Case Study: Preparing for the next global crisis

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Project lightspeed: A case study in research ethics and accelerated vaccine development

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Abstract
The COVID-19 pathogen led to a fast expanding pandemic because it proved lethal in certain populations but could be transmitted by persons who appeared healthy. As a result, researchers came under unprecedented time pressure to develop a vaccine. This case study focuses on the first COVID-19 vaccine, which was approved for use in humans, known as Comirnaty, the BioNTech-Pfizer COVID-19 vaccine or Vaccine BNT162b2. With the benefit of hindsight, we show how close collaboration with regulators and trust-based decisions meant that the race for a COVID-19 vaccine was won without purposefully infecting healthy participants with an infectious agent that can cause severe illness or death and for which no rescue therapy had existed.

Keywords
Vaccine development, COVID-19, research ethics, clinical trials, project lightspeed, BioNTech

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Introduction – the challenge

The COVID-19 pandemic put researchers under unprecedented time pressure to develop a vaccine. The speed with which the COVID-19 pathogen developed into a pandemic (U.S. Department of Defence, 2023: 150) illustrates the seriousness of the challenge. Patient Zero is assumed to have been infected in China in mid-November 2019. On 30th January 2020, the World Health Organization (WHO) declared a *Global Public Health Emergency*, which was upgraded to a pandemic less than 2 months later on 11th March 2020. By the end of the year, the WHO – using excess deaths figures – estimated the global death toll from COVID-19 in 2020 at over 3 million (World Health Organisation, 2023).

It was clear that 'vaccines are needed to protect from SARS-CoV-2, the virus causing COVID-19' (Speiser and Bachmann, 2020: 1). The normal duration of vaccine development for newly emerging pathogens is estimated to range from 10 to 15 years (Kalinke et al., 2022). Particularly fast advances, such as the development of the ERVEBOTM vaccine for Ebola, still took 5 years from start to regulatory approval (Wolf et al., 2021).

The German firm, BioNTech started its vaccine development under the name 'Project Lightspeed' on 27th January 2020 (Miller and Şahin, 2022: 42). Under 11 months later, on 8th December 2020, 91-year old UK resident Margaret Keenan received Comirnaty, also known as the BioNTech-Pfizer COVID-19 vaccine or Vaccine BNT162b2 (BBC, 2020).

The COVID-19 pandemic not only 'touched off an unprecedented search for vaccines and treatments' (Weijer, 2024), it also developed into a show case for research ethics discussions around human challenge trials (HCTs) versus traditional vaccine development (Rosenheck, 2022). On the one hand, it was argued that purposefully 'infecting younger participants at lower risk of complication with Covid-19 . . . could save thousands of lives' (Savulescu, 2020). This view was also promoted by the 1DaySooner initiative, which collected the names of tens of thousands of potential volunteers for HCTs in 2020 (1Day Sooner, 2020). On the other hand, it was maintained that HCTs for COVID-19 are 'Too Risky, Too Soon' (Dawson et al., 2020) because purposefully infecting healthy participants with an infectious agent that can cause severe illness or death and for which no rescue therapy exists is a major ethical challenge (Weijer, 2024).

With the considerable benefit of hindsight and knowing that vaccine development was undertaken without the implementation of HCTs, this case study, based on available literature, uses a research ethics lens to analyse *how* it was possible to develop an effective COVID-19 vaccine in under 11 months. The first section focuses on research governance questions, in particular the close collaboration with regulators. The second section broadens the topic to a wider ethical leadership question, namely the role of trust versus intellectual property agreements in collaborations with new partners. A conclusion summarises the lessons learned.

Close collaboration with regulators

Standard practice in vaccine development involves the following eight main stages:

(a) Design of vaccine candidates,
(b) toxicological studies on cell cultures and
(c) animals to establish the vaccine candidates' basic viability,
(d) clinical trials with a very small number of healthy volunteers (Phase 0) to gauge the metabolisation of the new substance in human beings,
(e) further trials involving several dozen healthy volunteers (Phase I) to establish the safety and immunogenicity of a vaccine candidate,
(f) further trials with several 1000 healthy volunteers (Phase II) to evaluate safety and immunogenicity and to accumulate data on the effects of different dosages to optimise the product, and
(g) further trials testing the vaccine candidate with tens of thousands of healthy volunteers to establish safety, immunogenicity and efficacy of the vaccine (Phase III) (Stern, 2020).
(h) The eighth stage involves obtaining (emergency) use authorisation for use in humans.

On 25th January 2020, the co-founders of BioNTech, Özlem Türeci and Uğur Şahin, decided to enter the COVID-19 vaccine development race. One day later, on 26th January 2020, Şahin had designed eight vaccine candidates (Miller and Şahin, 2022: 29) (step a).

The next steps require regulatory approval (FDA Center for Biologics Evaluation and Research, 2020). In the case of BioNTech, that involved approval from the Paul Ehrlich Institute (PEI), the German regulator for vaccine development at the Federal Ministry of Health. Based on prior good working relationships, Şahin persuaded senior PEI staff to provide a presentation slot for a planned vaccine study within a week rather than the 3 months this normally requires (Miller and Şahin, 2022: 46). PEI staff agreed on one condition. The BioNTech team had to provide a detailed briefing document about the vaccine development 2 days ahead of the meeting (Miller and Şahin, 2022).

German regulator PEI were not the only ones amenable to accelerated processes. Regulators across the globe were adapting their approaches to aide acceleration of vaccine development (Avorn and Kesselheim, 2020), including the Medicines and Healthcare Regulatory Agency (MHRA) in the UK (Mahase, 2020), the Food and Drug Administration (FDA) in the United States (Nania, 2020) and the European Medicines Agency (European Medicines Agency, 2020).

On 4th February 2020, BioNTech staff completed the briefing document detailing their plans to the PEI. The document included a:

> comprehensive rundown of every aspect of a potential drug's development, from the underlying technology to the raw materials and active ingredients that would be used, to the precise designs of preclinical safety studies on mice and primates. Normally, this would take between four and six weeks to complete. BioNTech had less than five days and was starting from scratch. It would have to move faster than it had been ever done before; indeed faster than anyone in the industry had ever moved (European Medicines Agency, 2020: 46).

At the regulator's (PEI) meeting with BioNTech staff on 6 February 2020, one ethically controversial proposal was raised, which would, however, accelerate the study significantly. The proposal was to run toxicological studies (steps b, c) in parallel with exposing a single healthy volunteer (step d) in a hospital setting to a very small dose of one vaccine candidate (European Medicines Agency, 2020: 56). As Özlem Türeci put it: 'Given our previous clinical experience with m-RNA vaccines, we felt that the toxicology study in animals would not tell us much more than we already knew (European Medicines Agency, 2020: 57)'.

This approach had already been approved by the US FDA for Moderna, the other company working on an mRNA-based COVID-19 vaccine (European Medicines Agency, 2020: 54). This is termed 'rolling review' and involves combined or overlapping phases in vaccine trials. The FDA also published guidance for the pharmaceutical industry about how to accelerate the development of COVID-19 vaccines (FDA Center for Biologics Evaluation and Research, 2020). In contrast to the FDA, the German regulator PEI refused this acceleration of clinical studies and BioNTech formally applied for approval of the toxicological studies, to run ahead of involving healthy volunteers (Miller and Şahin, 2022: 60).

On the same day that the WHO announced a global pandemic, 11th March 2020, BioNTech staff injected rodents with all vaccine candidates (Miller and Şahin, 2022: 123). On 27th March 2020, results showed that the immune reaction, catalysed by the vaccine candidates, had neutralised COVID-19 infections in rodents (Miller and Şahin, 2022: 126). From this stage onwards, it normally takes between 18 and 30 months to complete the preclinical stages of development (Kashte et al., 2021) . However, BioNTech staff had discovered that interim results from the toxicological studies can be accepted by regulatory authorities in times of crisis (Miller and Şahin, 2022) and the PEI did agree to this approach.

Still, even an interim report on toxicological studies in animals would be time-consuming. What was originally planned were three consecutive tests in rodents with 3 weeks in between the individual doses (Miller and Şahin, 2022: 160). It would then take at least 6 weeks until all doses had been administered and blood samples could be taken from the rodents to verify results. Further acceleration was deemed necessary. Given that the main expert for toxicology studies at BioNTech did not expect serious local reactogenicity (e.g. fever, sore injection point) in the rodents, she advised shortening the time between injections to 1 week (Miller and Şahin, 2022: 161). As a result, BioNTech was able to produce a 900-page interim toxilogical report in under 2 months (Miller and Şahin, 2022: 171).

Less than a month after the toxicology studies in rodents had started, on 22nd April 2023, the regulator approved Phase I and Phase II clinical studies for four vaccine candidates based on interim toxicology reports in rodents. A press release (BioNTech, 2020a) noted that:

> The dose escalation portion of the Phase 1/2 trial will include approximately 200 healthy subjects between the ages of 18 to 55 and will target a dose range of 1 μg to 100 μg aiming to determine the optimal dose for further studies as well as evaluate the safety and immunogenicity of the vaccine.

One day after obtaining the approval, the first human healthy volunteer was injected with one of the vaccine candidates (Miller and Şahin, 2022: 175). Astonishingly, the Oxford Team, which was developing the vaccine that later became known as the AstraZeneca vaccine, did the same thing on the same day. They injected the first healthy volunteer with a COVID-19 vaccine candidate. It seems that the BioNTech team was ahead of the Oxford Team by only 1 hour (Miller and Şahin, 2022: 175). At this point, Moderna was ahead of both competitor teams (Miller and Şahin, 2022: 177).

During the summer of 2020, results from the Phase I and II studies were so encouraging that the PEI approved Phase III studies on 7th September 2020. At this point, the number of candidate vaccines had been reduced to one: BNT162b2. According to the regulator (BioNTech, 2020b), 'the placebo-controlled trial evaluates the safety and efficacy of BNT162b2 in up to 30,000 participants between 18 and 85 years of age'.

Phase III studies were undertaken in Germany, the US, Brazil, Argentina, South Africa and Turkey and expanded to well over 40,000 healthy volunteers (Miller and Şahin, 2022: 202). The best possible scientific result would be high infection numbers in the placebo group, whilst showing full protection in the vaccine arm of the study without major adverse effects. Whilst AstraZeneca, Johnson & Johnson and Eli Lilly had to interrupt their Phase III COVID-19 vaccine studies to follow up on potential adverse effects, no such effects were observed for the BioNTech vaccine (Miller and Şahin, 2022: 212). Once the Phase III clinical trials were underway, the waiting began for enough COVID-19 infections to occur across all research participants for statistical significance. This is needed to enable the trial's independent data monitoring committee to analyse and compare the data for infections in the placebo and the vaccine arms of the study.

On 8th November 2020, the figures were clear. Ninety-four out of 43,538 healthy volunteers had contracted COVID-19: Ninety were in the placebo arm and only four in the vaccine arm of the study (Miller and Şahin, 2022: 214). This meant an approximate 90% efficacy of the BioNTech vaccine (Meredith, 2020).

During the development of the BioNTech/Pfizer COVID-vaccine, the 2023 Nobel Prize Laureate for Medicine, Dr Katalin Karikó (together with Drew Weissman),

was working on mRNA studies at the German laboratories of BioNTech. According to the New York Times, when she heard that the vaccine study results were positive, she turned to her husband, and said: 'Oh, it works, I thought so' (Kolata, 2023).

Whilst full regulatory approval of the final vaccine still required time (the US FDA only provided its full approval on 23th August 2021 (Food and Drug Administration, 2021)), emergency use authorisation in the UK (MHRA, 2020) made it possible for 91-year old Margaret Keenan to receive the BioNTech/Pfizer vaccine on 8th December 2020. As noted earlier, she was the first person worldwide to receive a COVID-19 vaccine outside of a research study.

> This initial authorization [from the UK] was followed by a rapid succession of authorizations or approvals for emergency use of BNT162b2 in several countries, with Bahrain, Canada, Mexico, Saudi Arabia and the USA being among the earliest (all prior to 14 December 2020) (Lamb, 2021: 495f).

From toxicological studies on cell cultures and animals, to healthy volunteer studies in all required phases, the BioNTech vaccine was developed and approved in under 11 months without avoiding any of the standard research ethics requirements for clinical trials.

In summary, the following accelerations were faciliated through close collaboration between BioNTech and the German regulator PEI:

- A 1 week, instead of a 3 months' wait for the first consultation meeting with the regulator.
- Under 1 week instead of over 1 month to prepare a full briefing document for the regulator.
- Accelerated preclinical development, including acceptance of interim results of toxicological studies by the regulator PEI and accelerated studies in rodents.
- Implementation of combined and overlapping clinical trial phases with rolling review of data being conducted by regulators.
- Emergency approval of the vaccine in under 11 months.

In addition to very close collaboration with regulators, one other main factor was responsible for the acceleration success: trust-based collaborations with new partners.[1]

Trust-based collaborations with new partners

As early as February 2020, 1 month after taking the decision to develop a COVID-19 vaccine, BioNTech staff started the search for a global partner to run phase III clinical trials (Miller and Şahin, 2022: 200) and provide the

manufacturing capacity to deliver hundreds of millions of vaccines. Pfizer and Fosun[2] were approached. At the time, BioNTech had 1300 employees, Pfizer 70,000 (Miller and Şahin, 2022: 156).

When Pfizer showed significant interest in collaboration, one ethical leadership decision was highly unusual but vital to accelerating the vaccine development, namely BioNTech's decision to release vaccine candidates to Pfizer *before* a collaboration agreement had been finalised.

The collaboration between BioNTech and Pfizer was officially announced on 17th March 2020, through a declaration of intent published at the Securities and Exchange Commission of the US government (SEC, 2020). After such a declaration of intent, the drafting process for a full collaboration agreement – which involves pharmaceutical intellectual property - normally takes at least 6 months (Miller and Şahin, 2022: 155). During this time, no proprietary technology (like BioNTech's vaccine candidates) would normally be shared. One day after the letter of intent was signed, Uğur Şahin, the co-founder of BioNTech, instructed his disbelieving team to 'share everything' (Miller and Şahin, 2022: 154).

This decision subordinated financial interests to live-saving interests, even though BioNTech 'had accumulated more than €400 million of debt in 11 years [and] needed to raise more money soon' (Miller and Şahin, 2022: 38). The willingness to share proprietary knowledge with a much more powerful competitor (Pfizer) shows ethical leadership in extremely difficult circumstances (Leisinger, 2020). In today's globally competitive business world, priority was given to saving lives over corporate interests.

Lessons learned

As this COVID-19 case study has shown, it is possible to develop a life-saving vaccine with over 90% efficiency in under 1 year in accordance with existing principles of good clinical practice.

Around the world, regulators worked closely with vaccine developers to consult on study design and on which stages of research, if any, could overlap. Not only was the BioNTech-Pfizer COVID-19 vaccine developed faster than any competitor vaccine, it was developed faster in one of the most highly regulated research governance systems in the world. The German regulator required that all vaccine development stages from toxicological to animal studies, and all phases of clinical trials had to be adhered to. Efficiency was achieved by the combining and overlapping of vaccine development phases and by regulators implementing rolling review of clinical trial data.

Despite adhering to these very strict research ethics regulations, the BioNTech-Pfizer COVID-19 vaccine was faster than competitors, including competitors who were using the allegedly accelerating human challenge trial set-up, for instance,

two studies in the UK purposefully infected volunteers with COVID 19 (Zarley, 2023). To date, the results of only one COVID-19 human challenge study have been published and 'what is striking about this study is the length of time from inception to publication—2 years' (Weijer, 2024), about twice as long as the time needed for the BioNTech-Pfizer vaccine.

Prioritising the saving of millions of lives by what one might call 'rolling legal agreements' was an ethical leadership decision that is exceptional. The vaccine development process was accelerated significantly by risking the security of company assets (BioNTech vaccine candidates). The completion of legal agreements for proprietary technology can add up to 6 months to standard collaborations but BioNTech leaders decided to share the vaccine candidates with only a letter of intent in place. One could note that this shows a deeply developed sense of responsibility, that is, the ability to respond to extraordinary circumstances with extraordinary decisions and activities.

Since Karikó and Weissman's groundbreaking findings on how mRNA can interact with human immune systems, for which they gained the 2023 Nobel Prize in Medicine, other mRNA-based vaccines for communicable diseases are in development. For influenza, shingles, HIV, malaria, rabies, tuberculosis and zika clinical studies are at least in Phase I and some in Phase II of clinical development (vfa, 2023).

The elephant in the room of all COVID-19 vaccine success stories, including the BioNTech-Pfizer COVID-19 vaccine, is the 'unprecedented investment' (Weijer, 2024). Improving pandemic preparedness cannot be ensured without further 'long-term investment in basic research and knowledge accumulation for pathogens of concern' (Bok et al., 2021: 1645).

What is reassuring about this case study – from an ethics perspective – is that a major breakthrough in vaccine development speed was compatible with the full protection of human participants in vaccine research through existing principles of good clinical practice.

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Notes

1. For efficiency gains through intensive shift working, postponing holidays etc, see Miller and Şahin (2022). For the significant contribution two German philanthropist financiers made to the mRNA research at BioNTech see a series of articles in the German Manager Magazin (n.d.)
2. The second collaboration with a large vaccine manufacturer, Shanghai-based Fosun, is not detailed here due to space constraints.

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