Research round-up

Highlights from vaccine trials. By Elizabeth Svoboda

Mosaic approach to HIV vaccine trials

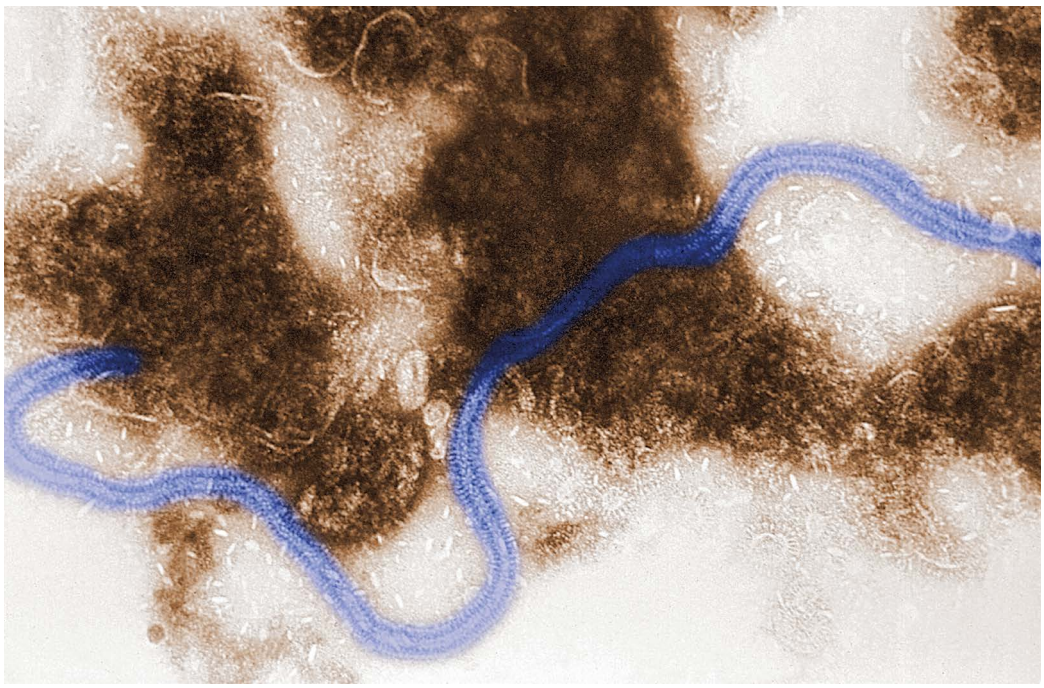
A vaccine for HIV has long been elusive because the virus comes in many different guises. A 'mosaic' vaccine, which includes snippets of variants of HIV from around the world, now entering a phase III trial could change that.

In a phase I/II trial published last year and led by Dan Barouch at Harvard Medical School in Boston, Massachusetts, more than 80% of participants showed a robust immune response to the best-performing version of the experimental vaccine. The volunteers produced a range of antibodies that bound specifically to different HIV strains, and the researchers saw clear evidence of phagocytosis, in which immune cells surround and digest cells infected with the HIV virus.

These outcomes have raised hopes that this vaccine — set to be the fifth tested for efficacy in humans — will perform well in a phase III trial. The trial, scheduled to start before the end of the year, is aiming to recruit 3,800 men and transgender people who have sex with men, transgender people or both. Unlike the phase I/II trial, this trial will show whether the vaccine prevents people from getting the virus. Results are expected in 2023.

Although antiretroviral therapy has reduced the burden of HIV around the world, the stakes for these trials remain high, because a safe and reliable vaccine is needed to end the pandemic entirely, say HIV specialists.

Lancet **392**, 232–243 (2018)



SCIENCE SOURCE/SPL

Transmission electron micrograph image of human respiratory syncytial virus (blue).

A precision-engineered RSV jab

It might not be as notorious as the flu, but respiratory syncytial virus (RSV), which causes cold-like symptoms, kills 160,000 people globally per year, and is especially serious for infants and older people. At the moment, there is no effective vaccine. However, a new candidate based on the virus, but with a precise tweak to the structure of one of its surface proteins, has shown signs of generating a substantial immune response in early trials in people.

To mount an effective defence against RSV, the body needs to churn out large numbers of antibodies against the virus. Many of those target a protein on its surface — known as the fusion glycoprotein, or F protein — that is crucial to it fusing with host cells. But previous RSV vaccine candidates could not create a sufficient immune response because the F protein changes shape once the virus enters a cell, rendering antibodies against its pre-fusion form less effective.

Because the pre-fusion form of the F protein generates the stronger immune response, Barney Graham at the US National Institutes of Health's Vaccine Research Center, Bethesda, Maryland, and his colleagues engineered a partial version of RSV with an F protein that could not change shape. The researchers hoped that providing a form of the protein locked in this state would allow the body to generate enough antibodies to ward off future infection.

In a phase I trial, 40 adults who were given the vaccine churned out 7–15 times more RSV-fighting antibodies than were present before vaccination — an increase that persisted for months. This is a larger antibody response than is seen in people after natural RSV infection. Subsequent trial phases, however, must prove not only that the vaccine boosts RSV antibody levels but also that it either prevents the disease or, at least, reduces its severity.

Science **365**, 505–509 (2019)

Malarial parasite trapped in the blood

An experimental vaccine for malaria can produce antibodies in humans that lock the disease-causing parasite *Plasmodium falciparum* outside red blood cells. Malaria symptoms are the result of the parasite multiplying inside these cells and causing them to burst, so researchers hope that this approach will lessen the damage caused.

Despite an array of drugs and mosquito-killing agents, malaria remains a deadly scourge in low- and middle-income countries. Attempts to create a vaccine against the parasite during the blood stage of its life cycle have flopped because the antibodies

created fail to stop the parasite entering red blood cells. Matthew Higgins at the University of Oxford, UK and his colleagues, therefore, opted to target a crucial parasite protein called PfRH5. This protein binds to the host's red blood cells to allow the parasite access — like a key opening a door. Blocking PfRH5 locks the parasite out of the cells, and thereby prevents it from damaging them.

During a phase I trial, the scientists collected the blood of people who'd received the vaccine, sequenced the genes that produced their antibodies, and used the genes to make more antibodies. The researchers then tested how strongly the antibodies reacted to the PfRH5 protein. Of the 17 distinct antibodies they found, 7 strongly inhibited the parasite by preventing PfRH5 from binding to red blood cells. The team also identified another antibody that slows PfRH5's binding rate. Although this antibody doesn't stop PfRH5 from binding, it is still helpful because it buys time for the other antibodies to act.

The team is now planning a version of the vaccine that creates more of the antibodies that block or stall PfRH5, and fewer of the ones that have little or no effect.

Cell **178**, 216–228.e21 (2019)

Antibiotics lower vaccine effectiveness

Antibiotics wreak havoc on the microbes in our gut. Signature side effects include diarrhoea or constipation, but the toll might be more than just digestive. A study published in September suggests that the depletion of gut microbes that follows antibiotic use can make the influenza vaccine less effective in people with low natural immunity.

During a two-part trial, Bali Pulendran at Stanford University in California and his colleagues gave flu vaccines to a total of 33 adults. Participants in the second phase of the trial hadn't encountered the virus recently or received the flu vaccine in three years, and were therefore considered to have low immunity. The scientists gave half the participants a course of broad-spectrum antibiotics, including neomycin, vancomycin and metronidazole. Gut-microbe diversity plummeted in all volunteers treated with antibiotics, but people with low levels of flu immunity also produced very few antibodies in response to the flu vaccine, meaning they might be more prone to develop the disease if exposed to the virus. People who did not receive antibiotics in either phase, however, displayed a normal antibody response to the flu jab, showing they were protected from the vaccine strains.

"People who take a course of antibiotics might have a weaker immune boost from the flu injection."

The results hint that some people who take a course of antibiotics might have a weaker immune boost from their yearly flu injection. Although the mechanism is not yet clear, the researchers note that production of bile acids such as lithocholic acid dropped 1,000-fold in people treated with antibiotics. Normally, gut bacteria help to manufacture these acids, which are known to regulate immune activity. The researchers think that when gut microbes are depleted, impaired lithocholic acid production might interfere with the body's ability to create a normal immune response to the flu vaccine.

Cell **178**, 1313–1328 (2019)

A bulwark against chlamydia

More common than gonorrhoea, syphilis and HIV combined, chlamydia has been the subject of vaccine research for more than half a century — without much success. But now a candidate vaccine for the sexually transmitted bacterial infection, which can cause infertility and chronic pain, has generated a strong immune response in early trials in people.

Previous uses of weakened chlamydia bacteria have failed to produce enough antibodies for long-lasting immunity. So Peter Andersen at Statens Serum Institut in Copenhagen and his colleagues isolated a protein on the surface of the bacterium called the major outer membrane protein, which had evoked a strong antibody response in animal tests. The team then tweaked its structure so that it could generate immunity to multiple strains of the bacterium.

In a phase I trial, the researchers gave 35 women aged 19 to 45 either a version of the vaccine that included aluminium hydroxide, or one that included lipid molecules or a placebo. Each participant received five doses of vaccine — three injected and two sprayed into the nose. Although both the aluminium hydroxide and the lipid-molecule variants created a robust immune response in all the volunteers compared with the placebo, the vaccine with lipid molecules performed best, generating more than five times as many chlamydia antibodies as did the other formulation.

The researchers are planning a phase II study of the lipid-variant vaccine. If its effectiveness is confirmed in further trials, it will be of particular benefit to girls and young women in low- and middle-income countries — a demographic with a high incidence of chlamydia. However, because the vaccine is based on an engineered protein rather than a live attenuated version of the bacterium, it could prove expensive to produce.

Lancet Infect. Dis. **19**, 1091–1100 (2019)

CAR-T takes on solid tumours

Lab-modified immune cells called chimeric antigen receptor (CAR) T cells are widely used to treat blood cancers. Darrell Irvine at the Massachusetts Institute of Technology, Cambridge, and his colleagues have developed a vaccine that could allow CAR-T cells to also attack solid-tumours.

Solid tumours tend to suppress immune cells. To address this problem, the team joined a specific antigen that boosts CAR-T cell activity to a molecule with a lipid tail that hooks onto albumin proteins in blood. Once in the blood, the vaccine molecules attach themselves to albumin and are carried to the lymph nodes, which regulate the body's immune responses. The molecules' lipid tails penetrate the surfaces of lymph-node cells, and the embedded surface antigens stimulate the activity of tumour-fighting CAR-T cells.

The team tested the vaccine in mice with glioblastoma, melanoma and breast tumours. In about 60% of mice that received the vaccine with an infusion of CAR-T cells, tumours disappeared completely. Tumours did not shrink in mice that received only CAR-T cells.

The authors also found that human cells studded with CARs rev up activity of tumour-fighting cells, indicating the vaccine could prove viable in people. The developers of the approach plan to test it in clinical trials in the next few years.

Science **365**, 162–168 (2019)

online

For the latest research highlights published by *Nature* visit nature.com/research-highlights