous study available for 4138 live births (286 deaths). Of these, 255 records were missing sex, birthday or exit day, which left 3883 children (282 deaths). <u>Selected for inclusion in review:</u> 3072 unvaccinated children or children with BCG [Groups 0 and I in the paper].	<u>SES:</u> NR <u>Child's health:</u> birth weight, current weight, length/height, common childhood morbidities <u>Other:</u> NR <u>Age:</u> Yes <u>Gender:</u> Yes	<u>Vaccines more likely among:</u> no information <u>Mortality more likely among:</u> no information	<u>Frequency:</u> 3 monthly visits <u>Method:</u> Vaccination card at home or when the child was brought to the clinic for immunization. <u>Vaccinated:</u> Children with a recorded BCG vaccine <u>Unvaccinated:</u> Children without a recorded vaccine, children whose vaccination card wasn't seen. <u>Dead children:</u> Data were available for 282/286 dead children <u>Approach:</u> Landmark	<u>DTP:</u> High probability of DTP co-intervention (none of the children had received DTP; follow-up stopped on receipt of DTP) <u>MV:</u> Moderate probability of MV co-intervention (follow-up to 1 year; 25% of the whole cohort received MV in the first year) <u>Other:</u> No information is provided about any of the co-interventions	All-cause mortality likely collected at 3 monthly visits at home.	Unadjusted analysis based on mortality rates in first 12 months, follow-up censored at receipt of DTP. But result is not more extreme than an adjusted analysis that also includes children who had DTP before BCG [MRR=0.41, Table 5].

High risk of bias in selection of participants into the study (vaccinated group was selected according to future events (children subsequently DTP vaccinated excluded))

High risk of bias due to confounding (unadjusted comparison of two groups)

High risk of bias in measurement of vaccination (unvaccinated group included those children whose card wasn't seen)

High risk of bias due to departures from intended interventions (high probability of co-intervention with DTP and MV)

Low risk of bias in measurement of outcomes

Moderate risk of bias due to missing outcome data

Moderate risk of bias in selection of the reported result

Overall: High risk of bias (no adjustment for age; assumptions about vaccination status)

Result selected	Sample	Confounders measured (*adjusted for)	Comparability of groups	Ascertainment of vaccine status	Co-interventions	Ascertainment of mortality	Data & analysis
India A #741 Hazard ratio (adjusted) = 0.44 (0.29, 0.66) Table 4, model I (No DTP, BCG)	Observational comparison. Live births between August 1998 and February 2002. Of the 13,294 infants born 11,619 were born alive and enrolled. Of these 10,274 were alive as of 7 days old (meaning approx 1250 died). <u>Selected for inclusion in review:</u> Child-time before receipt of DTP	<u>SES:</u> Wood fuel, Have roof, Lease land, Own cattle, Maternal Education, Electricity, TV <u>Child's health:</u> Birth weight <u>Other:</u> Mother's prior live births, season <u>Age:</u> Yes* <u>Gender:</u> Yes	<u>Vaccines more likely among:</u> higher birth weight, higher SES (hard roof, electricity, TV, maternal education) <u>Mortality more likely among:</u> those SES categories associated with lower vaccination coverage (using wood fuel, owning cattle, owning/leasing land)	<u>Frequency:</u> Fortnightly <u>Method:</u> Mother questioned at visits, if mother couldn't remember the vaccination card was checked if in the house <u>Vaccinated:</u> Children with reported vaccine <u>Unvaccinated:</u> No reported vaccination, a different code was used for children who received an unknown vaccine. <u>Dead children:</u> No information <u>Approach:</u> Probably retrospective: vaccination information collected retrospectively but not fully clear what vaccination times were used in the analysis. But only a 2-week window between visits.	<u>DTP:</u> Low probability of differential co-intervention (children who had received BCG only). <u>MV:</u> Low probability of differential co-intervention (follow-up to 6 months). <u>Other:</u> Part of a vitamin A trial. No information about any of the other co-interventions	Fortnightly visits	Cox proportional hazards model. Censoring at earliest of death, 6 months of age, loss to follow-up and receipt of first unknown vaccine.

High risk of bias in selection of participants into the study (follow-up begins at 1 week, after some BCG vaccinations)

High risk of bias due to confounding (no adjustment for SES or child's health, likely confounding SES)

High risk of bias in measurement of vaccination (retrospective collection of vaccination data)

Moderate risk of bias due to departures from intended interventions

Low risk of bias in measurement of outcomes

Moderate risk of bias due to missing outcome data

Moderate risk of bias in selection of the reported result

Overall: High risk of bias (no adjustment for SES or child's health; retrospective collection of vaccination data)

Result selected	Sample	Confounders measured (*adjusted for)	Comparability of groups	Ascertainment of vaccine status	Co-interventions	Ascertainment of mortality	Data & analysis
India G #9463 MRR (unadjusted) = 0.12 (0.09, 0.16) Computed from rates in Table 3 (0-5 weeks)	Observational comparison. Live study births from 1 January 2006 to 31 December 2011 in 28 villages in Ballabgarh. A total of 12,142 births with immunization details were available. A total of 11,390 had complete information on confounders and were included in analyses. <u>Selected for inclusion in review:</u> Time during which most recent vaccine was BCG between 0 and 5 weeks.	<u>SES:</u> Mother's education, fathers education, caste, wealth index <u>Child's health:</u> Access to health care, presence of a health facility in the village <u>Other:</u> Birth order <u>Age:</u> Yes <u>Gender:</u> Yes All included in analyses.	<u>Vaccines more likely among:</u> no information <u>Mortality more likely among:</u> no information	<u>Frequency:</u> Monthly work plan <u>Method:</u> Fortnightly visits added to computer database. <u>Vaccinated:</u> Recorded as having received BCG as last vaccine based on computerized system <u>Unvaccinated:</u> Recorded as not having received any vaccines based on computerized system <u>Dead children:</u> N/A <u>Approach:</u> Used date of vaccination, although likely to be quite accurate.	<u>DTP:</u> Low probability of differential DTP (follow-up to 6 weeks) <u>MV:</u> Low probability of differential MV (follow-up to 6 weeks) <u>Other:</u> No information is provided about any of the co-interventions	All-cause mortality Visits / computerized system.	Unadjusted mortality ratios. Children included in each group from receipt of vaccine until receipt of another vaccine or any other exit criteria. Exit criteria were 9 months of age, end of study or migration.

Moderate risk of bias in selection of participants into the study

Very high risk of bias due to confounding (unadjusted analysis, with importantly different ages in vaccinated and unvaccinated periods)

Moderate risk of bias in measurement of vaccination

Moderate risk of bias due to departures from intended interventions

Low risk of bias in measurement of outcomes

Moderate risk of bias due to missing outcome data

Moderate risk of bias in selection of the reported result

Overall: Very high risk of bias (confounding by age)

Result selected	Sample	Confounders measured (*adjusted for)	Comparability of groups	Ascertainment of vaccine status	Co-interventions	Ascertainment of mortality	Data & analysis
Malawi #664 MRR (adjusted) = 0.45 (0.16, 1.23) Table 2B (children present) BCG vs No BCG	Observational comparison. Live births between July 1995 and February 1997. The cohort includes approximately 95% of newborn children (N=803). Of these 36 were still born and 16 died during first week (no vaccines). <u>Selected for inclusion in review:</u> 751 children present at monthly anthropological examinations.	<u>SES:</u> Maternal schooling, district <u>Child's health:</u> Weight for age, height, twinning <u>Other:</u> HIV status of mother*, birth order, season of birth, religion, maternal age & present for examination* <u>Age:</u> Yes* <u>Gender:</u> Yes	<u>Vaccines more likely among:</u> no information <u>Mortality more likely among:</u> no information (but <i>associated</i> with HIV infection, twinning, religion, district, travelling and weight for age)	<u>Frequency:</u> Monthly visits up until 18 months, quarterly from 18 to 60 months. <u>Method:</u> Vaccination card, information verified from health centre records. <u>Vaccinated:</u> Vaccine recorded on card / health centre records <u>Unvaccinated:</u> Assumed children without evidence of vaccination were unvaccinated. <u>Dead children:</u> No information <u>Approach:</u> Landmark <u>Comment:</u> "Almost all children received the vaccines in the planned sequence."	<u>DTP:</u> High probability of differential DTP co-intervention (follow-up to 8 months; censored in analysis) <u>MV:</u> Low probability of differential MV co-intervention (follow-up to 8 months) <u>Other:</u> No information provided for any pre-defined co-interventions.	No information, likely collected at monthly visits.	Cox proportional hazards model. Estimates refer to BCG as most recent vaccine. Children were censored at 8 months. Absent children censored in analysis until they were again examined. Small differences in MR for BCG between retrospective and landmark approaches.

Moderate risk of bias in selection of participants into the study

High risk of bias due to confounding (no adjustment for SES or child's health)

High risk of bias in measurement of vaccination (assumptions about non-vaccination)

High risk of bias due to departures from intended interventions (high probability of co-intervention with DTP and MV)

Low risk of bias in measurement of outcomes

Moderate risk of bias due to missing outcome data

Moderate risk of bias in selection of the reported result

Overall: High risk of bias (no adjustment for SES or child's health; assumptions about non-vaccination)

Result selected	Sample	Confounders measured (*adjusted for)	Comparability of groups	Ascertainment of vaccine status	Co-interventions	Ascertainment of mortality	Data & analysis
Papua New Guinea #784 Hazard ratio (adjusted) = 0.17 (0.09, 0.34) Table 5a, 29 days-5 months	Observational comparison. Children born under demographic surveillance, registered within 60 days of birth and who survived more than 28 days were included. 6665 children born between 1989 and 1994. 2617 were excluded for a number of reasons, 117 died aged <29 days. Thus 4048 were included in survival analysis. <u>Selected for inclusion in review:</u> 3937 who were aged 29 days-5 months	<u>SES:</u> Region <u>Child's health:</u> Twin <u>Other:</u> Hep B*, pneumococcal vaccine*, birth order*, birth year, death of older sibling, birth interval from previous sibling, multiple births, mother's age*, propensity score*, DTP* <u>Age:</u> Yes* <u>Gender:</u> Yes*	<u>Vaccines more likely among:</u> children born to mothers less than 23 and older than 35. <u>Mortality more likely among:</u> no information	<u>Frequency:</u> Monthly clinics but frequent disruptions. Clinic cards bought to office monthly for entry of dates. <u>Method:</u> Clinic cards held by nurses and child's health books kept by mothers <u>Vaccinated:</u> Vaccination recorded on clinic records <u>Unvaccinated:</u> No vaccine recorded on clinic cards <u>Dead children:</u> Cards kept by nurses for 1 year after last attendance, likely to have information for dead children. <u>Approach:</u> Unclear; vaccination information appears to be prospectively recorded for living and dead children.	<u>DTP:</u> High probability of differential DTP co-intervention (follow-up to 6 months) <u>MV:</u> Low probability of differential MV co-intervention (follow-up to 6 months) <u>Other:</u> No information about other co-interventions	Reported during monthly demographic surveillance. Determined by verbal autopsy.	Cox proportional hazards model with propensity score adjustment. All vaccine included in model. Censoring at migration or end of the study period.

High risk of bias in selection of participants into the study (children had to survive to 29 days to be included)

High risk of bias due to confounding (no adjustment for SES or child's health, adjustment for future DTP)

Moderate risk of bias in measurement of vaccination

High risk of bias due to departures from intended interventions (high probability of co-intervention with DTP)

Low risk of bias in measurement of outcomes

Moderate risk of bias due to missing outcome data

Moderate risk of bias in selection of the reported result

Overall: High risk of bias (no adjustment for SES or child's health, adjustment for future DTP; late start of follow-up)

Senegal 1996-1999

<i>Result selected</i>	<i>Sample</i>	<i>Confounders measured (*adjusted for)</i>	<i>Comparability of groups</i>	<i>Ascertainment of vaccine status</i>	<i>Co-interventions</i>	<i>Ascertainment of mortality</i>	<i>Data & analysis</i>
Senegal D #9433 MRR (adjusted) = 0.98 (0.5, 1.9) Table 1	Observational comparison. 4133 children born and registered in study area between Sept 1996 and Dec 1999. 4102 included in the analyses. <u>Selected for inclusion in review:</u> Among 4421 children who followed the WHO strategy or were unvaccinated	<u>SES:</u> Health centre area* <u>Child's health:</u> NR <u>Other:</u> Year of vaccination*, season of vaccination* <u>Age:</u> Yes* <u>Gender:</u> Yes	<u>Vaccines more likely among:</u> no information <u>Mortality more likely among:</u> no information	<u>Frequency:</u> Every 3 months after mid 1997 <u>Method:</u> Project records and then vaccination card <u>Vaccinated:</u> All vaccines are provided and recorded by project team until mid 1997. Following this children with a noted vaccine and date were considered vaccinated. <u>Unvaccinated:</u> Those with no recorded vaccine. After mid 1997 this also includes children with no information available. <u>Dead children:</u> Generally no information provided <u>Approach:</u> Landmark	<u>DTP:</u> High probability of differential DTP co-intervention (follow-up to 24 months; censored at receipt of DTP). <u>MV:</u> High probability of differential MV co-intervention (follow-up to 24 months; censored at receipt of MV). <u>Other:</u> No information provided for any of the co-interventions.	No information	Cox proportional hazards model. Censored at 24 months of age, registration of next vaccine, death or migration.

Moderate risk of bias in selection of participants into the study
 High risk of bias due to confounding (no adjustment for child's health)
 High risk of bias in measurement of vaccination (children with no information included as unvaccinated, and further bias towards null from landmark approach)
 High risk of bias due to departures from intended interventions (high probability of co-intervention with DTP and MV)
 Low risk of bias in measurement of outcomes
 Moderate risk of bias due to missing outcome data
 Moderate risk of bias in selection of the reported result
 Overall: High risk of bias (no adjustment for child's health; co-intervention with DTP and MV)

3 Risk-of-bias assessments for non-randomized studies of DTP

Bangladesh 1986-2001

Result selected	Sample	Confounders measured (*adjusted for)	Comparability of groups	Ascertainment of vaccine status	Co-interventions	Ascertainment of mortality	Data & analysis
Bangladesh #9477 MRR (adjusted) = 0.52 (0.31, 0.87) Table 3	Observational comparison. Based on children born between 1986 and 1999. 37,894 children were followed between 6 weeks and 9 months of age. <u>Selected for inclusion in review:</u> Children who received BCG only (N=670) versus children who received BCG followed by DTP1 (N=5740)	<u>SES:</u> Maternal education*, asset score* <u>Child's health:</u> Distance from hospital <u>Other:</u> Birth order*, religion*, maternal age*, Period (year of birth) <u>Age:</u> Yes* <u>Gender:</u> Yes* <u>BCG:</u> Yes (all children had received BCG)	<u>Vaccines more likely among:</u> Higher education <u>Mortality more likely among:</u> Lower education, lowest asset score.	<u>Frequency:</u> Every 2 weeks until Jan 1998, once a month since then <u>Method:</u> Monthly immunization days, community worker vaccinates children on this day and records them in record keeping book. <u>Vaccinated:</u> Children with a recorded BCG and DTP1 vaccination. <u>Unvaccinated:</u> Children with recorded BCG vaccine but no recorded DTP1 vaccine. <u>Dead children:</u> No information. <u>Approach:</u> Information updated on day vaccine given.	<u>BCG:</u> Low probability of differential BCG co-intervention (only included children who received BCG before DTP). <u>OPV:</u> OPV nearly always given with DTP. <u>MV:</u> Low probability of differential MV co-intervention (follow-up to 9 months). Censoring at MV. <u>Other:</u> No information about any other co-interventions.	Cause of death ascertained by verbal autopsy. Twenty of the 712 deaths were due to accidents; these deaths have been excluded from the analysis.	Cox proportional hazards model with time varying covariates. Censored deaths due to trauma or accidents, and at date of MV if received before 9 months. Repeated analysis without 30 day lag period & got consistent results (data not shown).

Moderate risk of bias in selection of participants into the study

High risk of bias due to confounding (no adjustment for child's health)

Moderate risk of bias in measurement of vaccination

Moderate risk of bias due to departures from intended interventions

Low risk of bias in measurement of outcomes

Moderate risk of bias due to missing outcome data

Moderate risk of bias in selection of the reported result

Overall: High risk of bias (no adjustment for child's health)

Result selected	Sample	Confounders measured (*adjusted for)	Comparability of groups	Ascertainment of vaccine status	Co-interventions	Ascertainment of mortality	Data & analysis
Benin #9372 Odds ratio (adjusted) = 2.2 (0.93, 5.22) Table 2	Case-control study. Cases: All children who died between January 1986 and October 1987 and before the age of 3 years. Controls: selected from register of all children in the area, matched for age, sex and village of residence. "Some 74 cases and 230 controls were available for analysis" with 1-4 matched controls per case. "Children who were born and died within the interval of about 3 months between surveys were rarely reported. 2 infants who were known to have died within one month of birth were excluded. All other children had at least attained 4 months of age." <u>Selected for inclusion in review:</u> 91 children who were unvaccinated and 41 children who had 1 DTP dose.	<u>SES:</u> Socioeconomic score* (no details how this is calculated) <u>Child's health:</u> Weight for age* <u>Other:</u> NR <u>Age:</u> Yes (matched*) <u>Gender:</u> Yes (matched*) <u>BCG:</u> Yes	<u>Vaccines more likely among:</u> No information <u>Mortality more likely among:</u> Lower socioeconomic status	<u>Frequency:</u> None <u>Method:</u> Preventive child care cards, kept at the communal health centre. <u>Vaccinated:</u> Children with a vaccine recorded by vaccination team during visits to the village. <u>Unvaccinated:</u> Children with no recorded vaccine. Vaccination card could not be found for 10 children (1 case, 9 controls).	<u>BCG:</u> No information on co-administration <u>OPV:</u> Co-administered with DTP. <u>MV:</u> No information. High probability of differential co-intervention (follow-up 4-35 months) <u>Other:</u> No information provided for any other co-interventions.	When a child under 3 died the interviewer recorded the symptoms parents mentioned. A medical doctor subsequently visited the household to establish a probable cause of death.	Analysis by conditional logistic regression.

Moderate risk of bias in selection of participants into the study.

High risk of bias due to confounding (despite matching, some key confounders were not addressed)

Moderate risk of bias in measurement of vaccination

High risk of bias due to departures from intended interventions (likely co-interventions including MV)

Low risk of bias in measurement of outcomes

Moderate risk of bias due to missing outcome data

Moderate risk of bias in selection of the reported result

Overall: High risk of bias (likely confounding; unknown BCG co-administration; likely co-interventions including MV)

Result selected	Sample	Confounders measured (*adjusted for)	Comparability of groups	Ascertainment of vaccine status	Co-interventions	Ascertainment of mortality	Data & analysis
Burkina-Faso #799 Risk ratio (adjusted) = 1 (0.6, 1.67) Table 3 (vaccination status at first visit, ratio of BCG and DTP to BCG)	Observational comparison. During 1985 and 1993, 9412 births were registered. 204 stillbirths and 123 infants with no recorded month of birth were excluded leaving 9085 infants. <u>Selected for inclusion in review:</u> Children who survived until first visit (up to 7 months of age).	<u>SES:</u> Area* <u>Child's health:</u> Child's health service use, diarrhoea*, fever, cough and malnutrition during first year <u>Other:</u> Age of mother, age of father, number of wives, mode of delivery, dispensary in village*, family health service use*, birth season*, birth period <u>Age:</u> Yes* <u>Gender:</u> Yes <u>BCG:</u> All received BCG, but not clear when.	<u>Vaccines more likely among:</u> Boys, children in Yako, older mothers, modern delivery mode, dispensary in village, frequent health service use (child & family), having diarrhoea, fever, cough & malnutrition, being born Mar-Oct, being born after 1988 in Pissila and 1989 in Yako. <u>Mortality more likely among:</u> Boys, Pissila, younger mothers, more wives, modern delivery, no dispensary, frequent child's health service use, rare family health service use, having diarrhoea, fever, cough & malnutrition, born Nov-Feb, birth in 1986-88 in Pissila and 1987-89 in Yako.	<u>Frequency:</u> Every 6 months although in 1993-5 the average interval was 12 months <u>Method:</u> Vaccination cards <u>Vaccinated:</u> Vaccination recorded on vaccination card. <u>Unvaccinated:</u> Children with no vaccine recorded or whose card weren't seen <u>Dead children:</u> When child died, belongings were discarded including vaccination cards <u>Approach:</u> Landmark, based on vaccination status at first visit only.	<u>BCG:</u> "Most of the vaccinated children received either BCG followed by DTP or the vaccines simultaneously"; no information on proportions. <u>OPV:</u> No information <u>MV:</u> High probability of differential MV co-intervention (follow-up 6 months from first visit (which was in the first 6 months of life)). <u>Other:</u> No information	Collected 6-monthly during visits.	Cox proportional hazards model. Follow-up began at first visit (before 7 months). Censoring at 2 nd visit, 6 months after 1 st visit, out-migration or death.

High risk of bias in selection of participants into the study (children had to survive to first visit to be included)

High risk of bias due to confounding (likely confounding, including by SES)

High risk of bias in measurement of vaccination (children assumed unvaccinated when card not seen)

High risk of bias due to departures from intended interventions (some received BCG simultaneously; likely co-interventions including MV)

Low risk of bias in measurement of outcomes

Moderate risk of bias due to missing outcome data

Moderate risk of bias in selection of the reported result

Overall: High risk of bias (potential selection bias; co-administration of BCG; assumptions about non-vaccination; likely con-intervention with MV)

Result selected	Sample	Confounders measured (*adjusted for)	Comparability of groups	Ascertainment of vaccine status	Co-interventions	Ascertainment of mortality	Data & analysis
Ghana A #3294 MRR (adjusted) = 2.39 (0.82, 6.99) Computed from rates in Table 5 (row 3. vs row 2.)	Observational comparison. Children enrolment into placebo arm of a vitamin A trial (N=6882). 3330 children aged 6-35 months; 3082 included in analysis (excluding those with no information on health card, or health card known to exist but not seen). <u>Selected for inclusion in review:</u> 665 children who had health cards confirming receipt of DTP or no DTP (and no MV) [Groups 2 and 3 in the paper]	<u>SES:</u> Zone* and radio in compound* <u>Child's health:</u> Ever breastfed, still breastfeeding, MUAC, measles before enrolment, previously admitted to hospital, weight for age* <u>Other:</u> NR <u>Age:</u> Yes* <u>Gender:</u> Yes <u>BCG:</u> BCG scar.	<u>Vaccines more likely among:</u> Children still breastfeeding, lower weight for age children and children more likely to have been hospitalized <u>Mortality more likely among:</u> no information	<u>Frequency:</u> Every 4 months <u>Method:</u> Vaccination cards <u>Vaccinated:</u> Children whose card was seen and had received DTP. <u>Unvaccinated:</u> Children whose card was seen and had not received DTP. <u>Dead children:</u> Vaccination status not updated for children who died between visits. <u>Approach:</u> Landmark <u>Comment:</u> There is also a 'no health card' group, which could be treated as an unvaccinated group. However. "15% of children without a health card had a BCG scar. These children may have lost the card or never been issued one."	<u>BCG:</u> Co-administered with DTP in 76% of children. <u>OPV:</u> "Most children had registered an OPV at the same time as a DTP vaccine" [#401]. <u>MV:</u> High probability of differential MV co-intervention (86% received MV either simultaneously with DTP or before DTP). <u>Other:</u> Many missing vaccines given in first 4 months of enrolment (50% additional DTP, 50% MV), although these appear evenly balanced between groups. Only included children who had received placebo in vitamin A trial. No information provided about any of the other co-interventions.	Deaths were identified through visits and independently by key informants based in the community. Follow-up procedures were independent of the vaccination status of the child.	Cox proportional hazards model. Vaccination status at enrolment was a fixed term variable during follow-up.

Very high risk of bias in selection of participants into the study (included children were 6-35 months, so early effects of DTP on mortality not considered)

High risk of bias due to confounding (likely confounding)

Moderate risk of bias in measurement of vaccination

Very high risk of bias due to departures from intended interventions (high proportion of co-administration with BCG and with MV)

Low risk of bias in measurement of outcomes

Moderate risk of bias due to missing outcome data

Moderate risk of bias in selection of the reported result

Overall: Very high risk of bias (selection of children into the study; high proportion of co-administration with BCG; high proportion of co-administration with MV)

Result selected	Sample	Confounders measured (*adjusted for)	Comparability of groups	Ascertainment of vaccine status	Co-interventions	Ascertainment of mortality	Data & analysis
Ghana C #9464 Hazard ratio (adjusted) = 0.15 (0.14, 0.16) Table II, DTP1	Observational comparison. 17,967 children born between 1 st January 1998 and 31 st December 2004. Selected for inclusion in review: All	<u>SES</u> : Mother's education*, poverty status* <u>Child's health</u> : NR <u>Other</u> : Mother's age <u>Age</u> : Yes* <u>Gender</u> : No <u>BCG</u> : Yes	<u>Vaccines more likely among</u> : BCG recipients <u>Mortality more likely among</u> : Lower education, higher poverty.	<u>Frequency</u> : Annual collection of vaccination status <u>Method</u> : Annual survey <u>Vaccinated</u> : Unclear <u>Unvaccinated</u> : Unclear <u>Dead children</u> : No information <u>Approach</u> : Unclear <u>Comment</u> : "Annual updates of immunization status and educational attainment and indicators of socioeconomic status are linked to the demographic register."; "Models for the analysis presented here are based on the status of each child at the time of last observation with respect to the WHO definition."	<u>BCG</u> : No information <u>OPV</u> : Usual to be given simultaneously with DTP <u>MV</u> : High probability of differential MV co-intervention (follow-up to 5 years) <u>Other</u> : No information	All-cause mortality, quarterly visits	Time conditional HR. No description of any censoring.

Low risk of bias in selection of participants into the study

Very high risk of bias due to confounding (high degree of confounding with BCG)

Insufficient information to assess risk of bias in measurement of vaccination (high risk of bias or possibly very high risk of bias: cannot tell how vaccination status was defined; retrospective approach may have been used)

Very high risk of bias due to departures from intended interventions (high degree of co-intervention with MV)

Low risk of bias in measurement of outcomes

Moderate risk of bias due to missing outcome data

Moderate risk of bias in selection of the reported result

Overall: Very high risk of bias (high degree of co-intervention with other vaccines; unable to judge methods for determining vaccination status from publication)

<i>Result selected</i>	<i>Sample</i>	<i>Confounders measured (*adjusted for)</i>	<i>Comparability of groups</i>	<i>Ascertainment of vaccine status</i>	<i>Co-interventions</i>	<i>Ascertainment of mortality</i>	<i>Data & analysis</i>
Guinea-Bissau A #25 MRR (adjusted) = 4.33 (1.54, 12.2) Table 3 (DRR, BCG at birth)	Observational comparison. Low birth weight cohort examining early vs late BCG. 2343 children randomized in original trial. Of these, 1855 children were seen at 2 months and card was seen for 1830 children (99%). <u>Selected for inclusion in review:</u> 935 children who received BCG at birth and whose card was seen at 2 month visit	<u>SES:</u> Mother's education <u>Child's health:</u> Birth weight, twinning, breastfeeding, MUAC*, Ballard score, weight gain, weight at 2 months, weight for age, length, height for age, head circumference & abdominal circumference <u>Other:</u> Study area, birth order, consultations, mother died, maternal MUAC, mother's age, ethnicity & living with father <u>Age:</u> Yes* <u>Gender:</u> Yes* <u>BCG:</u> All received BCG at birth	<u>Vaccines more likely among:</u> older mothers, mothers with more schooling, families with fewer twins and Bandim. "The delayed DTP (unvaccinated) group had significantly lower anthropometric indices suggesting that the healthier children received DTP early" <u>Mortality more likely among:</u> No information	<u>Frequency:</u> Data only collected at 2 months <u>Method:</u> Vaccination cards were examined and all vaccine dates were noted. <u>Vaccinated:</u> Children with DTP recorded on card. <u>Unvaccinated:</u> Children with no DTP recorded on card. Didn't include children with no information. <u>Dead children:</u> Asked to see cards of dead children <u>Approach:</u> Landmark. Only vaccination status at 2 months used.	<u>BCG:</u> Not co-administered. <u>OPV:</u> No information <u>MV:</u> Low probability of differential MV co-intervention ("A total of 13 children received MV at 4.5-5 months as part of a trial of early MV"; children censored at MV). <u>Other:</u> Sample comes from a trial also of vitamin A, so this was balanced. More than two thirds of the children in the no DTP group received DTP during follow-up.	All-cause mortality collected at 3 monthly visits. Verbal autopsy was conducted by a clinician 3 months after death.	Cox proportional hazards model. Censoring at death, MV, migration or the 6 month visit, whichever came first.

High risk of bias in selection of participants into the study (follow-up begins after DTP vaccinations)

High risk of bias due to confounding (likely confounding from SES and child's health)

Moderate risk of bias in measurement of vaccination

High risk of bias due to departures from intended interventions (substantial DTP vaccination in the no DTP group).

Low risk of bias in measurement of outcomes

Moderate risk of bias due to missing outcome data

Moderate risk of bias in selection of the reported result

Overall: High risk of bias (likely confounding; DTP co-intervention in the no-DTP group)

<i>Result selected</i>	<i>Sample</i>	<i>Confounders measured (*adjusted for)</i>	<i>Comparability of groups</i>	<i>Ascertainment of vaccine status</i>	<i>Co-interventions</i>	<i>Ascertainment of mortality</i>	<i>Data & analysis</i>
Guinea-Bissau D #9466 Risk ratio (adjusted) = 1.74 (1.1, 2.75) Text of paper	Observational comparison. 10,298 children born alive of which 686 died, 90 moved and 770 were too young before the first visit. 8752 were alive at first visit and their survival ascertained at the second visit. 8104 were under 7 months at first visit. DTP given from 6 weeks <u>Selected for inclusion in review:</u> 5274 children aged under 0-6 months at first visit and who either had a vaccination card examined or had no card. Children followed-up until next visit or 6 months later if next visit was later than that (children aged up to 12 months). Results may refer to 4418 children.	<u>SES:</u> Cluster*, maternal education, latrine <u>Child's health:</u> MUAC, well, birth at home <u>Other:</u> Season, period, maternal tetanus, maternal age, birth order, ethnicity, previous dead children, length of follow-up* <u>Age:</u> Yes* <u>Gender:</u> Yes <u>BCG:</u> Yes*	<u>Vaccines more likely among:</u> children who had more contact with health system, mothers who received tetanus during pregnancy and who gave birth outside the home. They also had larger MUAC, younger mothers, had fewer children, have a latrine and not belong to Balanta or Pepel ethnicity. <u>Mortality more likely among:</u> no information	<u>Frequency:</u> Visits every 5-7 months on average <u>Method:</u> Vaccination card <u>Vaccinated:</u> Children whose card was seen and vaccine recorded <u>Unvaccinated:</u> Children who had no date or were declared not to have received the vaccine. Also children with no card. <u>Dead children:</u> No information <u>Approach:</u> Landmark. Only vaccination status at first visit used (aged 0-6 months).	<u>BCG:</u> No information <u>OPV:</u> Almost always co-administered with DTP <u>MV:</u> Moderate probability of differential co-intervention with MV (children potentially followed up to maximum of 12 months, and 791 children received MV between 7 and 11 months). <u>Other:</u> No information provided for any other co-interventions.	Information on mortality was obtained at subsequent visits (meaning children had to be visited twice to be included in the study).	Cox proportional hazards model. "There was no loss to follow-up because it was always possible to get information on all children from relatives living in the same compound". Analysis repeated excluding children considered unvaccinated because they had no card.

High risk of bias in selection of participants into the study (follow-up begins after DTP vaccinations)

High risk of bias due to confounding (likely confounding not adjusted for)

High risk of bias in measurement of vaccination (assumed no card meant unvaccinated)

High risk of bias due to departures from intended interventions (likely MV co-intervention)

Low risk of bias in measurement of outcomes

Moderate risk of bias due to missing outcome data

Moderate risk of bias in selection of the reported result

Overall: High risk of bias (likely confounding; assumptions about non-vaccination; co-intervention with MV)

Guinea-Bissau 1984-1985

Result selected	Sample	Confounders measured (*adjusted for)	Comparability of groups	Ascertainment of vaccine status	Co-interventions	Ascertainment of mortality	Data & analysis
Guinea-Bissau E #851 Risk ratio (adjusted) = 1.92 (1.04, 3.52) Text of paper, p. 377	Observational comparison. 1984-1987, when DTP first introduced into the area. The sample was 1657 infants examined between 2 and 8 months of age (DTP from 3 months although some as early as 2 months). May be children who were never registered as they were not reported during pregnancy and they died or moved before they had the chance to be seen at one of the mobile bi-annually visits. Children followed-up until next visit or 6 months later if next visit was later than that (children presumably aged up to 14 months). Few had previously received BCG. <u>Selected for inclusion in review: All</u>	<u>SES: Region*</u> <u>Child's health: Weight for age</u> <u>Other: Season*, period*</u> <u>Age: Yes*</u> <u>Gender: Yes*</u> <u>BCG: Yes*</u>	<u>Vaccines more likely among: No information.</u> <u>Mortality more likely among: No information.</u> No DTP tended to have lower weight for age z-scores, which was associated with higher mortality. These scores not used as many unvaccinated children not weighed as they were travelling.	<u>Frequency: 6 monthly</u> <u>Method: BHP records / vaccination cards</u> <u>Vaccinated: BHP provided vaccine / saw vaccination card with date of vaccine</u> <u>Unvaccinated: Those who were examined on days no vaccines were available, children travelling or absent, children examined but too sick to be vaccinated and children who were 2 months old.</u> <u>Dead children: No information</u> <u>Approach: Landmark</u>	<u>BCG: No information</u> ("few children had received BCG first, the proportion increasing from 1% to 29% between 1984 and 1987"). <u>OPV: Co-administered with DTP from 1984/5</u> <u>MV: Low probability of differential co-intervention (up to 18% received MV during 6 months of follow-up, but proportion appears similar for DTP and no DTP groups).</u> <u>Other: Up to 40% rate of DTP vaccinations were received during the 6 months of follow up: more in the DTP group.</u> No information on other co-interventions.	Mortality recorded at 6 monthly visits. If a child did not attend examinations assistants visited the compound to inquire whether the child was travelling, had moved, or died. Cause of death was reviewed and children who died as the result of an accident were censored.	Cox proportional hazards model. Censoring at earliest of 6 months of follow-up, death, migration or new examination.

High risk of bias in selection of participants into the study (follow-up could begin after DTP vaccination)

High risk of bias due to confounding (no adjustment for child's health)

High risk of bias in measurement of vaccination (unvaccinated group may include vaccinated children, and bias towards null from landmark approach)

High risk of bias due to departures from intended interventions (high rate of subsequent DTP vaccinations)

Low risk of bias in measurement of outcomes

Moderate risk of bias due to missing outcome data

Moderate risk of bias in selection of the reported result

Overall: High risk of bias (no adjustment for child's health; assumptions about non-vaccination)

Guinea-Bissau 1989-1999

Result selected	Sample	Confounders measured (*adjusted for)	Comparability of groups	Ascertainment of vaccine status	Co-interventions	Ascertainment of mortality	Data & analysis
Guinea-Bissau P #2622 Risk ratio (adjusted) = 1.58 (0.36, 7.02) Text of paper, p. 18	Observational comparison. 774 children aged 5 weeks to 5 months of whom 313 had vaccination card inspected in preceding 3 months. Of 2065 aged 6-20 months, of whom 1178 had their card inspected, 220 had not received MV. <u>Selected for inclusion in review:</u> All children aged 5 weeks-20 months who had not received MV (N=533).	<u>SES:</u> Ownership of pigs <u>Child's health:</u> Breastfeeding, Infections, Hospitalization, Arm circumference <u>Other:</u> Living with mother <u>Age:</u> Yes* <u>Gender:</u> Yes* <u>BCG:</u> Virtually all children vaccinated with BCG	<u>Vaccines more likely among:</u> No information <u>Mortality more likely among:</u> No information	<u>Frequency:</u> Every 3 months <u>Method:</u> Vaccination cards & local health centre records. <u>Vaccinated:</u> Vaccine recorded on vaccination card, registration of vaccine at local health centre. <u>Unvaccinated:</u> No vaccine recorded on vaccination card, registration of vaccine at local health centre. <u>Dead children:</u> No information <u>Approach:</u> Landmark, using vaccination status at the last home visit in the 3 months before the start of the war.	<u>BCG:</u> No information. <u>OPV:</u> Co-administrated with DTP <u>MV:</u> Low probability of differential MV co-intervention (low vaccination rate during war period). <u>Other:</u> No information provided about any other co-interventions	Evaluated from onset of war (7 June 1998) until 31 August 1998. Information obtained when routine surveillance was resumed in Sept 1998. Reviewed verbal autopsies to establish cause of death.	Cox proportional hazards model. No information about censoring.

Very high risk of bias in selection of participants into the study (follow-up begins after DTP vaccinations, and restriction to sample determined by subsequent MV)

High risk of bias due to confounding (no adjustment for SES or child's health)

High risk of bias in measurement of vaccination (children without vaccination card assumed unvaccinated)

Moderate risk of bias due to departures from intended interventions

Moderate risk of bias in measurement of outcomes

Moderate risk of bias due to missing outcome data

Moderate risk of bias in selection of the reported result

Overall: Very high risk of bias (follow-up begins after DTP vaccinations, and restriction to sample determined by subsequent MV)

Result selected	Sample	Confounders measured (*adjusted for)	Comparability of groups	Ascertainment of vaccine status	Co-interventions	Ascertainment of mortality	Data & analysis
India A #741 Hazard ratio (adjusted) = 1.64 (0.87, 3.07) Computed from results in Table 4, model I (ratio of 'DTP, BCG' to 'No DTP, BCG')	Observational comparison. Live births between August 1998 and February 2002. Of the 13,294 infants born 11,619 were born alive and enrolled. Of these 10,274 were alive as of 7 days old. <u>Selected for inclusion in review:</u> All child-time after receipt of BCG.	<u>SES:</u> Wood fuel, Have roof, Lease land, Own cattle, Maternal Education, Electricity, TV <u>Child's health:</u> Birth weight <u>Other:</u> Mother's prior live births, season <u>Age:</u> Yes* <u>Gender:</u> Yes <u>BCG:</u> All received BCG	<u>Vaccines more likely among:</u> Higher birth weight, higher SES (hard roof, electricity, TV, maternal education) <u>Mortality more likely among:</u> Those SES categories associated with lower vaccination coverage (using wood fuel, owning cattle, owning/leasing land)	<u>Frequency:</u> Fortnightly <u>Method:</u> Mother questioned at visits, if mother couldn't remember the vaccination card was checked if in the house <u>Vaccinated:</u> Children with reported vaccine <u>Unvaccinated:</u> No reported vaccination, a different code was used for children who received an unknown vaccine. <u>Dead children:</u> No information <u>Approach:</u> Probably retrospective: vaccination information collected retrospectively but not fully clear what vaccination times were used in the analysis. But only a 2-week window between visits.	<u>BCG:</u> Co-administration unlikely as median time of BCG is 2.7 weeks. <u>OPV:</u> Co-administered with DTP <u>MV:</u> Low probability of differential co-intervention (follow-up to 6 months). <u>Other:</u> Part of a vitamin A trial. No information about any of the other co-interventions	Fortnightly visits.	Cox proportional hazards model. Effect estimate for review obtained using ratio of HRs for "DTP, BCG" vs "No DTP, BCG". Censoring at earliest of death, 6 months of age, loss to follow-up and receipt of first unknown vaccine.

Moderate risk of bias in selection of participants into the study

High risk of bias due to confounding (no adjustment for SES or child's health, likely confounding by SES)

High risk of bias in measurement of vaccination (retrospective collection of vaccination data)

Moderate risk of bias due to departures from intended interventions

Low risk of bias in measurement of outcomes

Moderate risk of bias due to missing outcome data

Moderate risk of bias in selection of the reported result

Overall: High risk of bias (likely confounding; retrospective collection of vaccination data)

India 1987-1989

Result selected	Sample	Confounders measured (*adjusted for)	Comparability of groups	Ascertainment of vaccine status	Co-interventions	Ascertainment of mortality	Data & analysis
India E #8996 MRR (unadjusted) = 1.11 (0.3, 4.12) Computed from Table 4, comparison of groups I and II	Observational comparison. Live births between December 1987 and November 1989 in 45 contiguous villages. Analysis files from a previous study available for 4138 live births (286 deaths). Of these, 255 records were missing sex, birthday or exit day, which left 3883 children (282 deaths). <u>Selected for inclusion in review:</u> 1723 children with BCG or BCG followed by DTP [Groups I and II in the paper].	<u>SES:</u> NR <u>Child's health:</u> birth weight, current weight, length/height, common childhood morbidities <u>Other:</u> NR <u>Age:</u> Yes <u>Gender:</u> Yes <u>BCG:</u> All received BCG	<u>Vaccines more likely among:</u> ("Children with the best nutritional status were vaccinated first") <u>Mortality more likely among:</u> NR Birth weights similar in the two groups.	<u>Frequency:</u> 3 monthly visits <u>Method:</u> Vaccination card at home or when the child was brought to the clinic for immunization. <u>Vaccinated:</u> Children with a recorded BCG and DTP vaccines. <u>Unvaccinated:</u> Children with a recorded BCG vaccine. <u>Dead children:</u> Data were available for 282/286 dead children <u>Approach:</u> Landmark	<u>BCG:</u> No co-administration <u>OPV:</u> Given simultaneously <u>MV:</u> Moderate probability of MV co-intervention (9% received MV simultaneously with DTP; follow-up to 1 year; 25% of the whole cohort received MV in the first year) <u>Other:</u> No information	All-cause mortality at 3-monthly visits at home.	Unadjusted analysis based on mortality rates in first 12 months

Moderate risk of bias in selection of participants into the study

Very high risk of bias due to confounding (unadjusted comparison of children of different ages)

Moderate risk of bias in measurement of vaccination

High risk of bias due to departures from intended interventions (co-administration and co-intervention with MV)

Low risk of bias in measurement of outcomes

Moderate risk of bias due to missing outcome data

Moderate risk of bias in selection of the reported result

Overall: High risk of bias (unadjusted analysis; co-intervention with MV)

Result selected	Sample	Confounders measured (*adjusted for)	Comparability of groups	Ascertainment of vaccine status	Co-interventions	Ascertainment of mortality	Data & analysis
India G #9463 MRR (unadjusted) = 0.28 (0.2, 0.4) Computed from Table 3 (6 weeks – 8 months), BCG+DTP vs BCG only	Observational comparison. Live study births from 1 January 2006 to 31 December 2011 in 28 villages in Ballabgarh. A total of 12,142 births with immunization details were available. A total of 11,390 had complete information on confounders and were included in analyses. <u>Selected for inclusion in review:</u> Child-time during which most recent vaccine was BCG or DTP between 6 weeks and 8 months.	<u>SES:</u> Mother's education, fathers education, caste, wealth index <u>Child's health:</u> Access to health care, presence of a health facility in the village <u>Other:</u> Birth order <u>Age:</u> Yes <u>Gender:</u> Yes All included in analyses. <u>BCG:</u> Yes	<u>Vaccines more likely among:</u> no information <u>Mortality more likely among:</u> no information	<u>Frequency:</u> Monthly work plan <u>Method:</u> Fortnightly visits added to computer database. <u>Vaccinated:</u> Recorded as having received DTP as last vaccine based on computerized system (approx. 90% had received BCG) <u>Unvaccinated:</u> Recorded as having received BCG as last vaccine based on computerized system (some received DTP beforehand) <u>Dead children:</u> N/A <u>Approach:</u> Used date of vaccination, although likely to be quite accurate.	<u>BCG:</u> No co-administration <u>OPV:</u> No information <u>MV:</u> No co-administration. Low probability of differential MV (follow-up to 8 months; 'censored' at next vaccine) <u>Other:</u> No information	All-cause mortality from visits/computerized system.	Unadjusted mortality ratios. Children included in each group from receipt of vaccine until receipt of another vaccine or any other exit criteria. Exit criteria were 3 years of age, end of study or migration. Sensitivity analyses conducted using 2 week lag period.

Moderate risk of bias in selection of participants into the study

Very high risk of bias due to confounding (unadjusted comparison with importantly different ages in BCG and DTP periods)

Moderate risk of bias in measurement of vaccination

Moderate risk of bias due to departures from intended interventions

Low risk of bias in measurement of outcomes

Moderate risk of bias due to missing outcome data

Moderate risk of bias in selection of the reported result

Overall: Very high risk of bias (confounding, particularly by age)

Result selected	Sample	Confounders measured (*adjusted for)	Comparability of groups	Ascertainment of vaccine status	Co-interventions	Ascertainment of mortality	Data & analysis
Malawi #664 MRR (adjusted) = 3.19 (0.8, 12.8) Table 2 (only children present)	Observational comparison. Live births between July 1995 and February 1997. The cohort includes approximately 95% of newborn children (N=803). Of these 36 were still born and 16 died during first week (no vaccines). Selected for inclusion in review: Children present at monthly anthropological examinations.	<u>SES</u> : maternal schooling, district <u>Child's health</u> : weight for age, weight for height, twinning <u>Other</u> : HIV status of mother*, birth order, season of birth, religion, maternal age & present for examination <u>Age</u> : Yes* <u>Gender</u> : Yes <u>BCG</u> : Yes	<u>Vaccines more likely among</u> : no information <u>Mortality more likely among</u> : no information (but associated with HIV infection, twinning, religion, district, travelling and weight for age)	<u>Frequency</u> : Monthly visits up until 18 months, quarterly from 18 to 60 months. <u>Method</u> : Vaccination card, information verified from health centre records. <u>Vaccinated</u> : Vaccine recorded on card / health centre records <u>Unvaccinated</u> : Assumed children without evidence of vaccination were unvaccinated. <u>Dead children</u> : No information but used both methods <u>Approach</u> : Landmark <u>Comment</u> : "Almost all children received the vaccines in the planned sequence."	<u>BCG</u> : NR <u>OPV</u> : Nearly always co-administered <u>MV</u> : Low probability of differential MV co-intervention (follow-up to 8 months) <u>Other</u> : No information provided for any pre-defined co-interventions.	No information, likely collected at monthly visits.	Cox proportional hazards model. Absent children censored in analysis until they were again examined. No information about amount of missing data for dead children in retrospective approach. Large differences in MR for DTP between retrospective and landmark approaches.

Moderate risk of bias in selection of participants into the study

High risk of bias due to confounding (no adjustment for SES or child's health)

High risk of bias in measurement of vaccination (assumptions about non-vaccination)

Moderate risk of bias due to departures from intended interventions

Low risk of bias in measurement of outcomes

Moderate risk of bias due to missing outcome data

Moderate risk of bias in selection of the reported result

Overall: High risk of bias (no adjustment for SES or child's health; assumptions about non-vaccination)

Papua New Guinea 1989-1994

<i>Result selected</i>	<i>Sample</i>	<i>Confounders measured (*adjusted for)</i>	<i>Comparability of groups</i>	<i>Ascertainment of vaccine status</i>	<i>Co-interventions</i>	<i>Ascertainment of mortality</i>	<i>Data & analysis</i>
Papua New Guinea #784 Hazard ratio (adjusted) = 0.48 (0.22, 1.09) Table 6 (DTP1, 29 days-5 months)	Observational comparison. Children born under demographic surveillance, registered within 60 days of birth and who survived more than 28 days were included. 6665 children born between 1989 and 1994. 2617 were excluded for a number of reasons. Thus 4048 were included in survival analysis. <u>Selected for inclusion in review:</u> 2788 who had received BCG before 6 months, who survived the first month of life.	<u>SES:</u> Region <u>Child's health:</u> Twin <u>Other:</u> Hep B*, pneumococcal vaccine*, birth order, birth year*, death of older sibling, birth interval from previous sibling, multiple births, mother's age*, MV*, subsequent DTP doses* <u>Age:</u> Yes* <u>Gender:</u> Yes <u>BCG:</u> All children had received BCG but may have been after DTP.	<u>Vaccines more likely among:</u> children born to mothers less than 23 and older than 35. <u>Mortality more likely among:</u> no information	<u>Frequency:</u> Monthly clinics but frequent disruptions. Clinic cards bought to office monthly for entry of dates. <u>Method:</u> Clinic cards held by nurses and child's health books kept by mothers <u>Vaccinated:</u> Vaccination recorded on clinic records <u>Unvaccinated:</u> No vaccine recorded on clinic cards. <u>Dead children:</u> Cards kept by nurses for 1 year after last attendance, likely to have information for dead children. <u>Approach:</u> Unclear; vaccination information appears to be prospectively recorded for living and dead children.	<u>BCG:</u> Co-administration not reported, but evidence that many BCG vaccinations were after 1 month. <u>OPV:</u> Co-administered with DTP <u>MV:</u> Low probability of differential MV co-intervention (follow-up to 6 months) <u>Other:</u> Pigbel vaccine co-administered with DTP. Hep B introduced at birth. No information about other co-interventions.	Reported during monthly demographic surveillance. Determined by verbal autopsy.	Cox proportional hazards model. Censoring at death, migration, 6 months or the end of the study period.

Moderate risk of bias in selection of participants into the study

High risk of bias due to confounding (no adjustment for SES or child's health)

Moderate risk of bias in measurement of vaccination

High risk of bias due to departures from intended interventions (co-administration of pigbel)

Low risk of bias in measurement of outcomes

Moderate risk of bias due to missing outcome data

Moderate risk of bias in selection of the reported result

Overall: High risk of bias (TO ADD)

Result selected	Sample	Confounders measured (*adjusted for)	Comparability of groups	Ascertainment of vaccine status	Co-interventions	Ascertainment of mortality	Data & analysis
Philippines #555 Hazard ratio (adjusted) = 0.87 (0.33, 2.29) Text of paper (p. 1025)	Observational comparison. Children aged up to 30 months who had received a BCG vaccine and had complete baseline data (N=14,334/18,964). <u>Selected for inclusion in review:</u> 10,231 were included in the landmark analysis.	<u>SES:</u> Maternal education* and TV & radio ownership*, household cluster*. <u>Child's health:</u> Prenatal care and birth weight* <u>Other:</u> None <u>Age:</u> Yes* <u>Gender:</u> Yes* <u>BCG:</u> All children had received BCG but may have been with or after DTP.	<u>Vaccines more likely among:</u> Higher maternal education and prenatal care from a nurse/midwife. As well as being male, low birth weight and no TV ownership. <u>Mortality more likely among:</u> Lower maternal education, TV/radio ownership & low birth weight	<u>Frequency:</u> Every 6 months <u>Method:</u> Examination of vaccination card/clinic records. <u>Vaccinated:</u> Children whose card was seen and a vaccine was noted. <u>Unvaccinated:</u> If mother/caregiver didn't know if child had received vaccine / no vaccine received. <u>Dead children:</u> Vaccination status was collected post-mortem. <u>Approach:</u> Landmark	<u>BCG:</u> Probably co-administered with DTP in some children. <u>OPV:</u> Co-administered with DTP <u>MV:</u> High probability of differential MV co-administration (follow-up to 30 months, but censored at receipt of MV). <u>Other:</u> No information is provided for any of the co-interventions	Death information was obtained via post mortem interviews.	Cox proportional hazards model. Estimate adjusted by sex obtained as meta-analysis of estimates in boys and girls. Censored at receipt of MV or receipt of unknown vaccine, 30 months of age, outmigration or study end.

Very high risk of bias in selection of participants into the study (Inclusion of children up to 30 months of age at start of follow-up)

High risk of bias due to confounding (likely confounding not adjusted for)

High risk of bias in measurement of vaccination (considered unvaccinated if mother did not know whether vaccinated)

No information on risk of bias due to departures from intended interventions (MV received during long follow-up time; insufficient information about co-administration of BCG: claimed to be high in a letter)

Low risk of bias in measurement of outcomes

Moderate risk of bias due to missing outcome data

Moderate risk of bias in selection of the reported result

Overall: Very high risk of bias (selection of children too long after vaccination)

Senegal 1996-1999

<i>Result selected</i>	<i>Sample</i>	<i>Confounders measured (*adjusted for)</i>	<i>Comparability of groups</i>	<i>Ascertainment of vaccine status</i>	<i>Co-interventions</i>	<i>Ascertainment of mortality</i>	<i>Data & analysis</i>
Senegal D #9433 MRR (adjusted) = 1.37 (0.54, 3.47) Computed from results in Table 1 (ratio of DTP1 to 'BCG not yet DTP' (BCG-first group))	Observational comparison. 4133 children born and registered in study area between Sept 1996 and Dec 1999. 4102 included in the analyses. <u>Selected for inclusion in review:</u> Among 319 children who followed the WHO strategy	<u>SES:</u> Health centre area* <u>Child's health:</u> NR <u>Other:</u> Year of vaccination*, season of vaccination* <u>Age:</u> Yes* <u>Gender:</u> Yes* <u>BCG:</u> All children had received BCG	<u>Vaccines more likely among:</u> No information <u>Mortality more likely among:</u> No information	<u>Frequency:</u> Every 3 months after mid 1997 <u>Method:</u> Project records and then vaccination card <u>Vaccinated:</u> All vaccines are provided and recorded by project team until mid 1997. Following this children with a noted vaccine and date were considered vaccinated. <u>Unvaccinated:</u> Those with no recorded vaccine. After mid 1997 this also includes children with no information available. <u>Dead children:</u> Generally no information provided <u>Approach:</u> Landmark	<u>BCG:</u> No co-administration <u>OPV:</u> Usually co-administered with DTP. <u>MV:</u> High probability of differential MV co-intervention (follow-up to 24 months; censored at receipt of MV). <u>Other:</u> No information provided for any of the co-interventions.	No information	Cox proportional hazards model. Censored at 24 months of age, registration of next vaccine, death or migration.

Moderate risk of bias in selection of participants into the study

High risk of bias due to confounding (no adjustment for child's health)

High risk of bias in measurement of vaccination (children with no information included as unvaccinated, and further bias towards null from landmark approach)

High risk of bias due to departures from intended interventions (high probability of MV)

Low risk of bias in measurement of outcomes

Moderate risk of bias due to missing outcome data

Moderate risk of bias in selection of the reported result

Overall: High risk of bias (no adjustment for child's health)

4 Risk-of-bias assessments for randomized trials of measles vaccine

Guinea-Bissau 1989-1999

Result selected	Sample	Allocation or randomization	Blinding and co-interventions	Ascertainment of mortality	Data & analysis
Guinea-Bissau H #2543 Risk ratio (unadjusted) = 1 (0.2, 4.92) Text of paper (p. 825) (also described in #3896, #1468, #2202, #9343)	300 children randomised to MV or IPV at 6 months. 19 moved or died before receiving the 9 month MV vaccination. (#1468) <u>Selected for inclusion in review:</u> All 300 children.	<u>Allocation:</u> "Randomisation was done on a per patient basis and was done with a list of random numbers." (#3896)	<u>Blinding of participants:</u> Control children received IPV <u>Blinding of vaccine administrators:</u> No information <u>Co-interventions and departures from allocated intervention:</u> Half the children were randomised to receive either placebo or vitamin A with their vaccine.	No details <u>Blinding of outcome assessors:</u> Probably not, but objective outcome.	<u>Missing data:</u> No information <u>Analysis:</u> Not clear

Unclear risk of bias due to confounding (allocation may be unconcealed and no information about similarity of groups)
 Moderate risk of performance bias due to departures from intended interventions (participants knew vaccination status)
 Low risk of detection bias in measurement of outcomes
 Unclear risk of attrition bias due to missing data
 Unclear risk of bias in selection of the reported result
 Overall: Moderate risk of bias (due to knowledge of vaccination status)

Guinea-Bissau 1989-1999

Result selected	Sample	Allocation or randomization	Blinding and co-interventions	Ascertainment of mortality	Data & analysis
Guinea-Bissau S #2202 MRR (unadjusted) = 0.94 (0.53, 1.67) Computed from rates in Table 3 (Second two-dose trial; combined across 3+ and 0-2 doses of DTP) (also described in #482)	Randomized trial of MV at 6 and 9 months vs OPV at 6 months and MV at 9 months. All children born between September 1994 and October 2001 and registered before 6 months of age. (#2202). War started on 7 th June 1998, the war ended in May 1999. Mortality was considerably higher during this period. <u>Selected for inclusion in review:</u> Apparently at least 8511 children randomized (Table 1)	<u>Allocation:</u> No details regarding randomisation process and how allocation of MV v IPV was done.	<u>Blinding of participants:</u> Control children received IPV <u>Blinding of vaccine administrators:</u> No information <u>Co-interventions and departures from allocated intervention:</u> No information	No details <u>Blinding of outcome assessors:</u> Probably not, but objective outcome.	<u>Missing data:</u> No information <u>Analysis:</u> Cox proportional hazards model (#2202)

Unclear risk of bias due to confounding (no information about allocation process)

Moderate risk of performance bias due to departures from intended interventions (participants knew vaccination status)

Low risk of detection bias in measurement of outcomes

Unclear risk of attrition bias due to missing data

Unclear risk of bias in selection of the reported result

Overall: Moderate risk of bias (due to knowledge of vaccination status)

Result selected	Sample	Allocation or randomization	Blinding and co-interventions	Ascertainment of mortality	Data & analysis
Guinea-Bissau C #1731 Risk ratio (adjusted) = 0.67 (0.38, 1.19) Table 2 (4.5-9 months, all children) (also described in #9436, #9343, #433)	Between August 2003 and April 2007 6648 children were enrolled, 6417 were included in the main analysis. Half received vaccine at 4.5 months and half received nothing. All children received MV at 9 months. <u>Selected for inclusion in review:</u> All	<u>Allocation:</u> "The mothers or guardians were asked to select an envelope with the allocation number that defined to which group the child belonged. We randomised children to one of three equal sized groups by using block randomisation with 24 envelopes per bag. Block randomisation was organised within the whole study area and not by health centre. The data manager, who was not involved in the recruitment of children, prepared bags with 24 numbered envelopes indicating the randomisation group. These numbers could not be seen by the doctor informing and obtaining consent from the mothers or guardians. A new bag was opened only when the previous one was empty." "No major differences existed in the demographic, socioeconomic, and health related background factors between children included in the early two dose measles vaccine arm (group A) and the two groups with measles vaccine at 9 months of age (groups B +C) (table 1)."	<u>Blinding of participants:</u> No, "No placebo was given." <u>Blinding of vaccine administrators:</u> No "However, the health workers, doctors, and nurses in the paediatric ward and at the health centres do not inspect the vaccination cards of sick children to guide the treatment, and they were not aware of the purpose of the study." <u>Co-interventions and departures from allocated intervention:</u> None apparent.	Visit to health centre at 9 plus 3 monthly home visits. <u>Blinding of outcome assessors:</u> Probably no, although the outcome is objective. "However, the health workers, doctors, and nurses in the paediatric ward and at the health centres do not inspect the vaccination cards of sick children to guide the treatment and they were not aware of the purpose of the study."	<u>Missing data:</u> "The study was not perfectly balanced with respect to drop-out. As we tested specific strains of measles vaccine, children who had received measles vaccine elsewhere before they attended the 9 month vaccination session were censored in the study because the strain and quality of their measles vaccine would not be known. We excluded more children at the 9 month vaccination session in groups B and C than in group A (fig 1)." 231 children were excluded from the main analysis (80 children had had measles infection before enrolment at 4.5 months of age (five died), 131 children were enrolled within 25 days of the third DTP vaccination as opposed to 4 weeks after (seven died), 18 children were enrolled twice (none died); 2 children who had the wrong age recorded; they were both one year older than originally assumed (neither died). "A further 17 children received the wrong type of measles vaccine at 9 months of age and they have been censored in the analysis from the date of this vaccination (none died)." <u>Analysis:</u> Cox proportional hazards model with age as underlying time.

Low risk of bias due to confounding

Moderate risk of performance bias due to departures from intended interventions (participants knew vaccination status)

Low risk of detection bias in measurement of outcomes

Moderate risk of attrition bias due to missing data (imbalance in drop-out)

Unclear risk of bias in selection of the reported result

Overall: Moderate risk of bias (due to knowledge of vaccination status)

Nigeria c.1961

Result selected	Sample	Allocation or randomization	Blinding and co-interventions	Ascertainment of mortality	Data & analysis
Nigeria #8985 Risk ratio (unadjusted) = 0.41 (0.14, 1.15) Computed from counts in text (page 144)	Children from under-5s hospital clinic in Ilesha. Over 2000 children between 6 months and 2 years accepted an invitation for vaccination. attended, record cards available for 1962 children. <u>Selected for inclusion in review:</u> All 1962 with record cards at follow-up.	<u>Allocation:</u> “By a system of random numbers, these children were divided into two equal groups”.	<u>Blinding of participants:</u> Probably yes since placebo was apparently used. “The other group was a control one, receiving gamma globulin and inert material identical with that used in the culture of the virus”. <u>Blinding of vaccine administrators:</u> Unclear. Another study reported in the paper is described as “This was not a blind study, since the investigators knew which children had received measles vaccine”, suggesting that this might not be the case for the current study. <u>Co-interventions and departures from allocated intervention:</u> None apparent.	Not clear. “At the end of the trial period at the Ilesha Hospital 1962 record cards were Available”; “Among the children in this trial there were 17 known deaths”. It is not clear whether these two sources are linked. The paper reports that “the follow-up had to be made in a crowded and over-worked clinic”. <u>Blinding of outcome assessors:</u> Probably no, although the outcome is objective.	<u>Missing data:</u> Number randomized not reported, but known to be over 2000. It is not clear whether the numbers of deaths relate to the children with record cards or the larger number randomized. <u>Analysis:</u> None.

Unclear risk of bias due to confounding (no information on randomization procedure)

Low risk of performance bias due to departures from intended interventions

Unclear risk of detection bias in measurement of outcomes

Moderate risk of attrition bias due to missing data (unknown number at start of study)

Unclear risk of bias in selection of the reported result

Overall: Moderate risk of bias

5 Risk-of-bias assessments for non-randomized studies of measles vaccine

Bangladesh 1977-1985

Result selected	Sample	Confounders measured (*adjusted for)	Comparability of groups	Ascertainment of vaccine status	Co-interventions	Ascertainment of mortality	Data & analysis
Bangladesh B #6509 Hazard ratio (adjusted) = 0.51 (0.42, 0.62) Text of paper (page 110)	Matched cohort. 9133 children aged 9-60 months in vaccination area received MV. An unvaccinated match was found (based on month of birth) for 8135 children. The remaining 998 children were not included in the analyses. Although MV started in March 1982, events (e.g. mortality) were started in October 1982 so survival has only been analysed from October. One unvaccinated child was included twice so the second pair was excluded resulting in 8134 pairs. <u>Selected for inclusion in review:</u> All	<u>SES:</u> maternal education* <u>Child's health:</u> NR <u>Other:</u> Size of dwelling*, number of siblings* <u>Age:</u> Yes* <u>Gender:</u> Yes* In analyses which included covariates 635 children were excluded due to missing information. <u>BCG:</u> Yes <u>DTP:</u> Yes	<u>Vaccines more likely among:</u> no information <u>Mortality more likely among:</u> no information BCG coverage 48% and 39% in the two areas DTP coverage 50% and 51% in the two areas	<u>Frequency:</u> N/A <u>Method:</u> A detailed record keeping system contained details on the vaccination status and date of vaccination of all children aged <5 years in the study area. <u>Vaccinated:</u> Children who lived in a MV area (blocks A & C) who had already received MV. <u>Unvaccinated:</u> Children in blocks B & D where no MV campaign running and who had not received MV.	<u>DTP:</u> No information on co-administration <u>Other:</u> No information	Community health workers visited households every second week and reported to the field assistants of the Demographic Surveillance System.	Cox proportional hazards model for paired survival data. Censoring at moving, end of study.

Moderate risk of bias in selection of participants into the study

High risk of bias due to confounding (phased introduction of vaccines into two areas; matching by birth date only)

Moderate risk of bias in measurement of vaccination

Insufficient information to assess risk of bias due to departures from intended interventions

Low risk of bias in measurement of outcomes

Moderate risk of bias due to missing outcome data.

Moderate risk of bias in selection of the reported result.

Overall: High risk of bias (matching by birth date only)

Bangladesh 1986-2001

<i>Result selected</i>	<i>Sample</i>	<i>Confounders measured (*adjusted for)</i>	<i>Comparability of groups</i>	<i>Ascertainment of vaccine status</i>	<i>Co-interventions</i>	<i>Ascertainment of mortality</i>	<i>Data & analysis</i>
Bangladesh A #797 Hazard ratio (adjusted) = 0.93 (0.65, 1.34) Table 5	Observational comparison. Based on 39,625 children born between Jan 1 1986 and Jan 1 2000. 1731 excluded because they died (1600) or migrated (131) before 42 days (vaccines start at 6 weeks). <u>Selected for inclusion in review:</u> Analysis of 36,650 for MV (1244 died (712) or migrated (532) before 9 months).	<u>SES:</u> Maternal education*, asset score* <u>Child's health:</u> distance from hospital, MUAC (not used, too much missing data) <u>Other:</u> birth order*, religion*, maternal age* <u>Age:</u> Yes* <u>Gender:</u> Yes* <u>BCG:</u> Yes* <u>DTP:</u> Yes* (number of DTP vaccinations)	<u>Vaccines more likely among:</u> older mothers, higher education, not first born, higher asset score (least poor), non Muslims, closer to hospital <u>Mortality more likely among:</u> older mothers, lower education, first born (DTP)/third born (MV), lowest asset score.	<u>Frequency:</u> every 2 weeks until Jan 1998, once a month since then <u>Method:</u> Monthly immunization days, community worker vaccinates children on this day and records them in record keeping book. <u>Vaccinated:</u> Children given vaccine during immunization day <u>Unvaccinated:</u> Children with no vaccine recorded <u>Dead children:</u> Status based on vaccines received up to 30 days before death. <u>Approach:</u> Information updated on day vaccine given.	<u>DTP:</u> 77% had received 3 doses of DTP by 9 months, this increased to 93% by 60 months. <u>Other:</u> No information	All deaths included except those due to trauma or accidents	Cox proportional hazards model with time varying covariates. Censored deaths due to trauma or accidents. Any subsequent DTP that occurred later than usual schedule was included as a covariate in the model. Reanalysed using 30 day lag period & got consistent results (data not shown).

Moderate risk of bias in selection of participants into the study

High risk of bias due to confounding (no adjustment for child's health)

Moderate risk of bias in measurement of vaccination

High risk of bias due to departures from intended interventions (16% received additional DTP doses after MV)

Low risk of bias in measurement of outcomes

Moderate risk of bias due to missing outcome data.

Moderate risk of bias in selection of the reported result.

Overall: High risk of bias (no adjustment for child's health; some co-intervention with DTP)

Benin 1983-1987

<i>Result selected</i>	<i>Sample</i>	<i>Confounders measured (*adjusted for)</i>	<i>Comparability of groups</i>	<i>Ascertainment of vaccine status</i>	<i>Co-interventions</i>	<i>Ascertainment of mortality</i>	<i>Data & analysis</i>
Benin #9372 Odds ratio (adjusted) = 0.36 (0.16, 0.81) Table 2, up to 12 months	Case-control study. Cases: All children who died between January 1986 and October 1987 and before the age of 3 years. Controls: selected from register of all children in the area, matched for age, sex and village of residence. "Some 74 cases and 230 controls were available for analysis" with 1-4 matched controls per case. "Children who were born and died within the interval of about 3 months between surveys were rarely reported. 2 infants who were known to have died within one month of birth were excluded. All other children had at least attained 4 months of age." <u>Selected for inclusion in review:</u> 177 children who were unvaccinated and 75 children who were vaccinated at less than 12 months of age.	<u>SES:</u> Socioeconomic score* (no details how this is calculated) <u>Child's health:</u> Weight for age* <u>Other:</u> NR <u>Age:</u> NR <u>Gender:</u> NR <u>BCG:</u> Yes <u>DTP:</u> Yes (by dose)	<u>Vaccines more likely among:</u> no information <u>Mortality more likely among:</u> lower socioeconomic status	<u>Frequency:</u> <u>Method:</u> Preventive child care cards, kept at the communal health centre. <u>Vaccinated:</u> Children with a vaccine recorded by vaccination team during visits to the village. <u>Unvaccinated:</u> Children with no recorded vaccine <u>Dead children:</u> N/A	<u>DTP:</u> No information on co-administration <u>Other:</u> No information	When a child under 3 died the interviewer recorded the symptoms parents mentioned. A medical doctor subsequently visited the household to establish a probable cause of death.	Analysis by conditional logistic regression.

Moderate risk of bias in selection of participants into the study

High risk of bias due to confounding (despite matching, some key confounders were not addressed)

Moderate risk of bias in measurement of vaccination

Insufficient information for bias due to departures from intended interventions

Low risk of bias in measurement of outcomes

Moderate risk of bias due to missing outcome data.

Moderate risk of bias in selection of the reported result.

Overall: High risk of bias (key confounders were not addressed)

Burundi 1984-1988

<i>Result selected</i>	<i>Sample</i>	<i>Confounders measured (*adjusted for)</i>	<i>Comparability of groups</i>	<i>Ascertainment of vaccine status</i>	<i>Co-interventions</i>	<i>Ascertainment of mortality</i>	<i>Data & analysis</i>
Burundi #6889 MRR (unadjusted) = 0.3 (0.17, 0.52) Computed from rates in Table 5	Observational comparison. Door to door census of all households was done in January 1989 to identify children younger than 5. Children born since January 1984 and alive at 1 July 1988 were registered. A total of 1899 children were registered, of these 1442 had vaccination cards. 74% vaccinated between 9 and 23 months. <u>Selected for inclusion in review:</u> All	<u>SES:</u> NR <u>Child's health:</u> Measles infection, measles symptoms (fever, rash, cough, runny nose, red eyes, diarrhoea), hospitalized <u>Other:</u> Duration of outbreak <u>Age:</u> Yes <u>Gender:</u> NR <u>BCG:</u> No <u>DTP:</u> No	<u>Vaccines more likely among:</u> no information <u>Mortality more likely among:</u> no information	<u>Frequency:</u> None <u>Method:</u> Child home-based vaccination record <u>Vaccinated:</u> Children with MV and date on card <u>Unvaccinated:</u> Children with no vaccine on card and children with no card <u>Dead children:</u> Excluded from sample <u>Approach:</u> Used categorization of children according to previous vaccination or not	<u>DTP:</u> No information on co-administration <u>Other:</u> No information.	Deaths since 1 July 1988 were recorded during door to door census. Same households were visited in September 1989 to assess survival of children found during the January census.	Followed-up for 6 months 67 children received a non-measles vaccine after 9 months of age and had missed an opportunity for MV

Very high risk of bias in selection of participants into the study (children were enrolled up to age of 5 years, MV recommended from 9 months)

Very high risk of bias due to confounding (unadjusted analyses, previous vaccinations not considered)

High risk of bias in measurement of vaccination (unvaccinated group includes children assumed unvaccinated)

Insufficient information for risk of bias due to departures from intended interventions

Low risk of bias in measurement of outcomes

Moderate risk of bias due to missing outcome data.

Moderate risk of bias in selection of the reported result.

Overall: Very high risk of bias (children were enrolled up to age of 5 years; unadjusted analyses)

DR Congo 1973-1975

Result selected	Sample	Confounders measured (*adjusted for)	Comparability of groups	Ascertainment of vaccine status	Co-interventions	Ascertainment of mortality	Data & analysis
DR Congo #7108 MRR (unadjusted) = 0.29 (0.09, 0.98) Computed from survival probabilities in Table II (Group 1v vs Group 2)	Observational comparison. In May 1974 children born after 1 st June 1969 were entered into the study. Up to April 1977 children under 5 continued to be recruited. In total 7092 children were entered into the study and visited. Groups 1 & 2 consisted of children born between September 1974 and October 1975. 306 children in group 1 were invited for vaccine, of these 255 accepted. No other Ns are reported. <u>Selected for inclusion in review:</u> Children in Group 1v (invited for vaccination and accepted) and Group 2 (unvaccinated). Approx 600 children.	<u>SES:</u> None <u>Child's health:</u> weight, height, arm circumference (not used) <u>Other:</u> None <u>Age:</u> NR <u>Gender:</u> NR The authors report "there are no gross social differences between the two areas and both areas have the same health services." In addition they report that "their anthropometric data were identical." <u>BCG:</u> No <u>DTP:</u> No	<u>Vaccines more likely among:</u> no information <u>Mortality more likely among:</u> no information	<u>Frequency:</u> N/A <u>Method:</u> Invitation and attendance at clinic. <u>Vaccinated:</u> Children who attend an invitation for MV <u>Unvaccinated:</u> Children in area with no MV <u>Dead children:</u> N/A <u>Approach:</u> Categorization	<u>DTP:</u> No information <u>Other:</u> No information	3 monthly visits to study area.	Comparison of cumulative survival probabilities, 7-21 months. No data about vaccines during follow-up or if the unvaccinated children were later vaccinated.

Moderate risk of bias in selection of participants into the study

High risk of bias due to confounding (unadjusted analysis of groups)

Moderate risk of bias in measurement of vaccination

Insufficient information to assess risk of bias due to departures from intended interventions

Low risk of bias in measurement of outcomes

Moderate risk of bias due to missing outcome data.

Moderate risk of bias in selection of the reported result.

Overall: High risk of bias (unadjusted analysis of groups)

Result selected	Sample	Confounders measured (*adjusted for)	Comparability of groups	Ascertainment of vaccine status	Co-interventions	Ascertainment of mortality	Data & analysis
Ghana A #3294 MRR (adjusted) = 0.51 (0.29, 0.97) Table 4 (MRR MV/DTP all children)	Observational comparison. Children enrolment into placebo arm of a vitamin A trial (N=6882). 3330 children aged 6-35 months; 3082 included in analysis (excluding those with no information on health card, or health card known to exist but not seen). Selected for inclusion in review: 1793 children who had health cards confirming receipt of MV (plus DTP) or no MV (plus DTP) [Groups 3, 4, 5 and 6 in the paper]	<u>SES</u> : Zone* and radio in compound* <u>Child's health</u> : Ever breastfed, still breastfeeding, MUAC, measles before enrolment, previously admitted to hospital, weight for age* <u>Other</u> : NR <u>Age</u> : Yes* <u>Gender</u> : Yes <u>BCG</u> : BCG scar <u>DTP</u> : Yes (all had received at least 1 dose of DTP)	<u>Vaccines more likely among</u> : children still breastfeeding, lower weight for age children and children more likely to have been hospitalized <u>Mortality more likely among</u> : no information	<u>Frequency</u> : Every 4 months <u>Method</u> : Vaccination cards <u>Vaccinated</u> : Children whose card was seen and had received DTP and MV <u>Unvaccinated</u> : Children whose card was seen and had received DTP <u>Dead children</u> : Vaccination status not updated for children who died between visits. <u>Approach</u> : Landmark <u>Comment</u> : There is also a 'no health card' group, which could be treated as an unvaccinated group. However. "15% of children without a health card had a BCG scar. These children may have lost the card or never been issued one."	<u>DTP</u> : 86% of children who had received DTP & MV received them simultaneously or received at least one dose of DTP after MV <u>Other</u> : Many missing vaccines given in first 4 months of enrolment (50% additional MV), although these appear evenly balanced between groups. Only included children who had received placebo in vitamin A trial. No information provided about any of the other co-interventions.	Deaths were identified through visits and independently by key informants based in the community. Follow-up procedures were independent of the vaccination status of the child.	Cox proportional hazards model. Vaccination status at enrolment was a fixed term variable during follow-up.

Moderate risk of bias in selection of participants into the study

High risk of bias due to confounding (likely residual confounding)

Moderate risk of bias in measurement of vaccination

Very high risk of bias due to departures from intended interventions (high proportion of co-administration with MV)

Low risk of bias in measurement of outcomes

Moderate risk of bias due to missing outcome data.

Moderate risk of bias in selection of the reported result.

Overall: Very high risk of bias (likely residual confounding)

Result selected	Sample	Confounders measured (*adjusted for)	Comparability of groups	Ascertainment of vaccine status	Co-interventions	Ascertainment of mortality	Data & analysis
Ghana B #7190 Hazard ratio (unadjusted) = 0.78 (0.43, 1.41) Table 3, (group 4 vs group 2)	Observational comparison. Children who were born between October 1994 and December 1999 and for whom information is available in at least 1 of the annual vaccination surveys. The survey only collects information for living children so children who were born and died between successive visits were not included in the database. 24,053 children in the study area of which 17,753 are included and 6,300 are not included. Of the 17,753 mother's information was missing for 0.3% and these children were subsequently excluded resulting in 17,701 children <u>Selected for inclusion in review:</u> Time after receiving BCG/DTP3 & MV or BCG and DTP3 [Groups 2 and 4 in the paper].	<u>SES:</u> Mother's education, father's education, compound size <u>Child's health:</u> Cell location (health services delivery), distance to nearest health facility <u>Other:</u> Mothers age at birth, mother resident, father resident, age at first observation, distance to Navrongo town <u>Age:</u> Yes <u>Gender:</u> Yes <u>BCG:</u> Yes (all children had received BCG) <u>DTP:</u> Yes (all children had received all 3 doses of DTP)	<u>Vaccines more likely among:</u> no information <u>Mortality more likely among:</u> no information	<u>Frequency:</u> Annual collection of vaccination status <u>Method:</u> Inspection of vaccination cards or other written records. <u>Vaccinated:</u> children who have a recorded BCG, DTP3 and MV. <u>Unvaccinated:</u> Children with a recorded BCG and DTP3 vaccines. <u>Dead children:</u> Vaccination status not updated for children who died between birth and subsequent visit. <u>Approach:</u> Probably retrospective (suggestion that retrospectively collected dates of vaccination used in analysis)	<u>DTP:</u> Low probability of differential co-intervention of DTP (only included children who had received all 3 doses of DTP) <u>Other:</u> No information; only 2 months of follow-up used	Collected at 3 monthly intervals to village compounds and recorded on Navrongo Demographic Surveillance System	Cox proportional hazards model. Censoring at out-migration

Very high risk of bias in selection of participants into the study (children included only if seen in annual surveys)

High risk of bias due to confounding (unadjusted analysis of groups)

Very high risk of bias in measurement of vaccination (retrospective approach probably used)

Moderate risk of bias due to departures from intended interventions

Low risk of bias in measurement of outcomes

Moderate risk of bias due to missing outcome data.

Moderate risk of bias in selection of the reported result.

Overall: Very high risk of bias (children included only if seen in annual surveys; retrospective approach probably used)

Result selected	Sample	Confounders measured (*adjusted for)	Comparability of groups	Ascertainment of vaccine status	Co-interventions	Ascertainment of mortality	Data & analysis
Ghana C #9464 MRR (adjusted) = 0.14 (0.13, 0.16) Table II	Observational comparison. 17,967 children born between 1 st January 1998 and 31 st December 2004. <u>Selected for inclusion in review:</u> All	<u>SES:</u> Mother's education*, poverty status* <u>Child's health:</u> NR <u>Other:</u> Mother's age <u>Age:</u> Yes* <u>Gender:</u> No <u>BCG:</u> Yes <u>DTP:</u> Yes	<u>Vaccines more likely among:</u> BCG recipients <u>Mortality more likely among:</u> Lower education, higher poverty.	<u>Frequency:</u> Annual collection of vaccination status <u>Method:</u> Annual survey <u>Vaccinated:</u> Unclear <u>Unvaccinated:</u> Unclear <u>Dead children:</u> No information <u>Approach:</u> Unclear <u>Comment:</u> "Annual updates of immunization status and educational attainment and indicators of socioeconomic status are linked to the demographic register."; "Models for the analysis presented here are based on the status of each child at the time of last observation with respect to the WHO definition."	<u>DTP:</u> No information <u>Other:</u> No information	All-cause mortality, quarterly visits	Time conditional HR. No description of any censoring.

Low risk of bias in selection of participants into the study

Very high risk of bias due to confounding (high degree of confounding with BCG and DTP)

Insufficient information to assess risk of bias in measurement of vaccination (high risk of bias or possibly very high risk of bias: cannot tell how vaccination status was defined; retrospective approach may have been used)

Insufficient information to assess risk of bias due to departures from intended interventions

Low risk of bias in measurement of outcomes

Moderate risk of bias due to missing outcome data.

Moderate risk of bias in selection of the reported result.

Overall: Very high risk of bias (high degree of confounding with BCG and DTP)

Guinea-Bissau 1978-1983

Result selected	Sample	Confounders measured (*adjusted for)	Comparability of groups	Ascertainment of vaccine status	Co-interventions	Ascertainment of mortality	Data & analysis
Guinea-Bissau L #8668 Risk ratio (adjusted) = 0.51 (0.15, 1.81) Computed from counts in Table III (meta-analysis of risk ratios within two time periods)	Observational comparison. 143 children who were unvaccinated at the beginning of 1981. <u>Selected for inclusion in review:</u> All	<u>SES:</u> NR <u>Child's health:</u> weights measured quarterly until 3 years (not reported or used) <u>Other:</u> NR <u>Age:</u> Yes <u>Gender:</u> No <u>BCG:</u> No <u>DTP:</u> No	<u>Vaccines were likely among:</u> no information <u>Mortality was likely among:</u> no information	<u>Frequency:</u> Quarterly from beginning 1980 <u>Method:</u> Records kept by local health centre. <u>Vaccinated:</u> Children vaccinated since beginning of 1981 according to their central health file <u>Unvaccinated:</u> Unvaccinated at the beginning of 1981 according to central health file <u>Dead children:</u> N/A <u>Approach:</u> Categorization of children by vaccine given or not.	<u>DTP:</u> No information <u>Other:</u> No information	Mortality rates during 1 year of follow-up. Interviews were conducted with adult members of the household where measles had been reported to check information on measles infection. Any death within a month of an attack of measles was classified as a measles death.	Death rates during one year of follow-up in children aged 6-11 months at the beginning of 1981.

High risk of bias in selection of participants into the study (enrolment after vaccination likely to have happened)

High risk of bias due to confounding (crudely adjusted analysis)

Moderate risk of bias in measurement of vaccination

Insufficient information to assess risk of bias due to departures from intended interventions

Low risk of bias in measurement of outcomes

Moderate risk of bias due to missing outcome data.

Moderate risk of bias in selection of the reported result.

Overall: High risk of bias (enrolment after vaccination likely to have happened; crudely adjusted analysis)

Guinea-Bissau 1978-1983

Result selected	Sample	Confounders measured (*adjusted for)	Comparability of groups	Ascertainment of vaccine status	Co-interventions	Ascertainment of mortality	Data & analysis
Guinea-Bissau T #8670 Risk ratio (unadjusted) = 0.62 (0.2, 1.88) Computed from counts in Table 3 (Feb 1981-Mar 1982)	Observational comparison. 305 children under 5 were examined in June 1979. In March 1982 the registered population of children under 5 was 489. <u>Selected for inclusion in review:</u> Approximately 210 contributing to rates on MV vs no MV.	<u>SES:</u> NR <u>Child's health:</u> Weight for age (only at start of period in which child suffered measles have been used) <u>Other:</u> Season <u>Age:</u> Yes <u>Gender:</u> Yes <u>BCG:</u> No <u>DTP:</u> No	<u>Vaccines more likely among:</u> no information <u>Mortality more likely among:</u> no information	<u>Frequency:</u> Not updated? <u>Method:</u> No information <u>Vaccinated:</u> No information <u>Unvaccinated:</u> No information <u>Dead children:</u> No information <u>Comments:</u> Vaccination of measles susceptible children aged 6 months or older was introduced from Feb/March 1981.	<u>DTP:</u> No information <u>Other:</u> No information	All cause mortality and measles deaths. "Health problems are discussed with the village committee, which has been given the responsibility of registering deaths." "Inquiries have been made about children who do not turn up for a re-examination in order to find out if they have died, moved or left the area temporarily."	Unadjusted counts provided for vaccinated and unvaccinated children (also rates standardized to one year of follow-up, but not for both comparator groups)

Insufficient information to assess risk of bias in selection of participants into the study

High risk of bias due to confounding (unadjusted analysis, previous vaccines not considered)

Insufficient information to assess risk of bias in measurement of vaccination (cannot tell how vaccination status was defined)

Insufficient information to assess risk of bias due to departures from intended interventions

Low risk of bias in measurement of outcomes

Moderate risk of bias due to missing outcome data.

Moderate risk of bias in selection of the reported result.

Overall: High risk of bias (unadjusted analysis)

Guinea-Bissau 1984-1985

Result selected	Sample	Confounders measured (*adjusted for)	Comparability of groups	Ascertainment of vaccine status	Co-interventions	Ascertainment of mortality	Data & analysis
Guinea-Bissau M #6992 MRR (adjusted) = 0.34 (0.17, 0.68) Text of paper (p. 1046; value of 2.95 inverted)	Observational comparison. Children born between August 1984 and September 1985 who were registered in the area by 4 months. Children were followed until June 1987. 274 from Bandim 1 and 448 from Bandim 2. Selected for inclusion in review: All, excluding those vaccinated before 8.5 months of age with MV	<u>SES</u> : Area* <u>Child's health</u> : NR <u>Other</u> : NR <u>Age</u> : Yes* <u>Gender</u> : Yes* <u>BCG</u> : No <u>DTP</u> : No	<u>Vaccines more likely among</u> : no information <u>Mortality more likely among</u> : no information	<u>Frequency</u> : Every 3 months (Bandim 1), every 3-5 months (Bandim 2) <u>Method</u> : Vaccination cards. <u>Vaccinated</u> : Vaccine indicated on vaccination card <u>Unvaccinated</u> : No explicit definition given <u>Dead children</u> : No information <u>Approach</u> : "Vaccines regularly monitored in area so undoubtedly few vaccinated children classified as unvaccinated due to loss of the card"	<u>DTP</u> : No information <u>Other</u> : No information	Monthly visits in Bandim 1 to register deaths, visits are every 3-5 months in Bandim 2.	Cox proportional hazards model. Censoring at moving away

Moderate risk of bias in selection of participants into the study
 High risk of bias due to confounding (no adjustment for child's health or previous vaccines)
 Moderate risk of bias in measurement of vaccination
 Insufficient information to assess risk of bias due to departures from intended interventions
 Low risk of bias in measurement of outcomes
 Moderate risk of bias due to missing outcome data.
 Moderate risk of bias in selection of the reported result.
 Overall: High risk of bias (no adjustment for child's health or previous vaccines)

<i>Result selected</i>	<i>Sample</i>	<i>Confounders measured (*adjusted for)</i>	<i>Comparability of groups</i>	<i>Ascertainment of vaccine status</i>	<i>Co-interventions</i>	<i>Ascertainment of mortality</i>	<i>Data & analysis</i>
Guinea-Bissau D #2726 Risk ratio (adjusted) = 0.48 (0.27, 0.87) Text of paper	Observational comparison. 10,298 children born alive of which 686 died, 90 moved and 770 were too young before the first visit. <u>Selected for inclusion in review</u> : 4230 children aged 7-13 months at second visit and who either had a vaccination card examined or had no card. Children followed-up until next visit or 6 months later if next visit was later than that (children aged up to 18 months).	<u>SES</u> : Cluster*, maternal education, latrine <u>Child's health</u> : MUAC, well, birth at home <u>Other</u> : Season, period, maternal age, birth order, ethnicity, previous dead children, length of follow-up <u>Age</u> : Yes* <u>Gender</u> : Yes <u>BCG</u> : Yes* DTP: Yes	<u>Vaccines more likely among</u> : children who had more contact with health system, mothers who received tetanus during pregnancy and who gave birth outside the home. They also had larger MUAC, younger mothers, had fewer children, have a latrine and not belong to Balanta or Pepel ethnicity. <u>Mortality more likely among</u> : no information	<u>Frequency</u> : Visits every 5-7 months on average <u>Method</u> : Vaccination card <u>Vaccinated</u> : Children whose card was seen and vaccine recorded <u>Unvaccinated</u> : Children who had no date or were declared not to have received the vaccine. <u>Dead children</u> : No information <u>Approach</u> : Landmark. Only vaccination status at second visit used (aged 7-13 months).	<u>DTP</u> : Coverage for DTP 1 increased by approximately 10% between 9 and 17 months and by 30% for DTP3 during the same period. <u>Other</u> : No information	Information on mortality was obtained at subsequent visits (meaning children had to be visited twice to be included in the study).	Cox proportional hazards model. "There was no loss to follow-up because it was always possible to get information on all children from relatives living in the same compound". Analysis repeated excluding children considered unvaccinated because they had no card.

High risk of bias in selection of participants into the study (follow-up starts age 7-13 months)

High risk of bias due to confounding (likely confounding not adjusted for)

Moderate risk of bias in measurement of vaccination

Moderate risk of bias due to departures from intended interventions

Low risk of bias in measurement of outcomes

Moderate risk of bias due to missing outcome data.

Moderate risk of bias in selection of the reported result.

Overall: High risk of bias (follow-up starts age 7-13 months; likely confounding)

Guinea-Bissau 1999-2002

Result selected	Sample	Confounders measured (*adjusted for)	Comparability of groups	Ascertainment of vaccine status	Co-interventions	Ascertainment of mortality	Data & analysis
Guinea-Bissau G #9441 MRR (adjusted) = 0.7 (0.5, 0.98) Table 3, all children	Observational study within a randomized trial of vitamin A. Children aged 12-23 months who had their vaccination cards inspected between January 1999 and May 2006. This cohort included 16,921 children of whom 10,112 had their vaccination card inspected. <u>Selected for inclusion in review:</u> Children who had received MV and unvaccinated children at 12 months of age.	<u>SES:</u> Maternal education <u>Child's health:</u> Arm circumference <u>Other:</u> Maternal age, ethnicity <u>Age:</u> Yes* <u>Gender:</u> Yes <u>BCG:</u> Yes <u>DTP:</u> Yes	<u>Vaccines more likely among:</u> no information <u>Mortality more likely among:</u> no information	<u>Frequency:</u> None in urban area, 6 monthly in rural areas <u>Method:</u> Vaccination card <u>Vaccinated:</u> Children with a vaccine recorded <u>Unvaccinated:</u> Children with no recorded vaccine on card, only included child whose card was seen <u>Dead children:</u> N/A <u>Approach:</u> Landmark	<u>DTP:</u> In 2007 30% of MV administered simultaneously with or followed by DTP. <u>Other:</u> No information. 26% of measles unvaccinated children who had a card inspected at a subsequent visit had received MV during follow-up.	Followed through HDSS 6 monthly visits	Cox proportional hazards model. Effect of survival during following 6 months. Censoring at 6 months.

High risk of bias in selection of participants into the study (children included from 12-23 months, eligible for MV from 9 months)

High risk of bias due to confounding (no adjustment for SES or child's health)

Moderate risk of bias in measurement of vaccination

High risk of bias due to departures from intended interventions (co-administration and co-intervention of DTP, unvaccinated children receiving MV during follow-up)

Low risk of bias in measurement of outcomes

Moderate risk of bias due to missing outcome data.

Moderate risk of bias in selection of the reported result.

Overall: High risk of bias (children included from 12-23 months; no adjustment for SES or child's health)

Haiti 1981-1982

Result selected	Sample	Confounders measured (*adjusted for)	Comparability of groups	Ascertainment of vaccine status	Co-interventions	Ascertainment of mortality	Data & analysis
Haiti #7013 Odds ratio (adjusted) = 0.1 (0.02, 0.42)) Table 7 (all children, value 10.0 inverted)	Observational comparison. Door to door survey was done of all households between January and June 1985 to identify mothers who had births between October 1981 and April 1982. 1499 children were born during this period and 1381 survived until 9 months. Case children were born between October 1981 and April 1982 and died between 9 and 39 months. Control children were born in the same time interval and survived until 39 months or were alive at the time of the interview if younger than 39 months. <u>Selected for inclusion in review:</u> All	<u>SES:</u> Mother literate, mother works, house with cement walls, cement floors, porch on house, electricity in house, ownership of radio, number of rooms in house <u>Child's health:</u> Nutritional status (breastfeeding / solid foods), hospitalized after 9months of age <u>Other:</u> mother knowledge of rehydration, mother uses family planning, first born, maternal age, birth interval, crowding (more than 5 per house), mother's marital status. <u>Age:</u> Yes <u>Gender:</u> Yes Unclear but possible all variables controlled for <u>BCG:</u> No <u>DTP:</u> No	<u>Vaccines more likely among:</u> literate mothers, mothers with knowledge of rehydration, mothers who work, mothers who use family planning, children not first born, children without cement walls, houses with more than 1 room, mother not owning a radio. <u>Mortality more likely among:</u> birth interval greater than 24 months, hospitalized children,	<u>Frequency:</u> N/A <u>Method:</u> Records from MV trial, clinic records maintained by health centre <u>Vaccinated:</u> Children with recorded vaccine <u>Unvaccinated:</u> Children with no recorded vaccine <u>Dead children:</u> N/A <u>Approach:</u> Categorization into vaccinated or not. <u>Comments:</u> Of the 620 children who participated in the 1982 MV study, 306 were identified in 1985. 19 children had received MV subsequently and the remaining children were unvaccinated.	<u>DTP:</u> No information <u>Other:</u> No information	Information was obtained during the interview about any deceased children including date and age of child.	Stepwise logistic regression stratified by confounders. Deaths after 39 months of age were excluded from the analysis.

High risk of bias in selection of participants into the study (restricted to children who survived to 9 months and whose mother still around 4-5 years after birth)

High risk of bias due to confounding (unadjusted analysis)

Moderate risk of bias in measurement of vaccination

Insufficient information to assess risk of bias due to departures from intended interventions

Low risk of bias in measurement of outcomes

Moderate risk of bias due to missing outcome data.

Moderate risk of bias in selection of the reported result.

Overall: High risk of bias (restricted to children who survived to 9 months and whose mother still around 4-5 years after birth; unadjusted analysis)

India 1986-1991

Result selected	Sample	Confounders measured (*adjusted for)	Comparability of groups	Ascertainment of vaccine status	Co-interventions	Ascertainment of mortality	Data & analysis
India C #6720 MRR (unadjusted) = 0.34 (0.23, 0.51) Computed from cumulative frequencies in Table 3, with test-based confidence interval from log rank test	Observational comparison. 16,665 births were registered during the study period of which 3531 were excluded as they left the study area soon after birth to return to their father's home. <u>Selected for inclusion in review:</u> Children who received MV between 6-8 months of age and survived to 12 months. After 1100 excluded who had vaccine after 12 months: N=12034.	<u>SES:</u> No land, maternal education, paternal education, hut/kutch house <u>Child's health:</u> NR <u>Other:</u> NR <u>Age:</u> Yes* <u>Gender:</u> Yes* <u>BCG:</u> Yes (collected but not reported) <u>DTP:</u> Yes (collected but not reported)	<u>Vaccines more likely among:</u> families with land and parents with some education <u>Mortality more likely among:</u> no information	<u>Frequency:</u> Weekly visits to give information, child register updated periodically <u>Method:</u> Collected at weekly visits <u>Vaccinated:</u> Recorded measles vaccination <u>Unvaccinated:</u> No information <u>Dead children:</u> No information <u>Approach:</u> Vaccination status prior to start of follow-up used to categorize children	<u>DTP:</u> Coverage for DTP was over 90% at 12 months of age. No other information provided (censored at time of subsequent vaccinations). <u>Other:</u> No information	Weekly visits, deaths are reported by the part-time community health worker to the health aide. Simple verbal autopsy.	Unimmunized children who subsequently received immunization were censored at the time of immunization. Children who received vaccination after 12 months were excluded from further follow-up. Inclusion in the analyses was conditional on surviving the first year of life.

High risk of bias in selection of participants into the study (vaccine given from 6 months, had to survive to 12 months)

High risk of bias due to confounding (unadjusted analysis)

Moderate risk of bias in measurement of vaccination

Insufficient information to assess risk of bias due to departures from intended interventions

Low risk of bias in measurement of outcomes

Moderate risk of bias due to missing outcome data.

Moderate risk of bias in selection of the reported result.

Overall: High risk of bias (children had to survive to 12 months; unadjusted analysis)

India 1987-1989

Result selected	Sample	Confounders measured (*adjusted for)	Comparability of groups	Ascertainment of vaccine status	Co-interventions	Ascertainment of mortality	Data & analysis
India E #8996 MRR (unadjusted) = 0.31 (0.12, 0.8) Text of paper (p. 7305)	Observational comparison. Live births between December 1987 and November 1989 in 45 contiguous villages. Analysis files from a previous study available for 4138 live births (286 deaths). Of these, 255 records were missing sex, birthday or exit day, which left 3883 children (282 deaths). <u>Selected for inclusion in review:</u> Unvaccinated children or children with MV	<u>SES:</u> NR <u>Child's health:</u> birth weight, current weight, length/height, common childhood morbidities <u>Other:</u> NR <u>Age:</u> Yes <u>Gender:</u> Yes DTP: Yes BCG: Yes	<u>Vaccines were likely among:</u> no information <u>Mortality was likely among:</u> no information	<u>Frequency:</u> 3 monthly visits <u>Method:</u> Vaccination card at home or when the child was brought to the clinic for immunization. <u>Vaccinated:</u> Children with a recorded MV <u>Unvaccinated:</u> Children without a recorded vaccine at 12 months, children whose vaccination card wasn't seen. <u>Dead children:</u> Data were available for 282/286 dead children <u>Approach:</u> Children categorized by known vaccination status at 2-12 months.	<u>DTP:</u> Moderate probability of DTP co-intervention (some children had DTP out of sequence or simultaneous with MV) <u>Other:</u> No information	All-cause mortality likely collected at 3 monthly visits at home.	Unadjusted analysis based on mortality rates in first 12 months Follow-up from date of known MV

Moderate risk of bias in selection of participants into the study

High risk of bias due to confounding (unadjusted comparison)

High risk of bias in measurement of vaccination (unvaccinated group included those children whose card wasn't seen)

High risk of bias due to departures from intended interventions (some risk of DTP co-intervention)

Low risk of bias in measurement of outcomes

Moderate risk of bias due to missing outcome data.

Moderate risk of bias in selection of the reported result.

Overall: High risk of bias (unadjusted comparison; assumptions about non-vaccination)

India 1991-1998

Result selected	Sample	Confounders measured (*adjusted for)	Comparability of groups	Ascertainment of vaccine status	Co-interventions	Ascertainment of mortality	Data & analysis
India F #2580 OR (adjusted) = 0.36 (0.23, 0.56) Text of paper (after stratification, p. 246 (inverted))	Case-control study. Children aged 12-59 months born from 1991-1998 (MV from 10 months). The controls were chosen from a cohort of 15,578 born during the same period and alive at the time of the study. They were matched for age, sex, family size and area of residence. Overall 318 cases and controls formed matched pairs <u>Selected for inclusion in review: all</u>	<u>SES: Area*</u> (matching), mother's literacy, father's education, father's occupation, caste* <u>Child's health: NR</u> <u>Other: Mother's age, father's age, mother employed, family size*</u> (matching) <u>Age: Yes*</u> (matching) <u>Gender: Yes*</u> (matching) <u>BCG: Yes</u> (collected but not reported) <u>DTP: Yes</u> (collected but not reported)	<u>Vaccines more likely among: no information</u> <u>Mortality more likely among: no information</u>	<u>Frequency: NR</u> ("routine visits") <u>Method: Project database</u> examined to identify children who had died between 12-59 months. <u>Vaccinated: No details, likely children recorded as receiving MV</u> <u>Unvaccinated: No details, likely children with no recorded MV</u> <u>Dead children: N/A</u> <u>Approach: Exposure defined as vaccinated before 12 months old</u>	<u>DTP: No information</u> <u>Other: No information</u>	Collected as part of the Comprehensive Rural Health Services Project at Ballabgarh, no specific details provided.	Adjusted odds ratio

Moderate risk of bias in selection of participants into the study

High risk of bias due to confounding (matching and adjustment unlikely to address all confounders)

Moderate risk of bias in measurement of vaccination

Insufficient information to assess risk of bias due to departures from intended interventions

Low risk of bias in measurement of outcomes

Moderate risk of bias due to missing outcome data.

Moderate risk of bias in selection of the reported result.

Overall: High risk of bias (matching and adjustment unlikely to address all confounders)

<i>Result selected</i>	<i>Sample</i>	<i>Confounders measured (*adjusted for)</i>	<i>Comparability of groups</i>	<i>Ascertainment of vaccine status</i>	<i>Co-interventions</i>	<i>Ascertainment of mortality</i>	<i>Data & analysis</i>
India G #9463 MRR (unadjusted) = 0.41 (0.24, 0.7) Computed from rates in Table 3 (9-15 months), BCG, DTP + MV v BCG + DTP	Observational comparison. Live study births from 1 January 2006 to 31 December 2011 in 28 villages in Ballabgarh. A total of 12,142 births with immunization details were available. A total of 11,390 had complete information on confounders and were included in analyses. <u>Selected for inclusion in review:</u> Children whose most recent vaccine was DTP or MV between 9-15 months	<u>SES:</u> Mother's education, fathers education, caste, wealth index <u>Child's health:</u> Access to health care, presence of a health facility in the village <u>Other:</u> Birth order <u>Age:</u> Yes <u>Gender:</u> Yes <u>BCG:</u> Yes <u>DTP:</u> Yes	<u>Vaccines more likely among:</u> no information <u>Mortality more likely among:</u> no information	<u>Frequency:</u> Monthly work plan <u>Method:</u> Fortnightly visits added to computer database. <u>Vaccinated:</u> Recorded as having received MV as last vaccine based on computerized system (approx. 98% had received BCG and DTP) <u>Unvaccinated:</u> Recorded as having received DTP as last vaccine based on based on computerized system <u>Dead children:</u> N/A <u>Approach:</u> Used date of vaccination, although likely to be quite accurate.	<u>DTP:</u> Low probability of differential co-intervention of DTP (98% had received DTP prior to MV) <u>Other:</u> No information is provided about any of the co-interventions	Visits / computerized system.	Unadjusted mortality ratios. Children included in each group from receipt of vaccine until receipt of another vaccine or any other exit criteria. Exit criteria were 3 years of age, end of study or migration. Sensitivity analyses conducted using 2 week lag period.

Moderate risk of bias in selection of participants into the study

Very high risk of bias due to confounding (unadjusted comparison of time after BCG vaccine with time after DTP vaccine)

Moderate risk of bias in measurement of vaccination

Moderate risk of bias due to departures from intended interventions

Low risk of bias in measurement of outcomes

Moderate risk of bias due to missing outcome data.

Moderate risk of bias in selection of the reported result.

Overall: Very high risk of bias (unadjusted comparison of time after BCG vaccine with time after DTP vaccine)

Result selected	Sample	Confounders measured (*adjusted for)	Comparability of groups	Ascertainment of vaccine status	Co-interventions	Ascertainment of mortality	Data & analysis
Malawi #664 Hazard ratio (adjusted) = 0.42 (0.16, 1.14) Table 2B (children present) MV v No MV	Observational comparison. Live births between July 1995 and February 1997. The cohort includes approximately 95% of newborn children (N=803). Of these 36 were still born and 16 died during first week (no vaccines). <u>Selected for inclusion in review:</u> Children present at monthly anthropological examinations. 669 children in period 9 months to 18 months of age	<u>SES:</u> maternal schooling, district <u>Child's health:</u> weight for age, weight for height, twinning <u>Other:</u> HIV status of mother*, birth order, season of birth, religion, maternal age <u>Age:</u> Yes* <u>Gender:</u> Yes <u>BCG:</u> Yes <u>DTP:</u> Yes	<u>Vaccines more likely among:</u> no information <u>Mortality more likely among:</u> no information (but <i>associated</i> with HIV infection, twinning, religion, district, travelling and weight for age)	<u>Frequency:</u> Monthly visits up until 18 months, quarterly from 18 to 60 months. <u>Method:</u> Vaccination card, information verified from health centre records. <u>Vaccinated:</u> Vaccine recorded on card / health centre records <u>Unvaccinated:</u> Assumed children without evidence of vaccination were unvaccinated. <u>Dead children:</u> No information but used both methods <u>Approach:</u> Landmark <u>Comment:</u> "Almost all children received the vaccines in the planned sequence."	<u>DTP:</u> Low probability of differential co-intervention of DTP (almost all children received vaccines in the planned sequence) <u>Other:</u> No information provided for any pre-defined co-interventions.	No information, likely collected at monthly visits.	Cox proportional hazards model; no information about censoring. Absent children censored in analysis until they were again examined. No information about amount of missing data for dead children in retrospective approach.

Low risk of bias in selection of participants into the study

High risk of bias due to confounding (no adjustment for SES or child's health)

High risk of bias in measurement of vaccination (assumptions about non-vaccination)

Moderate risk of bias due to departures from intended interventions

Low risk of bias in measurement of outcomes

Moderate risk of bias due to missing outcome data.

Moderate risk of bias in selection of the reported result.

Overall: High risk of bias (no adjustment for SES or child's health; assumptions about non-vaccination)

Papua New Guinea 1989-1994

<i>Result selected</i>	<i>Sample</i>	<i>Confounders measured (*adjusted for)</i>	<i>Comparability of groups</i>	<i>Ascertainment of vaccine status</i>	<i>Co-interventions</i>	<i>Ascertainment of mortality</i>	<i>Data & analysis</i>
Papua New Guinea #784 MRR (adjusted) = 0.48 (0.18, 1.26) Table 6 (6-11 months)	Observational comparison. Children born under demographic surveillance, registered within 60 days of birth and who survived more than 28 days were included. 6665 children born between 1989 and 1994. 2617 were excluded for a number of reasons. Thus 4048 were included in survival analysis. <u>Selected for inclusion in review:</u> 2618 who had received BCG before 6 months	<u>SES:</u> Region <u>Child's health:</u> Twin <u>Other:</u> Hep B*, pneumococcal vaccine*, birth order, birth year*, death of older sibling, birth interval from previous sibling, multiple births, mother's age*, propensity score <u>Age:</u> Yes* <u>Gender:</u> Yes <u>BCG:</u> All children had received BCG <u>DTP:</u> Yes* (number of doses)	<u>Vaccines more likely among:</u> children born to mothers less than 23 and older than 35. <u>Mortality more likely among:</u> no information	<u>Frequency:</u> Monthly clinics but frequent disruptions. Clinic cards bought to office monthly for entry of dates. <u>Method:</u> Clinic cards held by nurses and child's health books kept by mothers <u>Vaccinated:</u> Vaccination recorded on clinic records <u>Unvaccinated:</u> No vaccine recorded on clinic cards. <u>Dead children:</u> Cards kept by nurses for 1 year after last attendance, likely to have information for dead children. <u>Approach:</u> Unclear; vaccination information appears to be prospectively recorded for living and dead children.	<u>DTP:</u> Coverage for DTP2 increased by 21% between 6 and 12 months of age and by 37% for DTP3 <u>Other:</u> No information. Large increase in pneumococcal polysaccharide (PncPS) vaccine during follow-up, may be associated with MV	Reported during monthly demographic surveillance. Determined by verbal autopsy.	Cox proportional hazards model. Censoring at death, migration, 6 months or the end of the study period.

Moderate risk of bias in selection of participants into the study

High risk of bias due to confounding (no adjustment for SES or child's health)

Moderate risk of bias in measurement of vaccination

High risk of bias due to departures from intended interventions (risk of co-intervention with DTP and PncPS)

Low risk of bias in measurement of outcomes

Moderate risk of bias due to missing outcome data.

Moderate risk of bias in selection of the reported result.

Overall: High risk of bias (no adjustment for SES or child's health; risk of co-intervention with DTP and PncPS)

Senegal 1985-1987

<i>Result selected</i>	<i>Sample</i>	<i>Confounders measured (*adjusted for)</i>	<i>Comparability of groups</i>	<i>Ascertainment of vaccine status</i>	<i>Co-interventions</i>	<i>Ascertainment of mortality</i>	<i>Data & analysis</i>
Senegal A #6904 MRR (unadjusted) = 0.99 (0.72, 1.37) Computed from rates in Table 2 (1985-1987, 9-23 months)	Observational comparison. Children born to a resident mother between February 1985 and January 1987. Of 2,417 children born during this period 2,093 were still under surveillance at 9 months of age. No routine MV until late 1986. Age of vaccination was much higher and more children were vaccinated after 12 months of age. <u>Selected for inclusion in review:</u> 2030 (assumed) with known vaccination status.	<u>SES:</u> NR <u>Child's health:</u> Measles infection <u>Other:</u> Season, year of birth, death of mother <u>Age:</u> Yes <u>Gender:</u> Yes <u>BCG:</u> No <u>DTP:</u> No	<u>Vaccines more likely among:</u> no information <u>Mortality more likely among:</u> rainy season	<u>Frequency:</u> Annual census <u>Method:</u> Vaccination cards for annual census visit. <u>Vaccinated:</u> Vaccine recorded on card <u>Unvaccinated:</u> No vaccine recorded on card <u>Dead children:</u> No information <u>Approach:</u> Landmark	<u>DTP:</u> No information <u>Other:</u> No information	Cause of death obtained through parental post-mortem interviews reviewed by 2 physicians who were blind to vaccine group.	Only included children who received the vaccine from 6 months. Children vaccinated after having had measles infection were considered unvaccinated. A few children who received HT MV after STD MV were censored at the day of revaccination.

Moderate risk of bias in selection of participants into the study

High risk of bias due to confounding (age-unadjusted analysis of groups)

High risk of bias in measurement of vaccination (annual data collection)

Insufficient information to assess risk of bias due to departures from intended interventions

Low risk of bias in measurement of outcomes

Moderate risk of bias due to missing outcome data.

Moderate risk of bias in selection of the reported result.

Overall: High risk of bias (age-unadjusted analysis of groups; annual data collection)

Senegal 1987-1989

<i>Result selected</i>	<i>Sample</i>	<i>Confounders measured (*adjusted for)</i>	<i>Comparability of groups</i>	<i>Ascertainment of vaccine status</i>	<i>Co-interventions</i>	<i>Ascertainment of mortality</i>	<i>Data & analysis</i>
Senegal B #6904 MRR (unadjusted) = 0.68 (0.42, 1.1) Computed from rates in Table 2 (1987-1989, 9-23 months)	Observational comparison. Children born to a resident mother between February 1987 and January 1989. 2,467 children born during this time. Of these 2,118 lived in the study area after the age of 9 months. MV trial during this time period, placebo group and those who did not receive their vaccine were offered MV at 10 months. <u>Selected for inclusion in review:</u> 1159 (assumed) with known vaccination status.	<u>SES:</u> NR <u>Child's health:</u> Measles infection <u>Other:</u> Season, year of birth, death of mother <u>Age:</u> Yes <u>Gender:</u> Yes <u>BCG:</u> No <u>DTP:</u> No	<u>Vaccines more likely among:</u> no information <u>Mortality more likely among:</u> rainy season	<u>Frequency:</u> Annual census which was supplemented with weekly surveillance visits to all compounds in the study area. <u>Method:</u> Most MV has been provided by the project. <u>Vaccinated:</u> Vaccine provided by project <u>Unvaccinated:</u> No vaccine provided by project <u>Dead children:</u> No information <u>Approach:</u> Date of vaccination known.	DTP: No information Other: No information	Cause of death obtained through parental post-mortem interviews reviewed by 2 physicians who were blind to vaccine group.	Compared from 9 months as this has been the official age for receiving MV. Only included children who received the vaccine from 6 months. Children vaccinated after having had measles infection were considered unvaccinated. A few children who received HT MV after STD MV were censored at the day of revaccination.

Moderate risk of bias in selection of participants into the study
 High risk of bias due to confounding (age unadjusted analysis of groups)
 Moderate risk of bias in measurement of vaccination
 Insufficient information to assess risk of bias due to departures from intended interventions
 Low risk of bias in measurement of outcomes
 Moderate risk of bias due to missing outcome data.
 Moderate risk of bias in selection of the reported result.
 Overall: High risk of bias (age unadjusted analysis of groups)

Senegal 1989-1996

<i>Result selected</i>	<i>Sample</i>	<i>Confounders measured (*adjusted for)</i>	<i>Comparability of groups</i>	<i>Ascertainment of vaccine status</i>	<i>Co-interventions</i>	<i>Ascertainment of mortality</i>	<i>Data & analysis</i>
Senegal C #740 MRR (unadjusted) = 0.98 (0.75, 1.27) Table 3 (first cohort)	Observational comparison. 8277 children born between Sept 1989 and August 1996. Children were excluded if they received BCG and DTP on different occasions. This resulted with 7796 children <u>Selected for inclusion in review</u> : All	<u>SES</u> : Maternal education <u>Child's health</u> : NR <u>Other</u> : Number of siblings who died before 2, number of siblings, mother's age, birth rank, BCG/DTP <u>Age</u> : Yes <u>Gender</u> : Yes <u>BCG</u> : Yes <u>DTP</u> : Yes MV was too strongly associated to assess the association between MV and mortality separately among recipients and non-recipients of BCG/DTP.	<u>Vaccines more likely among</u> : children who had received BCG, DTP <u>Mortality more likely among</u> : no information	<u>Frequency</u> : Weekly <u>Method</u> : Provided by project team <u>Vaccinated</u> : Children vaccinated by the project team <u>Unvaccinated</u> : Children not vaccinated by project team <u>Dead children</u> : No information <u>Approach</u> : Categorization <u>Comments</u> : "The project vaccinated all infants born in or migrated into the study area; hence vaccination status was completely accurate."	<u>DTP</u> : Ignored further doses of DTP <u>Other</u> : Also ignored further doses of YF, Polio and meningitis	During weekly visits	Proportional hazards model with time varying covariates. Children were included at birth and followed up to 2 years of age (or death or outmigration). Children receiving vaccines after inclusion were censored

Moderate risk of bias in selection of participants into the study

Very high risk of bias due to confounding (unadjusted analyses of groups, very high level of confounding by BCG/DTP)

Low risk of bias in measurement of vaccination

Insufficient information to assess risk of bias due to departures from intended interventions

Low risk of bias in measurement of outcomes

Moderate risk of bias due to missing outcome data.

Moderate risk of bias in selection of the reported result.

Overall: Very high risk of bias (unadjusted analyses of groups, very high level of confounding by BCG/DTP)

Senegal 1996-1999

<i>Result selected</i>	<i>Sample</i>	<i>Confounders measured (*adjusted for)</i>	<i>Comparability of groups</i>	<i>Ascertainment of vaccine status</i>	<i>Co-interventions</i>	<i>Ascertainment of mortality</i>	<i>Data & analysis</i>
Senegal D #9433 MRR (adjusted) = 0.55 (0.31, 0.98) Table 1 (MV with no known concurrent or subsequent DTP)	Observational comparison. 4133 children born and registered in study area between Sept 1996 and Dec 1999. 4102 included in the analyses. <u>Selected for inclusion in review:</u> 832 children who received MV according to the WHO strategy. Unvaccinated or BCG + DTP group?	<u>SES:</u> Health centre area* <u>Child's health:</u> NR <u>Other:</u> Year of vaccination*, season of vaccination* <u>Age:</u> Yes* <u>Gender:</u> Yes* <u>BCG:</u> All children had received BCG <u>DTP:</u> All children had received DTP	<u>Vaccines more likely among:</u> no information <u>Mortality more likely among:</u> no information	<u>Frequency:</u> Every 3 months after mid 1997 <u>Method:</u> Project records and then vaccination card <u>Vaccinated:</u> All vaccines are provided and recorded by project team until mid 1997. Following this children with a noted vaccine and date were considered vaccinated. <u>Unvaccinated:</u> Those with no recorded vaccine. After mid 1997 this also includes children with no information available. <u>Dead children:</u> Generally no information provided <u>Approach:</u> Landmark	<u>DTP:</u> Low probability of differential DTP co-intervention (analysis of children who received MV with no known concurrent or subsequent DTP) <u>Other:</u> No information	No information	Cox proportional hazards model. Censored at 24 months of age, registration of next vaccine, death or migration.

Moderate risk of bias in selection of participants into the study

High risk of bias due to confounding (no adjustment for child's health)

High risk of bias in measurement of vaccination (children with no information included as unvaccinated, and further bias towards null from landmark approach)

Moderate risk of bias due to departures from intended interventions

Low risk of bias in measurement of outcomes

Moderate risk of bias due to missing outcome data.

Moderate risk of bias in selection of the reported result.

Overall: High risk of bias (no adjustment for child's health; assumptions about vaccination)