Next-generation influenza B vaccines provide broad and long-lasting protection against flu viruses in preclinical tests

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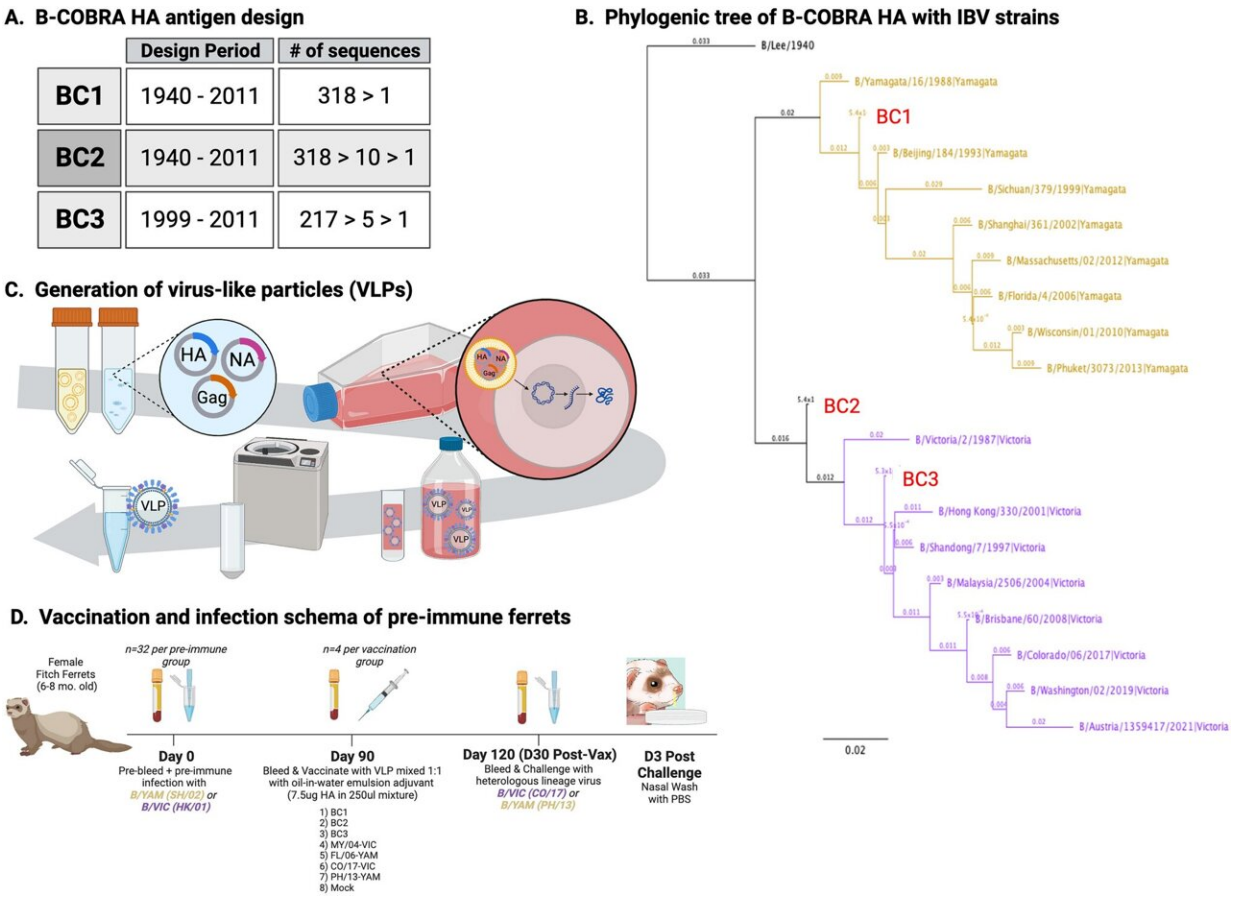

B-COBRA HA antigens for the vaccination and infection of pre-immune ferrets. Credit: *Scientific Reports* (2023). DOI: 10.1038/s41598-023-43003-2

Recent preclinical results indicate novel next-generation vaccine candidates developed at Cleveland Clinic protect against multiple strains of influenza and last longer than vaccines currently in use.

The vaccines are part of Cleveland Clinic's global vaccine research program, led by Ted Ross, Ph.D., Global Director of Vaccine Development at Cleveland Clinic. Published in *Scientific Reports*, the study credits the preclinical success of the influenza B vaccines to novel technology called Computationally Optimized Broadly Reactive Antigens (COBRAs).

Current vaccines use small, non-infectious parts of the virus or bacterium called antigens to train the immune system against infection. Keeping that immunity current can require yearly updates as the pathogen mutates, like for the flu vaccine. COBRAs are antigens designed to train the immune system's response more broadly to anticipate any changes.

"Seasonal influenza vaccines are mostly effective against pathogens with antigens matching the vaccine formulation," says study first author Michael Carlock, program manager in Dr. Ross's lab and Ph.D. student at the University of Georgia. "Viruses like to mutate constantly. If their antigens change too much, our immune system won't recognize them as the pathogen that the vaccine trained them to fight. We constantly need to update our vaccines to keep up with these new variants and mutations."

Further complicating the issue, a strain can mutate into multiple variants, and multiple strains of the same virus can break out at the same time. Vaccines made using an antigen specific to one strain or variant aren't always as effective against another.

Vaccine developers currently use a combination of statistics and public

health data to predict what flu strains will be the most common that year. They use antigens from those strains to make their vaccines. However, often by the time vaccines are manufactured and distributed, strains can mutate and render the vaccines less effective, Carlock says.

"Between 2001 and 2012, the influenza B strain used to make the flu shot matched the main influenza B strain infecting the population about 50% of the time," he says, "The vaccines weren't as effective as they could have been. That's part of why some flu seasons are worse than others."

The COBRA technology, says Carlock, eliminates the guesswork from antigen selection to protect against multiple diverse strains of the virus. The technology uses public databases of sequences and bioinformatic programs to analyze hundreds of flu strains over years' worth of flu seasons. The analysis identifies conserved regions of antigens most likely to be present in many viral strains and least likely to mutate over time.

The computer models behind COBRA can be used in multiple viruses, including influenza, SARS-CoV-2, HIV, respiratory syncytial virus (RSV) and many insect-borne viruses. Carlock and Dr. Ross say the success of their influenza B vaccine candidates serves as a proof-of-concept for COBRA as a whole.

When the influenza B COBRA vaccines were tested in preclinical models, they performed even better than expected. They protected against multiple strains of influenza B and even protected against strains between the two different lineages of influenza B. There was also evidence that the COBRA vaccines are longer-lasting than current technology.

"We used old strains isolated prior to 2013 to design these vaccines, but they protected against new strains circulating in 2023," says Carlock.

"The vaccines that public health officials actually made from and used against those strains ten years ago cannot protect against modern viruses. Our COBRA vaccines provide broad, long-lasting protection against many viruses over many years."

Clinical trials are planned to test the effectiveness of COBRA-based influenza vaccines against influenza in humans.

"The preclinical success of these vaccines is exciting because it shows our platform's promise in addressing public health threats effectively and proactively," Dr. Ross says. "As we continue to expand Cleveland Clinic's global vaccine research, technologies like COBRA are critical to serving the communities we reach all over the world."

More information: Michael A. Carlock et al, A computationally optimized broadly reactive hemagglutinin vaccine elicits neutralizing antibodies against influenza B viruses from both lineages, *Scientific Reports* (2023). DOI: 10.1038/s41598-023-43003-2

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