

Do childhood vaccines have non-specific effects on mortality?^a

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Abstract A recent article by Kristensen et al. suggested that measles vaccine and bacille Calmette–Guérin (BCG) vaccine might reduce mortality beyond what is expected simply from protection against measles and tuberculosis. Previous reviews of the potential effects of childhood vaccines on mortality have not considered methodological features of reviewed studies. Methodological considerations play an especially important role in observational assessments, in which selection factors for vaccination may be difficult to ascertain. We reviewed 782 English language articles on vaccines and childhood mortality and found only a few whose design met the criteria for methodological rigor. The data reviewed suggest that measles vaccine delivers its promised reduction in mortality, but there is insufficient evidence to suggest a mortality benefit above that caused by its effect on measles disease and its sequelae. Our review of the available data in the literature reinforces how difficult answering these considerations has been and how important study design will be in determining the effect of specific vaccines on all-cause mortality.

Keywords Measles vaccine; Diphtheria-tetanus-pertussis vaccine/adverse effects; BCG vaccine; Infant mortality; Measles/mortality; Sudden infant death/etiology; Tuberculosis, Pulmonary/mortality; Review literature (*source: MeSH, NLM*).

Mots clés Vaccin antimorbilleux; Vaccin diphtérie-tétanos-coqueluche/effets indésirables; Vaccin BCG; Mortalité nourrisson; Rougeole/mortalité; Mort subite nourrisson/étiologie; Tuberculose pulmonaire/mortalité; Revue de la littérature (*source: MeSH, INSERM*).

Palabras clave Vacuna antisarampión; Vacuna difteria-tétano-pertussis/efectos adversos; Vacuna BCG; Mortalidad infantil; Sarampión/mortalidad; Muerte súbita infantil/etiología; Tuberculosis pulmonar/mortalidad; Literatura de revisión (*fuentes: DeCS, BIREME*).

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يمكن الاطلاع على الملخص بالعربية في صفحة ٨٢٥

Introduction

A recent article by Kristensen et al. (1) suggested that measles vaccine and bacille Calmette–Guérin (BCG) vaccine might reduce mortality beyond what is expected simply from protection against measles and tuberculosis. The authors argued that measles vaccine was associated with dramatic reductions in mortality in the absence of measles disease, and that the reductions in mortality were unlikely to be due to selection factors associated with vaccination because analysis of children vaccinated with diphtheria–tetanus–pertussis vaccine (DTP) showed the opposite effect — that is, mortality was higher in DTP-vaccinated children than in children who had not received DTP (1). The Kristensen study raised at least three important questions that have implications for public policy (2, 3). First, does the introduction of vaccines into populations result in disease-specific reductions in mortality other than those expected? Second, is the receipt of some vaccines associated with an increase in mortality? Third, which observational study designs can best answer the latter question by controlling for selection factors associated with receipt of vaccination? If some vaccines

produce unexpected effects on mortality and some study designs are better able to address the above issues, there would be important implications for vaccine implementation and the planning of clinical trials and post-marketing surveillance.

We undertook a structured review that included considerations of study methodology to explore potential relationships between vaccines and childhood mortality (4–6).

Methods and Results

Identification of articles

We performed a structured review of articles describing childhood vaccines and mortality. Search, review, and selection criteria were developed before the initiation of the study. MEDLINE (1966 to March 2001), EMBASE (1980 to March 2001), and Current Contents were searched in March 2001. Studies of death were identified using the subject headings: “mortality”, “cause of death”, “sudden infant death”, “fatal outcome”, “death certificates”, and “death, sudden”. Studies of vaccine components were identified using the subject headings “diphtheria toxoid”, “diphtheria–tetanus–pertussis vaccine”, “tetanus toxoid”,

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“diphtheria-tetanus-pertussis vaccine”, “bacterial vaccines”, “bcg vaccine”, “measles vaccine”, “mumps vaccine”, “polio vaccine”, “polio vaccine, oral”, and “rubella vaccine”. Studies of deaths and studies of vaccines were then combined and limited to studies of infants or children, studies in humans, and studies written in English.

One of the authors (TGB) reviewed the abstract of each of the 782 articles identified using the above search strategy and excluded articles that did not include children, study the vaccines of interest, include a control group, or assess mortality. If information regarding exclusion criteria was not included in the abstract, or was unclear ($n = 102$), the full article was independently reviewed by two other authors (WOC, MRG). At this stage of our review, articles were excluded for the above reasons or if they described only condition-specific mortality (that is, from a single condition such as diarrhoea or cancer).

Assessment of methodological quality

All articles that met the screening criteria were then reviewed by two of the authors (WOC, MRG) using assessment of methodological issues developed a priori. Study design was incorporated into assessment of methodology to account for differences among cohort studies and case-control studies. Methodological criteria included: (1) completeness of mortality ascertainment (i.e. was there independent verification of death? Was cause of death determined by a health care practitioner?); (2) adequacy of follow-up (i.e. was there differential follow-up among study groups?); (3) consideration of sociodemographic differences between study populations (i.e. was any attempt made to control for living conditions, parental education, or family income?); (4) comparability of vaccinated and unvaccinated children and potential reasons for vaccination vs non-vaccination (i.e. were children who were unvaccinated different from vaccinated children with respect to socioeconomic status, use of health care, or overall health status?); and (5) absence of a strong co-intervention (i.e. did children in the study receive health-related interventions as a part of being in the study?) (4–6).

Selected articles

From the 782 studies identified in the original literature search, 753 were excluded (Fig. 1). We reviewed the remaining 29 articles and their reference lists, and from these we identified an

additional six studies that met our review criteria. This gave us a total of 35 articles describing 24 separate observational studies. Twelve of these 24 studies compared differences in mortality among children receiving standard measles vaccine and unvaccinated children. Three of these 12 investigations attempted to focus on measles-specific mortality by counting only deaths following documented measles infection, but they are included here because of the difficulty in accurately assigning the cause of death to measles. The other nine measles vaccine studies compared all-cause mortality among vaccinated and unvaccinated children. Two of these studies also compared mortality among children with and without exposures to DTP, BCG, and polio vaccines. There were four studies of the risk of sudden infant death syndrome (SIDS) associated with DTP vaccine.

Measles vaccine and deaths following measles

Three studies enumerated both measles infections and deaths following measles infection among vaccinated and unvaccinated children (Table 1, web version only, available at: <http://www.who.int/bulletin>) (7–9). In the two studies from Kenya (7, 8), the incidence of measles was nearly 40% among unvaccinated children, whereas it was much lower in Ghana (3.6%) (9). Vaccinated children experienced 40–70% fewer cases of measles and 62–86% fewer deaths following measles. The absolute reduction of deaths was high in the Kenya studies (2.1% and 3.6%) and much lower in Ghana (4.9 per 1000 person years of follow-up). There was no enumeration of deaths among vaccinated and unvaccinated children who did not have symptomatic measles illness.

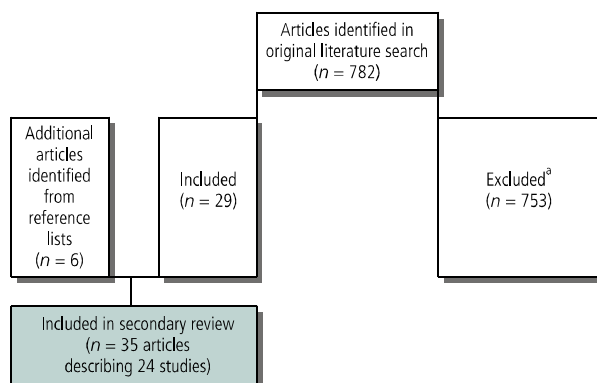
Measles vaccine and all-cause mortality

Nine studies evaluated all-cause mortality among vaccinated and unvaccinated children without regard to measles illness (Table 2, web version only, available at: <http://www.who.int/bulletin>) (1, 10–18). None of the nine studies was a randomized controlled trial. The age of the study children at the time of vaccination ranged from 6 to 13 months, except for one study (11, 12) in which children were vaccinated up to 60 months of age. Follow-up ranged from 4 to 54 months, with five of the studies following children until their fifth birthday (10–14, 17).

Two studies met all five criteria for high-quality observational studies as outlined above (10–12). In the Kasongo Project from Zaire (10), 291 vaccinated children were compared with 345 unvaccinated children (Table 2, web version only, available at: <http://www.who.int/bulletin>). Mortality in the two groups was comparable at baseline and measles illness was present in the study area. Mortality was carefully ascertained and study children were followed to their fifth birthday. Children in the vaccinated group were vaccinated at a mean age of 8.8 months, with vaccination coverage reported to be 83%. There were no important differences in sociodemographics or health status between the two groups. In the study from Bangladesh (11, 12), 8135 vaccinated children were compared with 8135 unvaccinated children in the Matlab Field Study Area. Mortality was assessed through visits by health care workers every two weeks in the field area. Mortality was comparable at baseline among the two groups and measles disease was present in the study area. Children were followed to their fifth birthday and the mean age of vaccinated children was 9 months, with a vaccination coverage of 82%.

In these two studies that met all five criteria for study quality, there was a 31% reduction in mortality among children

Fig. 1. Selection of articles



^a No control group ($n = 262$); commentary or review ($n = 245$); no specific group of vaccinated children ($n = 159$); not a study of mortality ($n = 60$); children not included ($n = 20$); mortality from only a single cause ($n = 7$).

in the vaccinated population in Zaire (10) and a 46% reduction in mortality among children in the vaccinated population in Bangladesh (11, 12) compared with childhood mortality in the selected unvaccinated populations. The absolute reductions in mortality — that is, the decreases in the overall expected mortality rate among the vaccinated cohorts — in the two studies were 2.1% and 1.8%, respectively.

The other seven studies all compared vaccinated and unvaccinated children in the same population and did not enumerate factors associated with health status that may have been associated with vaccination. The decreases in mortality in these studies tended to be greater (35% to 85%) than the two studies above and the absolute reductions in mortality (available for four of these studies) were 2.1–5.3% (Table 2, web version only, available at: <http://www.who.int/bulletin>). Although the study of Kristensen et al. (1) reported a reduction in mortality of 52%, which was similar to the other studies, the absolute reduction in mortality was extremely high given the short follow-up (4 months).

DTP vaccine and SIDS

Four studies, described in five papers, assessed the relationship between DTP vaccine and SIDS (Table 3) (19–23). These studies assessed 884 SIDS deaths among more than 350 000 children in England, France, and the USA. Three of these studies had adequate assessment of mortality and follow-up (19–21) but only one of them accounted for sociodemographic differences among study groups (19). None had strong co-interventions. In all four studies, vaccinated children were compared with unvaccinated children.

Reported relative reductions in SIDS mortality associated with DTP vaccine ranged from 30–80%, which were statistically significant in two of the four studies (19, 20). Notably, the large US study, which involved detailed maternal interviews and analyses that controlled for child and maternal factors, reported a statistically significant 30% decrease in the risk of SIDS associated with DTP immunization (19).

Other vaccines and non-specific mortality

Two of the studies from West Africa comparing mortality among those who did and did not receive measles vaccine (Table 1, web version only, available at: <http://www.who.int/bulletin>) also compared mortality among unvaccinated children and children receiving other vaccines (1, 18). Both of these studies had adequate assessment of mortality and adequate follow-up, although only one included sociodemographic factors (18). In the other study, there was a strong co-intervention present (1).

In the study from Benin West Africa (18), although the estimated increase in mortality following one dose of DTP and one dose of oral poliovirus vaccine (OPV) was elevated compared with unvaccinated children (relative risk = 2.2), this increase was not statistically significant. The risk estimate decreased with increasing numbers of DTP doses from 2.2 at one dose of DTP to 0.7 at four doses. With respect to BCG vaccine, the estimate for mortality reduction in vaccinated vs unvaccinated children was 0.38.

In the study from Guinea-Bissau (1), one dose of DTP (and OPV, which was almost always given with DTP) vaccine was associated with increased mortality. As in the Benin, West

Table 3. Studies assessing the relationship between DTP^a vaccine and mortality due to SIDS^b

Study information							Methodology assessment				Mortality	
Study	Type of study	Location	Years of study	No. of births	No. of SIDS cases	No. of controls	Complete ascertainment of mortality?	Adequate follow up?	Consider socio-demographics?	Vaccinated and unvaccinated comparable?	Absence of strong co-intervention?	Relative reduction in mortality (%) ^c
Hoffman et al., 1987	Matched case-control	United States	1978–9	347 800	716	757	Yes	Yes	Yes	No	Yes	40 (30 to 50)
Walker et al., 1987	Matched case-control	United States	1972–83	26 500	29	262	Yes	Yes	No	No	Yes	80 (60 to 95)
Pollock et al., 1984	Cohort	England	1978–80	10 028	4	3	Yes	Yes	No	No	Yes	40 (-30 to 90)
Bouvier-Colle et al., 1989; Flahaut et al., 1988	Matched case-control	France	1986	— ^d	135	401	Yes	No	No	No	Yes	30 (-10 to 50)

^a DTP = diphtheria and tetanus toxoids and pertussis vaccine.
^b SIDS = sudden infant death syndrome.
^c Numbers in parentheses are 95% confidence intervals.
^d Not reported.

Africa study, the estimate of mortality risk declined with increasing numbers of DTP vaccines received. For children who received BCG vaccine only, there was a significant reduction in mortality risk. Because children who weighed less than 2500 g did not receive BCG, there was a separate analysis for children aged 1 to 2 months who were either unvaccinated or vaccinated with BCG after the first month of life. Compared with children who remained unvaccinated, infants less than 6 months of age who were vaccinated with BCG after the first month of life experienced a significant reduction in mortality.

Comment

A recent study (1) suggested that in countries where childhood mortality is high, receipt of measles vaccine may confer benefits even in the absence of measles infections; however, higher mortality was suggested for children who were vaccinated with DTP and/or polio vaccines compared with those who were not (24). Our review of the English language literature of controlled observational studies of childhood vaccines and mortality yielded relatively few studies, and only two met all our methodological criteria (10–12). These criteria included: complete ascertainment of mortality, adequate follow-up, control for potential bias related to differences between vaccinated and unvaccinated children, and lack of a strong health-related co-intervention. Of note, no study directly addressed the key question of evidence of mortality differences among vaccinated and unvaccinated children in a population with concurrent morbidity and mortality surveillance in children who did not develop the target infection.

We considered the two studies from Zaire and Bangladesh (10–12) to be the strongest methodologically because they avoided the problem of selection bias associated with vaccine receipt; for example, vaccination may be strongly linked to other health practices. These two studies suggested that measles vaccine saved the lives of 2–3% of children in populations where disease was endemic, the vaccine was introduced, and uptake of vaccine was relatively high. These reductions were similar to those found in the studies reviewed here (7, 8) in which measles incidence was high and mortality was measured in defined periods following measles disease. These effects are also consistent with previous estimates of measles-associated mortality — that is, 2–4% mortality in the month following measles in countries where virtually all children contract measles and where childhood mortality is relatively high (25).

In several studies, strong mortality differences between vaccinated and unvaccinated children were observed in the absence of obvious measles-associated disease in the population. Measles-associated deaths may be particularly difficult to identify correctly; for example, in the malnourished or immunocompromised child a rash might not be present (26–28). Measles infection is also more severe among malnourished populations, and infection itself causes malnutrition and persistent growth delays (26–28). Because of these prolonged effects, infected children often experience prolonged increased mortality for 6 to 12 months following acute infection (27). Thus, it may be difficult to distinguish measles-associated deaths from “non-specific” mortality.

Most of the other studies reviewed suggested greater decreases in mortality associated with receipt of measles vaccine, often over shorter time periods, and in some cases as mentioned above, with no evidence of measles illness. This suggests that

other baseline differences between vaccinated and unvaccinated children may have been responsible for at least some of the observed differences in death rates. This is a type of selection bias that has also plagued studies of DTP and SIDS.

Studies of DTP vaccine and SIDS reported a strong protective effect of vaccination, even in the large US study that included careful collection of and control for multiple maternal and infant characteristics that were potential confounding factors (19). A previous review of similar data by the United States Institute of Medicine (29) concluded that there were probably strong differences between vaccinated and unvaccinated children that were not easily identifiable. Because the differences between vaccinated and unvaccinated children were believed to be so important, and virtually impossible to identify and control for adequately, several investigators ultimately included only vaccinated children and examined the timing of SIDS in relation to DTP vaccine (29). These latter studies, which were considered methodologically stronger, showed no link between DTP vaccine and SIDS.

In studies of the effects of other vaccines on mortality, two studies suggested increased mortality in children who received DTP vaccine (1, 18). In both of these studies, mortality risk decreased with increasing numbers of DTP vaccine, suggesting that receipt of only one DTP vaccine (rather than all recommended doses) might be associated with poorer health status. BCG vaccination gave a level of protection from mortality. Because selection factors for receipt of BCG vaccine are significant, randomized controlled trials or, in their absence, observational designs that compare similar vaccinated and unvaccinated populations will be necessary to determine the true effect of BCG vaccine on overall mortality.

We were unable to perform formal meta-analysis on the included studies because study populations were heterogeneous, only two studies were considered to be methodologically strong, and the studies involved different age groups and different periods of follow-up.

Conclusions

In the absence of randomized controlled trials, innovative ways to assess the impact of vaccine programmes are warranted. First, clinical trials of vaccines should incorporate safety and mortality assessments in the design. Second, observational studies should attempt to identify and control for important differences between vaccinated and unvaccinated children that may contribute to childhood mortality. Third, post-marketing surveillance of vaccines in both the developed and the developing world are needed to detect unexpected adverse events as well as unexpected beneficial effects of vaccines on childhood mortality. Ongoing monitoring of child mortality is a key outcome, especially in areas of the world where childhood mortality is high. With the introduction of new vaccines a broad look at vaccine effectiveness against morbidity and mortality is warranted. For example, in the Gambia, *Haemophilus influenzae* vaccination showed an unpredicted protection against pneumonia in vaccine trials (30). The natural differences in the start-up time of new programmes in similar and adjacent geographical areas can provide an opportunity for such assessments (24).

Recommendations

Our review highlights the enormous impact of measles on childhood mortality and the tremendous contribution of measles

vaccine in reducing mortality. The provocative article by Kristensen (1) has raised questions that should be addressed using study designs that address some of the limitations identified in studies selected for our review. Time-series designs might be possible in studies that included large populations of children with careful measurement of mortality and a well-defined intervention point such as a mass immunization campaign. In situations where vaccine programmes are implemented over time due to cost or other constraints, comparison of mortality in carefully selected populations who receive vaccines in sequential order might be possible. Finally, in circumstances where a new vaccine is introduced or a new age at vaccination is being studied, randomized controlled trials with a large sample size would allow comparison of mortality among vaccinated and

unvaccinated children. Whatever the study design, designs that avoid selection factors for vaccine should be used to further address these questions. ■

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Conflicts of interest: PFW receives support for clinical trials of experimental, new vaccines from Wyeth-Lederle Vaccines, Merck, and Aviron. MRG is paid by Merck to chair an endpoint committee for clinical trials on anti-inflammatory drugs and has received a non-restricted educational grant from Merck to study vaccine use in nursing homes.

Résumé

Les vaccins de l'enfance ont-ils des effets non spécifiques sur la mortalité ?

Un article récent de Kristensen et al. donne à penser que le vaccin antirougeoleux et le BCG (bacille Calmette-Guérin) pourrait entraîner une diminution de la mortalité qui dépasse ce que l'on peut attendre de la simple protection contre la rougeole et la tuberculose. Les études antérieures sur les effets potentiels des vaccins de l'enfance sur la mortalité n'ont pas tenu compte des caractéristiques méthodologiques. Or celles-ci revêtent une importance particulière dans les évaluations résultant d'observations, pour lesquelles il peut être difficile d'objectiver les facteurs de sélection pour la vaccination. Nous avons passé en

revue 782 articles en anglais sur les vaccins et la mortalité de l'enfant et nous avons constaté que seuls quelques-uns d'entre eux répondaient à des critères méthodologiques rigoureux. Si les données étudiées laissent entendre que le vaccin antirougeoleux entraîne bien la baisse de mortalité escomptée, il n'y a pas suffisamment de preuves pour envisager un effet dépassant celui obtenu par sa simple action contre la rougeole et ses séquelles. Notre examen de la littérature confirme la difficulté de ces questions et l'importance de la conception des études pour déterminer l'effet de chaque vaccin sur la mortalité globale.

Resumen

¿Tienen las vacunas infantiles efectos inespecíficos en la mortalidad?

En un reciente artículo de Kristensen et al. se sugería que la vacuna antisarampionosa y la vacuna BCG (bacilo de Calmette-Guérin) reducen quizá la mortalidad más de lo que cabe esperar sólo de un efecto de protección contra el sarampión y la tuberculosis. En revisiones anteriores de los efectos potenciales de las vacunas infantiles sobre la mortalidad no se han considerado las características metodológicas de los estudios examinados. Las consideraciones metodológicas, sin embargo, tienen una función muy importante en las evaluaciones observacionales, en las que los factores de selección para la vacunación pueden ser difíciles de determinar. Tras examinar

782 artículos en inglés sobre las vacunas y la mortalidad en la niñez, sólo hallamos unos cuantos cuyo diseño satisficiera los criterios de rigor metodológico. Los datos examinados indican que la vacuna antisarampionosa reduce en efecto la mortalidad, pero no hay evidencia suficiente para afirmar que tenga un efecto adicional en la mortalidad aparte del relacionado con el sarampión y sus secuelas. Nuestra revisión de los datos extraídos de la bibliografía corrobora lo difícil que es intentar responder a esas consideraciones y la importancia del diseño de los estudios a la hora de determinar el efecto de determinadas vacunas en la mortalidad por todas las causas.

ملخص

هل للقاحات الأطفال تأثيرات لانوعية على معدلات المراضة

باللغة الانكليزية حول اللقاحات والمراضة لدى لأطفال ووجدنا أن القليل من هذه المقالات كان تصميمه موافقاً لمعايير منهجية صارمة. وتشير المعطيات التي تمت مراجعتها إلى أن هناك بينات غير كافية للبرهنة على منافع في المراضة تزيد عما تسببه الإصابة بالحصبة وبعاقيها. وتؤكد حصيلة مراجعتنا للمعطيات المتوافرة في الأدب الطبي على صعوبة الإجابة على هذه التساؤلات حول تأثيرات بعض اللقاحات على معدل الوفيات العام.

خلاصة: أشار مقال نشر مؤخراً لكريستنسن وزملائه إلى أن لقاحي الحصبة وعصيات كالميت وغيران قد تنقص معدلات المراضة لأقل مما هو متوقع منها، وأن ذلك ينتج ببساطة عن اتقاء الحصبة والسل. إلا أن المراجعات التي أجريت سابقاً لم تأخذ بالاعتبار ملامح المنهجيات المتبعة في الدراسات التي تمت مراجعتها. فللاعتبارات المنهجية دور هام في التقديرات الملاحظة، إذ يصعب تعيين عامل اختيار اللقاحات. وقد قمنا بمراجعة 782 مقالة مكتوباً

References

1. Kristensen I, Aaby P, Jensen H. Routine vaccinations and child survival: follow-up study in Guinea-Bissau, West Africa. *BMJ* 2000;321:1435-50.
2. Fine P. Commentary: an unexpected finding that needs confirmation or rejection. *BMJ* 2000;21:1439.
3. Shann F. Non-specific effects of vaccines in developing countries. *BMJ* 2000;321:1423-4.
4. Mulrow CD, Cook DJ, Davidoff F. Systematic reviews: critical links in the great chain of evidence. *Annals of Internal Medicine* 1997;126:389-91.
5. Meade MO, Richardson WS. Selecting and appraising studies for a systematic review. *Annals of Internal Medicine* 1997;127:531-7.
6. Counsell C. Formulating questions and locating primary studies for inclusion in systematic reviews. *Annals of Internal Medicine* 1997;127:380-7.
7. Burstrom B, Aaby P, Mutie DM, Kimani G, Bjerregaard P. Severe measles outbreak in western Kenya. *East African Medical Journal* 1992;8:419-23.
8. Burstrom BO, Aaby P, Mutie DM. Child mortality impact of a measles outbreak in a partially vaccinated rural African community. *Scandinavian Journal of Infectious Diseases* 1993;25:763-9.
9. Dollimore N, Cutts F, Binka FN, Ross DA, Morris SS, Smith PG. Measles incidence, case fatality, and delayed mortality in children with or without Vitamin A supplementation in rural Ghana. *American Journal of Epidemiology* 1997;146:646-54.
10. Influence of measles vaccination on survival pattern of 7–35-month-old children in Kasongo, Zaire. The Kasongo Project Team. *Lancet* 1981;1:764-7.
11. Clemens JD, Stanton BF, Chakraborty J. Measles vaccination and childhood mortality in rural Bangladesh. *American Journal of Epidemiology* 1988;128:1330-9.
12. Koenig MA, Khan MA, Wojtyniak B. Impact of measles vaccination on childhood mortality in rural Bangladesh. *Bulletin of the World Health Organization* 1990;68:441-7.
13. George K, Joseph A, Muliylil J, Abraham S, Bhattacharji S, John KR. Measles vaccination before nine months. *Tropical Medicine and International Health* 1998;3:751-6.
14. Kumar G, Anand K, Kant S, Kapoor SK. Scale for identification of "at risk" families for underfive deaths. *Indian Journal of Pediatrics* 2000;67:411-7.
15. Holt EA, Boulos R, Halsey NA, Boulos LM, Boulos C. Childhood survival in Haiti: protective effect of measles vaccination. *Pediatrics* 1990;85:188-94.
16. Aaby P, Knudsen K, Jensen TG. Measles incidence, vaccine efficacy, and mortality in two urban African areas with high vaccination coverage. *Journal of Infectious Diseases* 1990;162:1043-8.
17. Aaby P, Samb B, Simondon F. A comparison of vaccine efficacy and mortality during routine use of high-titre Edmonston-Zagreb and Schwarz standard measles vaccines in rural Senegal. *Transactions of the Royal Society of Tropical Medicine and Hygiene* 1996;90:326-30.
18. Velema JP, Alihonou EM, Gandaho T, Hounye FH. Childhood mortality among users and non-users of primary health care in a rural West African Community. *International Journal of Epidemiology* 1991;20:474-9.
19. Hoffman HJ, Hunter JC, Damus K. Diphtheria-tetanus-pertussis immunization and sudden infant death: results of the national institute of child health and human development cooperative epidemiological study of sudden infant death syndrome risk factors. *Pediatrics* 1987;79:598-611.
20. Walker AM, Jick H, Perera DR, Thompson RS, Knauss TA. Diphtheria-tetanus-pertussis immunization and sudden infant death syndrome. *American Journal of Public Health* 1987;77:945-51.
21. Pollock TM, Miller E, Mortimer JY, Smith G. Symptoms after primary immunisation with DTP and with DT vaccine. *Lancet* 1984;2:146-9.
22. Bouvier-Colle MH, Flahaut A, Messiah A, Jougla E, Hatton F. Sudden infant death and immunisation: an extensive epidemiological approach to the problem in France — winter 1986. *International Journal of Epidemiology* 1989;18:121-6.
23. Flahaut A, Messiah A, Jougla E, Bouvet E, Perrin J, Hatton F. Sudden infant death syndrome and diphtheria/tetanus toxoid/pertussis/poliomyelitis immunisation [letter]. *Lancet* 1988;1:582-3.
24. Aaby P, Samb B, Simondon F, Seck AM, Knudsen K, Whittle H. Non-specific beneficial effect of measles immunisation: analysis of mortality studies from developing countries. *BMJ* 1995;311:481-5.
25. Aaby P, Clements CJ. Measles immunization research: a review. *Bulletin of the World Health Organization* 1989;67:443-8.
26. Assaad F. Measles: Summary of worldwide impact. *Review of Infectious Diseases* 1983;5:452-9.
27. Hull HF, Williams PJ, Oldfield F. Measles mortality and vaccine efficacy in rural West Africa. *Lancet* 1983;972-5.
28. Koster FT, Curlin GC, Aziz KM, Haque A. Synergistic impact of measles and diarrhoea on nutrition and mortality in Bangladesh. *Bulletin of the World Health Organization* 1981;59:901-8.
29. Howson CP, Howe CJ, Fineberg HV, editors. *Adverse effects of pertussis and rubella vaccines*. Washington (DC): National Academy Press; 1991.
30. Mulholland K, Hilton S, Adegbola R. Randomised trial of Haemophilus influenzae type-b tetanus protein conjugate for prevention of pneumonia and meningitis in Gambian infants. *Lancet* 1997;349:1191-7.

Table 1. Studies assessing mortality following measles infection among vaccinated and unvaccinated children

Study information				Methodology assessment					Reduction in mortality							
Study	Location	Years of study	Age of participants (months)	Complete ascertainment of mortality?	Adequate follow-up?	Consider socio-demographics?	Vaccinated and unvaccinated comparable?	Absence of strong co-intervention?	No. of children		% of children developing measles ^a		% of child deaths ^a		Reduction in mortality	
									Vaccinated	Unvaccinated	Among vaccinated children	Among unvaccinated children	Among vaccinated children	Among unvaccinated children	Relative	Absolute
Burstrom et al., 1992	Kenya	1985–6	1–120	Yes	Yes	No	No	Yes	158	177	22.8 (36)	37.9 (67)	1.3 (2)	3.4 (6)	62	2.1
Burstrom et al., 1993	Kenya	1987–8	1–59	Yes	Yes	No	No	Yes	310	167	13.5 (42)	35.9 (60)	0.6 (2)	4.2 (7)	86	3.6
Dollimore et al., 1997	Ghana	1989–91	0–95	Yes	Yes	No	No	Yes	14 299 py ^b	22 760 py ^b	1.1 (153)	3.6 (808)	0.1 (15)	0.6 (136)	82	4.9/1000 py ^b

^a Numbers in parentheses are number of deaths.

^b py = person-years.

Table 2. Studies assessing the relationship between measles vaccine and childhood mortality

Study information				Methodology assessment							Reduction in mortality					
Study	Type of study	Location	Years of study	Age at vaccine (months)	Age at end of follow-up (months)	Complete ascertainment of mortality?	Adequate follow-up?	Consider socio-demographics?	Vaccinated and unvaccinated comparable?	Absence of strong co-intervention?	% child deaths for cohort studies		No. of cases for case-control studies	No. of controls for case-control studies	Reduction in mortality (%)	
											No. of deaths/vaccinated	No. of deaths/unvaccinated			Relative	Absolute
Kasongo Project, 1981 Clemens et al., 1988;	PC ^a	Zaire	1974–77	8–12	60	Yes	Yes	Yes	Yes	Yes	4.8 (14) ^b	6.9 (24) ^b	– ^c	– ^c	31 (NA) ^d	2.10
Koenig et al., 1990	CC ^e , PC	Bangladesh	1982–85	9–60	60	Yes	Yes	Yes	Yes	Yes	2.4 (195)	4.2 (339)	–	–	46 (35 to 55) ^f	1.80
George et al., 1998	RC ^g	India	1986–91	6–12	60	Yes	Yes	Yes	No	Yes	1.1 (94)	3.2 (37)	–	–	66 (NA)	2.10
Kumar et al., 2000	NCC ^h	India	1991–95	10	60	Yes	Yes	Yes	No	Yes	– ⁱ	– ⁱ	849	849	54 (37 to 67)	–
Holt et al., 1990	PC, CC	Haiti	1982–85	6–13	39	Yes	No	Yes	No	Yes	1.3 (3)	6.6 (70)	–	–	85 (37 to 96)	5.30
Aaby et al., 1990	PC	Guinea-Bissau	1984–87	9	30	Yes	Yes	No	No	Yes	NA	NA	–	–	66 (32 to 83)	–
Aaby et al., 1996	RC	Senegal	1989–91	9–10	60	Yes	Yes	No	No	Yes	4.3 (65)	6.7 (24)	–	–	35 (-3 to 60)	2.40
Kristensen et al., 2000	PC	Guinea-Bissau	1990–96	9	13	Yes	Yes	No	No	Yes	1.8 (19)	4.0 (94)	–	–	52 (13 to 73)	2.20
Velema et al., 1991	NCC	Benin West Africa	1986–87	9–12	35	Yes	Yes	Yes	No	No	–	–	74	230	64 (19 to 84)	–

^a PC = prospective cohort.

^b Numbers in parentheses are number of deaths.

^c Study is not a case-control study.

^d NA = information not available in paper.

^e CC = case-control.

^f Numbers in parentheses are 95% confidence intervals.

^g RC = retrospective cohort.

^h NCC = nested case-control.

ⁱ Study is not a cohort study.