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BOOK REVIEW

Gregory Zuckerman: *A shot to save the world: the inside story of the life-or-death race for a COVID-19 vaccine*

Portfolio/Penguin, 2021

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In December 2019, infections with a previously unknown virus were reported from Wuhan, China. By March, this virus, subsequently named SARS-CoV-2, had spread around the world. Initial preventive measures were limited to non-pharmaceutical interventions; masking, social distancing, and environmental hygiene. Although public health professionals knew a targeted vaccine would be needed to stop transmission of the virus, many scientists were convinced that it could be years until a safe effective vaccine was produced. Dr. Anthony Fauci, director of the U.S. National Institute of Allergy and Infectious Disease, said March 2020 "the earliest the US could possibly get a vaccine would be in 12 or even 18 months, at least."[1] The vaccine previously developed in the shortest amount of time was to protect against mumps—and that took four years. Not only were predictions that it would take time to develop a vaccine but our expectations were low—a vaccine that protected against 50% of infections would be a triumph. Spoiler alert! The Pfizer-BioNTech mRNA vaccine, a highly effective, safe vaccine, received emergency use authorization (EUA) from the FDA less than one year after the new virus was identified with EUA of two additional vaccines quickly following. Gregory Zuckerman's latest book *The Shot to Save the World* recounts the decades-long research that underlay the rapid development of not one, but three vaccines against the SARS-CoV-2 virus.

All immunizations work essentially identically—the body's immune system is introduced to an agent or part of an agent, so that the body can defend itself if it encounters that agent again. Up until last year, there were basically four platforms; that is, the type of technology used to manufacture vaccines, in licensed vaccines in the United States. The oldest method is to take a virus or bacteria and inactivate it, so that it cannot cause an infection. One type of influenza vaccine is an example, as is the hepatitis A vaccine. Some vaccines use just part of the virus or bacteria—for example, those against the human papillomavirus (HPV) or pertussis. We also have vaccines that use an attenuated, or weakened, virus, precluding the virus from causing disease—the measles, mumps, rubella (MMR) vaccine is an example of this type. Lastly, we get protection against some bacterial diseases such as tetanus by creating immunity to the toxin the bacteria produces rather than to the bacteria itself. Each of these methods has its benefits and drawbacks and can be used for certain pathogens but not others.

The race to develop a vaccine against SARS-CoV-2 was intense with high stakes. The field was crowded—by late July 2020 there were over 165 vaccine candidates in development and more than 30 in clinical trials using different methodologies. Zuckerman's book tells the story of how two platforms that had not been employed in U.S. licensed vaccines previously were studied, modified, and finalized. Messenger RNA (mRNA) was discovered 60 years ago—it serves as the conduit to interpret genetic material into proteins. By injecting mRNA for virus proteins, the body will read this mRNA and produce virus proteins that the immune system can then recognize, providing future protection against that virus. These proteins cannot cause disease as they do not comprise the complete virus. The second successful technique described involves inserting parts of the SARS-CoV-2 genetic material into a harmless virus, often adenovirus, so that when this mild virus replicates in the body, proteins of the inserted virus are made as well, initializing an immune response to those proteins. Again, no

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[1] https://www.businessinsider.com/us-top-virus-expert-coronavirus-vaccine-12-18-months-away-2020-3, accessed 25 April 2020.

complete COVID virus is included in the jab so there is no possibility of infection with it. Novavax's work on development of a traditional platform for the SARS-CoV-2 vaccine is mentioned, but not followed in as great detail, perhaps because it uses a more conventional platform and has not yet received FDA emergency use authorization.

While many of us may only have heard about mRNA and adenovirus vector vaccines in the context of SARS-CoV-2, Zuckerman's extensively researched book begins this story over 40 years before this pandemic virus appeared with attempts to develop a vaccine to protect against HIV, something we are still waiting for. The book ends with FDA authorization of two mRNA (Moderna and Pfizer) and one adenovirus vector vaccines (Johnson & Johnson). This is not a straightforward, simple, story and Zuckerman helpfully includes a cast of characters for the companies involved, which includes Moderna, BioNTech, AstroZeneca, and Novavax, governmental scientists, as well as other individuals who contributed.

Development of a vaccine for which billions of people throughout the world would be eligible was both a high risk and high reward endeavor with the anticipated result of both saving lives and making money. The role of government funding through Operation Warp Speed (a less potentially confusing tag could have been chosen) played a major role as development of a new vaccine was estimated in 2019[2] to cost between 31 and 68 million dollars, probably more for a newly-identified virus. However, while Pfizer-BioNTech contracted with Operation Warp Speed to sell vaccine doses, they did not sign a contract for upfront development of the vaccine, perhaps fearing bureaucratic red tape. Moderna and AstroZeneca did accept government monies for vaccine development.

A Shot to Save the World is both a business book and a science book, with the science accessible to most readers (Zuckerman is not a scientist and there are a few minor scientific misstatements, such as confusing preventative with therapeutic vaccines). As vaccine development progressed, the advantages of an mRNA vaccine platform became apparent. However, there were multiple technical and business-related issues that had to be overcome, and Zuckerman does a good job of explaining these setbacks and successes. There was criticism of "science by press release" as the traditional peer-review procedure was sidestepped. The book does a good job of stressing that science is not a solitary activity and does not occur in a linear fashion. There are many failures, also known as opportunities to learn, along the way. Science takes persistence, as well as intuition and smarts. It's a complicated story told in detail.

While the science is ultimately crucial in developing new technologies, it's not the only aspect that needs to be considered—there's human psychology as well. As scientists had to make a final decision on vaccine design, Pfizer CEO Albert Bourla and senior scientist Mikael Dolsten began to have second thoughts. Nobel prize in Economic Sciences winner Daniel Kahneman had been hired a few years previously to talk about decision-making red flags including the "bandwagon effect" (also known as the Abilene Paradox[3]; when people do something primarily because other people are doing it, regardless of their own beliefs[4]) and "ostrich bias" (a type of confirmation bias where we avoid negative or new information and proceed in the direction we've chosen.[5]) They were worried that scientists were making one, or both, of these mistakes. Only one vaccine design could go forward, however, and a decision was made. Key Pfizer players had a difficult few weeks until the data came in showing that they had made a correct choice. Recognizing that these psychological defenses can play a role can help improve decision making, but luck still plays a role.

I assume in an attempt to humanize the scientists, a great deal of information not relevant to the story of vaccine development (clothes worn, daily schedules, family issues) are included. I do not really care what the dog's name is or the scientist's alcohol of choice. My favorite piece of minutiae was about the scientist who wore the same clothing uniform each day to shave 3 minutes off of getting ready for work. Heated disputes between the players are detailed, as is the intense competition to be the first to publish new findings. Scientists need money to fund their research, and that is a constant struggle in the academic and business worlds. The toil this enormous workload took on the scientists is telling, and some seem to have suffered from PTSD following a year of non-stop work. The paucity of women in this story points to the challenges women face, particularly those with children, in extremely competitive environments where 80 hour weeks are the minimum, and work/life balance is non-existent. The lives of many of these scientists overwhelmed me, and I was unclear whether Zuckerman was admiring their dedication or including so much detail to comment on the, what I found sad, lack of balance in their lives. However, not all the major players were men. Dame Sarah Gilbert, a vaccinologist at Oxford's prestigious Jenner Institute and co-founder of the University's spin-out company, Vaccitech (which develops vector vaccines), is credited with a major role in developing the Oxford/AstraZeneca vaccine.

But succeed they did and I, for one, am grateful these protective vaccines were available less than 12 months

[2] https://www.thelancet.com/journals/langlo/article/PIIS2214-109X(18)30346-2/fulltext

[3] https://en.wikipedia.org/wiki/Abilene_paradox

[4] https://www.investopedia.com/terms/b/bandwagon-effect.asp

[5] https://thedecisionlab.com/biases/ostrich-effect

after identification of this new pandemic virus. All three U.S. authorized vaccines were shown to be safe and incredibly effective in preventing infection, hospitalization, and death. However, vaccines do not save lives, jabs in arms do, and developing a vaccine is a technical, albeit, complicated problem. Convincing the public to receive such a vaccine is a "wicked" problem and one that public health could have approached in a better manner, not anticipating the tremendous backlash from the anti-vax campaign and the role of social media in propagating false information. Many in Communities of Color were apprehensive about a government-sanctioned vaccine due to historical exploitation. Public health's messaging that a vaccine was all we would need to stop the pandemic also did great damage to the overall campaign to prevent transmission and infection. Instead, we need to employ a "Swiss cheese" model with layers of protection including vaccine, particularly for those who may not respond to the vaccine optimally and for whom infection could have serious consequences.

So what is ahead? On the one hand, these vaccines, constructed to protect us against the original SARS-CoV-2 virus, appears to be less effective against preventing infection with the newer variants that have evolved, such as delta and omicron. However, the vaccines are still doing an excellent job of protecting against hospitalization and death, which in the end, is what is essential. Will this be true for future variants that arise? Time will tell, but the good news is that these vaccines can be easily modified to protect against evolved SARS-CoV-2. The optimal timing of boosters is still being determined, as we understand more about how vaccine-induced immunity lasts in the context of new variants. While we have these incredible protections against the pandemic virus, the situation continues to evolve and research continues.

The research by these scientists, followed in this book, as well as others, have laid the groundwork for future medical advances. While the book stops with authorization of these three vaccines, scientists currently are working on using mRNA technology for a myriad of other applications, including new vaccines against influenza, rabies, and Zika viruses. In addition, mRNA as a platform for therapeutics is being investigated for protein replacement therapy and the treatment of some genetic diseases.

A Shot to Save the World is a fascinating peek into the race to develop vaccines quickly and safely for a new virus. I would recommend it to anyone interested in the science and the business aspects of developing immunizations, as well as the struggles scientists face in both their personal and professional lives as they try to save the world.