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EDITORIAL

On the Respiratory Syncytial Virus Vaccine

See review article by Kahlon *et al.*

With this issue of the *Journal* is the short review, "The Impact of the COVID-19 Pandemic on Respiratory Syncytial Virus", and during its submission to publishing process, the U.S. Food & Drug Administration (FDA) approved a respiratory syncytial virus (RSV) vaccine for adults in May—twice. Generally, RSV accounts for 60,000 to 160,000 adults being hospitalized per year, and the virus kills 6,000 to 10,000 adults per year. The highest risk factors are age ≥65 years, heart disease, lung disease, and immunosuppression. From the perspective of viruses, SARS-CoV-2 and COVID-19 dominated the winter respiratory seasons of 2020–21 and 2021–22. From the perspective of the research scientists, their decades-long work on a vaccine for RSV was interrupted by the COVID-19 pandemic as resources shifted from RSV to SARS-CoV-2. The remaining work accelerated, however, after the pandemic waned in 2022–23. The history of an RSV vaccine is worth mentioning to appreciate the recent progress that has been made, including the release and approval of multiple vaccines.

The study of an RSV vaccine came on the heels of a very successful polio vaccine in the mid-1950s. The polio vaccine was a whole inactivated vaccine, so a whole inactivated RSV vaccine was made in the mid-60s—with disastrous consequences. In a study of 31 infants, 20 became infected, 16 were hospitalized and two died.[1] Although inactivated vaccines are supposed to be safer than live vaccines, even safe for immunocompromised patients, the vaccine stimulated an autoimmune response that caused RSV vaccine–associated enhanced respiratory disease (VAERD), which progressed to a storm of cytokines and subsequently sepsis. It was two decades before any meaningful research was performed on RSV.

The meaningful research in question turned out to be with the fusion glycoprotein F, otherwise known as the F protein. In the mid-1980s, with the technology available, it was merely a blurry spot, but a very important blurry spot. It would be two more decades, before the atomic-level structure of the RSV F protein would be determined.[2] The location of this protein is on the surface of the RSV (much like the spike protein on a SARS-CoV-2 virus), and its function is to bind an RSV to a human cell. It exists in two forms: a prefusion state and a postfusion state. The problem with prefusion F protein is that it naturally progresses into the postfusion state. Research on vaccine candidates using the postfusion F protein elicited an antibody response that was not robustly neutralizing. In children, it did not last longer than 3 months, which did not carry them through an entire respiratory season. The challenge was to create an F protein that stayed in its prefusion state.

Dr. Richard Plemper describes the prefusion state of the F protein as a volcano with a huge boulder sitting in the crater at its top. It is relatively stable, but once that volcano is jiggled, the boulder roles down the side, releasing an enormous amount of potential energy (*i.e.*, energy is released as the prefusion F protein transitions into the postfusion state) and lies in a postfusion state that is impossible to reverse—imagine rolling a large boulder up the side of a volcano. So, the prefusion state F protein was mutated to keep it in that form, and it was used as a vaccine to initiate a more robust immune response.

Before the prototype vaccine studies were finished, COVID-19 emerged, delaying further development—this was the impact of COVID-19 on RSV vaccine research. On the other hand, RSV research to that point positively affected the COVID-19 vaccine. The studies that were performed to mutate RSV's F protein and keep it in its prefusion state were applied to the spike protein of SARS-CoV-2, expediting the creation of a COVID-19 vaccine. This the impact of RSV vaccine research on the COVID-19 pandemic. While SARS-CoV-2 was raging, disease from RSV was nearly absent. Work continued with SARS-CoV-2 vaccines as that virus' own rate of mutation was incredibly fast, necessitating new vaccines. Eventually, RSV returned with an epidemic of its own in 2022–23. This was likely, in part, due to an increase in susceptible persons set up by the lack of infection with RSV during the previous two years as a result of isolation, masking, and hand washing for COVID-19. Work on a vaccine for SARS-CoV-2 continued to delay RSV vaccine research until 2022 when phase III studies (re)started.

Three RSV vaccines have well publicized data from phase III studies (**Table 1**).[3–5] The Centers for Disease Control and Prevention (CDC)'s Advisory Committee on Immunization Practices (ACIP) met June 21–23, 2023, to review the data on the vaccines recently approved by the FDA and make a recommendation. The group voted 13 to 1 to recommend a one-dose regimen for patients 60–64 years of age, and 9 to 5 to recommend a one-dose regimen for patients ≥65 years.

There is still no FDA-approved vaccine for infants, and the adult RSV vaccines are not appropriate for infants because their immune systems respond differently than adults' do.

Table 1. Summary of results from clinical trials of RSV vaccines.

Vaccine	Age (years)	One-dose VE		2-dose VE	LRTI	Systemic events	
		1-year	2-year	2-year		Vaccine	Placebo
RSV prefusion F protein (GSK; Papi *et al.*)*	≥60	94.1%	67.2%	67.1%	94.1%	15.8%	14.9%
RSV prefusion F protein (Pfizer; Walsh *et al.*)*	≥60	66.7%			85.7%	27%	26%
Ad26.RSV.preF (Janssen; Falsey *et al.*)	≥65				80%	41.4%	16.4%

Abbreviations: LRTI, lower respiratory tract infection; VE, vaccine efficacy.
* FDA-approved.

Remember, nearly all adults have encountered RSV—most are infected by 2 years of age—whereas infants are naïve to RSV exposure; this is what caused vaccine-associated enhanced respiratory disease in some infants in the 1960s. That was a lesson learned the hard way, but a lesson nonetheless in the long path towards a successful RSV vaccine. The vaccine for adults is here, and an RSV vaccine for children is hopefully soon to come.

Forest Arnold, DO MSc

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