**Letters**

**Do measles vaccines have non-specific effects on mortality?**

**Editor** – Cooper et al. (1) reviewed the non-specific effects on mortality of childhood vaccines. Although there are numerous studies detailing mortality following measles vaccination (MV) (2), only two studies cited in their article (3, 4) satisfied the authors’ methodological criteria. The Zaire (3) and Bangladesh (4) studies compared mortality in areas with MV to adjacent areas without MV. The MV-associated relative mortality reductions were 31% and 46% and the absolute reductions were 2.1% and 1.8%. Since the case-fatality rate was assumed to be 2–4%, Cooper et al. concluded that there was insufficient evidence to suggest a mortality benefit above that caused by the prevention of measles infection. Hence, they questioned our non-specific effects hypothesis (2) after having excluded almost all MV studies. However, even the two studies retained (3, 4) in the Cooper et al. article support the existence of non-specific effects.

First, Cooper et al. have not analysed the two studies in the same manner. In the Bangladesh study (4), measles-vaccinated children were compared to measles-unvaccinated children, whereas in the Zaire study (3), only 83% of children in the vaccinated area received MV. If vaccinated children from the vaccinated area are compared with unvaccinated children from the adjacent area, the relative mortality reduction was 48% (3, Table 1) giving an absolute reduction of 3.0%. Children in Bangladesh were vaccinated between 9 and 60 months of age; the difference in the proportion of children who died was 1.8% and it was this proportion which was used to indicate the absolute reduction. However, if accumulated mortality is used to estimate the absolute reduction as in Zaire (3), the absolute reduction seen in Bangladesh would be around 3.9% (4, Fig. 3). The relative (48%, 46%) and absolute (3.0%, 3.9%) reductions in the Zaire and Bangladesh studies were similar to the estimates seen in the less methodologically rigorous studies (1, 2).

Interestingly, all of the study designs have yielded similar estimates (2–6), including: studies of mortality before and after the introduction of MV (2), blind studies with ineffective vaccine (2), and randomized studies (2, 6).

Second, the assertion that the absolute reduction corresponds to measles-associated mortality is not supported by any study (2, 5, 6). Cooper et al. claim that MV-associated mortality differences were not examined in areas with concurrent morbidity and mortality surveillance (1). In fact, we reanalysed the Bangladesh study to determine the MV-associated mortality reduction that could be explained by the prevention of measles infection (5); surprisingly, prevention of measles infection accounted for very little of the reduction. When measles cases were censored in the survival analysis, the relative reduction changed merely from 49% to 43%. Mortality was lower after measles infection than among measles-uninfected children (2, 5). (There were no similar data from Zaire.) In Zaire, the difference in accumulated measles incidence for vaccinated and unvaccinated children was 25%, with a case-fatality rate of 7%, indicating that the measles-associated mortality reduction would be less than 2% in 5 years of age. In the first year following measles vaccination, when less than 2% of those vaccinated would have died from measles, the absolute reduction was 3.8% (3, Table 2). Therefore, prevention of measles infection in Bangladesh or Zaire cannot explain the MV-associated mortality reduction (2).

Without large randomized trials, the MV-associated mortality reduction cannot be assessed with certainty. However, there are many indications that MV has beneficial non-specific effects. First, the prevention of measles does not explain the observed MV-associated mortality reduction (2–6). Second, the beneficial effect was greatest in the first 6–12 months after MV (2, 5). However, this contradicts the prevention-of-meadles-deaths hypothesis since the effect should be greater for older children, among whom measles accounts for a larger proportion of all deaths (2, 5).

Third, the beneficial effect of MV has been shown to be greater for girls (2, 6). Fourth, although both vaccines were protective, standard measles vaccine was associated with lower mortality for girls than the high-titre vaccine (2). These trends cannot be explained by the epidemiology of measles infection.

Standard MV is associated with a mortality reduction greater than that caused only by prevention of measles. Given the consistency of these findings (2), the mechanisms of the beneficial effects of MV should be explored and the mortality effects of other routine vaccinations reassessed (2, 5, 6).

**Conflicts of interest:** none declared.

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