

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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Condom use within marriage: a neglected HIV intervention

Editor – We were surprised by the findings of Ali et al. (1) suggesting that a massive shift from the use of oral contraceptive pills to condoms may result in a slight decrease in the total number of pregnancies observed. The primary explanation for this unexpected result appears to be a flaw in their analysis.

In their model, Ali et al. hypothetically assumed that all of the 20 875 observed pill episodes were replaced by condom episodes. Although condoms are less effective than pills for preventing pregnancy, condom episodes tend to be substantially shorter than pill episodes. In addition, the period during which no contraceptive method is used is shorter after discontinuation of condoms than after discontinuation of pills; pregnancies that occurred during these periods were included in the authors' analysis. Consequently, the total number of pregnancies associated with the 20 875 episodes was lower in the hypothetical situation than in the observed data (5072 versus 5130, respectively). Conversely, replacement of the 4786 observed condom episodes with that same number of pill episodes resulted in a minor increase in the number of pregnancies associated with these episodes (from 1106 observed to 1125 in the hypothetical situation). The combined effect was a decrease by 39 pregnancies.

However, it was inappropriate to have replaced the longer pill episodes with shorter condom episodes (and vice versa) in the model without adjusting for the difference in episode duration. If such an adjustment had been included in the model, large-scale switching from more effective to less effective contraceptive methods would undoubtedly have been shown to considerably increase the total number of pregnancies, at least among the contraceptive users.

We agree with the authors that vigorous condom promotion is vital in areas of high HIV/STI prevalence, but we should not discount the adverse effect

that success in this effort might have on unintended births and abortions. ■

Conflicts of interest: none declared.

Elizabeth Raymond¹ & James Trussell²

1. Ali MM, Cleland J, Shah IH. Condom use within marriage: a neglected HIV intervention. *Bulletin of the World Health Organization* 2004;82:180-6.

Response to Raymond & Trussell

Editor – We thank Raymond & Trussell for their interest in our paper (1). Before addressing their concerns, we take this opportunity to further explain the methodology that we used.

The multiple decrement life-table method was used to estimate the proportion of all episodes starting 4–39 months prior to the survey that: 1) were still continuing at the time of the survey; 2) had ended in method- or user-failure; and 3) had been discontinued for method-related reasons or because of no further need.

These calculations were performed on the pill and the condom data separately. Pregnancies resulting from contraceptive failure were counted and classified into four categories: wanted, mistimed, unwanted and terminated. For discontinued episodes, outcomes at 12 months were estimated using multiple decrement life-tables with the following possible outcomes: still at risk, switched to another method, or became pregnant. These pregnancies were further classified into the above-mentioned four categories. Pregnancies that occurred within 12 months of discontinuation were attributed to the last discontinued method, but those that occurred after 12 months were attributed to the non-use of a contraceptive method. This latter distinction is arbitrary but reasonable.

This method was the basis for the results reported in Table 3 of our paper. It is worth noting that a substantial majority of all pregnancies stemmed from the non-use of any contraceptive method. The hypothetical estimates

were obtained by reversing the number of condom and pill episodes. Multiple-decrement life-table procedures were then applied to obtain the hypothetical numbers of pregnancies.

Contrary to Raymond & Trussell's concern, our method did take into account the fact that pill episodes are longer than condom episodes and that pills are a more effective contraceptive than condoms. Table 1 showed that fewer condom than pill episodes were continuing at the time of the survey (57% versus 44%) and that the pill has a lower failure rate (6.3% versus 9.1%). The superiority of the pill in terms of pregnancy prevention entered the calculations. While it is true that the number of pregnancies resulting from contraceptive failure is higher in the hypothetical data than the observed scenario (1978 versus 1769), this is offset by the fact that those who discontinued using condoms switched to another method more promptly than those who discontinued the pill. After adjustment for education level and residence, the number of pregnancies attributable to discontinuation is lower in the hypothetical data than the observed scenario (4219 versus 4469, respectively).

We agree that the results are surprising, even counter-intuitive, but we believe that our methodology was sound and our findings valid. Assessments of the reproductive implications of large shifts in choice of contraceptive method need to take into consideration discontinuation and its consequences as well as failure rates. What was also surprising, and of considerable policy importance, was the finding that even in countries with a high contraceptive prevalence, approximately 70% of unwanted and mistimed births were attributable to non-use. ■

Conflicts of interest: none declared.

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1. Ali MM, Cleland J, Shah IH. Condom use within marriage: a neglected HIV intervention. *Bulletin of the World Health Organization* 2004;82:180-6.

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Tailoring antenatal visits: quality over quantity

Editor – The article by Lumbiganon et al. (1), which describes Thailand's decision to reduce the number of antenatal visits from approximately eight to five, based on evidence gathered by WHO (2) that fewer visits have no adverse consequences for the woman or her baby, raises several points that require clarification.

First, the article reports that in the original research: "Some women in the studies, especially those in developed countries, expressed dissatisfaction with the reduced number of visits."

For Thailand too, Lumbiganon et al. state: "... some women were concerned about the long intervals between visits, particularly women who had been pregnant before and who were familiar with having shorter intervals".

A qualitative study among women and providers of the new model also found some dissatisfaction with fewer visits, including among women and providers in Thailand, but again, few details are offered (3). This raises questions about the nature of women's dissatisfaction with fewer visits and whether pregnant women need more than medical attention from antenatal care. One of the main goals of the new model is to strengthen the information component within fewer visits; however, perhaps this component has not been improved adequately. Perhaps women also want to be able to ask questions more frequently related to the preg-

nancy and delivery; perhaps they want reassurance that everything is all right or advice on whether something they are experiencing is reason for concern. In the paper by Lumbiganon et al., there were no qualitative data from interviews with the women themselves. There was almost no description of the nature of the women's dissatisfaction, how it could be resolved or how to ensure that the women's informational and other non-biomedical needs could be met in fewer visits.

Second, while the original research notes that in cases of illness or complications an increased number of visits may be required, the paper by Lumbiganon et al. does not mention whether the number of visits recommended will be influenced by the presence of HIV in pregnancy. In Thailand and many other countries, pregnant women are tested for HIV early in pregnancy and should be counselled. If they are HIV- positive and have low immune status they will require antiretroviral drugs throughout pregnancy; or, if their immune status is still high enough, they will require antiretroviral drugs in the latter stages of pregnancy and at delivery to reduce perinatal HIV transmission. In Thailand, women are advised not to breastfeed and should be counselled on how to feed their babies safely. Will this not affect the number and timing of visits and if so, how? ■

Conflicts of interest: none declared.

Marge Berer¹

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