You don't have to be a COVID vaccine rejectionist to want to fully understand the nonspecific effects (NSE) of vaccines

The world's attention is presently focused on the mRNA vaccines, which may turn out to be the most revolutionary vaccines ever produced. However, very few doctors, and certainly not the public, have any awareness at all of the nonspecific effects of vaccines (NSEs). The specific effect of a vaccine is immunity to a target infection; the nonspecific effect refers to the off-target effects of all vaccines. These can be positive or negative. The beneficial effects are improved immunity to a variety of infections and all-round health, and the negative effects are the inverse—a predisposition to off-target diseases and immune dysregulation, whilst still conferring immunity to the targeted pathogen. These discoveries have surprised the scientific community and left researchers scratching their heads as to how and why such important effects could have been overlooked by epidemiologists for over a century.

It began with observations made in the small West African nation of Guinea-Bissau from 1979. Anthropologist Peter Aaby was sent to investigate malnutrition in the country but found none. Instead, he ran headlong into a measles epidemic compounding pre-existing endemic infections, which resulted in half of all children dying before the age of five. Guinea-Bissau had the sad distinction of having the fourth highest child mortality rate in the world. Aaby must have felt like a lone mariner in a tropical storm. Blindsided, he immediately set about obtaining measles vaccines. At the time, the conventional wisdom was that such vaccination efforts against measles were not the main priority for African countries.

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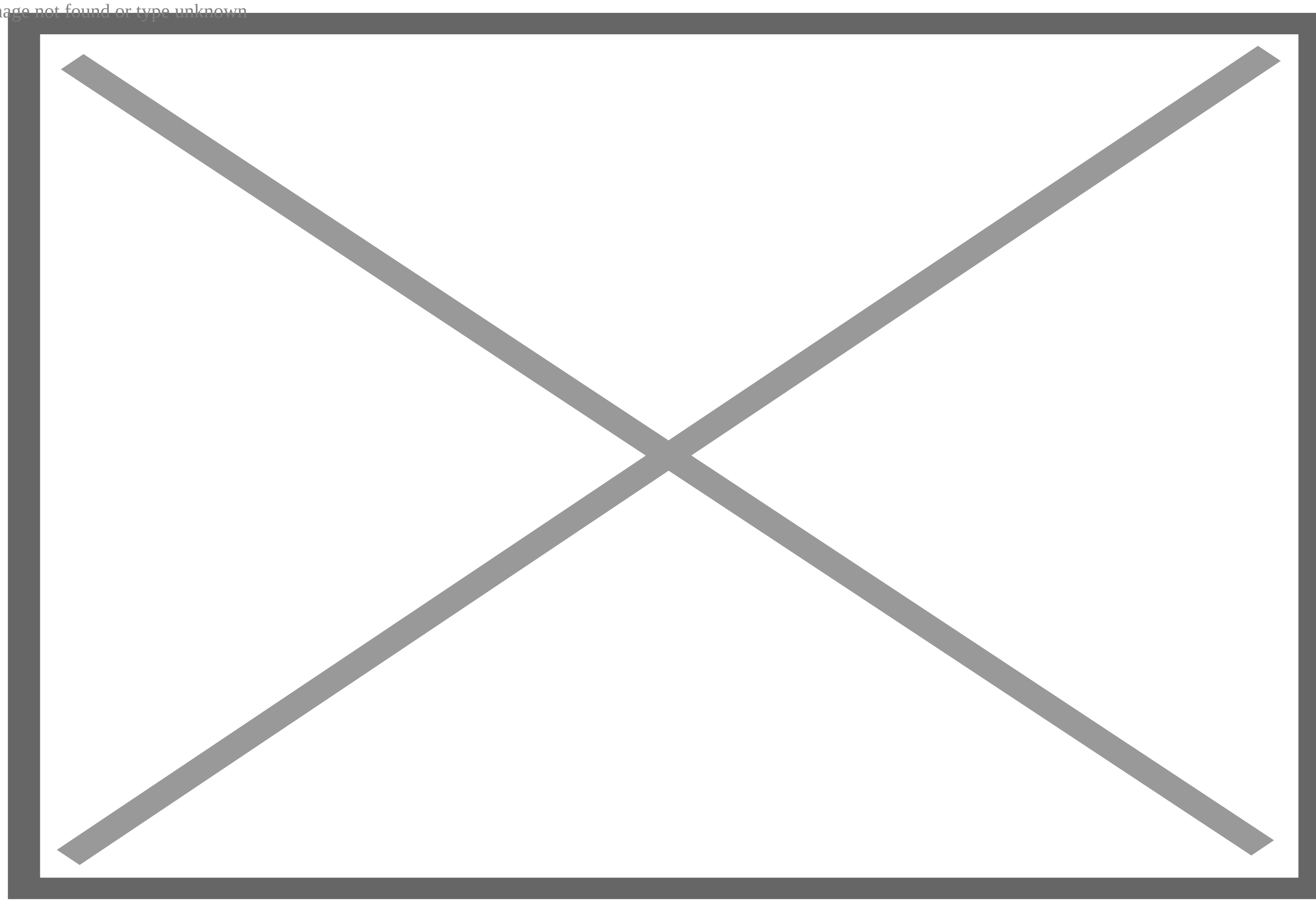

Mother and child from Guinea-Bissau. Credit: Elizabeth Stevens/Oxfam

Aaby was taken aback by what occurred following mass vaccination against measles: the rate of all-cause mortality among the children dropped by far more than could be explained by the measles decline alone. Children were not only not dying from measles, but they weren’t succumbing to a number of other diseases either. In an interview at the 2019 European Congress of Clinical Microbiology and Infectious Disease (ECCMID), Aaby pointed out that measles epidemiological models predict a mortality decline of 15 percent in the first 12 months. Instead, Aaby witnessed a reduction in all-cause mortality in children of more than 50 percent. Aaby had stumbled upon the NSE of a vaccine. This discovery prompted the creation of the Bandim Health Project (BHP), a health and demographic surveillance system.

Greatly encouraged by the measles experience, Aaby set about introducing the DTP vaccine for diphtheria, tetanus, and pertussis. But to his surprise, all-cause deaths increased from 200 to 275 per 1,000! Aaby had discovered that the live vaccines such as those used to combat measles, smallpox, BCG (TB), and oral polio reduced all-cause mortality, and non-live (inactivated) vaccines had the opposite effect. From then until 2015, all-cause mortality in Guinea-Bissau continued to decline in a saw-toothed fashion to 75 per 1,000—an 85 percent overall reduction. This was a staggering result. As Aaby states: “I don’t think this is something that has ever been achieved before.”

Today, the BHP has published over 1,000 papers on their work in Bissau (not all of which are vaccine-related). Aaby has been officially credited as the discoverer of the vaccine NSE, and received Denmark’s most important prize in medicine, the Novo Nordisk. However, their team has met with bureaucratic resistance when they have tried to discuss the importance of NSEs. Aaby is the BHP director in Bissau. Christine Stabell Benn, the University of Southern Denmark’s Professor of Global Health and a well-published researcher on NSEs, is the BHP director in Copenhagen. Benn has worked with BHP since 1992, and she is trying to nuance the polarised debate over vaccinology. The first conference on NSEs was held at the Wellcome Genome Centre in England last February, in the form of the now-established Optimmunize movement, comprising vaccine researchers and medical specialists from a number of countries. This is intended to become a biennial event.

A summary of Aaby and Benn’s work was published in the *Lancet* recently, encapsulated in the form of the following six principles:

1. Live vaccines enhance immunity against off-target infections.
2. Inactivated or non-live vaccines increase the susceptibility of girls to off-target infections.
3. The most recently administered vaccine has the strongest NSE.
4. Combining live and non-live vaccines have variable NSEs.
5. The vaccination of children with live vaccines when maternal immunity is present (such as following birth) improves beneficial NSEs.
6. All vaccines may interact with other interventions or supplementation.

It now appears that two important concepts need investigation. First, given the sex differential effects of the world’s most widely used vaccine, DTP, males and females may need different vaccines for all targeted diseases. Professor Sabra Klein works at the Johns Hopkins Bloomberg School of Public Health and is co-director of the Johns Hopkins Centre for Women’s Health, Sex, and Gender Research. In an email, she told me: “I’ve always been concerned that documented detrimental NSEs are worse for females than males. There is a growing number of studies showing that infant girls have increased mortality after receiving high-titer measles vaccine (HTMV), which seems to be associated with the timing and order of receipt of the HTMV and diphtheria tetanus pertussis (DTP) vaccine. … Based on available data, among children under five years of age, NSEs whether beneficial or detrimental are more pronounced for girls than boys and we do not know why.” This is amplified by Benn in her criticisms of the roll-out of the RTS,S/AS01 malaria vaccine in Africa, where she claims it will have very negative effects for females.

All of the researchers working either in Bissau or on allied studies elsewhere are enthusiastic supporters of the BCG vaccine as a means of disease prevention due to its beneficial NSEs. BHP’s Dr. Frederik Schaltz-Buchholzer has been working on BCG research in Bissau for some time, particularly on the use of

BCG vaccine on sick and underweight neonates. He advocates the administration of BCG to very small and fragile babies, and he is insistent: “We have previously shown in three randomised controlled trials that if low birth-weight neonates are vaccinated at discharge from the hospital, the all-cause mortality drops by 38 percent, especially due to a reduced risk of death from fatal neonatal sepsis.”

Second, the current vaccine programmes need re-scheduling so that the live vaccine is always administered last. Professor Frank Shann from Australia’s Melbourne University has estimated that a simple re-scheduling of the current vaccines in use could save the lives of six million children annually—not to mention the substantial reductions in negative NSEs such as asthma, eczema, allergies, and predisposition to off-target infections.

Most people associate vaccination with childhood, but increasingly, more adults are being advised to get more vaccines. This trend accelerated with the development of the influenza vaccine, prior to which most baby boomers had only received a handful of vaccines as children and perhaps the occasional DTP vaccine as adults, for tetanus protection following a wound. With the COVID vaccines quite possibly becoming an annual occurrence, this trend will continue. In an email, Dr. Schaltz-Buchholzer told me he questions whether the Johnson & Johnson and AstraZeneca vaccines can be considered live vaccines (and therefore imparting beneficial NSEs) in the accepted sense, and furthermore that the overall NSEs remain uncertain at this stage. Perhaps they offer none of the advantages of their forebears, or perhaps we’ll see a new era of vector vaccines with more promising NSEs.

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Credit: Amanda Perobelli/Reuters

Medical science has made the same mistakes with vaccines as it has made with various drugs such as opioids: the overreach of use, often in low-risk situations. However, there is a way forward through the more frequent administration of live vaccines, together with the development of new ones, and careful re-sequencing so that live vaccines are administered last.

Set against Benn's optimism is the persistence of the antivax movement which has arguably arisen from the seemingly glib dismissal of patients' concerns about negative NSEs. In contrast, they are not aware of positive NSEs. The BHP research has shown the smallpox, oral polio, BCG (TB), and measles vaccines greatly reduce all-cause mortality and morbidity, with the former three being responsible for large reductions in hospital admissions over the course of a recipient's lifetime. During his interview at the ECCMID, Peter Aaby said, "Any system of medicine which does not allow for the fact it may be wrong isn't a good system. … You all think we know what our vaccines are doing—we don't!" Cherry-picked quotesby the antivax movement are clarion calls to the lay public. The medical approach of browbeating and belittling those with concerns hasn't worked, but they press on with the same strategy. A new strategy is required that balances authority with humility.

Meanwhile, researchers are focussed on the priorities of getting the message about NSEs to the public, and on the urgent need for research and vaccine re-sequencing. Discussions at the first Optimmunize conference centred on present research and trials on both of these things. Particular attention was paid to re-sequencing, the principle that a live vaccine should always be administered last, and the incompatibility of certain vaccines being administered concurrently. "Unfortunately," wrote Australian Professor Frank Shann in a 2013 paper, "policymakers have been all too ready to dismiss the nonspecific effects of vaccines as quirky findings based on flimsy evidence. Now that substantial evidence from randomized trials and immunologic studies suggests that these effects are important, it is time for strong international support for the conduct of randomized trials to test the effects of BCG, measles vaccine, and DTP on all-cause mortality in children in high-mortality regions."

David McLelland trained as a phytotherapist. Retired since 2017, he now disseminates research on the nonspecific effects of vaccines. Follow him on Twitter @docdave53

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