Commentary: Non-specific effects of measles vaccine—more grist for the mill

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This paper represents another in a series of publications by Peter Aaby and colleagues on unexpected and ‘non-specific’ effects of vaccines. For several years, these authors have argued in particular that the benefits of measles vaccines are greater than that which can be explained by protection against measles virus. This time they re-analyse data from an evaluation of measles vaccine carried out in the early 1980s in the Matlab demographic surveillance population associated with the International Centre for Diarrhoeal Disease Research, Bangladesh (ICDDR,B), comparing mortality between areas in which Schwarz strain measles vaccine was (areas A and C) and was not (areas B and D) offered to children between 9 and 60 months of age: 8134 vaccinated children are compared with an equal number of children, matched for age (within one month) within the non-vaccinated area. The analysis (employing a proportional hazards model for paired survival data) is not as clearly presented as some readers might wish (e.g. we are not told the age distributions of the compared populations nor are we shown the death rates by age), but the differences are striking, indicating that the vaccinated children experienced only about half the mortality (for assigning deaths as attributable to measles or not. There was an analysis was greatest during the 6 months following vaccination. Secondly, it uses data on reported measles in the population—and finds that removal of reported measles-associated deaths reduces the overall protection against death from 49% to 43%; from which they argue there is ample room for non-specific effects. Thirdly, the authors look at mortality trends post reported measles disease, and find that after heightened mortality during the 3 months following acute measles, these ex-cases experienced lower mortality than unvaccinated non-cases. Fourthly, they find suggestive evidence that vaccination reduced mortality even in children who reported having already experienced measles at the time of vaccination. Each of these bits of evidence is used to support the argument that measles vaccine has beneficial effects beyond those attributable merely to protection against measles disease.

For critics searching for alternative explanations to these findings, a major issue is the comparability of the two populations. It was not a randomized controlled trial, and as luck would have it, the areas compared were not perfectly comparable. The area which received the vaccine was better off according to several indicators: the mortality rates were approximately 10% higher in the unvaccinated area both before and after the measles vaccination and the maternal tetanus and BCG vaccination coverages were appreciably higher in the vaccinated than in the non-vaccinated areas, suggestive of differences in health services or accessibility between the areas. In addition, the vaccinated children were by definition a compliant population (only 82% of the children in areas A and C accepted the vaccination). On the other hand, the authors note that coverage of the other Expanded Programme on Immunization (EPI) vaccines was similar between the areas and argue that the various population differences could not explain the observed difference in mortality.

Another issue is that of measles diagnoses, which is crucial for assigning deaths as attributable to measles or not. There was a clear difference in mortality between the two populations. For assigning deaths as attributable to measles or not. There was a clear difference in mortality between the two populations. The simplest conventional explanation would be to attribute this to a combination of (1) lower background mortality risks in the A and C populations even without the vaccine, and (2) the effect of measles vaccine to protect against measles infection or disease-associated mortality. The authors argue that measles can only explain a minority of the difference. Unfortunately, the vast majority of measles diagnoses were not confirmed, but based only upon parental histories. Though the authors refer to studies indicating a high validity to measles diagnoses in this population, the evidence is not entirely convincing. Only 29% of unvaccinated area children were reported to have had measles by the age of 5. The authors admit that a quarter of the cases may have gone undiagnosed, but it is possible that the underascertainment was even greater than this. Unfortunately there are apparently no serological data that might be used to confirm the true cumulative seroprevalence of measles in this population and thereby to measure the underascertainment. Measles virus infection is generally considered to be rarely subclinical, and underascertainment means that cases were not recognized, for whatever reason. One may legitimately wonder how many deaths in the unvaccinated populations were associated in some way with unrecognized measles infections or disease. Interestingly, Clemens et al. who carried out the initial case-control study in this population, noted (as do Aaby et al. in the present paper) that the vaccine appeared to protect against deaths attributed to diarrhoea, respiratory illness, and malnutrition, and commented that these were ‘causes of death which
could plausibly be related to measles’. Indeed, it was recognized by investigators working at the ICDDR,B in the early 1980s that measles surveillance in Matlab was not comprehensive. In contrast, the Matlab Demographic Surveillance System maintained superb surveillance for deaths and other vital events. For that reason, the initial publication on this topic by Clemens et al.2 focused only on deaths and intentionally excluded consideration of measles cases.

The issue of non-specific effects of vaccination is an interesting and important one, and deserves serious research to assess its magnitude (if any) and possible mechanisms. These effects have, to date, been reported from developing country populations subject to high infant and child mortality, in which immune modulation by measles vaccine (e.g. a shift towards a Th1 cytokine profile?), might enhance protection against a variety of infectious agents. Unfortunately, the only data we have to date are based upon non-randomized studies, which inevitably are prone to selection bias—children who receive vaccines are in general better off, and at lower mortality risk (even without the vaccines), than are children who do not receive vaccines. Such is the injustice of the world. Perhaps the only way to settle this particular debate will be to wait until wild measles virus is in fact eradicated from the world, and an ethical committee is willing to allow a placebo-controlled trial of measles vaccine to assess its potential to lower mortality! A more practicable approach would be to study the question in a population with high-quality morbidity as well as mortality surveillance, in order to get a confident handle on the true incidence of measles and on any causes of deaths which occur more in non-vaccinees than in vaccinees.

References