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MILESTONE 13

Another layer of protection

Read any textbook on vaccination and you will learn that vaccines protect against their target diseases by inducing immune memory to specific pathogen components. However, interesting observations throughout vaccine history have suggested that some live vaccines offer additional benefits by protecting against unrelated infections. These early observations were dismissed or overlooked until a series of studies led by Peter Aaby in Guinea-Bissau, West Africa, in the late 1970s and 1980s showed that measles vaccination had beneficial effects on all-cause mortality that could not be explained by protection against measles alone. Since then, similar nonspecific effects have been reported for other types of live vaccine in both high-income and low-income regions of the world.

When the Bacillus Calmette–Guérin (BCG) vaccine against tuberculosis was introduced in the 1920s (MILESTONE 5), Albert Calmette noted that general mortality in vaccinated children was four times less than in unvaccinated children. Calmette concluded by asking whether BCG vaccination "confer[s] on the organism a special aptitude to resist those other infections which are so frequent in young children?" Carl Näslund noted similar effects on all-cause mortality after introduction of the BCG vaccine in Sweden in 1927. Writing in French, he was the first to refer to nonspecific immunity ("une immunité non spécifique"), although he concluded that the effects were likely owing to selection bias.

As well as the BCG vaccine, Mikhail Chumakov and his wife Marina Voroshilova showed in clinical studies carried out in the Soviet Union in the 1970s that prophylaxis with oral polio vaccine (OPV) could reduce morbidity from influenza and other respiratory infections by 70–80%. But like Calmette and Näslund before, the nonspecific effects noted by Chumakov and Voroshilova were consigned to vaccine history.

Then in 1978, Aaby arrived in Guinea-Bissau. He observed that the very high measles fatality rate locally was independent of nutritional status, which contradicted the prevailing view that measles vaccination would have limited effectiveness because many of the children were too frail to survive in any case. The first measles vaccination campaigns ran in Guinea-Bissau in 1979 and 1980 and the results of these campaigns led Aaby to champion the concept of nonspecific effects of vaccines. By comparing the general mortality rate before and after vaccination in results published in 1984, he estimated a reduction of more than 50%. As measles normally caused 10–15% of all deaths in Guinea-Bissau, protection from measles alone could not account for this large reduction in mortality. Furthermore, there was little difference in vaccine efficacy against death when including or excluding death from measles. In an analysis published in 1995 of 10 cohort and two case–control studies from Bangladesh, Benin, Burundi, Guinea-Bissau, Haiti, Senegal and Zaire, Aaby concluded that "measles vaccine may confer a beneficial effect which is unrelated to the specific protection against measles disease."

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Early detractors noted the observational nature of many of these studies, but the results have since been repeated for various live vaccines in a range of settings. For example, a population-based cohort study of Danish children involving Aaby's long-term collaborator Christine Stabell Benn showed that the live measles–mumps–rubella (MMR) vaccine was associated with reduced risk of hospital admission for any infection. Randomized controlled trials (RCTs) are difficult to carry out for vaccines that are already part of the routine schedule, but the recommendation for delayed BCG vaccination in low-birthweight infants in Guinea-Bissau enabled Aaby and colleagues to show in three RCTs that BCG vaccination at birth reduced neonatal mortality by 38% in low-birthweight infants compared with later vaccination.

As a result of these studies, a systematic review sponsored by the World Health Organization concluded in 2016 that the BCG vaccine and measles vaccine have effects on mortality that are "more than would be expected through their effects on the diseases they prevent"— a reminder that we have much still to learn about the protective effects of vaccines.

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Nature Reviews Immunology

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