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 difference would be less than 2% before 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-measles-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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