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.1 Subsequent studies2–7 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,8 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,9,10 and is speculated to be linked to a Th1 type immune response.7 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.6,7,11 In rural India, a different epidemiological setting, a ‘long-term’ beneficial effect of BCG vaccine on all-cause childhood mortality, however, is not observed.8 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.12 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,13 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.14 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.15 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.16 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.17 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.18 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.19 Finally, the variations in childhood mortality rates20 as well as in the vaccination coverage levels21 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,22 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.23

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

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References


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

From PABLO LARDELLI-CLARET, JUAN DE DIOS LUNA-DEL-CASTILLO and JOSÉ JUAN JIMÉNEZ-MOLEÓN

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...