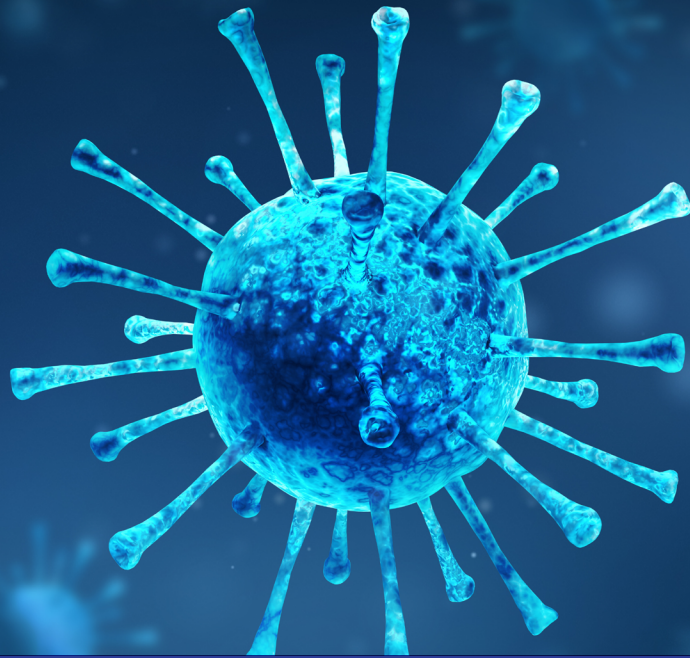


Leveraging Biosimulation to Inform Optimal Use of COVID-19 Vaccines



By Dr. Piet van der Graaf, SVP

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As the world struggles to address the vast demand for, and limited supply of, regulatory-approved COVID-19 vaccines, experts are investigating scientific approaches to maximize those precious resources.

Biosimulation, which integrates computer-aided modeling and simulation with pharmaceutical science, provides potent intelligence to support decision making on these crucial issues. It can help answer questions like:

- Do elderly people require a higher dose of the COVID-19 vaccine because their immune system becomes less effective with age?
- Might a lower vaccine dose be effective for young people?
- Can the interval between doses be increased to free up vaccine to allow more people to get their first dose earlier?
- Can people receive their first dose of one vaccine and their second dose of a different vaccine?
- How long does a vaccine's antibody response last? Will a booster shot be required in a year?
- If people have had COVID-19, should they still get a vaccine, and do they need the full dose?
- Are the answers to these questions the same for populations of different ethnicity?

The beauty of Certara's biosimulation models is that they allow researchers to study how a drug or a biologic is handled by the human body in computer-generated, virtual patients. They enable virtual computer-based trials to be conducted that may be impractical or unethical to perform with real subjects due to a range of recruitment challenges such as age, concurrent diseases, comedications, or an impaired hepatic or renal system. They generally yield results much faster and at a lower cost than actual clinical studies and are often used to streamline, optimize, and sometimes replace studies. *This speed factor is pivotal for COVID-19, especially as we grapple with how to optimize the vaccine supply chain.*

Biosimulation is a powerful and proven technology. Certara and our partners have been using biosimulation to support the development of drugs and biologics, including new modalities such as gene therapies, and to optimize immuno-oncology combinations for many years. These biosimulation technologies have been adopted by major pharmaceutical and biotechnology companies, academia and global regulatory agencies.

Developing the COVID-19 Vaccine Model

Certara established a biosimulation consortium with seven major pharmaceutical companies in 2017 to build a mechanistic model of the human immune system. The consortium wanted to predict when administering a biological therapeutic, such as an antibody, would generate an undesired immunogenic response in the body. Immunogenicity is a major challenge because it lowers a patient's exposure to, and hence the benefits derived from, the biological therapeutic. It can also cause immune-related adverse clinical events.

Certara's immunogenicity model has been validated using data from more than 20 clinical case studies that were either provided by consortium members or published in the scientific literature. It has also been presented to global regulatory agencies several times and is being applied today to the development of new biologics.

As the COVID-19 pandemic gripped the world, the Certara team quickly realized that its immunogenicity model could be reworked and extended for use as a COVID-19 vaccine model. Instead of trying to minimize the immune response as was the goal for the original immunogenicity model, the team switched its focus to maximizing the immune response for the COVID-19 vaccine. To be effective, a vaccine needs to induce an immune response and create an immune memory in the body. Then, the next time the virus, which looks very much like the vaccine protein, enters the body, the body will recognize it and respond very quickly.

Once the principle was confirmed, the team inputted part of the COVID-19 virus sequence (as a hypothetical COVID-19 vaccine) into the newly modified model and demonstrated that it would generate an immune response. Then, they calibrated the model using the structure of actual COVID-19 vaccines and were able to replicate all the published data for each of them. Essentially, they demonstrated that they could predict with a virtual trial the outcomes of an actual clinical trial using those vaccines. The model also allows the team to predict immunological responses that may not be measurable in actual patients, such as the level of memory B cells, which is used to compare and optimize various dosing schedules in the virtual trials.

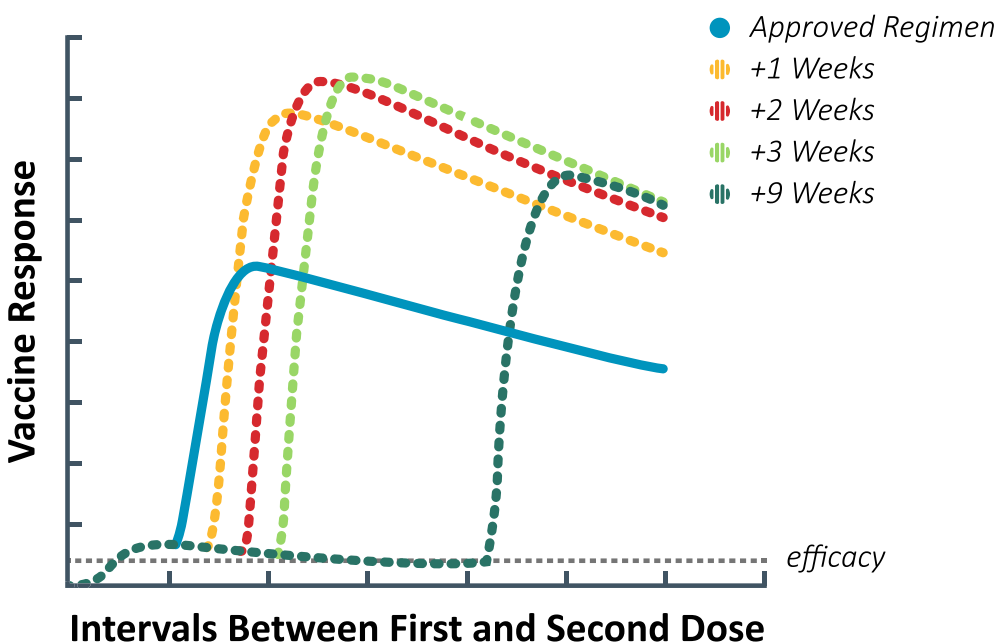
Certara’s COVID-19 vaccine model is now being used to investigate dose selection for different populations and determine optimal timing for the second vaccine dose. Results from the COVID-19 vaccine model have already been submitted to a global regulatory agency to support clinical trial designs.

Evaluating the Optimal Dose for Young and Elderly People

Certara’s vaccine model generates virtual populations of different ages, allowing a series of virtual clinical trials to be run using the COVID-19 vaccine model in order to determine which vaccine dose will generate the maximum antibody response for each age group. The model leverages Certara’s Simcyp™ Simulator, which features proprietary genetic, physiological and epidemiological databases to create virtual patients with different characteristics, such as age, ethnicity or disease state. For example, we can predict whether elderly people would be better served by receiving a higher dose of vaccine and whether younger people could generate a robust antibody response with a lower dose. If so, it may be possible to split vaccine doses between older and younger populations, ensuring that they all get the right dose to generate the optimal antibody response.

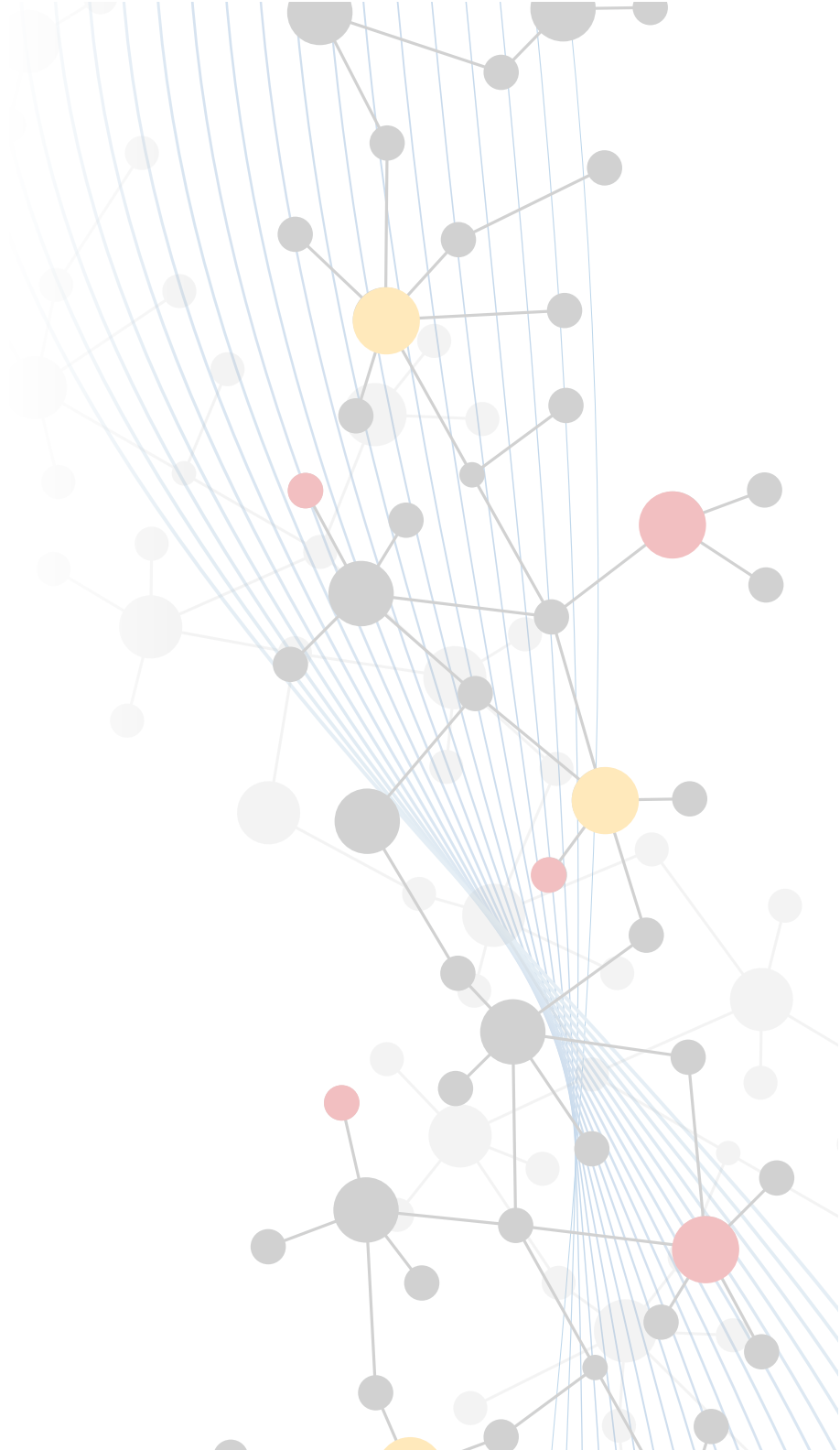
Determining the Best Dosing Interval

The COVID-19 vaccine model shows in graphical form the antibody response (or how many antibodies a person produces against the COVID-19 virus) when the second vaccine dose is given three, four, six or 12 weeks after the first dose. Antibody response is used as a surrogate for efficacy in vaccinology and is considered the best biomarker. This approach can show when the maximum antibody response is generated by the second vaccine dose and at what interval after the first dose that response begins to diminish. For example, in the hypothetical case below, the data show how long the second dose can be delayed before it starts to have a negative impact on the level of antibody response generated. This information is used to guide the next clinical steps.



Conclusion

Biosimulation with Certara’s COVID-19 vaccine model can help answer many important questions about how to best use the world’s limited supplies of COVID-19 vaccines. The use of this approach is especially important as recruitment for ongoing clinical trials diminishes, especially in western countries. Most important, biosimulation employs well-established scientific approaches and existing clinical and real-world data to inform healthcare decisions that will impact us all.



About Certara

Certara is a leading provider of decision support technology and consulting services for optimizing drug development and improving health outcomes. Certara's solutions, which span the drug development and patient care lifecycle, help increase the probability of regulatory and commercial success by using the most scientifically advanced modeling and simulation technologies and regulatory strategies. Its clients include hundreds of global biopharmaceutical companies, leading academic institutions and key regulatory agencies.

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