A flurry of RSV vaccine research may result in a protective immunization in the not-too-distant future

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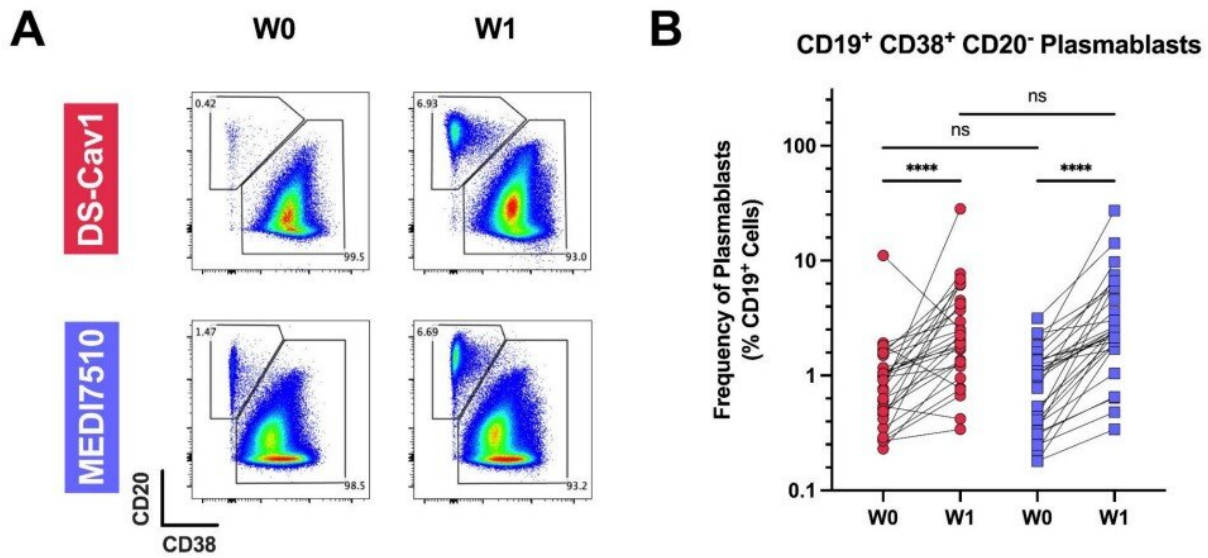

Plasmablasts at W0 and W1 post-vaccination. (A) Representative plasmablast plots are shown for a single participant vaccinated with DS-Cav1 (pre-F, N = 30) or MEDI7510 (post-F, N = 30) at week 0 (W0) and week 1 (W1). Cells were gated on live, singlet, lymphocytes then $CD19^+$ prior to gating $CD38^+$ $CD20^-$ plasmablasts. (B) Plasmablast frequency is denoted as percentage of $CD19^+$ cells. **** denotes P Science Translational Medicine (2022). DOI: 10.1126/scitranslmed.ade0424

A new analysis of how the immune system responds to both older and

newer investigational vaccines for respiratory syncytial virus—RSV—will help inform the ultimate translation of an immunization from the laboratory to actual clinical usage.

The research couldn't arrive at a more crucial time. The unexpected, and dramatic, worldwide escalation of RSV cases in recent months helped demonstrate why a vaccine to prevent the infectious illness is so critically needed. Each year, RSV is responsible for 1 in 50 pediatric deaths worldwide, according to researchers at Wilhelmina Children's Hospital in the Netherlands, where medical researchers recently completed a study on RSV.

The majority of those deaths occur among infants too young to fight the viral disease. But the infectious agent also is a killer of frail, older adults, data from the World Health Organization show, making the development of an effective vaccine a medical priority to prevent unnecessary deaths at opposite ends of the human age spectrum.

"There is currently no licensed vaccine for respiratory syncytial virus," writes Dr. Lauren Chang, who with a large team of colleagues at the Vaccine Research Center of the National Institute of Allergy and Infectious Diseases in Bethesda, Maryland, produced a comprehensive study analyzing potential RSV vaccines.

Most recent RSV vaccine candidates function by eliciting antibodies against the so-called fusion protein of RSV, reports Chang, lead author of the new research, which included scientists at AstraZeneca's Vaccine and Immune Therapies division in Gaithersburg, Maryland.

The pathogen uses its fusion protein to infect human cells and initiate the rapid cascade of deleterious events that result in full-blown infection.

The aim of the research was not only to compare investigational

vaccines, but to elucidate how different types of RSV vaccines engage the immune system. Not intended as an aim of the research is the peek it provides into the future, revealing the type of RSV vaccine possessing the most promise to eventually win regulatory approval.

"Here, we assessed the effect of RSV fusion protein conformation on B cell responses," Chang added, referring to her team's findings, which are published in the journal *Science Translational Medicine*.

The fusion protein, also known as the F protein, is primarily responsible for attaching to and penetrating host cells, infecting them. The F protein is also responsible for the subsequent cell-to-cell spread or "the syncytium formation" during RSV infection.

Syncytium formation means the fusion of many RSV infected cells glommed together; hence, the name, respiratory syncytial virus. RSV is classified into two subtypes, A and B, whose dominance alternates during different epidemic seasons.

"We compared the magnitude and quality of the serological and B cell responses across time points and vaccines," Chang continued. "We measured RSV A and B neutralization," Chang wrote, referring to antibody activity on the seasonal types of the infection. But the team dug deeper and studied different types of RSV vaccines and how each was able to interact with B cells and elicit antibody responses.

It was a comprehensive study for a complex viral infection. The pathogen has an affinity for epithelial cells in the lungs and other parts of the pulmonary tree. The infection's complexity is the reason newborns and the frail elderly can find the infection difficult, if not impossible, to shake.

Until the so-called "tripledemic" in recent months, not many people had

not heard of RSV, unless they or someone close had dealt with the respiratory infection, doctors say.

But the unexpected combo of the flu, COVID-19 and RSV, not only made RSV a household name, it familiarized broad swaths of the global population with yet another seasonal respiratory threat. RSV tends to infect the lower respiratory tract and is the cause of millions of infections worldwide annually, according to the World Health Organization.

Research by Chang and her colleagues at the Vaccine Research Center of NIAID, arrives more than a half century after the first efforts to develop an RSV vaccine.

Attempts to produce an RSV date back to the 1960s, but initial efforts were unsuccessful because they were marred by an ineffective vaccine. Scientists at the time had developed an RSV shot that induced a severe—and in two cases lethal—lung inflammatory response during the first natural RSV infection after vaccination of RSV-naive infants, according to the WHO.

Concerns regarding the faulty immunization "hindered development of alternative RSV vaccines for many years," experts at the WHO asserted in a statement. Nevertheless, in recent years, increased understanding of the biology of RSV and associated technological advances have resulted in multiple vaccine candidates now in clinical development, some of which may receive regulatory approval in the near future.

It is from this growing number of investigational vaccines over the years that Chang and colleagues were able to compare vaccine types.

The team examined how vaccine candidates prompt the emergence of antibodies against the fusion protein of RSV. Earlier vaccines were

based on the inactivated post-fusion form of the protein, while newer candidates tend to use a stabilized version of the active pre-fusion conformation. Few studies had ever directly compared the two vaccine strategies—at least, not until now.

Chang and colleagues comprehensively compared the antibody-generating capabilities of pre-fusion RSV type of vaccine and the post-fusion type. The researchers analyzed antibodies in serum samples from individuals who received either the DS-Cav1 pre-fusion vaccine, or the MEDI7510 post-fusion immunization.

Although both vaccines elicited antibodies against the fusion protein, antibodies from the pre-fusion immunization were better at neutralizing both the A and B subtypes of RSV in culture. Chang and colleagues concluded that, in terms of vaccine types, a prefusion stabilized prefusion RSV F vaccine elicits B cell responses with greater breadth and potency than a post-fusion F vaccine.

Further work showed this was partly because the prefusion vaccine elicited antibodies that can bind to additional sites on the F protein that weren't present in the post-F form.

In a related Focus article, also published in *Science Translational Medicine*, Dr. Mark Peeples of Nationwide Children's Hospital in Columbus, Ohio, comments on the research by Chang and her collaborators.

Peeples notes that the new findings about antibody binding may also apply to other viruses, such as SARS-CoV-2. The findings by Chang and the team "are important not only for RSV and COVID-19 vaccine development, but also for the development of vaccines against other enveloped viruses," he concluded.

More information: Lauren A. Chang et al, A prefusion-stabilized RSV F subunit vaccine elicits B cell responses with greater breadth and potency than a postfusion F vaccine, *Science Translational Medicine* (2022). DOI: 10.1126/scitranslmed.ade0424

Mark E. Peeples, Next-generation RSV vaccines avoid flipping out, *Science Translational Medicine* (2022). DOI: 10.1126/scitranslmed.ade9984