Interview with Maria Major

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Maria Major

Maria Major is a medical field advisor in vaccines for Pfizer. She has worked in the vaccine industry since 1998 starting at Merck (chicken pox, meningococcal, HPV, Zoster vaccines), then Novartis (influenza, meningococcal vaccines), and for the past five and a half years at Pfizer (pneumococcal, meningococcal, COVID-19 vaccines). She graduated from Western University with a BSc in biology, holds an MPH from the University of Waterloo, and is in the final stages of completing her PhD in public health at the University of Waterloo. Her research interests include the epidemiology and population impact of vaccines.

UTMJ: Could you tell us a bit about yourself?

MM: I'm a Field Medical Advisor for Pfizer Vaccines. I have been working in the vaccine industry for the last 26 years, working on over 10 vaccines starting with chickenpox back in 1996. For the last 6 years, I've worked at Pfizer in Medical Affairs. It has been very exciting here at Pfizer with the commitment to go all-in on this vaccine. I feel like we're all running on adrenaline.

UTMJ: Before we dive in, tell us a bit about the role of a Field Medical Advisor and your work in Medical Affairs.

MM: There are many steps in vaccine development. There is basic science or product development, clinical development, and then end-user data communication. Scientists responsible for research and development don't have the capacity to communicate their research nationally. They may attend special meetings with regulators, but they rely on Medical Affairs to present the data to guideline committees, governments, public health, and researchers. We also address local vaccine research priorities and questions that require information beyond what is available in the product monograph. Finally, they call it field work because I work out of my home! The work is engaging due to the diversity and interesting people.

UTMJ: We know Pfizer-BioNTech has developed a messenger RNA (mRNA) vaccine against COVID-19, could you take us through the timeline from inception to distribution?

MM: Since 2018, Pfizer and BioNTech were investigating mRNA technology to develop an influenza vaccine. However, after SARS-CoV-2 was sequenced on January 12, 2020, they saw potential in using that genetic code to produce a SARS-CoV-2 vaccine and put the influenza project on hold. By March 2020, we began to investigate 4 vaccine candidates. SARS-CoV-2 was declared a pandemic on March 12, 2020, so you can see that this was happening very quickly. Prior, there were no approved mRNA vaccines but there was ongoing research using mRNA. Thus, while less conventional, we proceeded with this innovative approach.

New vaccine development usually takes around 10 years, meaning it would be unlikely to impact the pandemic. However, Pfizer's CEO, Albert Bourla, asked the research team what was needed to develop a vaccine this year. This timeline was shocking, but they made a list of requirements. Then, they were given a blank check, essentially to make it happen. It felt unrealistic to promise the world a COVID-19 vaccine this quickly, but the dedicated funding and flexibility to explore new processes removed corporate barriers.

After identifying the vaccine candidates, we developed an adaptive clinical trial design to test them safely in humans. We flattened the process and conducted each research phase in parallel rather than sequentially, thus saving time. The clinical trial was registered as a Phase I/II/III trial and was published in the New England Journal of Medicine with initial immunogenicity trial results from Phase II. Once we established early positive safety and immunogenicity data from Phase II, we initiated the Phase III efficacy trial in parallel. The pandemic meant endpoints accrued quickly, allowing sufficient efficacy data collection to submit to regulators and acquire interim authorization. The ongoing trials evaluate safety and efficacy data, though it is no longer blinded. In early 2021, the protocol was updated, including evaluation of the vaccine in younger children (the amended protocol was published in Nature).

No steps were skipped regarding safety evaluation. Regulators evaluated safety data daily and independent safety committees unblinded trial data weekly to evaluate safety. Additionally, we developed manufacturing capacity and produced doses while still in Phase II. We had produced nearly 74 million doses in 2020 when the emergency licensing was only provided on December 12, 2020. Typically, we'd never produce vaccine before a product is licensed due to the financial risk. We like to say we did not take any safety risk, only financial risk.

UTMJ: How does the mRNA vaccine work compared to other vaccine types?

MM: The vaccine consists of an mRNA molecule that codes for the full spike protein of the SARS-CoV-2 virus, contained within a novel delivery system – the lipid nanoparticle. The vaccine is injected intramuscularly, is taken up by the lymphatic system, and enters cells where the mRNA is then released into the cytoplasm. The mRNA uses ribosomes to produce copies of the SARS-CoV-2 spike protein. This is then presented to the immune system (MHC Class-I/II) where it generates both humoral (production of neutralizing antibodies) and cell-mediated (production of both CD4+ and CD8+ cells) immune responses.

The difference between mRNA technology and conventional vaccines is that the mRNA vaccine doesn't deliver antigens, rather your cells make them. Most vaccines work by delivering an antigen, to which your body generates an immune response. For example, this includes protein sub-unit or split virus vaccines (influenza, hepatitis B), virus-like particle vaccines (HPV), live-attenuated vaccines (chicken pox, MMR), or conjugated carbohydrate vaccines that protect against encapsulated bacterial pathogens (HiB, PCV).

UTMJ: Why did Pfizer-BioNTech decide to use a lipid nanoparticle delivery system?

MM: The delivery system is a proprietary lipid nanoparticle developed by a Vancouver-based Canadian company, Acuitas Therapeutics. It is positively charged and made of 4 lipids, allowing easy passage through cell membranes. While one of the lipid components is polyethylene glycol (PEG), which may be allergenic in some individuals (the vaccine is contraindicated those with a known allergy to any of its components), it will not generate antibodies, avoiding the issue of vector immunity. This means you can administer additional doses to boost the immune response or protect against new variants, if needed, without changing the delivery system.

UTMJ: Considering this is a completely new platform, were there any roadblocks throughout development?

MM: There was never certainty this would succeed, but retrospectively, everything turned out well. It helped that there was already a research team in place investigating mRNA technology, as their findings were applied to development of this vaccine. The BioNTech collaboration was an ideal partnership, with complementary expertise. Pfizer had experience in conducting Phase III clinical trials and the manufacturing capacity to produce a large number of doses, while BioNTech had developed an innovative mRNA platform.

Most roadblocks were eliminated by the financial commitment made by Pfizer's CEO and the willingness of stakeholders (like regulators) to be flexible in developing new evaluative vaccine processes. Now we are reflecting on what we might keep from this newfound agility! Not that everything should be treated like an emergency – everyone involved with the pandemic is exhausted and has made tremendous personal sacrifices. We would all like a little bit of normalcy, but we are also considering our lessons learned to improve vaccine development efficiency.

UTMJ: On the efficiency note, tell us about the regulatory changes and frameworks necessary to get the vaccine approved so quickly.

MM: In Canada, the vaccine has an Interim Order Authorization. This is an emergency regulatory tool used to authorize products quickly with certain restrictions. Things got done quickly on a regulatory level because Health Canada was very proactive. By October 2020, Health Canada invited file submissions for COVID-related vaccines or treatments to be reviewed on a rolling basis. Typically, we would submit the clinical data to the regulator after the trials are complete, then receive a decision afterwards. During this period, new clinical data cannot be added to your submission unless it addresses specific questions (e.g. clarifying data or manufacturing processes). New data submissions usually result in rescinding and re-submitting applications, ultimately lengthening the process. Here, the so-called "rolling submission" allowed for the submission of new data in real-time for Health Canada's review. This interim process was an important contribution to the availability of COVID-19 vaccines in Canada.

UTMJ: We understand there are several SARS-CoV-2 variants circulating. What happens if a variant escapes vaccine coverage?

MM: One advantage of the mRNA platform is not needing to grow virus to produce a protein antigen. All you need is the genetic code of the antigen to produce the vaccine. This means we can make changes to a vaccine, adapting it to an emerging variant for example. It is possible to re-program the mRNA template to produce a new vaccine in around 6 weeks. Currently, the Pfizer-BioNTech COVID-19 vaccine demonstrates real world effectiveness against some of the circulating COVID-19 variants (such as B.1.117), and we continue to gather effectiveness data as new variants emerge. Of course, it is not unreasonable to assume there may be a variant that could escape vaccine coverage at some point in the future. The current vaccine works, so there is no reason to stop production and divert resources to create a different vaccine, but it is highly reassuring to know that we could produce a vaccine tailored to a new variant in about 6 weeks (excluding the time needed for regulatory approval).

UTMJ: The Pfizer vaccine is given in two doses. Why is this and will we need more boosters in the future?

MM: We expected boosting might be necessary. The vaccine performs reasonably well after one dose, but immunogenicity and efficacy are significantly improved after administration of the second dose, which may indicate that there is better protection durability with 2 doses. The 21-day period (the interval used in clinical trials) allows the

body to fully generate the priming immune response. Then the second dose generates a robust boost of that response without interference.

The need for additional boosters is currently unknown but something we are watching carefully. This is the first ever mRNA vaccine, so we do not have a model for the duration of protection. Current data shows immunogenicity and effectiveness lasts for at least 6 months after two doses and that research is ongoing.

UTMJ: What are the current efforts at Pfizer-BioNTech focused on?

MM: Currently, we are investigating use of the vaccine in special populations like pregnant women, youth, immunocompromised populations, etc. We are also evaluating real world effectiveness in Israel, and we are starting a study in South Africa to investigate effectiveness against another variant of concern (B.1.351). An important area of research is stability. Currently the vaccine needs to be stored at ultra-cold temperatures which creates issues for cold chain management and distribution of the vaccine. We recently registered a trial to evaluate the immunogenicity of a lyophilized version of the vaccine, which wouldn't require ultra-cold storage. Solving this issue will allow us to expand the use of this technology to develop other vaccines such as influenza.

UTMJ: You mentioned there were multiple candidates. Are any of them still being investigated that could be part of future vaccine production?

MM: Two of the four candidates use the full COVID-19 spike protein while the other two were just the receptor binding domain subunits of the spike. Using the full spike protein might be why we see such great efficacy against variants, as opposed to the receptor binding domain, which turned out be more highly mutable. The other spike protein candidate we are still looking at uses self-amplifying RNA (saRNA), meaning when it enters the body, it can self-replicate. This could mean we would only need to give one dose. However, since this vaccine is working, the main questions we're looking at now are related to special populations, improving the storage temperature, and ensuring coverage of any variants of concern that may emerge.

UTMJ: What are some of the future implications of the mRNA platform?

MM: BioNTech is engaged in many early-stage research collaborations, applying their mRNA technology to develop cancer treatments. Pfizer is currently collaborating with BioNTech on the use of mRNA for the development of vaccines, specifically influenza. The agility of this platform makes it very practical for quickly scaling up manufacturing in emergencies as well as responding to viral mutations.