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Project Lightspeed

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Overview:

This report summarises the development of the BionTech/Pfizer vaccine as relevant to research ethics and integrity issues.

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Acknowledgements

This case study relies heavily on background information presented in Joe Miller, Özlem Türeci and Uğur Şahin, The Vaccine: Inside the Race to Conquer the COVID-19 Pandemic, (New York: St. Martin's, 2022). All quoted examples of unorthodox decision processes are taken from this seminal book in post-COVID leadership studies. To avoid unnecessary replication of the source, only MTS and respective pages numbers are mentioned.

1. Executive Summary

Context

Fast expanding pandemic due to pathogen being transmitted by persons who feel healthy;

Unprecedented time pressure;

Enormous disease load with increasing lethality;

New technology platform accepted (mRNA) – but necessity to develop a full set of safety and immunogenicity data for each vaccine candidate.

Responsible acceleration

Early contact with regulators to get them on board with the new technology (mRNA);

Co-authoring scientific papers on mRNA with scientists from regulatory bodies – joint learning curve;

Prepare the Briefing Book for regulatory agency that normally takes 4 – 6 weeks in less than a week

Produce a brochure for medical personnel on "How to use mRNA based vaccines"

Test multiple vaccines in parallel;

Elimination of idle periods throughout all phases of the development process:

- Prepare for essential preclinical facts in labs, on rodents;
- Compile a checklist of safety requirements for trials with healthy volunteers,
- Identify partners that could help run trials worldwide;
- Organise around-the-clock shifts, 7 days a week;

Start clinical trials (Phase I) in agreement with regulatory agencies on the basis of an interim toxicology report – experience from previous (flu-) mRNA-vaccines showed that potential side effects would show up within one week;

Business as usual for Phase II and Phase III study

"Invest risk capital" to prepare production processes;

Expand manufacturing capacity early to potentially supply a vaccine to anyone who wanted it.

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2. Introduction and Context

Why This Case Study?

Beyond the widespread panic induced by the virus itself, COVID-19 unleashed a broader fear that the international community might now be faced with "an era of pandemics". (Fleming 2021) The prospect of future global health crises, some perhaps many times more devastating than COVID-19, can no longer be ignored; mitigation of human loss and socio-economic harm will require quick reactions by all relevant solution-stakeholders.

Research and development is a vital part of this puzzle: Highest standards of ethics and integrity must be kept up despite time pressure. In addition, there are significant ethical challenges to be faced in the areas of intellectual property, pricing and competition law.

> The following case study deals with lessons learned from a small company - BioNTech - whose astounding success in the research, development and mass production of an effective vaccine saved millions of lives.

Violations of ethical standards never occur in isolation; they are always embedded in broader institutional cultures of (ir-)responsibility, which in turn are shaped by the behavior of respective individual leaders. This case study addresses both the specific ethical challenges faced by those working under the time pressure of a mounting pandemic and the institutional context in which they were operating.

Under the leadership of scientists Özlem Türeci and Uğur Şahin, the BioNTech team managed to develop, clinically test and mass-produce an effective vaccine against COVID-19 (COMIRNATY) in less than 10 months. The leadership couple's focused mindset, extraordinary work ethos and outstanding leadership created an enabling environment based on mutual trust, shared values and a common understanding of BioNTech's purpose. This leadership provided fertile ground for the development of exceptional levels of motivation among all stakeholders involved. Many actors went well beyond their comfort zones without compromising standards of ethics and integrity. Focus on the overarching goal - an effective vaccine in the shortest possible time - took precedence over the pursuit of (short-term) profit.

The Project Lightspeed experience represents a concise compendium of best practices for leadership as well as a model for future collaborations among stakeholders committed to an ambitious common goal. BioNTech's decision-makers took the road less travelled, and that has made all the difference. (Frost 1915)

Results of the LANCET COVID-19 Commission

When the World Health Organization (WHO) first learned of a novel coronavirus strain (later named SARS-CoV-2) on December 31st 2019, only a handful of scientists (and even fewer politicians) raised the alarm. Three and a half years later, the human loss is estimated to be at least 20 million deaths and myriad complications from several hundred million infections. (WHO 2023 /IHME 2023) The estimated economic damage lies in the order of hundreds of billions of Euros; long-term social costs, not to mention the general setback in the implementation

of the Agenda 2030 for Sustainable Development, may be added to the grisly COVID bill. The Lancet Commission on Lessons for the Future from the COVID-19 Pandemic came to an alarming conclusion:

> This staggering death toll is both a profound tragedy and a massive global failure at multiple levels. Too many governments have failed to adhere to basic norms of institutional rationality and transparency, too many people—often influenced by misinformation— have disrespected and protested against basic public health precautions, and the world's major powers have failed to collaborate to control the pandemic.
>
> The multiple failures of international cooperation include:
> (1) the lack of timely notification of the initial outbreak of COVID-19;
> (2) costly delays in acknowledging the crucial airborne exposure pathway of SARS-CoV-2, the virus that causes COVID-19, and in implementing appropriate measures at national and global levels to slow the spread of the virus;
> (3) the lack of coordination among countries regarding suppression strategies;
> (4) the failure of governments to examine evidence and adopt best practices for controlling the pandemic and managing economic and social spillovers from other countries;
> (5) the shortfall of global funding for low-income and middle-income countries (LMICs), as classified by the World Bank;
> (6) the failure to ensure adequate global supplies and equitable distribution of key commodities—including protective gear, diagnostics, medicines, medical devices, and vaccines—especially for LMICs;
> (7) the lack of timely, accurate, and systematic data on infections, deaths, viral variants, health system responses, and indirect health consequences;
> (8) the poor enforcement of appropriate levels of biosafety regulations in the lead-up to the pandemic, raising the possibility of a laboratory-related outbreak;
> (9) the failure to combat systematic disinformation; and
> (10) the lack of global and national safety nets to protect populations experiencing vulnerability. (The Lancet 2022, p.1224)

The Commission, however, also noted some "important bright spots in the national and global responses to COVID-19. The most important has been the public-private partnership for the rapid development of vaccines". (The Lancet 2022, p. 1236) The death toll, burden of illness and overall economic cost, in other words, would have been dramatically higher without the availability of effective vaccines developed with record speed thanks to unprecedented modes of research cooperation and other forms of collaboration.

3. Stakeholders for a Global Solution

The Challenge of a Covid Vaccine

There are by definition no simple solutions to complex problems: even the best will in the world among key actors can be eroded if it is not supported by a functioning network of communication and resource allocation among stakeholders. When several actors work together, joint success depends on an efficient and fair

distribution of responsibility. Responsibility is understood in this context as the duty to observe a range of legal, technical, moral, social, cultural and other standards. A clear distribution of societal responsibility must therefore be defined - and duties clearly assigned - to the respective parties. As there are problems that the market can solve and others that it cannot, it is vital to establish where market solutions should be given priority and where government should intervene through regulation and/or the provision of financial resources and public services. (Leisinger 2022, chapter 4)

While the basic structure of a fair societal division of labor is relatively clear, exact delimitations are defined in specific situations by the leadership personalities involved. Strong leaders will go beyond what is expected of them in orthodox definitions of a fair distribution of responsibility: they will make sure that what has to be done to achieve a particular goal is actually done; and they will refrain from excusing inaction by pointing to other actors' responsibilities. In the case under consideration, such a maximalist approach to the responsibilities of leadership made a huge real-world difference.

Much of what needs to be done to mitigate the medical and socio-economic harms arising from global pandemics is now known - and as a matter of fact *was* already known before the outbreak of COVID-19. The main elements of harm reduction include: strengthening national health systems, particularly primary health care; improving cooperation and coordination among solution-stakeholders; and a "vaccination-plus strategy". (Gates 2022, The Lancet 2022)

It remains to be seen to what extent the "new normal" of post-COVID global public health policy will be characterized by the lessons learned in the past years, the importance of vaccines, in any case, should now be more obvious than ever. The key ingredients for success in making effective COVID vaccines available in record time were: outstanding leadership and a motivating corporate culture at companies like BioNTech; extraordinary professional support from regulatory authorities, unprecedented international scientific exchange and collaboration; and significant financial investments in the new mRNA technology before the outbreak of COVID-19.

All stakeholders pointed out that first and foremost safety and effectiveness of a potential vaccine candidate had to be established and that a lowering of standards due to time pressure and disease load was unacceptable.

Financial stakeholders

Successful research into complex problems depends on adequate financial resources. Since 2020 the central banks of many countries, as well as the World Bank and the International Monetary Fund (IMF), have made hundreds of billions of Euros available for the fight against COVID and its tragic consequences. (The Lancet 2022, p. 1261ff.) The European Investment Bank and private organisations like the Bill & Melinda Gates Foundation have also provided significant funding for vaccine research and development from clinical trials to production and distribution.

National governments around the world, moreover, supported vaccine research and development in their own unique ways. By ordering enormous quantities of vaccine before they were actually available, several national governments facilitated the global cashflow ultimately required to bring the vaccine to patients. Private

companies also invested large amounts for the same purposes. While there is always a need for “more” (particularly in low- and middle-income countries), the volume of global finance mobilized in the context of COVID-19 was certainly impressive.

Pharmaceutical companies normally finance research and development from their own resource pools created by profits from past and current revenues. In the case of BioNTech - a start-up focusing on cutting-edge cancer medicines - this was not possible: there was no financial cushion available from earlier profitable sales (the company, indeed, faced substantial accumulated debts in the runup to the COVID outbreak). On the whole, capital markets were not interested in financing a small start-up working with a non-mainstream mRNA technology. (SCNAT 2022) Two important exceptions to this rule were the biotech investors Thomas and Andreas Strüngmann; their daring vision and enthusiasm for highly risky new projects like those of Özlem Türeci and Uğur Şahin constitute an important contemporary example of financial valor. (personal communication with Thomas Strüngmann) The investors’ big-picture mindset - their refusal to be constrained by short-termism - was one of the key determinants of BioNTech’s eventual success.

Before BioNTech was founded in 2008 the Strüngmann brothers had invested a substantial amount in the couple’s predecessor company, Ganymed. Türeci and Şahin urgently needed substantial amounts of money to finance their high-risk research and respective clinical trials, but they also wanted to make sure that financial investors did not interfere in scientific decision-making. The normal model for investors in this sector is to invest in young companies in order to support their development for a period of time, with the ultimate goal of making the company an attractive asset for a larger potential buyer.

Thomas and Andreas Strüngmann, unusually drawn to Şahin and Türeci’s professional ethos and vision, decided differently. They agreed to a no-questions-asked clause, meaning in practice that he and his brother Andreas would not be able to interfere in the company’s internal affairs for at least the first two years. In other words, Şahin and Türeci were free to go in whichever research directions they liked. In addition, Athos, the investment arm of the Strüngmann family, agreed to forfeit the right to force a sale until 2023, thereby guaranteeing the researchers fifteen years in which to operate as they deemed necessary (MTS p.135).

Driven by his firm belief that mRNA-based medicines and vaccines would have a revolutionary impact on the treatment of cancers, Uğur Şahin had already hired a team of scientists before the final agreement with Athos was signed, financing their salaries out of his own private savings. Thanks to the Strüngmann up-front investment, the leadership couple and their team was able to continue the research and development that culminated, 12 years later, in the desperately needed COVID-19 vaccine.

Subsequent financial support from the German government and the European Commission were immensely important for the success of the BioNTech Covid vaccine, but without the entrepreneurial intuition of Thomas and Andreas Strüngmann years earlier - their trust in the scientific and managerial capabilities of Şahin and Türeci as well as their courage to invest significant amounts of money in a new technology (mRNA) with very few strings attached - this life-saving vaccine would not have become available.

Regulatory Authorities

Like any other medicine, vaccines against COVID-19 undergo a thorough screening process in order to make sure they are safe for patients (or at least safe insofar as potential benefits significantly outweigh potential risks). Comprehensive toxicological studies in test tubes on cell cultures and animals establish the vaccine's basic viability, followed by clinical trials on a small number of healthy volunteers, the main goal of which is to gauge the metabolization of the new substance in human beings (Phase 0). Trials establishing the safety of a vaccine candidate can only be started once baseline human tolerance had been established. (Phase I).

In Phase II, different groups of patients are given different dosages of the vaccine in order to accumulate data on the effects of different dosages and to optimize the final product. Phase III involves the testing of many thousands of patients over a longer period of time in order to explore potential long-term side-effects. All phases are necessary to establish safety for patients. The overriding mission of regulatory institutions is to protect research participants from harm and to ensure that any future innovative medicine or vaccine can be used safely.

In view of the inhuman medical experiments carried out on helpless prisoners during the Nazi era, German guidelines for clinical trials are very rigorous. As per its existing modus operandi in cancer-drug trials, BioNTech did not shy away from more stringent German processes; though it could easily have done so, the company refused to run its trials in a country with less stringent regulatory requirements.

Project Lightspeed (an obvious homage to the urgency of the endeavor) needed regulators to come on board from the beginning, e.g. to co-create a checklist of safety requirements for clinical trials with the new mRNA technology. In this context, the Paul Ehrlich Institute (PEI) played a particularly active role (it had already been instrumental in developing a regulatory framework for mRNA vaccines). More important still for the BioNTech case was the fact that the PEI had worked with start-ups using mRNA (including BioNTech) to ensure that the molecule was safe to administer to humans.

Türeci, Şahin and other BioNTech experts had attended PEI-run research retreats at which the frontiers of medical research were discussed in detail. In this way, innovators and regulators were able to learn together about novel technologies (including mRNA). These joint learning opportunities allowed for the development of a collegial relationship between the PEI and BioNTech staff. Experts from the two institutions deepened their relationships with each other and developed mutual trust in their respective expertise. As a result, PEI experts developed deep knowledge about mRNA and could be counted upon to take sudden advances in the field seriously. (MTS p.45) Although the PEI was initially more optimistic about the controllability of the pandemic through conventional measures - masks and social distancing - than BioNTech's experts (and therefore felt less time pressure), consensus was reached on all contentious issues without compromising patient safety and within the time limits set - despite differing assessments of key challenges.

At all levels of evaluation, regulators are forced to make stringent assessments of the particular importance of specific scientific data. In this process, however, they also have to make value judgments of ethical relevance, e.g. on the acceptability of potential side-effects or - more difficult still - on whether potential risks to participants of clinical trials would be more than outweighed by the potential benefits of a medicine or vaccine. Judgments of this kind are not only data-driven; human judgment is also influenced, to a certain extent, by the quality of one's relationships with those who present data. A company with a proven track record for creating the highest possible

transparency, not only around the expected strengths of their ideas but also with regard to potential weaknesses and unknown factors, will be able to develop the kind of trust over time that can tip the scales of an evaluation. This principled openness to critical exchange proved to be a central element in BioNTech's campaign to convince regulatory experts that what they were proposing was safe enough to try under close supervision.

Also the role of the US regulatory institutions was remarkable: In a virtual hearing of the US House Committee of Energy and Commerce on the subject of "Pathways to a Vaccine: Efforts to Develop a Safe, Effective and Accessible Covid 19 vaccine" all witnesses from pharmaceutical companies (Pfizer, Moderna, AstraZeneca, Novavax and Merck) praised the professional collaborative spirit of FDA and the stringency of its guidelines. The virtual hearing can be listened to by clicking the picture:

Maintaining good relationships with experts from regulatory authorities and other stakeholders - on whose goodwill one depends - is always prudent, but in the case of Project Lightspeed, it was decisive.

4. BioNTech and its founders

The company

BioNTech is a small biotechnology company founded in 2008 in Mainz (Germany) by Özlem Türeci, Uğur Şahin, and the oncologist Christoph Huber. Its mission statement is ambitious:

> "We are committed to improving the health of people worldwide with our fundamental research and our work in the area of development of immunotherapies utilizing the full potential of the immune system to fight cancer, infectious diseases and other serious diseases. We believe in scientific rigor, innovation and passion as driving forces. BioNTech was founded by scientists and physicians to translate science into survival by combining fundamental research and operational excellence." (BioNTech 2022.1)

Before tackling the COVID-19 vaccine, BioNTech had focused its research work on immunotherapy for cancer, but the company had also worked on developing vaccines against influenza, tuberculosis and HIV at different times. (BioNTech 2022.2) In October 2019 the company was listed on the NASDAQ Global Select Market under the ticker symbol BNTX.

Özlem Türeci and Uğur Şahin

The success of BioNTech would not have been possible without two extraordinary personalities, Özlem Türeci and Uğur Şahin. The couple's excellent leadership, professional ethos, personal work ethic and general ability to motivate people inside and outside the company to go beyond their comfort zone all helped to create a culture of trustful collaboration with stakeholders. This climate of trust proved to be a decisive element of success in the context of the race for a COVID-19 vaccine. Such leadership requires not only executive competence and a corresponding willingness to make difficult decisions, but also an institutional setting with a culture based on clear inner compasses repelling infringements of ethics and integrity.

Joe Miller went so far as to say that "it was the sheer will of two people that got us to this place. The vaccine's key ingredient was not RNA. It was Uğur Şahin and Özlem Türeci." (MTS p. 248) This statement can be substantiated by examining the couple's work between January and December 2020, the legacy of which we explore in the following section.

5. Elements of Success

Intuition Combined with Mathematics

At a time when only a few scientists were aware of the existence of a hitherto unknown virus in China, Uğur Şahin was already aware that something "different" was developing. He tirelessly collected available evidence of asymptomatic person-to-person transmission and sought to quantify the Wuhan's status as a national and international transit hub. Comfortable in the realm of advanced mathematics, Şahin added his virological insights to project a nightmare scenario in early January 2020: the local outbreak in Wuhan had the potential to become a global pandemic.

Belief in Biotechnology

At a time when mainstream researchers and most pharmacology experts at major pharmaceutical corporations viewed mRNA research as pie-in-the-sky science fiction, Türeci and Şahin were convinced that this small molecule had specific features that could be leveraged in the fight against diseases. As an mRNA drug would only contain a few lines of genetic code, it could be engineered and produced quickly:

> "The relative simplicity of the technology made it easier to isolate antigens (…) and copy their genetic code into a synthetic mRNA template. Once the strand was introduced into a patient's body, their cells would do the rest of the work." (MTS p.22)

Şahin had used the molecule in his cancer research with the goal of mobilizing patients' immune systems to fight the disease on their own. In skin cancer research, most notably, mRNA-based approaches have already yielded promising results. (MTS p.24). Şahin was convinced that an mRNA-based vaccine could help to save lives and mitigate the socioeconomic impact of the new coronavirus.

Courage, Commitment and Perseverance

On January 24, 2020, with accumulated debts of more than 400 million Euros for their cancer research, Şahin and Türeci privately committed to developing a vaccine against a virus whose existence had only been acknowledged by the WHO less than four weeks earlier. By January 26, Şahin had already designed eight different vaccine candidates. (MTS p.29) Convinced that tens, perhaps hundreds of millions of lives could be lost without a prompt and effective vaccine, Şahin and Türeci were willing to run an enormous risk: if they failed in their endeavors to develop an effective vaccine before the competition, the economic consequences for BioNTech would be disastrous. In a worst-case scenario, committed employees would lose their jobs and BioNTech would lose intellectual property built up over many years to the liquidator.

At a subsequent BioNTech board meeting, the leadership couple explained their all-in decision: a full-blown global pandemic would be a danger to BioNTech's employees anyway.

> "Why wait for others to guide the world out of this looming crisis if BioNTech had the capability to do so itself? Shouldn't we at least make an effort?" (MTS p.39)

Another example of the pair's commitment to finding the best possible solutions under time pressure was the last-minute switch from the vaccine candidate originally planned for clinical trials (BNT162b1) to a more promising alternative (BNT162b2.9). All documents for the b1 candidate had already been filed, and supply-chain specialists had already developed plans to produce tens of thousands of doses for global clinical trials (Phase III). A day before the start of production, however, new data on the b2.9 alternative pointed in the direction of a better safety and efficacy profile: b2.9 would give the immune system a larger area to target, and it was predicted to be more effective at disrupting the virus's docking mechanism. (MTS p.171) Such a late change would be difficult on its own, but also conflict with Pfizer's[1] established standard procedures; the switch, however, was nevertheless achieved, and Pfizer remained on board as the partner for global registration, production and marketing. The bold call to change the vaccine candidate despite some missing data points – and with all the logistical challenges that such a late change entailed – ultimately translated into enhanced efficacy and user safety.

Other individuals naturally played important roles in the development of the vaccine, most notably Albert Bourla (Chairman and CEO of Pfizer) but also Kathrin Jansen and the aforementioned Strüngmann brothers. Bourla not only had the courage to trust Şahin's assessments in complex decision processes, but he also stood firm in a difficult political situation: US President Donald Trump was exerting intense public pressure to circumvent safety standards and regulatory requirements. Trump wanted a timely success story to support his re-election campaign; Bourla resisted. (MTS p.210)

Maintaining Safety Standards Under Time Pressure

When the BioNTech team started its work on the vaccine in February 2020, the time frame assumed as "normal" for the development and emergency approval of a vaccine ranged from five to eight years (and with an overall price tag in the hundreds of millions of Euros). With the deadly Ebola virus, clinical phases alone had lasted nearly four years. Given the mathematical calculations and projections Şahin had made and knowing that person-to-

[1] The relationship between BioNTech and Pfizer is explained below.

person transmission rates were significant, such a timeframe would lead to a historically unprecedented death toll and impose epoch-shattering economic and social cost with further deadly consequences of their own.

As any delay in the development of the vaccine would raise the death toll, the BioNTech team did its utmost to accelerate processes and save time. In Şahin's words, "only the laws of physics would be an acceptable limit." The internal name for the vaccine drive - Project Lightspeed - reflected this ambition.

To speed things up, Uğur Şahin completely rewrote the vaccine-maker's playbook: he could not afford to test a prototype, discard it if it didn't work, and repeat the process over and over again. Instead he decided to build and test multiple vaccines *in parallel*, sending several designs at once into preclinical trials. (MTS p.35f) Sequential processes were conducted contemporaneously with the goal of achieving the same overall safety standards: all signs would be rigorously tested in the lab, on animals, and eventually on humans. At any stage, vaccine candidates not found to be sufficiently safe or effective would be abandoned. The candidate which best survived this gauntlet would be mass-produced. (MTS p.36).

Also to be mentioned here as a major precondition to make the vaccine available in record time are the risky pre-investments all pharmaceutical companies potentially producing the vaccine made in parallel to ongoing phase III clinical trials, i.e. before emergency authorization was given:

- Increasing and expanding existing manufacturing capacities plus hiring and acquiring additional production facilities;
- Increase efficiencies in the processes by incorporating lessons learned from other diseases (e.g. flu vaccines);
- Hiring and training additional personnel to work 7 days / 24 hours;
- Increase number of doses to be drawn from the serum vials, and, finally
- Do whatever can be done in parallel instead of consecutively.

All such investments would have been lost if vaccine candidates would not meet the safety and effectiveness expectations.

An Enabling Corporate Culture

In all phases of Project Lightspeed, Şahin and Türeci's work ethics was exceptional and they expected the same of their employees. Processes that would normally take months would have to be completed within weeks; "idle periods" would have to be eliminated; shift rosters to ensure round-the-clock progress were instituted. It was taken as a matter of course that holiday plans would have to be postponed, weekends devoted to work, and everyone available whenever needed for as long as it took.

In general, business leaders who expect such extreme levels of performance have to answer the purpose question. (HHL 2018) In BioNTech's case, generic pressure to achieve "more", "faster" and "better" would not have been credible goals on their own. (HHL 2018, McKinsey 2020) Şahin and Türeci were able to stimulate employee enthusiasm for this punishing new rhythm by providing a convincing answer to the purpose question. The "why?" was made clear to everyone: saving hundreds of millions of lives and preventing untold socioeconomic harm to billions more. If the pressure exerted on BioNTech staff had been perceived as unreasonable by even a small minority, the project would not have been as successful as it eventually became. Extraordinary "war-mode" levels

of individual motivation were enhanced by a feeling of collegial togetherness developed over years of professional collaboration in the BioNTech environment. (MTS chapter 2)

Emphasis on Shared Goals over Private Successes

It soon became apparent that BioNTech would exhaust its own resources in the race for a COVID-19 vaccine. Beyond all streamlining of performance targets, elimination of efficiency gaps and changes in work processes, BioNTech would not be able to win the race on its own; solving a global problem of such dimensions would inevitably require partners all over the world, decentralized clinical trials and regulatory filings in multiple countries, global infrastructure for complex logistics, and above all marketing for the safety and efficacy of the vaccine. All this required collaboration with at least one of the major pharmaceutical companies.

Despite the obvious need to bring other partners on board, Şahin and Türeci were keen to maintain BioNTech's independence; as earlier experiences of "collaboration" had proven challenging. (MTS 140f.) Only meaningful independence would ensure that scientific excellence took precedence over the short-term returns of investors. What BioNTech had achieved in its negotiations with Thomas and Andreas Strüngmann would have to be replicated in discussions with Big Pharma.

The Chinese pharmaceutical company FOSUN and the US-based Pfizer eventually became members of the Project Lightspeed team. Initial disinterest, particularly on Pfizer's part, had to do with differences in judgment about the probable scale of the pandemic and corresponding demand for a vaccine, as well as broader reservations about the overall readiness of BioNTech's mRNA technology. The fact that Pfizer overcame its initial reservations about mRNA can be attributed not only to the persuasive scientific argumentation of Şahin and his team of BioNTech scientists, but also to the personal chemistry between the two key decision-makers, Uğur Şahin and Pfizer CEO Albert Bourla. Without mutual trust and a willingness to compromise on certain issues, it would not have been possible for Pfizer to agree to the basic rules of cooperation that Şahin proposed. (MTS p.150)

Şahin was concerned that a large company like Pfizer, with its established modus operandi, might slow down or otherwise curb the innovative dimension of the project. Pfizer eventually agreed that BioNtech's corporate independence was non-negotiable, but hesitating BioNTech employees still had to be persuaded of the merits of the new agreement: sharing all data with Pfizer, as they were told by Şahin they were now obliged to do, created the risk that the much larger company could misuse its newfound access to important data and later claim ownership of BioNTech-developed mRNA-based intellectual property. Such potential disputes, critics warned, could only be refuted in lengthy legal proceedings – if at all. Şahin was not to be dissuaded, however, from the principle of sharing all data; he did not want to allow well-meaning members of his own legal department and senior management team to stand in the way of the fast development of a vaccine that could save millions of lives.

The mutual trust and shared values between the two key decision-makers - Şahin and Bourla - allowed for a highly unorthodox agreement: normally, in the run-up to a comprehensive collaboration agreement between two companies, all terms and conditions are discussed line by line in detail between the respective business development teams, patent experts and legal counsel. This usually takes months - time that was not available in this case. Instead, Bourla and Şahin agreed to "start immediately and then let the paperwork come whenever it comes." (MTS p.150) Even more astounding if compared with normal practice in large companies, the Pfizer CEO

told staff not to spend a second worrying about budgets: they had a blank check for the coronavirus project. Reaching a common real-world goal, in short, took precedence over financial corporate interests. This trust-based decision culture accelerated the eventual success of the project by many months – and thus saved the lives of millions of people.

Responsible Acceleration

Under the unique circumstances of 2020, it was clear to BioNTech experts that toxicological studies on animals would have to be completed in a much tighter time window than the usual six months allotted to this phase of vaccine development. The analysis of earlier experiences with the development of vaccines against Ebola and other viral diseases provided crucial insights for legitimate accelerations of BioNTech's work on the COVID vaccine; these accelerations were then accepted by regulatory institutions like the PEI. One such innovation was to begin clinical trials on the basis of an interim toxicology report. Crucially, however, work was stopped and plans were amended every time a potential safety issue arose; throughout the process, opportunities to accelerate results were seized, but safety considerations were, whatever the circumstances were, not compromised. (MTS p.162) The task of launching the fastest human trials in BioNTech's history was naturally full of practical and ethical challenges, but the company had accumulated significant prior experience in administering mRNA medicines to cancer patients. BioNTech's respective experience was also known to the PEI.

Selection of volunteers to test the new coronavirus vaccine had been performed with the utmost care; safety and tolerability considerations remained the principal decision vectors. After the beginning of clinical studies in humans in particular, transparent communication was vital: not only regulators, but also the clinicians conducting the trials and above all the human beings receiving the trial vaccine would have to understand what was to be expected, namely that there are typically mild side-effects and symptoms associated with mRNA-based vaccines, but that these usually subside within a day or two. To create as much understanding as possible, BioNTech decided to produce a brochure, "essentially a user manual containing a rundown of the technology behind the vaccine. Its purpose was to eliminate surprises." (MTS p.164)

Özlem Türeci's exceptional aptitude for explaining complex issues to non-specialists had already proven to be a vital asset in the context of BioNTech's mRNA oncology trials. From this experience, and from early toxicology results with the new vaccine, it was quickly accepted among stakeholders that adverse reactions were most likely to be observed within the first twenty-four hours after administration. This allowed for rapid consensus on a shortening of the interval between the first and the second doses – not only in the trials but also later with patients receiving the vaccine.

When bureaucratic hurdles appeared that could not be overcome by scientific explanation and cross-reference with earlier studies, Şahin found innovative solutions. The Ethics Commission of the German state of Baden Württemberg, for example, insisted that all trial participants be tested for COVID-19 before receiving a vaccine. At the time, only a few specialized companies were able to perform reliable tests, and results were slow. Through Şahin's network it became possible to purchase machines to produce PCR equipment and the cartridges needed to accelerate testing and gain time for trials. (MTS p.173)

6. Critical Issues

Analytical Rigor versus Speed of Approval

Based on accelerated clinical data, intensive official discussions of the pros and cons of BioNTech's COVID-19 vaccine were able to be conducted within a single year of the outbreak in Wuhan. As a result, the U.S. Food and Drug Administration (FDA) sought fit to declare on December 10, 2020 that the benefits of the BioNTech vaccination (for recipients over 16 years of age) outweighed the risks of non-vaccination, and that emergency approval for mass production of the vaccine could hence be granted. The FDA's European counterpart, the EMA, followed suit on December 21, 2020.

There is an obvious tradeoff to be made between analytical rigor in order to achieve optimal safety for patients, on the one hand, and swift approval for a life-saving drug or vaccine on the other. Evidence of a high degree of efficacy and safety may already be convincing at an early stage Phase III, but according to the established rulebook, further testing should nevertheless be conducted to gain data on potential long-term issues. Dealing with such dilemmas in an acute emergency situation like the COVID-19 pandemic requires a clear hierarchy of values. There can be no hard-and-fast general rules in this sphere, context matters. Finding ethically acceptable solutions necessitates consensus finding among experts including social scientists and ethicists. In the present case, the efficacy and safety targets were achieved without any corners cut or safety standards lowered

, the vaccine was made available to the general public via emergency approval.

Pricing Policy

Pharmaceutical products are normally priced by the value an innovation holds for patients in comparison to other medicines already on the market; the value of COVID vaccines per vaccinated person was later calculated at around US$5,800 (Castillo et alia 2021). The value-based price of an innovation is usually the market price – actual production costs (raw material, manufacturing, etc.) are much too low to finance research investments. When it comes to defending prices, pharmaceutical companies usually cite research costs and the necessity of profit as an incentive for the development of future cures. (Cueni 2019) Public pressure, however, can lead to substantial price concessions. Price discussions between companies and state institutions are in any case characterized by contrasting basic philosophies and decision-making patterns.

Pfizer and BioNTech were indirectly criticized in the context of prices: successful development of the vaccine led to substantial earnings for both companies – and yet this income was partly derived from knowledge generated by public funding:

> "Despite having had a decisive role in funding the development of these vaccines, the US Government did not share in the market returns, and indeed purchased the vaccines from these companies on a commercial basis. (…) Typically, intellectual property that has been funded by the US Government ends up entirely in non-governmental hands, whether at universities or companies. This discrepancy leads to an inequitable outcome (the privatization of publicly funded wealth generation) and to an inefficient outcome (the underuse of intellectual property because of monopoly pricing by patent holders)." (The Lancet 2022, p.1256, also Reuters 2022 and Oxfam 2021)

Although a principle of fair distribution of financial gains holds in most stakeholder disputes, specific cases call for a differentiated analysis: large companies like Pfizer or Astra-Zeneca are qualitatively different actors than small companies like BioNTech. Astra-Zeneca had committed to selling its COVID-19 vaccine at cost during the pandemic, thus putting pressure on competing companies. BioNTech opted for a differential pricing system whereby poor patients in low-income countries could benefit from lower prices cross-subsidized by higher prices for patients in high-income countries, but it struggled to implement this system in the early stages: the company had accumulated 400 million Euros in debt, and according to the agreement with Pfizer would have to cover 50% of the costs of Project Lightspeed. While at-cost prices would have ruined BioNTech, a large company with a diversified product portfolio like Pfizer had many more options when it came to cross-subsidizing the vaccine. As prices for pharmaceuticals – particularly for life-threatening diseases – are always also a political issue, the final price is most often the result of negotiations between the state, insurance companies and the company.

7. Lessons Learned and Outlook

First and foremost, Project Lightspeed's swift and successful development of the BioNTech COVID-19 vaccine (COMIRNATY) can be explained by the work ethos and courageous leadership of Uğur Şahin and his wife, Özlem Türeci. The couple acted as role models for BioNTech's employees and created a corporate culture characterized by a quiet individual determination to do one's best and act with integrity. Project Lightspeed is a case study in leadership excellence and a prominent contemporary illustration of the significance of individual character. (see also Leisinger 2020 on leadership excellence)

Second, the best efforts of individual people may come to nothing if they are not embedded in a framework in which various solution-seeking stakeholders co-create to the best of their abilities. Şahin and Türeci were able to rely on a network of like-minded people willing to give their best and push the normal limits of what is considered possible. Project Lightspeed hence provides an important example of the value of solution-oriented stakeholder relationships with maximal transparency and truthfulness in all interactions.

Third, Project Lightspeed demonstrates that the existence of a purpose-driven, ethical corporate culture can facilitate the acceleration of work processes without neglecting safety concerns or violating ethical and integrity standards.

Fourth, Project Lightspeed is a splendid example of science and (business-led) technological innovation making a difference in global efforts to achieve the goals set in the Agenda 2030 for Sustainable Development. (United Nations 2015)

Last but not least, corporate action, as successful as it can be, provides no silver bullets: companies are part of a moving jigsaw puzzle where active coalitions must be forged and elements of non-competitive teamwork nurtured. (Smit et alia / McKinsey 2022): *Vaccines don't save lives, vaccinations do*: Without an appropriate health policy allocating resources according to prevailing disease patterns; without a functioning primary health care system that allows for early diagnosis and appropriate treatment or referral by community health workers;

without basic infrastructure (roads, electricity, etc.), and last but not least without overcoming widespread vaccination hesitation. even the best vaccine in the world cannot unfold its full potential.

Future pioneers of emergency solutions to global health problems, moreover, will face a series of ethical and legal challenges similar to those discussed here. Struggling with a specific stabilization problem in the mRNA molecule in the early spring of 2020, Şahin approached Barney Graham, a veteran immunologist and virologist at the U.S. National Institutes of Health (NIH). Graham had used modern bioengineering techniques to facilitate the development of vaccinations against viral diseases such as RSV (Human Respiratory-Syncytial-Virus) and MERS (Middle East Respiratory Syndrome Coronavirus). Graham's method, Şahin hoped, could help to solve his stabilization problem too.

Graham was already collaborating with BioNTech's mRNA rival Moderna, which was also working on a coronavirus vaccine. Şahin nevertheless trusted that he could count on a fellow scientist's sense of responsibility to help solve a global problem, and he was right: Graham had the knowledge Şahin needed and generously gave it to him.

Graham explained his constructive attitude in the following terms: "I am a public servant (… and the reason to help) is to make things go faster, go better." After discussions with Anthony Fauci, the head of the NIH's Infectious Disease Agency, Graham reported that "we had made a decision internally that we would not worry too much about IP or confidentiality". (MTS p.72)

A scientist's willingness to serve humanity in the midst of a crisis, however, has since become a legal bone of contention. In August 2022, Moderna sued Pfizer and its German partner BioNTech for patent infringement in the United States, alleging that the firm illegally copied technology Moderna had developed years before the pandemic. The outstanding verdict in this case will provide an important precedent for future scientific collaboration in pandemics and other global emergencies.

8. References

BioNTech (2022.1): Our mission. https://www.biontech.com/int/en/home.html (last access November 9, 2022);

BioNTech (2022.2): Therapeutic areas. https://www.biontech.com/int/en/home/research-and-innovation/therapeutic-areas.html (last access November 12, 2022);

Castillo J.C. et alia (2021): Market design to accelerate COVID-19 vaccine supply. SCIENCE vol.371 No. 6534 https://www.science.org/doi/10.1126/science.abg0889

Cueni Th. (2019): Fair Pricing – Striking the Balance. In: Health Policy Watch. https://www.healthpolicy-watch.org/fair-pricing-striking-the-balance/

Fleming S. (2021): EU must prepare for "era of pandemic", von der Leyen says. In: Financial Times, 28 Feb 2021.

Frost R (1915): The Road not Taken. https://www.theatlantic.com/magazine/archive/1915/08/a-group-of-poems/306620/

Gates B. (2022): How to Prevent the Next Pandemic. (Penguin Random House) New York; German edition: Wie wir die nächste Pandemie verhindern, (Piper) München;

HHL (2018): Das Leipziger Führungsmodell. Leipzig Graduate School of Management, 3. edn., Leipzig. https://www.hhl.de/leipzig-leadership-model/, accessed on 22.11.2022

Institute for Health Metrics and Evaluation (IHME): Covis-19 projections. https://covid19.healthdata.org/global?view=cumulative-deaths&tab=trend (last access May 4th, 2023);

Leisinger K. (2020): The Art of Leading. The Significance of Personality and Character on the Choice of Leadership Personalities in the Economy. (CRT Publications), Minneapolis;

Leisinger K. (2022): Integrity in Business and Society. Idealism without illusions. (CRT Publications), Minneapolis;

McKinsey Quarterly (August 2020): Igniting individual purpose in times of crisis.

Miller J., Türeci Ö., Şahin U. (2022): The Vaccine. Inside the Race to Conquer the Covid-19 Pandemic. St. Martin's Press, New York, also available in German as Projekt Lightspeed. Der Weg zum BioNTech-Impfstoff – und zu einer Medizin von morgen. (Rowohlt) Hamburg 2021;

National Library of Medicine (2020): Severe acute respiratory syndrome coronavirus 2 isolate Wuhan-Hu-1, complete genome. https://www.ncbi.nlm.nih.gov/nuccore/MN908947 (last accessed November 11, 2022);

Oxfam (2021): Vaccine monopolies make cost of vaccinating the world against Covid at least 5 times more expensive that it could be. https://www.oxfam.org/fr/node/17295

Reuters (2022): Pfizer COVID vaccine price hike to boost revenue for years, rivals may follow. https://www.reuters.com/business/healthcare-pharmaceuticals/pfizer-covid-vaccine-price-hike-seen-giving-revenue-boost-years-2022-10-21/;

Schweizerische Akademie der Naturwissenschaften (scnat): Was ist eine mRNA und welche Funktion hat sie? https://naturwissenschaften.ch/covid19-vaccination-explained/mrna_vaccines/was_ist_eine_mrna_und_welche_funktion_hat_sie_ (letzter Zugang 10.11.2022);

Smit S. / et alia / McKinsey & Company (2022): Towards a sustainable, inclusive, growing future: The role of business. https://www.mckinsey.com/featured-insights/sustainable-inclusive-growth/toward-a-sustainable-inclusive-growing-future-the-role-of-business (letzter Zugang 5.5.2023)

The LANCET Commission (2022) Lessons for the Future from COVIC-19 pandemic. https://www.thelancet.com/action/showPdf?pii=S0140-6736%2822%2901585-9 ;

United Nations (2015): Transforming Our World: The 2030 Agenda for Sustainable Development. https://sustainabledevelopment.un.org/content/documents/21252030%20Agenda%20for%20Sustainable%20Development%20web.pdf

US House Committee of Energy and Commerce (2021): Pathways to a Vaccine: Efforts to Develop a Safe, Effective and Accessible Covid 19 vaccine. https://www.youtube.com/watch?v=tnWwJPe7p2A

WHO (2015): Guidelines on the quality, safety and efficacy of Ebola vaccines. (WHO/BS/2015.2276)

WHO (2023): Press conference on Covid-19 and other global health issues, Statement Dr. Tedros Adhanom Ghebreeyesus (https://www.who.int/emergencies/diseases/novel-coronavirus-2019?adgroupsurvey=%7Badgroupsurvey%7D&gclid=EAIaIQobChMItYz7_Pbn_gIVj7myCh1vogZWEAAYASAAEgJWVvD_BwE