It is really about the non-specific effects of vaccines

By Peter Aaby and Christine Stabell Benn, University of Southern Denmark

A recent report in The Guardian Dec 19, 2025, about a hepatitis B vaccine (HBV) randomised controlled trial (RCT) in Guinea-Bissau was spiced with condemnations like 'highly unethical', 'extremely risky', 'reeks of a neocolonialist attitude', 'questionable research', 'endpoints are "very squishy"', etc. The Guardian readers are told about 'major issues with research conducted by Aaby and Stabell Benn'. The derogatory terms were justified with quotes from six professors.

Since none of the commentators had read the protocol, which has yet to be registered, the condemnations are an alarming indication of what is wrong in current discussions of vaccine "research". No data but lots of moral outrage and condemnation against researchers who may not share *public health authorities'* opinion about specific vaccines. This is particularly the case if the researchers whether we have enough data to decide which policies will contribute most to health for everybody. Apparently, the mindset in 'vaccinology' has become inquisitional-religious rather than curious and humble.

Underlying this discussion is the challenge that all current vaccination policies are based exclusively on whether the vaccine protects against the vaccine-targeted disease, e.g. measles vaccine (MV) against measles infection or DTP vaccine against diphtheria, tetanus, and pertussis infections. This was because historically it was not known that vaccines could have other effects. It is now clear that vaccines can stimulate the broader immune system. For a period after vaccination this can alter how the immune system defends itself against all kinds of disease organisms (not just the vaccine disease organism). In other words, vaccine may have health effects on morbidity/mortality beyond those that are explained by prevention of the vaccine-targeted disease. Such effects have been coined non-specific effects (NSEs) of vaccines. They are seen as long as a given vaccine is the most recent vaccine but may change once a new vaccine type is given.

The best-known example of NSEs is the high-titre measles vaccine (HTMV) which was recommended by WHO in 1989 after it had been shown to be fully protective against measles infection even when given at 4-6 months of age, while the children still had maternal measles antibodies. However, in the

following years studies from Guinea-Bissau, Senegal, Sudan and Haiti showed that HTMV was associated with two-fold increased female mortality. WHO had to withdraw the recommendation of HTMV in 1992.

Since this incident, we have studied all routinely used vaccines in Africa for their NSEs. Several important patterns have emerged.

First, live vaccines (MV, BCG against tuberculosis, oral polio vaccine (OPV), and smallpox vaccine) may have very strong beneficial effects, which are not explained by prevention of the vaccine-targeted disease. For example, BCG is recommended for its effect against tuberculosis but we and others have shown that BCG may also reduce the risk of dying from other infections that would otherwise have killed newborns in the first month of life. In 5 randomised clinical trials (RCTs) BCG reduced the risk of dying from all causes in the first month of life by 17% to 59%, and this was not explained by prevention of tuberculosis, which does not normally kill children that early.

Second, in contrast, in the African context, several non-live vaccines (DTP, Pentavalent vaccine, IPV (inactivated polio vaccine, RTS,S malaria vaccine, hepatitis B vaccine (HBV)) have been associated with increased mortality, particularly for females. For example, it turned out that the reason that HTMV was associated with higher female mortality was that HTMV was given so early at 4-6 months of age that most children received DTP after the measles vaccine. DTP is associated with higher female mortality, so this change in the sequence of vaccines was extremely important for the overall effect on survival.

The existence of NSEs of vaccines have numerous implications for public health but these are currently not taken into consideration by public health authorities. Within the current medical culture, the ultimate victory is to eradicate a disease – as happened with smallpox infection – and then vaccination can be stopped as the vaccine is no longer needed. However, if the vaccine has beneficial NSEs far beyond the protection against smallpox infection, stopping the vaccination could actually increase overall mortality because people no longer received the beneficial immune stimulation. Smallpox vaccine was stopped in 1980, but no researchers or public health authority examined what this meant for overall health in different countries. We have shown with data from Guinea-Bissau and Denmark that having a smallpox vaccination was associated with around 40% lower adult mortality than not having received the vaccine. So, stopping smallpox vaccine may not

have been a resounding success for public health. This may be very relevant now because current medical culture is hoping to eradicate both polio and measles infections and then stopping the corresponding live vaccines.

Before dismissing the trial of HBV at birth (HBV0), people should read the literature on NSEs of vaccines. In a larger study in Guinea-Bissau, where an annual cohort of children aged 7-10 months received 3 doses of HBV, the female-male mortality ratio was 2.20 (1.07-4.54) whereas it was only 0.96 (0.70-1.32) if the children had not received HBV. In a small study from Gambia of the vaccination cards from children who had died, girls who died at 2-4 months of age were more likely to have HBV and DTP as their last vaccination whereas boys were more likely to have received BCG ($p<0.01$). We are not questioning whether HBV0 is effective in stopping maternal transfer of hepatitis virus. The issue is whether the prevention comes at a prohibitive price. The HTMV was clearly protective against measles infections, but that protection came at the price of two-fold higher female mortality.

The moral outrage from academic celebrities seems unnecessary. Contrary to what some of the critiques claim, we will not withhold the vaccination from any children who would other have received it. HBV0 is not yet provided in Guinea-Bissau. However, all children in Guinea-Bissau are receiving HBV as part of the pentavalent vaccine at 6, 10 and 14 weeks of age. We will use the time until the HBV0 is introduced in 2027-2028 to test the overall health effects of HBV0. As a result of the trial more children, who would not otherwise have had it, are actually getting the vaccine. Children will also benefit from the additional access to better health care which accompany the RCT. And importantly, the trial will close an important gap in the knowledge about the broader health effects of HBV0.

So, the trial is not “highly unethical” as claimed in the Guardian’s headline unless it has become official heresy to test the overall health effects of vaccines. This is after all what parents want to know when vaccinating their child: “Will my child be overall healthier from this vaccine?”

**

The Bandim Health Project has worked 47 years in Guinea-Bissau to find ways of reducing child mortality; in this period under-5 mortality has declined 86%. This decline cannot be understood unless one looks at the non-specific immune stimulatory effects of the live vaccines: MV, BCG, and OPV. But knowing the NSEs of the live vaccines implies also that we have to assure that the non-live vaccines do not have negative effects. It would be unethical not to investigate.