Letters to the Editor

Is all-cause mortality a useful epidemiological endpoint in vaccine trials? An example of BCG (Bacille-Calmette-Guerine)

From ZUBAIR KABIR

Sirs—Since 1978, the WHO/UNICEF Expanded Programme on Immunization has led to steady reductions in childhood mortality from the vaccine preventable diseases both in developed and less-developed nations. Surprisingly, scant attention has been paid to the overall effect of routine vaccines. In general, we have taken vaccines and schedules that are effective in developed nations with low levels of child mortality and used them in high mortality populations without studying their effects on all-cause mortality.

As early as the mid-1970s, measles vaccination showed an overall improvement in the probability of child survival, for children aged 12–24 months old in particular. Subsequent studies on measles vaccination status and child mortality across different populations reported substantial reductions in overall mortality of at least 30%, particularly in high child mortality areas. A recent case-control study, using data collected prospectively, demonstrated that measles vaccination also reduced overall child mortality by 27%, especially in children aged 12–59 months old, in relatively low mortality populations of sustained high childhood vaccination coverage (more than 90%) over the past decade. This phenomenon has been termed the ‘non-specific beneficial’ effect of vaccines, and is speculated to be linked to a Th1 type immune response. Such a ‘spectacular’ finding, however, is not consistent with other routine childhood vaccines, such as BCG (Bacille-Calmette-Guerine), DTP (diphtheria, tetanus, pertussis), and OPV (oral polio vaccines).

The BCG vaccines are among the most widely used of all routine vaccines and their use and effectiveness are also controversial, although there is accumulating evidence of its wider effect on some non-targeted diseases, such as leprosy, asthma, and bladder cancer. The major differences in the protection afforded by BCG vaccine in various populations reflect determinants of protection that are still not understood. A non-specific protective effect of BCG vaccine on all-cause child mortality is reported in certain populations. In rural India, a different epidemiological setting, a ‘long-term’ beneficial effect of BCG vaccine on all-cause child mortality, however, is not observed. For example, children aged 12–59 months old who had received BCG vaccination in infancy had the same risk of dying from any cause compared with those without BCG during infancy. In addition to methodological issues, this observed variation underscores possible biological implications across the populations.

First, the protective effect of BCG, possibly linked to a potent Th1 response, which is normally observed in individuals during early infancy, may be offset by a mixed Th1/Th2 response with a more pronounced Th2 response later in life, as evident in animal models. This may also be attributed to any variations in mycobacterial ‘dose’ administered, which defines the Th1/Th2 nature of the immune response in individuals; for instance, a relatively low dose favours a Th1 response. Second, it is possible that the observed cell-mediated response to BCG vaccination wanes over a period of time in individuals subsequently infected with common tropical condition, such as onchocerciasis. In addition to such individual-specific explanations, there may be some observations at the population level. For instance, a Th1 response observed within a few weeks following BCG vaccination in a specific population may not be appreciable in another population even one year after the vaccination. Variations in the prevalence of tuberculosis (TB) infection or a higher prevalence of environmental mycobacteria in a specific population leading to a reduced as well as a less-persistent Th1 response may partly explain the observed difference. This heterogeneity in protection may be associated with natural immunity. The Indian setting, however, has a relatively low prevalence of childhood TB infection and the likelihood of environmental mycobacteria influencing the observation is less likely. Finally, the variations in childhood mortality rates as well as in the vaccination coverage levels across the populations may provide some clue to any underlying biological mechanisms.

Regional variations in vaccine protection on all-cause child mortality may indicate an underlying immunological mechanism of non-specific protection induced by vaccines in general. Such important biological implications may be elucidated in other vaccines targeted at infectious and tropical diseases, such as human immunodeficiency virus and malaria, which, unfortunately, are common causes of high childhood mortality in some specific populations. Non-specific effects of vaccines are best demonstrated in large randomized controlled trials, but these may be ethically inappropriate for vaccines, whose effectiveness is already well established. Nevertheless, the numerous vaccine trials currently underway worldwide, and probably a considerable number in the near future may offer rich opportunities for robust testing of such effects.

The potential utility of ‘all-cause mortality’ as an epidemiological endpoint in new vaccine trials is worth considering in high-mortality populations, in addition to surrogate measures, such as disease-specific morbidity or mortality, and indirect evidence, such as antibody or interferon-gamma response. The lack of evidence about the effect of vaccines on all-cause mortality can lead to serious errors, for instance, the use of high titre measles vaccine resulting in a higher mortality than standard titre vaccine in girls, and the failure to investigate the role of polysaccharide pneumococcal vaccine in children in high-mortality areas, because of poor antibody responses and poor protection against otitis media in children in developed nations.

Large vaccine trials using all-cause mortality as an epidemiological endpoint may be cost-effective in high-mortality nations.23

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populations, but need proper economic evaluations. Most importantly, non-specific effects, if biologically plausible, may give an insight into the causal pathway of the targeted diseases. In conclusion, the possible non-specific effect of vaccines merits attention in resource-poor countries, not only for formulating effective vaccination schedules in the future but also for guiding the policy-makers to more evidence-based tropical and infectious disease control policies.

Acknowledgement
Dr George Davey Smith and the referee for their valuable editorial comments.

References

Position on the moped, risk of head injury and helmet use: an example of confounding effect

From PABLO LARDELLI-CLARET,1 JUAN DE DIOS LUNA-DEL-CASTILLO2 and JOSÉ JUAN JIMÉNEZ-MOLEÓN1

Sirs—The example of confounding described below is of potential interest both from a teaching perspective and in the field of epidemiological research on the risk of head injury in moped riders.

We took data from the Spanish Registry of Traffic Crashes with victims to study the strength of association between position of the rider on the moped (the driver or the passenger) and risk of head injury in all 187 353 moped riders involved in a traffic crash with victims between 1990 and 1999 in Spain, and for whom information about helmet use was available. In the crude analysis (Table 1a), the frequency of head injury was similar for drivers and passengers; accordingly, the crude odds ratio (OR) for the association between being the driver and receiving a head injury was only 1.06. But when we stratified this estimate...
### Table 1
Crude, stratified and adjusted associations between the position on the moped, helmet use and head injury

#### 1a Effect variable: Head injury

<table>
<thead>
<tr>
<th>Exposure variable:</th>
<th>Crude analysis</th>
<th>Stratified analysis by helmet use</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Head injury</td>
<td>Non-head injury</td>
</tr>
<tr>
<td>Position on the moped</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Driver (exposed)</td>
<td>25 211</td>
<td>138 112</td>
</tr>
<tr>
<td>(15.4%)</td>
<td>(84.6%)</td>
<td></td>
</tr>
<tr>
<td>Passenger (non-exposed)</td>
<td>3537</td>
<td>2 0 4 9 3</td>
</tr>
<tr>
<td>(14.7%)</td>
<td>(85.3%)</td>
<td></td>
</tr>
<tr>
<td>OR = 1.06 (1.02–1.10)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

#### 1b. Effect variable: Helmet use

<table>
<thead>
<tr>
<th>Exposure variable:</th>
<th>Crude analysis</th>
<th>Stratified analysis by position on the moped</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Head injury</td>
<td>Non-head injury</td>
</tr>
<tr>
<td>Helmet use</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-helmeted (exposed)</td>
<td>20 921</td>
<td>64 422</td>
</tr>
<tr>
<td>(24.5%)</td>
<td>(75.5%)</td>
<td></td>
</tr>
<tr>
<td>Helmeted (exposed)</td>
<td>7 8 2 7</td>
<td>9 4 1 8 3</td>
</tr>
<tr>
<td>(7.7%)</td>
<td>(92.3%)</td>
<td></td>
</tr>
<tr>
<td>OR = 3.91 (3.80–4.02)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

#### 1c. Effect variable: Helmet use

<table>
<thead>
<tr>
<th>Exposure variable:</th>
<th>Crude analysis</th>
<th>Stratified analysis by head injury</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Helmeted</td>
<td>Non-helmeted</td>
</tr>
<tr>
<td>Position on the moped</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Driver (exposed)</td>
<td>9 3 5 4</td>
<td>6 9 7 6 9</td>
</tr>
<tr>
<td>(57.3%)</td>
<td>(42.7%)</td>
<td></td>
</tr>
<tr>
<td>Passenger (non-exposed)</td>
<td>8 4 5 6</td>
<td>1 5 5 7 4</td>
</tr>
<tr>
<td>(35.2%)</td>
<td>(64.8%)</td>
<td></td>
</tr>
<tr>
<td>OR = 2.47 (2.40–2.54)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\(^a\) Odds ratio (95% CI in parentheses).
Percentages are referred to the totals of exposed and non-exposed riders (by rows).
depending on helmet use, the corresponding values were considerably higher in both helmeted (1.40) and non-helmeted riders (1.41). As a result the OR estimate adjusted by helmet use (using unconditional logistic regression) was 1.41.

Careful assessment of the role of helmet use showed that this variable satisfied all three classical requirements for a confounder.1

1. It is causally related with the effect: for both drivers and passengers, the risk of head injury was much higher for non-helmeted than for helmeted riders (Table 1b).
2. It is associated with exposure, in the absence of effect. The OR for the association between helmet use and being the driver of the moped (Table 1c) was 2.61 in non-head-injured riders, a value similar to that obtained for head-injured riders (2.59).
3. It is not an intermediate step in the causal path between exposure and effect, as the strength of the association between being the driver of the moped and the risk of head injury was the same for helmeted as for non-helmeted riders.

Put simply, drivers of mopeds are at an intrinsically higher risk of suffering head injury than are passengers, but this increase is masked (confounded) by helmet use, because helmets (a device which strongly reduces the risk of head injury) are more frequently used by drivers than by passengers.

We have found no studies of the risk of head injury in moped riders that took this possible source of confusion into account. It is disappointing that we must usually resort to hypothetical data to teach our students how a confounding factor operates. For these reasons we hope that the real data presented in this letter will be useful for both teaching and research purposes.

Reference


WHO leads global effort on systematic reviews

From J VILLAR, AP BETRÁN, AM GÜLMEZOLGÜL and L SAY

Sirs—We read with interest the article by Dickersin on systematic reviews and meta-analysis of observational studies.1 She notes obstacles for conducting systematic reviews of observational studies as compared to those of intervention studies (randomized trials) of medical and non-medical forms of care. She also suggests steps to improve their methodological quality.

The World Health Organization (WHO) has been fully engaged in systematic reviews in the area of reproductive health for several years. It has now become necessary to expand this activity beyond the issues of effectiveness of interventions. For example, considerable information describing the incidence and prevalence of eclampsia, haemorrhage, abortion and other morbidities, and mortality is continuously generated. However, these efforts are not efficiently co-ordinated; data are of uneven quality, not synthesized, and overall results are seldom taken into consideration for service planning. We think that global effort similar to that made for randomized clinical trials (e.g. The Cochrane Collaboration) is needed to map the magnitude and distribution of reproductive morbidity and mortality, especially in developing countries.

With this concept in mind, the Department of Reproductive Health and Research of WHO is conducting a systematic review of maternal and perinatal morbidity and mortality covering published and unpublished studies from 1997 to 2002. The main objective of the review is to provide a comprehensive tabulation of available data on the prevalence/incidence of maternal morbidity and mortality globally. Through this systematic review we also aim to estimate case-fatality rates for maternal conditions, and calculate the proportion of maternal deaths that could be averted (population-attributable fraction) by eliminating or reducing the prevalence of selected morbidities.

As of October 2002, the protocol for the systematic review, including a generic form for data-extraction and a critical appraisal strategy have been developed and externally peer-reviewed, following the same procedures for any other research protocol supported by WHO. Internal and external methodological consultations with experts on analytical strategies have also taken place. Data abstraction has been completed for 1997 and over 1000 data entries were recorded. We expect that during 2003 over 5000 entries will be included in the WHO database.

Although efforts to develop methodologies for searching, critically appraising, and analysing data from observational studies exist, these focus largely on effects of health care interventions that are difficult or impossible to evaluate through randomized controlled trials (Cochrane methods groups). Conducting a systematic review of prevalence/incidence studies poses new challenges: developing a search strategy that has a satisfactory level of sensitivity and specificity is difficult; relevant studies are dispersed widely in many bibliographic databases, Internet sites, and grey literature. Other methodological difficulties include dealing with population- and institution-based data, and the lack of a standardized set of definitions of maternal conditions and diagnosis methods which affect results.2–4 Heterogeneity due to study design could be larger than real measurable changes over time or by regions, and may make pooling of results impossible.

The WHO systematic review will also assist in identifying a standard set of definitions for maternal morbidities, test a critical appraisal instrument for future reviews, and set a global database to guide epidemiological research. Eventually routine vital registration systems should be adopted in all developing countries; previous experiences in many countries in Latin America demonstrate that this is feasible. These efforts should result in better and sounder grounds for capturing, quantifying, and tackling the burden of reproductive ill-health.

To our knowledge, this is the first time that such global effort based on systematic review principles is being undertaken. Tackling this challenge requires active international collaboration
within the epidemiological community. Support from researchers in the field, university departments, governments, and non-governmental institutions could help ensure comprehensiveness. We invite all researchers to participate in this effort by providing WHO with any results that are not easily available by standard searching techniques so that they could be included in this systematic review. Appropriate credit to the sources will always be given. In her article Dr Dickersin also encourages the development of registers of observational studies, including a description of the variables examined. We agree that a register of large multicentre observational studies on maternal and perinatal mortality and morbidity should be started and offer the Department of Reproductive Health and Research at WHO as a secretariat for such a register.

References