How does vaccination thwart pneumococcal infection? Animal model uncovers 'capture and kill' scenario

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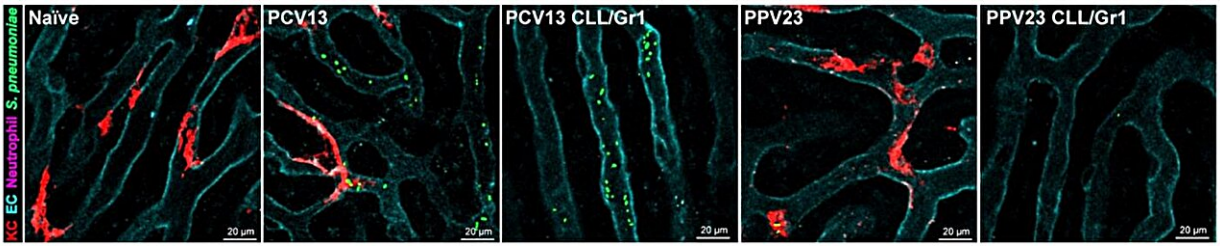

Representative IVM imaging of vaccine-activated capture of ST865 pneumococci in the liver sinusoids. Pneumococci, green; KCs, red; ECs, cyan; neutrophils, magenta. Credit: *Science Translational Medicine* (2023). DOI: 10.1126/scitranslmed.ade0054

In findings that are nothing short of surprising, scientists have demonstrated that the liver is the site where the immune system unleashes its assault on pneumococcal bacteria following vaccination against the potentially lethal pathogens.

For years, scientists had hypothesized, theorized, suggested and even guessed how pneumococcal bacteria are destroyed in the body after being flagged as a threat by vaccination.

New research shows that the immune system not only has a special place

for the organisms to be destroyed, but that a special pair of cells is involved in a "capture and kill" annihilation, preventing disease before it starts, the key benefit of vaccination.

A global team of vaccinologists in China, the United States and Switzerland sought explanations on how the annihilation unfolded, launching a deep dive into how two approved pneumococcal vaccines prompt the capture and kill response against Streptococcus pneumoniae.

Multiple strains of S. pneumoniae pose threats and the bacteria are notorious causes of meningitis, pneumonia and bloodstream infections. The researchers studied two leading pneumococcal vaccines: PCV13 and PPV23.

"Vaccination has substantially reduced the morbidity and mortality of bacterial diseases," asserted Dr. Juanjuan Wang, lead author of a series of experiments reported in *Science Translational Medicine*. The research confirmed how bacterial annihilation occurred—and which of the two vaccines prompted the most efficient immune response.

Vaccines are one of humanity's greatest technological achievements, having saved hundreds of millions of lives dating back to Edward Jenner's 1796 smallpox vaccine, which was developed in England during the reign of George III.

Most vaccines, Jenner's included, have been developed to fight viruses. And some of the world's best known vaccines have had a dramatic impact on public health, beating back a range of viral diseases—measles, the flu, mumps, polio, SARS-CoV-2, and more.

Vaccines aimed at bacteria are equally adept at thwarting disease and saving lives from devastating infectious agents. Immunizations that help the body repel bacterial infections include those developed to fight

diphtheria, pertussis and tetanus, along with the pneumococcal vaccines. Yet, what had remained a provocative—and unanswered research question—was how the body captured and killed pneumococcal bacteria when exposed.

Prior to the new research, scientists had suspected that after vaccination the immune system coaxed key cells, such as phagocytes, to migrate to sites of infection and destroy invading bacteria. But while that scenario was widely accepted, the core mechanisms of how it might work had remained unknown. Now, the international collaboration has produced an answer that is quite surprising.

"We report that vaccine-elicited immunity against invasive bacteria mainly operates in the liver," Wang wrote. "In contrast to the current paradigm that migrating phagocytes execute vaccine-elicited immunity against blood-borne pathogens, we found that invasive bacteria are captured and killed in the liver of the vaccinated host via various immune mechanisms that depend on the protective potency of the vaccine."

Wang, a vaccinologist at the Center for Infectious Disease Research at Tsinghua University in Beijing, underscored that mechanisms of vaccine-elicited pathogen clearance—how and where in the body the immune system got rid of invasive bacteria—had remained largely undefined, at least until now. And it took scientists on three continents to find the answer and reveal where the immune system annihilated disease-causing bacteria.

Turning to a mouse model, they were able to compare the effects of two well-known vaccines for Streptococcus pneumoniae, PCV13 and PPV23.

PCV13 is a so-called conjugate vaccine. PCV stands for pneumococcal

conjugate vaccine and the number 13 indicates the number of S. pneumoniae strains that it protects against. Conjugate vaccines are made up of two subunits—a weak antigen as one unit, and a strong antigen as a carrier unit. With both units, the immune system has a stronger response to the weak antigen, according to the U.S. Centers for Disease Control and Prevention.

The other vaccine analyzed in the investigation was PPV23, which is a polysaccharide vaccine. The initials stand for pneumococcal polysaccharide vaccine, which protects against 23 strains. A polysaccharide vaccine is designed to prompt immunity by exposing the immune system to sugars that swath the surface of nearly two dozen S. pneumoniae strains.

During the course of their experiments, the team was able to demonstrate a striking difference between the capture and kill capability prompted by the two vaccines. There was greater capture and kill efficacy detected with the PCV13 formulation. That vaccine was associated with an increased capture of circulating pathogens by hepatic endothelial cells.

PCV13 has long been considered more effective than PPV23, and Wang colleagues have now provided a reason for that difference. The researchers found that the more potent PCV13 induced higher amounts of IgG antibodies, and that PCV13 also more potently engaged Kupffer cells and epithelial cells in the liver.

Kupffer cells are macrophages—phagocytic white blood cells—that reside in the liver adhering to endothelial cells of blood vessels. Endothelial cells are the epithelial cells that line blood vessel walls. Because Kupffer cells are phagocytic, meaning, they ingest and destroy invasive microorganisms, their role is critical in the rough-and-tumble activity of capture and kill, Wang and colleagues found.

The team was able to confirm in their research that both Kupffer and endothelial cells captured S. pneumoniae in the bloodstream through a "zipper-like" mechanism before destroying them. The weaker PPV23 vaccine, by contrast, only engaged Kupffer cells and induced lower amounts of IgG antibodies. The scientists reported similar liver-based capture and kill patterns with vaccines against Neisseria meningitidis, a major cause of bacterial meningitis.

"With certain technical modifications, our findings may also be used for evaluation of vaccine candidates for viral pathogens that depend on viremia for dissemination," Wang concluded, noting that viremia is the presence of viruses in the bloodstream.

More information: Juanjuan Wang et al, Liver macrophages and sinusoidal endothelial cells execute vaccine-elicited capture of invasive bacteria, *Science Translational Medicine* (2023). DOI: 10.1126/scitranslmed.ade0054