Viewpoint

Non-specific Effect of Measles Vaccination on All-cause Child Mortality: Revisited

In this paper, we give an insight into the historical perspective of any underlying non-specific effect of measles vaccination on the overall cause of childhood deaths in high-mortality populations, such as the West African nations. During our process of discussion, we also provide a synopsis of various case-studies across different population settings supporting our evidence. We also outline a few controversies surrounding such a hypothesis, and the potential implications for addressing such issues from a child health perspective. The reader should be aware that this paper is not a systematic review or a meta-analysis of examining our research question. However, we have attempted to bring in a comprehensive perspective.

Almost 40 years ago, Hartfield and Morley(1) conducted a randomised controlled trial (RCT) in West Africa. They observed that 26 young children immunised with measles vaccine had no deaths when followed-up for 18 months, while three deaths were reported among the 27 control children immunised with DTP (Diphtheria, Tetanus, Pertussis) vaccine. Very little research on such effects was done in the 1960s and the early 1970s. However, there has been growing evidence on such effects in the 1980s and the 1990s from different epidemiological settings.

The first prospective cohort study published was the Kasongo Project in Zaire in 1981(2). This study demonstrated 48% relative reduction in overall child mortality between age groups 7 and 35 months following measles vaccination. The same study(2) reported 3.0% absolute reduction in overall child mortality, but the absolute reduction was apparently greater among the relatively young children.

In Guinea-Bissau, a three-fold decline in overall mortality among children aged 6 months to 3 years was reported, following the introduction of standard measles vaccination in 1979 at a time when no other intervention was implemented(3). Subsequent epidemiological studies across several developing countries (Bangladesh, Benin, Senegal, Haiti) observed similar findings(4). The possible explanation of preventing acute measles infection alone seems unlikely(5), although selection bias is an inherent methodological issue for such observational studies. Could measles infection be associated with excess mortality after the acute phase of infection, and does measles vaccine have much larger effects on survival by preventing both acute and delayed mortality?

The World Health Organization (WHO) introduced the standard Schwarz measles vaccination (SSMV) in the early 1980s for children more than 9 months old. Contemporaneously, the first high-titre Edmonston Zagreb vaccine trials were undertaken in Mexico by Sabin and in the Gambia by Whittle among children of four to six months of age(6). Though long-term protection had not been reported from such trials, the WHO in 1989 recommended high-titre measles vaccine (HTMV) for childhood immunisation at six months of age. Following this recommendation, a three-fold higher overall child mortality that was surprisingly more pronounced among

girls was observed in Guinea-Bissau(7). Similar findings were also reported from Senegal and Haiti in the 1990s(8). Consequently, WHO had to withdraw the HTMV vaccination programme in 1992 worldwide.

Subsequent observational studies in the 1990s confirmed that standard measles vaccination reduced overall child mortality in low-income countries, and such effects were more pronounced among girls(9,10). It was also demonstrated that HTMV is as effective as SSMV against measles infection. Such observations indicate that the reported higher female child mortality could not be explained due to vaccine inefficacy alone. Could there be any non-specific effects?

There could be a link between measles vaccination and measles infection epidemiology, as evidence suggests that both mild acute measles infection and standard measles vaccination can be associated with reduced overall child mortality(11). Also, post-hoc observations suggest that in pre-vaccination era there was no gender difference in child mortality, while one-third lower mortality was observed for girls than for boys in Senegal in the mid 1980s with SSMV trial (9,10). In summary, HTMV did not have the same non-specific 'beneficial' effect as SSMV, and also failed to explain the gender-specific effect. Could other routine vaccines have a role?

A recent study(12) reported that other routine childhood vaccines such as DTP might have non-specific 'harmful' effects on overall child survival. A few recent WHO-endorsed studies failed to support such a hypothesis(13-15), but were methodologically totally different and survival bias was a potential misclassification bias in these analyses(16,17). Interestingly, the hazard ratio (HR) reported for measles vaccine in one of these studies was 0.93 for children beyond 9 months old(14). On censoring the effect of DTP vaccines administered after 9 months of age in particular, the HR of measles vaccine was reduced to 0.61, suggesting a marked negative effect of DTP when given with measles vaccine(14). Furthermore, a recent re-analysis of data from different trials demonstrated that the sequencing of vaccination schedule (DTP in particular) could explain the gender-specific effect following high-titre measles vaccination (18). In other words, the female-male mortality ratio was 1·93 (1·33 – 2·81) for those who received DTP after HTMV, and 0·96 (0·69-1·34) for those who did not receive DTP after HTMV (p = 0·006) (18).

Although a recent review refuted non-specific effect of measles vaccines by excluding virtually all studies for methodological reasons(19,20), the following body of evidence fails to support such a 'rebuttal'. For examples, the prevention of measles infection alone cannot explain the impact of measles vaccination(4,5), the effect of measles vaccine is also stronger for girls (9,10,21), SSMV was associated with lower mortality than HTMV in randomised trials even though there was no difference in vaccine efficacy against measles infection(7,8,18), and randomised studies have found reduction in mortality unrelated to prevention of measles infection(2, 22).

Could there be any biological plausibility for such observations? Th1 and Th2 immunity are suggested to play some role, as a live vaccine like measles stimulates Th1 and an inactivated DTP vaccine stimulates a Th2 profile(12). It is possible that measles vaccine itself and measles infection activates heterologous immunity(23). More importantly, beneficial effect has also been demonstrated even in populations with relatively low child mortality rates and high measles vaccination coverage(24, 25).

Future directions

Since it is unethical to conduct RCTs for the current measles vaccine, trials of potential non-specific reduction in mortality can only be considered when evaluating new vaccines or through changes in the age of administration for routine vaccines. This issue may also be studied during campaigns in areas with low routine coverage. It is also necessary to evaluate the impact of other interventions being used simultaneously or differences in those who seek vaccination versus those who do not seek vaccination. Epidemiological study designs across different settings can be integrated with laboratory-based investigations for a better understanding of the underlying biological mechanism.

In conclusion, it could be worthwhile to consider 'all-cause mortality' as one of the epidemiological endpoints in future vaccine trials, and in the economic evaluations of such trials(26). The expert panel of the WHO Steering Committee in June 2004 also suggested a post-marketing surveillance of 'all-cause mortality' in persons receiving newly licensed vaccines in both developed and developing countries. Such initiatives could certainly expand the epidemiological evidence base of non-specific effect of vaccines on overall mortality for cost-effective public-health policy developments in low-income countries, such as Guinea-Bissau or India.

Conflict of Interest: Dr. Kabir was invited as a technical advisor to the WHO Steering Committee Meeting on Measles Vaccine Research Initiative at Geneva in June 2004.

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