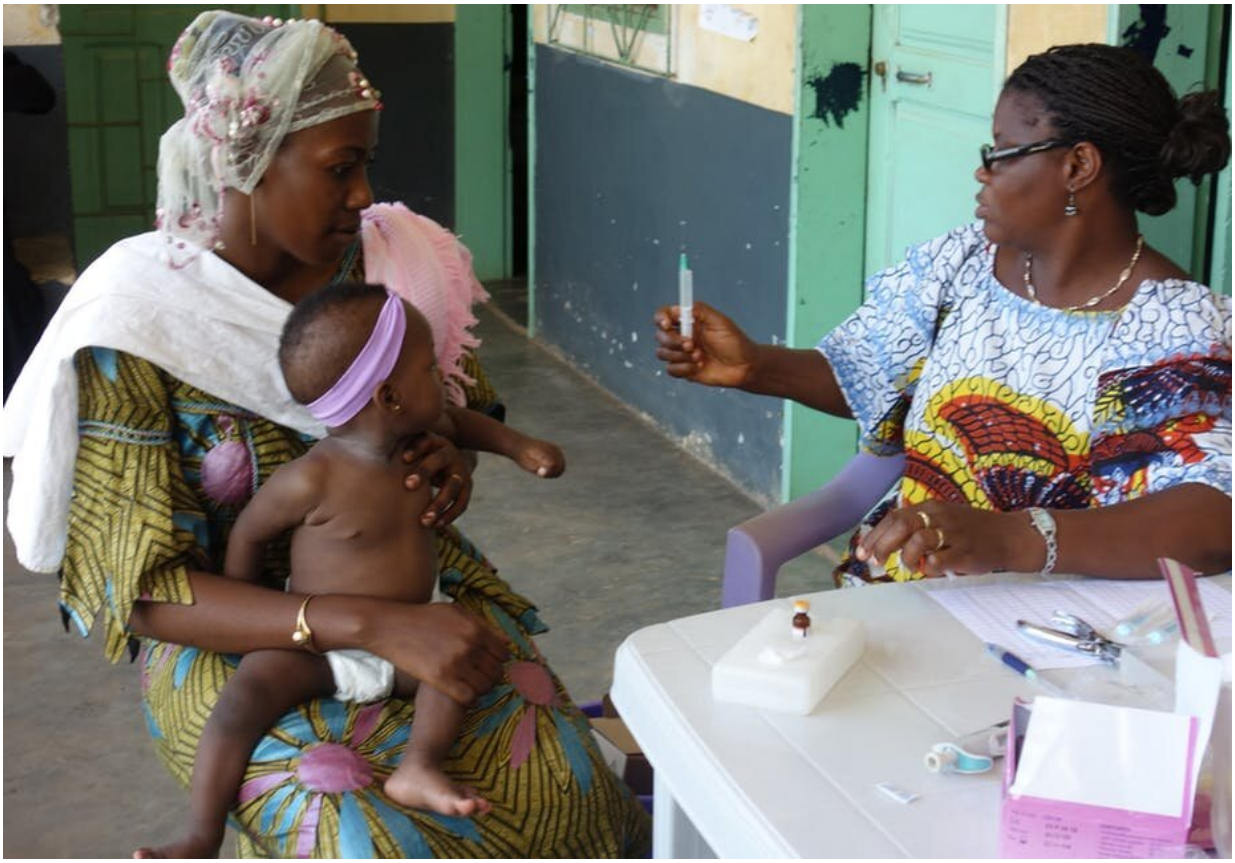
Vaccines have health effects beyond protecting against target diseases

January 11 2019, by Christine Stabell Benn



Child ready to receive measles vaccine, Bissau, Guinea-Bissau. Credit: Christine Stabell Benn, Author provided

A measles vaccine protects against measles infection. By introducing a bit of weakened virus, the immune system learns how to deal with it, so

when a real measles virus comes along, it can eliminate it. But does the immune system learn more from the vaccine? Recent research suggests, rather intriguingly, that it does.

Our group first noticed this phenomenon in Guinea-Bissau in West Africa over 30 years ago. We followed a large sample of the population, with regular home visits. The focus was on nutritional status, but as a service to the community, in December 1979, we provided a measles vaccine for all children. The following year, we observed something amazing: the measles vaccine reduced overall mortality by more than 70% - much more than could be explained by the prevention of measles infection, which only caused around 10-15% of all deaths at that time.

During further research, it became clear that the effect of these vaccines on overall health couldn't be explained by their disease-specific effects. Vaccines also affect the risk of other infections. We coined these effects the "non-specific effects" of vaccine.

Two types of vaccines

There are two major types of vaccines, live and non-live. Live vaccines contain the disease organism in a weakened form. They create a mild natural infection in the body, usually so mild that there are no symptoms. These vaccines give good protection against the disease they were designed for from the first dose. (Though these vaccines have the very rare potential to cause real disease, particularly in people with compromised immune systems.)

Non-live vaccines contain the killed disease organism or parts of it. They are not very good at stimulating the immune system and usually have to be given with a helper substance, known as an "adjuvant", and in several shots to give disease protection. The non-live vaccines can never create the real disease, so most doctors prefer them over live vaccines.

We have now investigated four live vaccines and six non-live vaccines, in Guinea-Bissau and other low-income countries, as well as in Denmark. A consistent pattern has emerged. The live vaccines reduce death and disease much more than can be explained by the specific protection. But the non-live vaccines, in spite of protecting against the vaccine disease, are associated with negative effects on health, including death, particularly for girls. Here are two examples.

BCG

BCG vaccine is a live vaccine against tuberculosis. It is recommended at birth in poor countries. But newborns with low birth weight are normally vaccinated later. We tested the effect of BCG vaccine on overall health in this group. We randomly allocated Guinean children who weighed less than 2.5kg to receive BCG at birth or the usual delayed BCG.

In the first month of life, deaths from any cause were reduced by more than a third in children who received the vaccine versus those who didn't. Children don't die from tuberculosis in the first month of life. But BCG reduced their risk of dying from sepsis and pneumonia – a purely non-specific effect of BCG, which had nothing to do with protection against tuberculosis.

In sub-Saharan Africa, BCG is often given with delay. Currently, only around 50% of all children, irrespective of weight, receive BCG at birth. If our results are correct, it would be possible to prevent 200,000 babies dying each year simply by making sure that all children received the BCG vaccine at birth.

DTP

Diphtheria, tetanus and pertussis (DTP) vaccine is a non-live vaccine

against three serious and potentially deadly diseases. So it has been assumed that introducing it would reduce overall mortality. But when we tested what had happened when the DTP vaccine was introduced in Guinea-Bissau, we were very surprised. In spite of protecting against the diseases, DTP-vaccinated children had fivefold higher mortality than children who didn't receive the vaccine.

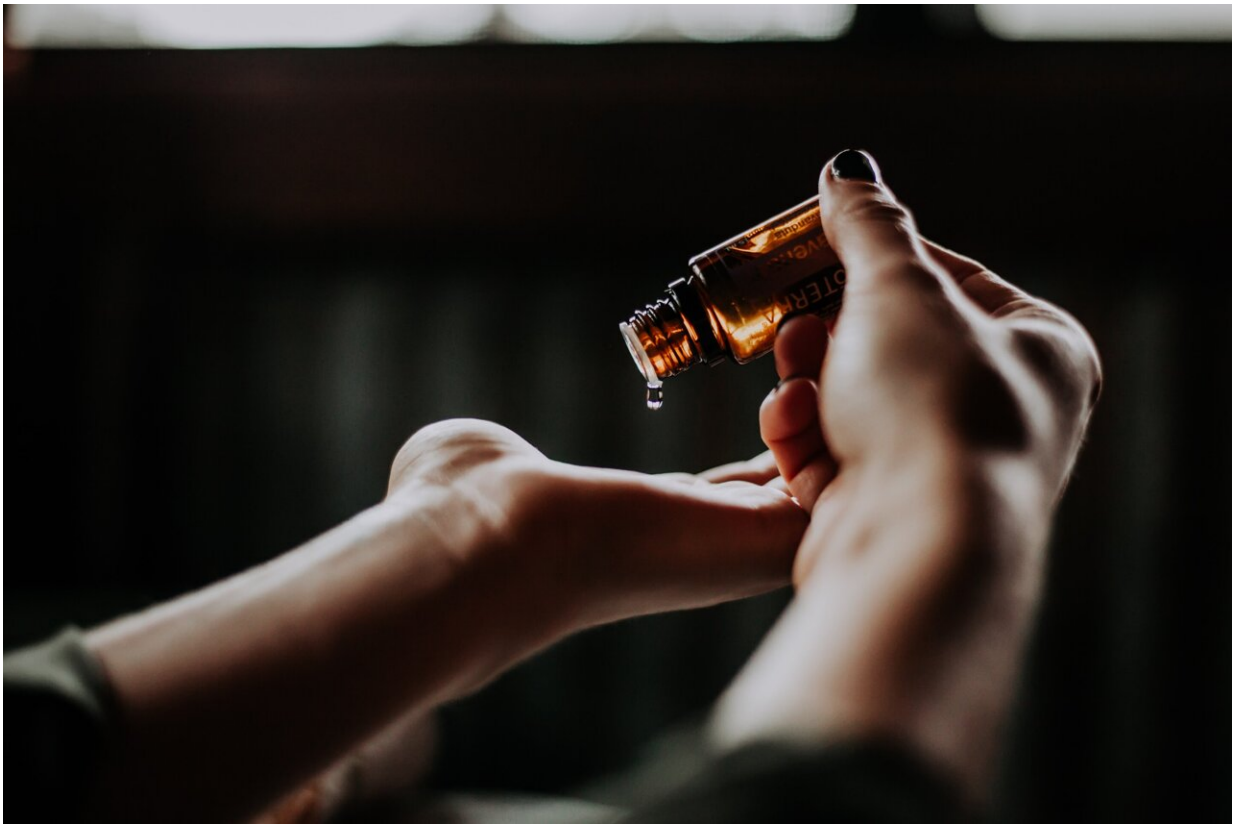
We have repeated this finding many times. Protection against diphtheria, tetanus and pertussis seems to come at a very high price: increased risk of dying from other infections, such as respiratory infections, particularly for females. Translated into absolute numbers, the results indicate that the use of DTP vaccine in sub-Saharan Africa may cost tens of thousands of female lives every year.

These are just two examples among many studies done by our team. Besides BCG, we have found beneficial non-specific effects of the live measles, smallpox and oral polio vaccines. And besides DTP, we have found negative effects in females of the non-live pentavalent vaccine (which combines immunisation against five diseases), as well as the inactivated polio, hepatitis B and H1N1 influenza vaccines, and we also predicted a negative effect of the new malaria vaccine in females.

Not many places have the kind of data needed to conduct these studies, but other research groups are now starting to replicate our findings in other poor regions of Africa and Asia. The same patterns have also been seen in wealthy countries. For instance, a recent US study found that the risk of getting hospitalised for other infections was halved among children who had a live versus a non-live vaccine.

The World Health Organisation recently reviewed the evidence for non-specific effects of the live BCG and measles vaccine and the non-live DTP vaccine and concluded that BCG and measles-containing vaccines could reduce overall mortality by more than expected, while higher all

cause mortality may be associated with receipt of DTP.



Credit: Unsplash/CC0 Public Domain

Effect of vaccines on the immune system

The immune system has traditionally been divided into the innate and the adaptive immune system, with the innate seen as the first line of defence, with no memory of previous pathogens. The adaptive has been seen as the place where the memory of disease organisms develops, which can be measured in the antibodies the disease creates. The protective effect of vaccines has largely been ascribed to the ability to

induce antibodies.

However, recent research has taught us that the immune system is more complex. The innate immune system also learns when exposed to a disease organism. In a recent experiment, we showed that volunteers who received a BCG vaccine four weeks before a yellow fever vaccine, had much less yellow fever virus in the blood, and this was because BCG vaccine trained their innate immune cells to become more vigilant. So we now have evidence that a vaccine can change the immune response to subsequent unrelated infections in humans. This goes a long way to explaining how vaccines can influence other diseases and overall health.

Hard to find what you're not looking for

Vaccines have been used for centuries. So if they have such profound effects on the risk of other diseases, why didn't we discover this a long time ago? The short answer is that you can't discover what you're not looking for.

Everybody has been convinced that vaccines only affected the target infection, so their effect on other infections and overall health was not studied. So while there are many studies that show that vaccines have protective effects, there is no data that shows that vaccines *only* have protective effects.

It is time to change our perception of vaccines: vaccines are not merely a protective tool against a specific disease, they affect the immune system broadly. In the case of live vaccines, the immune system is strengthened. In contrast, non-live vaccines seem to have a negative effect on the immune system in females.

The latter finding is an obvious cause for concern, particularly since it would be undesirable to stop using, say, the DTP vaccine, as it protects

against three severe diseases. Fortunately, there is something to do. It appears that if a live vaccine is given after a non-live vaccine, the negative effect of the non-live vaccine may be mitigated. So there is an urgent need for studies testing different sequences of live and non-live vaccines.

Studies into the overall health effects of vaccines are providing new insights about the immune system and how it may be trained by vaccines. Live vaccines seem to be potent immune trainers, and with this new knowledge we may be able to reduce global child mortality by more than a million deaths a year. With smarter use of vaccines, we may also be able to reduce disease and improve child health in wealthy countries.

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